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Table of Contents

Research Articles

- 1. RELATIONSHIP BETWEEN ANXIETY, DEPRESSION LEVELS AND COPING STYLE WITH STRESS AND SLEEP QUALITY OF PATIENTS WITH MYOCARDIAL INFARCTION**   
(Miyokard infarktüsü geçiren hastaların anksiyete, depresyon düzeyleri ve stresle baş etme yöntemleri ile uyku kalitesi arasındaki ilişki)  
Emel DEMİRBAŞ, Yunus KAYA.....344-355
- 2. NEW EVIDENCE-BASED PHYSIOTHERAPY APPROACHES IN THE TREATMENT OF PATELLOFEMORAL PAIN SYNDROME IN THE LAST FIVE YEARS**   
(Patellofemoral ağrı sendromu tedavisinde son beş yılda kanıta dayalı yeni fizyoterapi yaklaşımları)  
Musa ÇANKAYA, İlkin ÇITAK KARAKAYA.....356-364
- 3. OVERVIEW ON VASCULAR SURGERY**   
(Vasküler cerrahiye genel bakış)  
Serpil ŞAHİN.....365-369
- 4. ENCEPHALOCELE: RETROSPECTIVE ANALYSIS AND OUR CLINICAL EXPERIENCE**   
(Ensefalosel: retrospektif analiz ve klinik deneyimimiz)  
Elif BAŞARAN GÜNDOĞDU, Nermin KILICARSLAN.....370-378
- 5. INVESTIGATION OF GLOBAL TRENDS IN PUBLICATIONS ON SYPHILIS WITH BIBLIOMETRICS**   
(Sifiliz hakkındaki yayınların küresel eğilimlerinin bibliyometrik incelenmesi)  
Emine Kübra DİNDAR DEMİRAY, Sevil ALKAN, Cihan YÜKSEL.....379-386
- 6. EVALUATION OF CORNEAL AND LENS DENSITOMETRY WITH SCHEIMPFLUG IMAGING IN YOUNG BETA THALASSEMIA PATIENTS**   
(Genç beta talasemi hastalarında scheimpflug görüntülemeyle korneal ve lens dansitometrisinin değerlendirilmesi)  
Hafize Gökben ULUTAŞ, Elif Güler KAZANCI.....387-394
- 7. THE IMPACT OF ENDEMIC IRIS TAOCHIA ETHANOLIC EXTRACTS ON HUMAN LUNG ADENOCARCINOMA CELLS**   
(Endemik iris taoki etanolik özütlerinin insan akciğer adenokarsinoma hücreleri üzerindeki etkisi)  
Nezahat KANDEMİR, Emine ÇELİKOĞLU, Şevket KANDEMİR, Umut ÇELİKOĞLU, Önder İDİL, Canan Vejselova SEZER, Hatice Mehtap KUTLU.....395-403
- 8. GLOBAL TRENDS IN HEMOPHILIA RESEARCH**   
(Hemofili araştırmalarında küresel trendler)  
Can ÖZLÜ, Güray CEYLAN.....404-410
- 9. TIME-DEPENDENT RECEIVER OPERATING CHARACTERISTIC ANALYSIS AND APPLICATIONS IN THE FIELD OF MEDICINE**   
(Tıp alanında zaman bağımlı alıcı çalışma özellikleri analizi ve uygulamaları)  
Ceren EFE SAYIN, İlker ÜNAL.....411-416
- 10. THE RELATION BETWEEN THE URIC ACID LEVELS AND THE RECANALIZATION TIMES IN PATIENTS WITH CEREBRAL VENOUS THROMBOSIS**   
(Serebral venöz tromboz olan hastalarda ürik asit düzeyleri ile rekanalizasyon süreleri arasındaki ilişki)  
Fatma ŞİMŞEK.....417-423
- 11. THE EFFECT OF PERCEPTION OF DEATH ON SPIRITUAL WELL-BEING IN ADULTS**   
(Yetişkin bireylerde ölüm algısının manevi iyi oluş üzerine etkisi)  
Didem AYHAN, Hilal SEKİ ÖZ.....424-429

**12. EFFECT OF APACHE-II AND THE AGE-ADJUSTED CHARLSON COMORBIDITY INDEX AT PREDICTING MORTALITY IN PATIENTS WITH COVID-19** 

(Apache-ii ve yaşa ayarlanmış charlson koorbidite endeksi'nin Kovid-19'lu hastalarda mortalite öngörülemede etkisi)

Sermin EMINOGLU, Seyda Efsun OZGUNAY.....430-437

**13. WHERE IS TÜRKİYE IN ATAXIA REHABILITATION? BIBLIOMETRIC ANALYSIS STUDY** 

(Türkiye ataksi rehabilitasyonunda nerededir? Bibliyometrik analiz çalışması)

Fatma ERDEO, İsmail CEYLAN.....438-445

**14. DO HUMOR STYLES OF PATIENTS AFFECT THEIR INTENSIVE CARE EXPERIENCES?** 

(Hastaların mizah tarzları yoğun bakım deneyimlerini etkiliyor mu?)

Seher ÇEVİK AKTURA, Serdar SARITAŞ, Sultan TARLACI.....446-453

**15. THE EFFECT OF ATTITUDE TOWARDS UNCERTAINTY AND PERCEIVED CONTAMINATION COGNITION ON MENTAL STATUS OF NURSES DURING THE COVID-19 PANDEMIC** 

(Belirsizliğe karşı tutum ve algılanan kontaminasyon bilşinin Kovid-19 pandemisi sırasında hemşirelerin ruhsal durumlarına etkisi)

Mahmut EVLİ, Nuray ŞİMŞEK, Ömer ÖDEK.....454-462

**16. THE ASSESSMENT OF ANESTHESIA TECHNIQUES USED IN PATIENTS UNDERGOING CESAREAN SECTION: COMPARISON OF DAY AND NIGHT SHIFT PERIODS** 

(Sezaryen operasyonlarında uygulanan anestezi tekniğinin değerlendirilmesi: mesai içi ve dışı saatlerin karşılaştırılması)

Özlem ÖZKUMİT, Ayşe Neslihan BALKAYA, Elif EYGİ, Şükran ŞAHİN, Şefika Gülsen KORFALI.....463-470

**17. THE ROLE OF INFLAMMATORY MARKERS AND THE MODIFIED SYSTEMIC INFLAMMATORY SCORE IN BETHESDA CATEGORY 3 AND 4 PATIENTS FOR PREDICTION OF MALIGNANCY** 

(Bethesda kategorisi 3 ve 4 hastalarında malignitenin öngörülmesinde inflamatuvar belirteçlerin rolü ve değiştirilmiş sistemik iltihap skoru)

Sönmez OCAK, Ömer Faruk BÜK, Ahmet Can SARI, Ahmet Burak ÇİFTÇİ.....471-475

**18. SOCIAL INTELLIGENCE, SELF-EFFICACY, AND STRESS-COPING STYLES AS PREDICTORS OF EMOTIONAL INTELLIGENCE IN NURSING STUDENTS: A DESCRIPTIVE STUDY** 

(Hemşirelik öğrencilerinde duygusal zeka yönlendiricileri olarak sosyal zeka, kendi yetkililik ve stresle başa çıkma stilleri: belirleyici bir araştırma)

Alime SELÇUK TOSUN, Nurcan AKGÜL GÜNDOĞDU, Emine ERGİN, Neslihan LÖK.....476-483

**19. CONFIGURAL FREQUENCY ANALYSIS FOR MEDICAL SCIENCES WITH SPSS** 

(SPSS ile tıp bilimleri için yapılandırıcı frekans analizi)

Fatih ÜÇKARDEŞ.....484-489

**20. PATIENT CHARACTERISTICS, LOCATIONS AND HISTOPATHOLOGICAL FEATURES OF STEATOCYSTOMA MULTIPLEX CASES** 

(Steatosistom çoklu olguların hasta özellikleri, lokasyonları ve histopatolojik özellikleri)

Hilal BALTA, İlknur ÇALIK, Şenay ERDOĞAN DURMUŞ, Sevilay ÖZMEN, Ahmet Erkan BİLİCİ.....490-492

**21. DOES SHORT TERM DIETARY INTERVENTION CHANGE DIETARY CARBON FOOTPRINT?** 

(Kısa süreli beslenme müdahaleleri beslenme karbon ayak izini değiştirir mi?)

Feride AYYILDIZ, Büşra ATABİLEN, Hilal YILDIRAN.....493-499

**22. INVESTIGATION OF KNOWLEDGE LEVEL OF HEALTH PERSONNEL WORKING IN COVID-19 CLINICS AND COMPLIANCE WITH ISOLATION MEASURES** 

(Kovid-19 kliniklerinde çalışan sağlık personelinin bilgi düzeyi ve izolasyon önlemlerine uyumlarının incelenmesi)

Dudu ALPTEKİN, Derya GEZER, Esmâ GÖKÇE, Hamide ŞİŞMAN, Refiye AKPOLAT, Sevban ARSLAN.....500-506

**23. INVESTIGATION OF NURSING THESIS RELATED TO REIKI APPLICATION ON PAIN IN TÜRKİYE** 

(Türkiye’de ağrıya yönelik reiki uygulaması ile ilgili yapılmış hemşirelik tezlerinin incelenmesi)

Hamide ŞİŞMAN.....507-511

**24. THE EFFECT OF WORKING IN A HOSPITAL OFFERING PANDEMIC-RELATED SERVICES ON THE PERCEIVED STRESS AND ANXIETY LEVELS OF NURSES DURING COVID-19: A CASE OF TWO HOSPITALS** 

(Pandemiyle ilgili hizmet veren bir hastanede çalışmanın Kovid-19 sırasında hemşirelerin algılanan stres ve kaygı düzeylerine etkisi: iki hastane olgusu)

Züleyha KILIÇ, Tülay AYTEKİN AYDIN, Yurdağül GÜNAYDIN, Yunus HACIMUSALAR, Ayşe AYDINLI.....512-518

**25. GLOBAL TRENDS IN TRACHOMA** 

(Trahomada küresel trendler)

Mustafa YILMAZ, Emine Kübra DİNDAR DEMİRAY.....519-525

**26. THE EFFECT OF INDIVIDUAL EXERCISE AND GROUP EXERCISE TRAINING ON PHYSICAL PERFORMANCE IN HEALTHY WOMEN** 

(Sağlıklı kadınlarda bireysel egzersiz ve grup egzersiz eğitimlerinin fiziksel performans üzerine etkisi)

Tuğba GÖNEN, Yavuz YAKUT.....526-532

**27. ANALYSIS OF THE EFFECTIVENESS OF FIRST TRIMESTER NUCAL TRANSLUCENCE, FREE BETA-HUMAN CHORIONIC GONADOTROPIN, AND PREGNANCY-RELATED PLASMA PROTEIN-A IN PREDICTION OF PREGNANCY COMPLICATIONS** 

(Gebelik komplikasyonlarının tahmininde birinci trimester saydamlığı, serbest beta-insan koryonik gonadotropin ve gebelikle ilgili plazma protein-a etkinliğinin analizi)

Kamuran SUMAN, Zafer BÜTÜN, Musa BÜYÜK, Murat SUMAN, Banu DANE.....533-539

**28. THE EFFECT OF DISTANCE EDUCATION ON THE PROFESSIONAL COMPETENCE AND ACADEMIC MOTIVATION OF MIDWIFERY STUDENTS: A QUALITATIVE STUDY** 

(Uzaktan eğitimin ebelik öğrencilerinin mesleki yeterlilik ve akademik motivasyonu üzerine etkisi: kalitatif bir araştırma)

Sahika SIMSEK CETINKAYA, Demet GUNEY.....540-546

**29. SCIENTIFIC OUTPUTS OF HYPERTENSIVE RETINOPATHY** 

(Hipertansif retinopatinin bilimsel çıktıları)

Ayşe Nilüfer KÖYLÜOĞLU, Bünyamin AYDIN.....547-552

**30. EVALUATION OF COGNITIVE FUNCTIONS IN SCHIZOPHRENIC PATIENTS WITH THE MONTREAL COGNITIVE ASSESSMENT SCALE AND MINI-MENTAL STATE EXAMINATION** 

(Şizofrenik hastalarda bilişsel fonksiyonların montreal kognitif değerlendirme ölçeği ve minimal durum muayenesi ile değerlendirilmesi)

Serkan ZINCİR.....553-557

**31. CURRENT STATUS OF THALASSEMIA MINOR STUDIES** 

(Talasemi minör çalışmalarının mevcut durumu)

Güray CEYLAN, Can ÖZLÜ.....558-564

**Case Report**

**32. SPLENIC INFARCTION FOLLOWING THYROIDECTOMY: AN UNUSUAL CASE IN THE EMERGENCY DEPARTMENT** 

(Tiroidektomi sonrası splenik enfeksi: Acil bölümde olağanüstü bir olgu)

Nafis VURAL.....565-567

- 33. COVID-19 CASE PRESENTING WITH ANOSMIA AND RASH**   
(Anosmi ve döküntü ile başvuran Covid-19 vakası)  
*Serpil OĞUZ MIZRAKÇI*.....568-569
- 34. METHANOL INTOXICATION WITHOUT OPTIC ATROPHY AND CENTRAL DAMAGE**   
(Optik atrofi ve merkezi hasar olmadan metanol zehirlenmesi)  
*Fatma SÜMER*.....570-573
- 35. A RARE CASE OF SCALP MASS: CLEAR CELL HIDRADENOCARCINOMA**   
(Nadir bir skalp kültesi olgusu: Berrak hücreli hidradenokarsinoma)  
*Gözde KURTULUŞ, Serdar TOKMAK, Samet DINÇ, Adem KURTULUŞ*.....574-576

### **Review Articles**

- 36. EFFICACY OF POSTERIOR TIBIAL NERVE STIMULATION IN THE TREATMENT OF URINARY INCONTINENCE**   
(Üriner inkontinans tedavisinde posterior tibial sinir stimülasyonunun etkinliği)  
*Musa ÇANKAYA, Maria CİORBADJİ*.....577-584
- 37. EVALUATION OF CALCIUM ELECTROPORATION IN CANCER TREATMENT WITH IN VITRO, IN VITRO AND CLINICAL STUDIES**   
(In vitro, in vivo ve klinik çalışmalarla kanser tedavisinde kalsiyum elektroporasyonunun değerlendirilmesi)  
*Güney GÜRİSOY, Meriç Arda EŞMEKAYA, Zehra ÇİÇEK*.....585-590
- 38. A HOLISTIC APPROACH TO THE EFFECTS OF INTRAUTERINE ANTIMICROBIAL THERAPY ON PREGNANCY RATE AFTER ARTIFICIAL INSEMINATION IN DAIRY COWS**   
(Süt ineklerinde yapay tohumlama sonrası içi antimikrobial tedavinin gebelik oranı üzerindeki etkilerine bütünsel bir yaklaşım)  
*Ömer UÇAR, Deniz AĞIRBAŞ*.....591-596
- 39. EXAMINATION OF SOME FACTORS THAT MAY AFFECT LEARNING AND MEMORY IN THE SPACE ENVIRONMENT**   
(Uzay ortamında öğrenme ve belleğe etki edebilecek bazı faktörlerin irdelenmesi)  
*Serdar SARITAŞ, Pınar ÖZ*.....597-599
- 40. ANATOMY EDUCATION FROM THE PAST TO THE FUTURE**   
(Geçmişten geleceğe anatomi eğitimi)  
*Engin ÇİFTÇİOĞLU, Zeynep ALTUNTAŞ, Ezgi ÇİFTÇİOĞLU*.....600-605



## MİYOKARD İNFARKTÜSÜ GEÇİREN HASTALARIN ANKSİYETE, DEPRESYON DÜZEYLERİ VE STRESLE BAŞ ETME YÖNTEMLERİ İLE UYKU KALİTESİ ARASINDAKİ İLİŞKİ

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**Özet:** Bu araştırma, miyokard infarktüsü geçiren hastaların anksiyete, depresyon düzeyleri ve stresle baş etme yöntemleri ile uyku kalitesi arasındaki ilişkinin incelenmesi amacıyla tanımlayıcı olarak yapılmıştır. Araştırmanın örneklemini Koroner Yoğun Bakım Ünitesinde yatan 300 hasta oluşturmuştur. Araştırmanın verileri, Hasta Tanıtıcı Özellikler Soru Formu, Hastane Anksiyete-Depresyon Ölçeği, Stresle Başa Çıkma Tarzları Ölçeği ve Richard-Campbell Uyku Ölçeği kullanılarak toplanmıştır. Araştırma verilerinin değerlendirilmesinde; Kruskal-Wallis, Mann Whitney U ve Spearman's korelasyon analizleri kullanılmıştır. Araştırmaya katılan hastaların anksiyete (8,03±4,45) ve depresyon (9,28±4,75) puan ortalamaları sınırdadır bulunmuştur. Uyku kalitesi puan ortalaması (35,6±19,4) düşük bulunurken, stresle baş etme alt boyut puan ortalamaları, Kendine Güvenli Yaklaşım 22,4±3,4, Çaresiz Suçlayıcı Yaklaşım 19,8±4,5, Boyun Eğici Yaklaşım 14,1±3,1, İyimser Yaklaşım 14,9±2,6 ve Sosyal Destek Arama için 10,6±2,3 olarak bulunmuştur. Kendine Güvenli Yaklaşım, İyimser Yaklaşım ve Sosyal Destek Arama ile anksiyete ve depresyon arasında ise negatif yönde ilişki bulunurken, Çaresiz Suçlayıcı Yaklaşım ve Boyun Eğici Yaklaşım ile anksiyete ve depresyon düzeyleri arasında pozitif yönde ilişki bulunmuştur. Uyku kalitesi ile anksiyete, depresyon ve Çaresiz Suçlayıcı Yaklaşım ile arasında negatif yönde ilişki bulunurken, İyimser Yaklaşım ve Kendine Güvenli Yaklaşım ile aralarında pozitif yönde ilişki tespit edilmiştir. Sağlık çalışanları koroner yoğun bakım ünitelerinde miyokard infarktüsü geçiren hastaların ruhsal durumları değerlendirilmeli ve hastalara ruhsal destek sağlanmalıdır.

**Anahtar kelimeler:** Anksiyete, Baş etme, Depresyon, Miyokard infarktüsü, Uyku kalitesi

### Relationship between Anxiety, Depression Levels and Coping Style with Stress and Sleep Quality of Patients with Myocardial Infarction

**Abstract:** This research was conducted as a descriptive study to examine the relationship between anxiety, depression levels, coping styles and sleep quality in patients with myocardial infarction. The sample of the study consisted of 300 patients who were admitted to the coronary intensive care unit. The data of the study were collected by using the Patient Characteristics Questionnaire, the Hospital Anxiety-Depression Scale, the Stress Coping Style Scale, and the Richard-Campbell Sleep Questionnaire. In the evaluation of research data; Kruskal-Wallis, Mann Whitney U and Spearman's correlation analyzes were used. The mean scores of anxiety (8.03±4.45) and depression (9.28±4.75) the scores of the patients were found to be limit. While the sleep quality mean score was low (35.6±19.4), the sub-dimension mean scores for Stress Coping Style Scale were Self-confident Approach 22.4±3.4, Helpless Accusatory Approach 19.8±4.5, Submissive Approach 14.1±3.1, Optimistic Approach 14.9±2.6 and Seeking Social Support 10.6±2.3. While there was negative relationship between Self-confident, Optimistic, Seeking Social Support Approach and anxiety and depression, positive relationship was found between Helpless Accusatory and Submissive Approach and anxiety and depression levels. While there was negative correlation was found between the sleep quality scale and the Helpless Accusatory Approach, anxiety and depression, positive relationship was found between Optimistic, Self-confident Approach and sleep quality. Health care providers responsible for the care of patients with acute myocardial infarction followed up in the coronary intensive care unit should evaluate the mental health status of the patients and should be provided psychological support.

**Keywords:** Anxiety, Coping, Depression, Myocardial infarction, Sleep quality

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### 1. Giriş

Koroner arter hastalıkları (KAH) hem dünyada hem de ülkemizde morbidite ve mortalite oranlarını artırarak bireylerin yaşamsal bütünlüğünü tehlikeye sokan hastalıklar olarak tanımlanmaktadır. Gelişmiş ve

gelişmekte olan ülkelerde ölüm sebepleri arasında KAH ilk sırada yer alırken, Dünya Sağlık Örgütü (DSÖ) istatistiklerine göre ise kalp damar hastalıkları ilk 10 ölüm nedeni arasında birinci sırada yer almaktadır (Malakar ve ark., 2019; WHO, 2020). Türkiye İstatistik Kurumu (TÜİK)



2018 verilerine göre ülkemizde ölüm nedenleri arasında %38,4'lük oranı kalp damar sistemi hastalıkları oluştururken, kalp damar sistemi hastalıklarından kaynaklı ölümlerin %39,7'sini iskemik kalp hastalıkları oluşturmaktadır (TÜİK, 2018). KAH, kalbi besleyen ana koroner damarların ateroskleroz ve trombüs sonucunda ciddi tıkanıklık oluşması nedeniyle kalbin oksijen gereksiniminin karşılanmaması ile karakterize bir hastalıktır. Kalbin oksijen gereksiniminin karşılanmaması kalp kasında hipoksi ve iskemiye yol açabilmektedir (Durusoy ve ark., 2010). Hipoksi ve iskemi sonucunda koroner kan akımında azalma ile birlikte akut koroner sendroma (AKS) sebep olabilen patolojik bir süreç başlamaktadır (Thygesen ve ark., 2018). AKS'de hastanın elektrokardiyografi (EKG) dalgalarına bakılarak ST yükselmez Miyokard İnfarktüsü (NSTEMI - Non ST Elevation Myocardial Infarction) veya ST yükselmeli Miyokard İnfarktüsü (STEMI - ST Elevation Myocardial Infarction) gibi bireyin yaşamsal bütünlüğünü etkileyen ciddi sorunlara neden olmaktadır (Yalçınkaya, 2006). AKS metabolizma üzerinde oluşturduğu sorunlar nedeniyle koroner yoğun bakım ünitesine yatırılma sebepleri arasında ilk sırada yer almaktadır (Ceylan ve ark., 2011). AKS sonucunda oluşan MI'da mortalite oranının oldukça yüksek olmasının yanında, yaşamsal bütünlüğün devamı konusunda risklere ve birtakım psikososyal sorunlara neden olarak yaşam kalitesini olumsuz yönde etkilemektedir (Erşan ve ark., 2013). AKS sırasında oluşan ve etkisi uzun sürebilen şiddetli angina pectoris hastada kaygı, ölüm korkusu ve beraberinde günlük yaşama uyumda sorunlara neden olabilmektedir. AKS'ye bağlı meydana gelen MI sonucunda hastaneye yatma, uygulanan tedaviler, tekrar MI geçirme korkusu, ölüm korkusu ve kaygı sorunları hastalığın yanında birçok psikososyal sorunu da beraberinde getirmektedir (Akkaya ve ark., 2013; Dias ve ark., 2015). Hem yaşamsal önemi olan kalp üzerinde meydana gelen sorunlar hem de kronik hastalık tanısı almak ve yaşanan psikososyal sorunlar sıklıkla beraberinde ruhsal sorunlara da neden olabilmektedir (Yıldırım ve ark., 2016). Kronik kalp hastaları üzerinde yapılan çalışmalar değerlendirildiğinde hastaların yarısından fazlasında depresyon ve anksiyete bozukluklarının olduğu görülmektedir. Hastalarda ortaya çıkan psikiyatrik komorbiditeler tedavi sürecini olumsuz yönde etkilemenin yanında fiziksel hastalığın daha ağır seyretmesine, hastalığa uyumda sorunlara ve yaşam kalitesinde azalmaya neden olmaktadır (Aydemir ve ark., 2015). Hastaların yaşadıkları stres, kaygı ve depresyon gibi sorunlar, kardiyovasküler hastalıklarda kalbin oksijen gereksiniminde artışa neden olmakta ve hastalığa bağlı bu gereksinimin karşılanmaması nedeniyle mortalite oranlarının artmasına neden olan önemli birer risk faktörleridirler. Aynı zamanda yaşanan stres, kaygı ve depresyon gibi ruhsal sorunlar tekrarlı yatışlara neden olarak iyileşme sürecini de uzatmaktadır (Çam ve Nehir, 2011). MI geçiren hastalarla yapılan diğer çalışmalarda hastaların umutsuzluk ve depresyon düzeyinin yüksek olduğu ve bu durum nedeniyle hastanın hastalıkla baş

etmede yetersizliğe, kişiler arası ilişkilerde bozulmaya, fiziksel iyilik halinde ve iyileşme sürecinde sorunlara yol açtığı görülmektedir (Çam ve Nehir, 2011; Fırat Akçay ve Dereli, 2016).

Hastaların yaşadığı ruhsal sorunların kardiyovasküler sistem üzerindeki olumsuz etkileri nedeniyle hastalarda yoğun bakım ünitelerine tekrarlı yatışlara neden olabilmektedir. Yoğun bakım ünitesinde yatmakta olan hastalar hastaneye yatma, sevdiklerinden ayrı kalma, ölüm riski ile karşı karşıya kalma gibi nedenlerle kaygı ve depresyonun yanında hastane ortamına bağlı çeşitli stresörlere de maruz kalmaktadırlar. Hastaneye yatış, ağrı, hastalığın nasıl ilerleyeceği ve tam iyileşmenin olup olmayacağına yönelik kaygı, yoğun bakım ortamlarında duyuşsal uyaran eksikliği ya da fazlalığı, mahremiyet kaygısı, sıklıkla gerçekleştirilen tedavi ve bakım uygulamaları ve uyku problemleri hastalar için stres oluşturabilmektedir (Aktaş Yaman ve ark., 2015; Dias ve ark., 2015). Yoğun stres altında stres hormonları olarak da bilinen kortizol ve adrenalin salınımında meydana gelen artış kardiyak aktivitede artışa, bronkodilatasyona, solunum derinliğinin ve hızının artmasına neden olarak kalp üzerinde önemli etkileri olmaktadır. Bu bağlamda hastadaki stres ve stresörler etkin bir şekilde yönetilmediğinde hastada immün sistemin baskılanmasına, dolaşım sisteminde sorunlara, ruhsal ve sosyal zorlanmalara neden olarak hastanın yaşam kalitesinde ve iyilik halinde azalmaya ve ölüme yol açabilmektedir (Selye, 1952; Dias ve ark., 2015; Burford ve ark., 2017).

MI geçiren hastalar, hastalığın ortaya çıkardığı fiziksel ve ruhsal sorunlara bağlı olarak yorgunluk yaşayabilmekte ve uyku gereksinimleri artabilmektedir (Tenekeci ve Kara, 2016). Ancak hastaların psikososyal alanda yaşadıkları sorunlar, bilgi eksikliği, hastanede ortamı, kaygı, depresyon, etkisiz bireysel baş etme, ölüm kaygısı, belirsizlik ve umutsuzluk gibi duygular hastanın uyku örüntüsünde bozulmalara yol açabilmektedir (Karagözoğlu ve ark., 2007; Matsuda ve ark., 2017). Uyku hastanın hem fiziksel olarak dinlenmesinde hem ruhsal olarak kendisini toparlamasında önemli etkisinin olmasının yanında uyku esnasında meydana gelen fiziksel gevşeme, kan basıncının ve kalp atım hızının azalması MI'da yorulan kalbin dinlenmesini sağlar. Ancak, yaşanan psikososyal sorunlar, kaygı ve stres gibi etkiler hem uyku örüntüsünde sorunlara hem de yaşamsal bulgular üzerinde artışa neden olarak hastayı bütüncül olarak etkilemektedir (Trinder ve ark. 2012; Matsuda ve ark., 2017). Köklü (2019)'nün yaptığı çalışmada anksiyete ve uyku bozukluğu olan hastaların kalp hızının daha yüksek olduğu, stres düzeyinin artmasına bağlı olarak anksiyetenin arttığı ve uyku kalitesinin olumsuz etkilendiği bulunmuştur.

Bu araştırmada, MI sonrası koroner yoğun bakıma yatışı yapılan hastaların, anksiyete, depresyon ve stresle baş etme tarzı ile uyku kalitesi arasındaki ilişkinin belirlenmesi amaçlanmıştır. Araştırmada elde edilen veriler, MI geçiren hastaların yaşadıkları psikososyal

sorunların belirlenmesinin yanında hastaların tedavi ve bakımlarını şekillendirmede önemli katkı sağlayacağı düşünülmektedir. Bu nedenle, araştırma bulguları, hem hastalığın fiziksel tedavi ve bakımı hem de konsültasyon liyezon psikiyatrisi (KLP) kapsamında MI geçiren hastaların ruhsal tedavi ve bakımının planlanmasına yönelik önemli katkı sağlayacağı düşünülmektedir. Hastalarda ortaya çıkabilecek psikososyal sorunlara erken dönemde müdahale edilmesi hem fiziksel ve ruhsal iyilik halini artıracak hem de yaşam kalitesinin artmasına katkı sağlayacaktır.

## 2. Materyal ve Yöntem

### 2.1. Araştırmanın Tipi

Bu araştırma, miyokard infarktüsü tanısı ile yoğun bakım ünitesinde yatan hastaların anksiyete, depresyon düzeyleri ve stresle baş etme tarzları ile uyku kalitesi arasındaki ilişkiyi incelemek amacıyla tanımlayıcı ve ilişki arayıcı türde gerçekleştirilmiştir.

Bu araştırma da, araştırma amacı doğrultusunda aşağıdaki sorulara yanıt aranmıştır.

1. MI sonrası hastaların anksiyete, depresyon, stresle baş etme tarzları ve uyku kalitesi puan ortalamaları ne düzeydedir?
2. Hastaların anksiyete ve depresyon puanları ile stresle başa çıkma tarzları ve uyku kaliteleri arasında bir ilişki var mıdır?
3. Hastaların stresle başa çıkma tarzları ile uyku kaliteleri arasında bir ilişki var mıdır?

### 2.2. Araştırmanın Evren ve Örneklemi

Bu araştırma, İstanbul Sultangazi Haseki Eğitim ve Araştırma Hastanesi Koroner Yoğun Bakım Ünitesinde MI tanısı alarak yatan hastalarda gerçekleştirilmiştir. Araştırmanın evrenini, son bir yılda Haseki Eğitim ve Araştırma Hastanesi Koroner Yoğun Bakım Ünitesi'ne MI tanısı ile yatan hastalar oluşturmuştur. Son bir yılda Koroner Yoğun Bakım Ünitesi'ne 1022 MI tanısı alan hastanın yatışı yapılmıştır. Bu nedenle, araştırmanın evrenini, 1022 hasta oluşturmuştur. Araştırmanın örnekleminin hesaplanmasında ise evreni bilinen örneklem hesabı yapılmış, %95 güvenilirlikle ve %5 hata payıyla en az 280 hastanın dahil edilmesi gerektiği bulunmuş ve bu araştırmanın örneklemini 300 hasta oluşturmuştur. Araştırmaya dahil edilmede, Koroner Yoğun Bakım Ünitesine MI tanısı alarak yatma, en az bir gün yoğun bakım ünitesinde kalma, sorulan soruları anlayacak ve onam verecek düzeyde Türkçe okuma ve yazma becerisine sahip olma, ruhsal ve organik (deliryum) başka bir bozukluğunun olmaması, araştırmaya katılmaya gönüllü olması, yazılı ve sözlü onam verme kriterleri aranmıştır.

### 2.3. Veri Toplama Araçları

Araştırmanın verileri, Hasta Tanıtıcı Özellikleri Soru Formu, Hastane Anksiyete-Depresyon Ölçeği, Stresle Başa Çıkma Tarzları Ölçeği ve Richard-Campbell Uyku Ölçeği kullanılarak toplanmıştır.

#### 2.3.1. Hasta tanıtıcı özellikleri soru formu

Araştırmada, hastaların tanıtıcı özellikleri, araştırmacılar

tarafından hazırlanan ve 10 sorudan oluşan soru formu kullanılarak toplanmıştır. Bu formda, hastanın cinsiyeti, yaşı, medeni durumu, öğrenim durumu, gelir durumu, kronik hastalık ve hastaneye yatış öyküsü, sigara/alkol kullanma durumu, günlük uyku saati ve uyku süresinin yeterli olup olmadığını değerlendiren sorular bulunmaktadır.

#### 2.3.2. Hastane anksiyete-depresyon ölçeği (HADÖ)

HADÖ, bedensel hastalığı olan bireylerin anksiyete ve depresyon düzeyini değerlendirmek amacı ile Zigmond ve Snaith (1983) tarafından geliştirilmiştir. Türkçe geçerlik ve güvenilirlik çalışması Aydemir ve ark. (1997) tarafından yapılmıştır. HADÖ'de yer alan sorulardan yedi tanesi anksiyete belirtilerini, yedi tanesi de depresif belirtileri değerlendirmek üzere toplam 14 sorudan oluşmaktadır. Ölçek, dördümlük likert tipi ölçüm aracıdır ve her soruya verilecek yanıtlar 0-3 arası değişmektedir. Her bir alt boyut için puanlar ayrı ayrı hesaplanmakta, anksiyete ve depresyon alt boyutları için minimum 0 ve maksimum 21 puan alınabilmektedir. Alt boyutlardan alınan puanlar arttıkça anksiyete ya da depresyon semptomlarının da arttığı şeklinde yorumlanmaktadır. Alt boyutlar için kesme noktasının, anksiyete alt boyutu için 10 ve depresyon alt boyutu için 7 bulunmuştur. Güvenirlik çalışmasında, Cronbach alfa katsayısı anksiyete alt ölçeği için 0,85, depresyon alt ölçeği için 0,77 olarak bulunmuştur (Aydemir ve ark., 1997). Bu çalışmada, Cronbach alfa katsayısı ise anksiyete alt boyutu için 0,81, depresyon alt boyutu için 0,77 bulunmuştur.

#### 2.3.3. Stresle başa çıkma tarzları ölçeği (SBTÖ)

SBTÖ, Folkman ve Lazarus (1980) tarafından bireylerin stresle başa çıkma tarzını değerlendirmek için geliştirilmiş bir ölçüm aracıdır. Ölçeğin, Türkçe geçerlik ve güvenilirlik çalışması Şahin ve Durak (1995) tarafından yapılmıştır. Ölçek, toplamda 30 sorudan oluşmakta ve her bir soruya verilecek yanıtlar "Tamamen Uygun" (%100) ile "Hiç Uygun Değil" (%0) arasında değişen dördümlük likert tipi bir ölçektir. Ölçeğin beş alt boyutu bulunmaktadır. Kendine Güvenli Yaklaşım alt boyutu yedi sorudan, Çaresiz Yaklaşım sekiz sorudan, Boyun Eğici Yaklaşım altı sorudan, İyimser Yaklaşım beş sorudan ve Sosyal Desteğe Arama dört sorudan oluşmaktadır. Ölçekten elde edilen puanlar toplam puan olarak değil her bir alt boyuta göre puan ortalaması elde edilerek değerlendirilmektedir. Her bir alt boyuttan alınan puan arttıkça o alt boyutun daha fazla kullanıldığı şeklinde yorumlanmaktadır. Türkçe geçerlik ve güvenilirlik çalışmasında alt boyutların Cronbach alfa değerleri 0,47 ile 0,80 arasında değiştiği bulunurken (Şahin ve Durak, 1995), bu çalışma için Cronbach alfa değerlerinin 0,47 ile 0,79 arasında değiştiği bulunmuştur.

#### 2.3.4. Richard-Campbell uyku ölçeği (RCUÖ)

RCUÖ, Richards (1987) tarafından geliştirilen ölçek bireylerin uyku süreçlerini ve kalitelerini değerlendiren bir ölçektir. Ölçeğin, Türkçe geçerlik güvenilirliği Özlü ve Özer (2015) tarafından yoğun bakımda yatmakta olan hastalar ile yapılmıştır. Ölçek toplamda altı sorudan oluşmaktadır. Her bir soru görsel analog skala tekniği ile

0 ile 100 arasında yer alan çizelge üzerinde değerlendirilmektedir. Ölçekte her bir soru için skala üzerinden verilen puanlar ise "0-25" arası çok kötü, "76-100" arası çok iyi şeklinde değerlendirilmektedir. Ölçekten alınan puan seviyesi arttıkça uyku kalitesinin arttığı, puan seviyesi azaldıkça uyku kalitesinin azaldığı şeklinde değerlendirilmektedir. Ölçeğin Türkçe geçerlik ve güvenilirlik formunun Cronbach alfa değeri 0,91 olarak bulunurken (Özlu ve Özer, 2015), bu çalışma için Cronbach alfa değeri 0,95 olarak bulunmuştur.

#### 2.4. Araştırma Verilerinin Toplanması

Araştırma verileri, etik kurul ve kurum izninin ardından Sultangazi Haseki Eğitim ve Araştırma Hastanesi Koroner Yoğun Bakım Ünitesi'nde araştırmaya dahil edilme kriterlerini karşılayan, yazılı ve sözlü onam veren hastalardan toplanmıştır. Araştırma verileri 03.02.2021-01.06.2021 tarihleri arasında toplanmıştır. Ortalama her bir araştırma soru formunun tamamlanması 30 dakika sürmüştür.

#### 2.5. İstatistik Analiz

Araştırma verilerinin analizi için SPSS 25.0 Windows programı kullanılmıştır. Tanımlayıcı istatistikler; kategorik değişkenler için sayı ve yüzde, sayısal değişkenler için ortalama, standart sapma, minimum ve maksimum değerler, ortanca ve çeyrekler arası aralık olarak gösterilmiştir. Araştırma verilerinin normal dağılıp dağılmadığı Kolmogorov-Smirnov testi ile incelenmiş ve araştırma verilerinin normal dağılmadığı görülmüştür. Bu nedenle araştırma verilerinin analizinde, ikili grupların karşılaştırılmasında Mann Whitney U testi ve ikiden çok grupların karşılaştırılmasında ise Kruskal Wallis testi kullanılmıştır. Bağımlı değişkenler arasındaki ilişki ise Spearman Korelasyon Analizi ile değerlendirilmiştir (Önder, 2018).

### 3. Bulgular

Hastaların tanıtıcı özelliklerine bakıldığında, dörtte üçünün (%74,7) erkek, yarısından fazlasının (%57,3) 40-59 yaş aralığında olduğu, büyük çoğunluğunun (%80,7) evli olduğu, yarısından fazlasının (%60,0) ilköğretim mezunu ve (%56,0) gelirinin giderine eşit olduğu görülmektedir. Hastaların yarısından fazlasının (%63,3) en az bir kronik hastalığı olduğunu (hipertansiyon, diabetes mellitus vb.), daha öncesinden en az bir kez hastane yatış öyküsünün olduğunu (%67,0) ve sigara kullandığını (%52,0) belirtmiştir. Hastaların yarısından fazlası (%61,0) günlük

uyku süresinin 6-8 saat arası olarak tanımlarken ve yaklaşık dörtte üçü (%72,3) kendileri için uyku sürelerinin yeterli olduğu bildirilmiştir.

Tablo 1'de HADÖ, SBTÖ ve RCUÖ ölçüm araçlarından elde edilen puan ortalamaları, minimum, maksimum puanları, medyan değerleri, birincil ve üçüncül çeyreklik puanları verilmiştir. Hastaların HADÖ Anksiyete alt boyutu puan ortalaması 8,03±4,45, Depresyon alt boyutu puan ortalaması 9,28±4,75 olarak bulunmuştur. SBTÖ alt boyutlarının puan ortalamaları değerlendirildiğinde ise Kendine Güvenli Yaklaşım ortalaması 22,4±3,4, Çaresiz Suçlayıcı Yaklaşım ortalaması 19,8±4,5, Boyun Eğici Yaklaşım ortalaması 14,1±3,1, İyimser Yaklaşım ortalaması 14,9±2,6 ve Sosyal Destek Arama puan ortalaması 10,6±2,3 olarak bulunmuştur. Katılımcıların, RCUÖ'nün puan ortalaması 35,6±19,4 olduğu bulunmuştur.

Tablo 2'de hastaların tanıtıcı özelliklerine göre ölçek puanlarının farklılaşp farklılaşmadığı değerlendirilmiştir. Hastaların cinsiyetlerine göre HADÖ alt boyutlarından anksiyete ve depresyon puanlarının kadınlarda erkeklere göre yüksek olduğu bulunmuştur (P<0,05). SBTÖ alt boyutlarında ise erkeklerin Kendine Güvenli ve İyimser Yaklaşım alt boyutları puanları yüksek olduğu bulunurken, kadınların Çaresiz Suçlayıcı ve Boyun Eğici Yaklaşım puanları daha yüksek olduğu görülmektedir (P<0,05). RCUÖ toplam puanlarının ise erkeklerin kadınlara göre daha yüksek olduğu bulunmuştur (P<0,05).

Yaş gruplarına göre ise, 19-39 yaş grubunun anksiyete puanı 40-59 yaş grubuna göre yüksek bulunurken, 60 yaş ve üzeri grubun depresyon puanı 40-59 yaş grubuna oranla daha yüksek bulunmuştur (P<0,05). SBTÖ alt boyutlarından Kendine Güvenli Yaklaşım puanının 40-59 yaş grubunda 19-39 yaş grubuna kıyasla daha yüksek olduğu bulunurken (P<0,05), SBTÖ diğer alt boyutlarında ve RCUÖ toplam puanının da yaş grupları arasında istatistiksel olarak anlamlı birer fark bulunamamıştır (P>0,05). Bekarların anksiyete ve depresyon puanı evlilere göre daha yüksek bulunmuştur (P<0,05). Bekarların, SBTÖ alt boyutlarından Çaresiz Suçlayıcı Yaklaşım puanı daha yüksek bulunurken (P<0,05), evlilerin Sosyal Destek Arama ve İyimser Yaklaşım puanlarının daha yüksek olduğu bulunmuştur (P<0,05). SBTÖ diğer alt boyutlarının ve RCUÖ toplam puanının medeni duruma göre istatistiksel olarak farklılaşmadığı bulunmuştur (P>0,05).

**Tablo 1.** MI tanılı hastaların HADÖ, SBTÖ ve RCUÖ puan ortalamaları

Ölçüm Araçları	Alt Boyutlar	Ort.±SD (Min-Max)	Median (IQR)
HADÖ	Anksiyete	8,03±4,45 (0-21)	7 (4,25-7,00)
	Depresyon	9,28±4,75 (0-21)	9 (5,25-9,00)
SBTÖ	Kendine Güvenli Yaklaşım	22,4±3,4 (12-28)	22 (20-25)
	Çaresiz Suçlayıcı Yaklaşım	19,8±4,5 (9-32)	20 (17-23)
	Boyun Eğici Yaklaşım	14,1±3,1 (6-24)	14 (12-16)
	İyimser Yaklaşım	14,9±2,6 (8-20)	15 (13-16)
	Sosyal Destek Arama	10,6±2,3 (4-16)	11 (9-12)
RCUÖ	Toplam Puan	35,6±19,4 (5-92)	32,5 (21-49)

**Tablo 2.** MI tanılı hastaların tanıtıcı özelliklerine göre HADÖ, SBTÖ ve RCUÖ puanları

Hastanın Tanıtıcı Özellikleri (n)	HADÖ				SBTÖ			RCUÖ
	Anksiyete	Depresyon	Kendine Güvenli Yaklaşım	Çaresiz Suçlayıcı Yaklaşım	Boyun Eğici Yaklaşım	İyimser Yaklaşım	Sosyal Destek Arama	
<b>Cinsiyet</b>								
Kadın (76)	211,20	199,85	122,68	196,12	183,28	122,32	136,25	117,26
Erkek (224)	129,90	133,76	159,84	135,02	139,38	160,06	155,33	161,78
İstatistiksel Analiz	U: 3,898 P=0,0001	U: 4,761 P=0,0001	U: 6,397 P=0,001	U: 5,045 P=0,0001	U: 6,020 P=0,0001	U: 6,370 P=0,001	U: 7,429 P=0,0094	U: 5,986 P=0,0001
<b>Yaş</b>								
19-39 Yaş <sup>a</sup> (17)	198,06	130,56	104,38	141,74	138,15	125,62	170,94	189,71
40-59 Yaş <sup>b</sup> (172)	143,71	140,13	159,09	151,21	151,21	151,74	153,33	154,41
60 ve üzeri <sup>c</sup> (111)	153,73	169,92	144,26	150,74	151,29	152,39	142,98	138,44
İstatistiksel Analiz	KW= 6,344 P=0,04	KW= 8,790 P=0,01	KW= 7,125 P=0,02	KW=0,187 P=0,91	KW=0,369 P=0,83	KW=1,509 P=0,47	KW=2,002 P=0,36	KW=5,970 P=0,05
<b>Medeni Durum</b>								
Evli (242)	142,19	139,97	154,30	145,08	148,64	155,67	157,95	154,72
Bekar (58)	184,16	195,68	134,63	173,09	158,24	128,91	119,42	132,89
İstatistiksel Analiz	U=5,007 P=0,001	U=4,497 P=0,0001	U=6,097 P=0,119	U=5,707 P=0,027	U=6,569 P=0,447	U=5,766 P=0,034	U=5,215 P=0,002	U=5,996 P=0,085
<b>Eğitim düzeyi</b>								
Okur yazar <sup>a</sup> (27)	168,87	188,44	97,17	185,76	182,69	138,52	129,91	109,46
İlkokul <sup>b</sup> (180)	167,13	153,98	161,94	149,75	151,04	158,32	151,48	149,23
Ortaokul <sup>c</sup> (38)	149,26	144,37	144,42	160,34	164,84	150,92	142,01	166,95
Lise <sup>d</sup> (35)	148,71	125,63	145,84	127,34	117,57	133,63	158,36	169,66
Üniversite ve üzeri <sup>e</sup> (20)	161,48	123,18	139,25	131,45	132,55	125,03	171,83	152,53
İstatistiksel Analiz	KW=1,833 P=0,76	KW=10,707 P=0,03	KW=14,077 P=0,001	KW=8,467 P=0,07	KW=10,773 P=0,02	KW=5,103 P=0,27	KW=3,473 P=0,48	KW=9,170 P=0,05
<b>Eğilim Durumu</b>								
Gelir<Gider <sup>a</sup> (112)	174,48	175,75	142,46	166,42	159,50	139,45	147,49	142,09
Gelir=Gider <sup>b</sup> (168)	136,09	140,76	155,11	144,32	149,80	158,03	152,28	151,06
Gelir>Gider <sup>c</sup> (20)	137,28	90,93	156,83	113,28	105,93	149,10	152,38	192,90
İstatistiksel Analiz	KW=13,717 P=0,0001	KW=21,138 P=0,001	KW=1,555 P=0,45	KW=8,353 P=0,01	KW=6,566 P=0,03	KW=3,135 P=0,20	KW=0,219 P=0,89	KW=5,840 P=0,05
	a>b	a>b,c	b>a	a>b,c	a>d b>d c>d			

**Tablo 2.** MI tanılı hastaların tanıtıcı özelliklerine göre HADÖ, SBTÖ ve RCUÖ puanları (Devam)

Hastanın Tanıtıcı Özellikleri (n)	HADÖ				SBTÖ			RCUÖ Toplam Puan	
	Anksiyete	Depresyon	Kendine Güvenli Yaklaşım	Çaresiz Suçlayıcı Yaklaşım	Boyun Eğici Yaklaşım	İyimsiz Yaklaşım	Sosyal Destek Arama		
Kronik Hastalık Öyküsü	Evet (190)	156,27	162,91	146,32	158,25	152,94	147,71	149,13	139,91
	Hayır (110)	140,54	129,07	157,73	137,11	146,28	155,33	152,87	168,80
	İstatistiksel Analiz	U=9,354 P=0,121	U=8,092 P=0,001	U=9,655 P=0,270	U=8,977 P=0,041	U=9,986 P=0,519	U=9,919 P=0,460	U=10,189 P=0,716	U=8,437 P=0,005
Kronik Hastalık Öyküsü	Evet (201)	158,64	158,51	144,08	151,40	152,31	138,89	145,81	150,99
	Hayır (99)	133,97	134,24	163,53	148,67	146,82	174,07	160,02	149,52
	İstatistiksel Analiz	U=8,313 P=0,021	U=8,330 P=0,022	U=8,660 P=0,067	U=9,768 P=0,797	U=9,585 P=0,604	U=7,616 P=0,001	U=9,007 P=0,178	U=9,852 P=0,890
Günlük uyku süresi	6 saatten az <sup>a</sup> (72)	181,85	168,84	140,19	156,01	143,85	130,16	119,63	118,19
	6-8 saat arası <sup>b</sup> (183)	138,20	141,64	152,72	149,36	150,71	154,24	160,58	160,36
	8 saatten fazla <sup>c</sup> (45)	151,16	157,83	157,96	146,33	160,29	167,84	158,90	162,11
İstatistiksel Analiz	KW=12,840 P=0,001	KW=5,396 P=0,06	KW=1,481 P=0,47	KW=0,429 P=0,80	KW=1,007 P=0,60	KW=6,189 P=0,04	KW=12,259 P=0,001	KW=13,162 P=0,001	KW=13,162 P=0,001
Günlük uyku süresi yeterli algisi	Evet (217)	135,88	140,25	156,09	143,62	147,42	159,52	155,28	160,78
	Hayır (83)	187,36	175,80	135,90	168,48	158,56	126,93	138,01	123,63
	İstatistiksel Analiz	U=5,833 P=0,0001	U=6,781 P=0,001	U=7,793 P=0,070	U=7,513 P=0,026	U=8,336 P=0,317	U=7,049 P=0,003	U=7,968 P=0,119	U=6,775 P=0,001

Hastaların eğitim durumlarına göre anksiyete puanları arasında anlamlı bir farklılık bulunmazken (P>0,05), eğitim durumu okur-yazar olanların diğer tüm eğitim seviyelerine göre depresyon puanları daha yüksek bulunmuştur (P<0,05). SBTÖ alt boyutlarından Kendine Güvenli Yaklaşım puanlarının ilkökul, ortaokul ve lise mezunu olanların puanları okur-yazar olan gruba göre daha yüksek olduğu bulunmuştur (P<0,05). Boyun Eğici Yaklaşım puanlarının ise lise mezunu olan kişilerin okur-yazar, ilkökul ve ortaokul mezunlarına göre daha düşük olduğu bulunmuştur (P<0,05). SBTÖ diğer alt boyutlarının

ve RCUÖ toplam puanlarının eğitim durumuna göre istatistiksel olarak anlamlı düzeyde farklılaşmadığı bulunmuştur (P>0,05). Gelir durumlarına göre değerlendirildiğinde geliri giderine göre az olan hastaların, geliri giderine eşit olan hastalara oranla anksiyete düzeyi yüksek bulunurken, geliri giderinden az olan hastaların, geliri giderine eşit ve geliri giderinden fazla olan hastalara oranla depresyon düzeyleri de daha yüksek bulunmuştur (P<0,05). SBTÖ alt boyutlarından Çaresiz Suçlayıcı Yaklaşım puanlarının ise geliri giderinden az olan hastalarda diğer gelir durumlarına

göre daha yüksek olduğu bulunmuştur ( $P<0,05$ ). Geliri giderine eşit olan hastaların geliri giderinden fazla olan hastalara oranla Boyun Eğici Yaklaşım puanları daha yüksektir ( $P<0,05$ ). SBTÖ diğer alt boyutlarının ve RCUÖ toplam puanın hastaların gelir durumuna göre farklılaşmadığı bulunmuştur ( $P>0,05$ ).

Hastaların, kronik hastalığa sahip olup olmamasına göre anksiyete puanları arasında anlamlı bir farklılık bulunmazken ( $P>0,05$ ), kronik hastalığı olanların olmayanlara göre depresyon puanları daha yüksek bulunmuştur ( $P<0,05$ ). SBTÖ alt boyutlarında ise kronik hastalığı olan bireylerin olmayanlara göre Çaresiz Suçlayıcı Yaklaşım puanları daha yüksek bulunmuştur ( $P<0,05$ ). RCUÖ toplam puanının ise kronik hastalığı olmayan bireylerde olanlara göre daha yüksek olduğu bulunmuştur ( $P<0,05$ ). Daha öncesinde hastane yatış öyküsü olan hastaların olmayanlara göre anksiyete ve depresyon puanları daha yüksek bulunmuştur ( $P<0,05$ ). SBTÖ alt boyutlarından İyimser Yaklaşım puanlarının ise hastane yatış öyküsü olmayanlarda olanlara göre daha yüksek bulunmuştur ( $P<0,05$ ). SBTÖ diğer alt boyutlarının ve RCUÖ toplam puanının hastane yatış öyküsüne göre farklılaşmadığı bulunmuştur ( $P>0,05$ ).

Günlük 6 saatten az uyuyanların hastaların anksiyete puanları diğer gruplara göre daha yüksek olduğu bulunurken ( $P<0,05$ ), günlük uyku sürelerine göre depresyon puanlarının farklılaşmadığı bulunmuştur ( $P>0,05$ ). SBTÖ alt boyutlarından İyimser Yaklaşım ve Sosyal Destek Arama yaklaşımın puanlarının 6 saatten az uyuyanlarının diğer gruplara göre daha düşük olduğu bulunmuştur ( $P<0,05$ ). SBTÖ diğer alt boyut puanlarını ise uyku süreleri göre farklılaşmadığı bulunmuştur ( $P>0,05$ ). Gündelik yaşamda 6 saatten az uyuyanların diğer gruplara göre yoğun bakımda yattığı süreçte RCUÖ toplam puanlarının daha düşük olduğu saptanmıştır ( $P<0,05$ ).

Günlük uyku sürelerinin yeterlilik algısına göre ölçek puanları değerlendirildiğinde, uyku süresinin yetersiz olduğunu bildiren hastaların anksiyete ve depresyon puanları daha yüksek bulunmuştur ( $P<0,05$ ). SBTÖ alt boyutlarından, Çaresiz Suçlayıcı Yaklaşım puanı günlük uyku süresini yetersiz olarak bildiren hastalarda daha yüksek olarak bulunurken ( $P<0,05$ ), günlük uyku süresinin yeterli olduğunu bildiren hastaların İyimser Yaklaşım Puanları daha yüksek bulunmuştur ( $P<0,05$ ). Günlük uyku süresini yeterli olarak belirten hastaların yoğun bakım şartlarındaki RCUÖ toplam puanının günlük uyku süresini yetersiz olarak bildiren hastalara göre daha yüksek bulunmuştur ( $P<0,05$ ).

Tablo 3'te HADÖ alt boyutlarından Depresyon ve Anksiyete arasında pozitif yönde ve orta düzeyde anlamlı bir ilişki olduğu bulunmuştur ( $r=0,571$ ,  $P<0,05$ ). SBTÖ alt boyutlarından Kendine Güvenli Yaklaşım ile Anksiyete ( $r=-0,358$ ,  $P<0,05$ ) ve Depresyon ( $r=-0,392$ ,  $P<0,05$ ) arasında ise negatif yönde zayıf bir ilişki, Çaresiz Suçlayıcı Yaklaşım ile Anksiyete ( $r=0,464$ ,  $P<0,05$ ) ve Depresyon ( $r=0,409$ ,  $P<0,05$ ) arasında pozitif yönde orta düzeyde bir ilişki, Boyun Eğici Yaklaşım ile Anksiyete ( $r=0,121$ ,  $P<0,05$ ) ve Depresyon ( $r=0,156$ ,  $P<0,05$ ) arasında pozitif yönde zayıf bir ilişki, İyimser Yaklaşım ile Anksiyete ( $r=-0,373$ ,  $P<0,05$ ) ve Depresyon ( $r=-0,364$ ,  $P<0,05$ ) arasında negatif yönde zayıf bir ilişki, Sosyal Destek Arama ile Anksiyete ( $r=-0,212$ ,  $P<0,05$ ) ve Depresyon ( $r=-0,326$ ,  $P<0,05$ ) arasında negatif yönlü zayıf düzey bir ilişki olduğu belirlenmiştir. RCUÖ uyku kalitesi ile Anksiyete ( $r=-0,328$ ,  $P<0,05$ ), Depresyon ( $r=-0,358$ ,  $P<0,05$ ) ve SBTÖ alt boyutlarından Çaresiz Suçlayıcı Yaklaşım ( $r=-0,244$ ,  $P<0,05$ ) arasında negatif yönlü zayıf birer ilişki olduğu bulunurken, İyimser Yaklaşım ( $r=0,224$ ,  $P<0,05$ ) ve Kendine Güvenli Yaklaşım ( $r=0,206$ ,  $P<0,05$ ) aralarında pozitif yönde zayıf bir ilişki olduğu tespit edilmiştir.

**Tablo 3.** MI geçiren hastaların HADÖ, SBTÖ ve RCUÖ ölçüm araçları arasındaki korelasyon analizi sonuçları

Ölçüm Araçları		HADÖ Anksiyete	HADÖ Depresyon	SBTÖ Kendine Güvenli Yaklaşım	SBTÖ Çaresiz Suçlayıcı Yaklaşım	SBTÖ Boyun Eğici Yaklaşım	SBTÖ İyimser Yaklaşım	SBTÖ Sosyal Destek Arama
HAD Depresyon	r	0,571						
	P	<0,001						
SBTÖ Kendine Güvenli Yaklaşım	r	-0,358	-0,392					
	P	<0,001	<0,001					
SBTÖ Çaresiz Suçlayıcı Yaklaşım	r	0,464	0,409	-0,132				
	P	<0,001	<0,001	0,022				
SBTÖ Boyun Eğici Yaklaşım	r	0,121	0,156	0,103	0,456			
	P	0,042	0,006	0,075	<0,001			
SBTÖ İyimser Yaklaşım	r	-0,373	-0,364	0,617	-0,064	0,161		
	P	<0,001	<0,001	<0,001	0,268	0,005		
SBTÖ Sosyal Destek Arama	r	-0,212	-0,326	0,230	-0,233	-0,129	0,122	
	P	<0,001	<0,001	<0,001	<0,001	0,025	0,034	
RCUTOP	r	-0,331	-0,356	0,206	-0,244	-0,030	0,224	0,087
	P	<0,001	<0,001	<0,001	<0,001	0,602	<0,001	0,131

#### 4. Tartışma

Bu çalışma, MI sonrası koroner yoğun bakım ünitesinde yatan hastaların anksiyete, depresyon düzeyleri ve stresle başa çıkma tarzları ile uyku kaliteleri arasındaki ilişkiyi değerlendirmek amacıyla gerçekleştirilmiştir. Elde edilen bulgular literatür doğrultusunda tartışılmıştır.

Çalışmaya katılan hastaların %74,7'sinin erkek ve %57,3'nün 40-59 yaş aralığında olduğu, %63,3'ünün diyabet ve hipertansiyon ağırlıklı olmak üzere en az bir kronik hastalığının bulunduğu ve %52,0'sinin sigara kullandığı bulunmuştur. Literatürde, erkek cinsiyet, erkeklerde 45 yaş ve üzeri, kadınlarda ise 55 yaş ve üzeri olmak, diyabet ve hipertansiyon gibi kronik hastalıklara sahip olmak ve sigara kullanımı koroner arter hastalığı için en önemli risk faktörleri arasında yer almakta ve çalışmaya katılan hastaların çoğunluğunda bu risk faktörlerinin varlığı görülmüştür (Yalçınkaya, 2006; Ceylan ve ark., 2011; Malalar ve ark., 2019).

Çalışmamızda, kadın hastaların anksiyete ve depresyon düzeyleri anlamlı düzeyde yüksek bulunmuştur. SBTÖ alt boyutlarında ise erkeklerin Kendine Güvenli ve İyimser Yaklaşım alt boyut puan ortalamaları, kadınların ise Çaresiz Suçlayıcı ve Boyun Eğici Yaklaşım puan ortalamaları anlamlı derecede daha yüksek bulunmuştur. Literatür incelendiğinde kadınların erkeklere göre anksiyete ve depresyon düzeylerinin yüksek olduğu görülmektedir (Kutlu ve ark., 2016; Allabadi ve ark., 2019). Aynı zamanda, anksiyete ve depresyon gibi ruhsal durumların bireylerin kullandıkları baş etme yöntemleri ile ilişkili olabilmektedir. Bu çalışmada, erkeklerin daha fazla Kendine Güvenli ve İyimser Yaklaşım baş etme yöntemlerini, kadınların daha fazla Çaresiz Suçlayıcı ve Boyun Eğici baş etme yöntemlerini kullanması kadınların anksiyete ve depresyon düzeyinin yüksek olmasına neden olduğu düşünülmektedir. Yapılan çalışmalarda etkisiz baş etme yöntemlerinin ve stres puanlarının yüksek olmasının depresyon ve anksiyete ile ilişkili olduğu bulunmuştur, bu sonuçlar bizim çalışmamızla paralellik göstermektedir (Erşan ve ark., 2013; Dağlar ve Nur, 2014). RCUÖ uyku kalitesi toplam puanlarının ise erkeklerde anlamlı derecede daha yüksek olduğu bulunmuştur. Bu durumun, anksiyete, depresyon düzeyleri ve baş etme yöntemleri ile ilişkili olduğu düşünülmektedir. Özellikle, erkeklerin depresyon ve anksiyete düzeyinin düşük olması ve stresle etkili baş etme yöntemlerini daha fazla kullanmaları uyku kalitesini olumlu yönde etkileyebilmektedir. Literatürdeki araştırma sonuçları, çalışma bulgularını destekler niteliktedir ve erkeklerin uyku kalitelerinin daha yüksek olduğu görülmektedir (Matsuda ve ark., 2017; Akkaya ve ark., 2018).

Yaş gruplarına göre ölçek puanlarını değerlendirmek için yapılan analizde, 19-39 yaş grubunun anksiyete puanı 40-59 yaş grubuna göre anlamlı düzeyde yüksek bulunurken, 60 yaş ve üzeri grubun depresyon puanı 40-59 yaş grubuna oranla anlamlı olarak daha yüksek bulunmuştur. Erken yaşta MI geçirmiş olmak, hayati bir organ olan kalp ile ilgili bir hastalık tanısı almak ve bu hastalığın ölümcül olmasına yönelik yaşanan duyguların 19-39 yaş grubunun

anksiyete puanının yüksek olmasına neden olduğu düşünülmektedir. Aynı zamanda, genç hastaların iş yaşamında aktif olması, fiziksel yetersizlik korkusu, bakmakla yükümlü olduğu aile bireylerinin olması ve çalışmama düşüncesi anksiyete düzeyini arttıran faktörler arasında sayılabilir. Literatür incelendiğinde, MI geçiren hastalar arasında genç yaş grubunun anksiyete düzeyi yüksek bulunmuştur, bu sonuçlar çalışma bulguları ile benzerlik göstermektedir (Özer Canlı ve ark., 2009; Çam ve Nehir, 2011). 60 yaş ve üzerinin depresyon düzeyi 40-59 yaş grubuna göre anlamlı düzeyde yüksek bulunmuştur. Yaş ile birlikte kronik hastalıkların artışı, kronik hastalıkların günlük yaşam üzerinde oluşturduğu yetersizlikler, yaşamdan beklentilerin azalması, belirsizlik, ölüm korkusu ve eş kayıpları gibi sebeplerin depresyon düzeyini artırdığı düşünülmektedir. Aydemir ve ark., (2015) MI geçiren hastaların depresyon puanının yaş ile birlikte arttığını bulurken, Çam ve Nehir (2011) ise çalışma bulgularının aksine MI geçiren hastaların yaş ile birlikte depresyon düzeyinin azaldığını saptamışlardır. SBTÖ alt boyutlarından Kendine Güvenli Yaklaşım puanı 40-59 yaş grubunda 19-39 yaş grubuna kıyasla anlamlı derecede daha yüksek olduğu bulunmuştur. Bu durumun, yaş arttıkça bireyin kendini tanıma, belirsizlik, günlük olaylar ve hastalıklarla baş etme ve uyum becerilerinin artmasından kaynaklı olduğu düşünülmektedir. Özellikle, 40-59 yaş grubunun 19-39 yaş grubuna göre anksiyete puanlarının anlamlı derecede düşük çıkmasında stresle baş etme de Kendine Güvenli Yaklaşım puanının yüksek olmasının etkisi olabilmektedir. Ancak bu çalışmada, SBTÖ diğer alt boyut puan ortalamalarının yaşa göre farklılaşmadığı bulunmuştur. Benzer şekilde, Bayrak ve ark. (2019) MI geçiren hastalar ile yaptıkları çalışmada hastaların yaşına göre algıladıkları stres düzeyleri ve baş etme becerilerinin değişmediğini bulmuşlardır. Hastaların yaşına göre RCUÖ uyku kalitesi toplam puan ortalamalarının farklılaşmadığı bulunmuştur. Ancak literatürde koroner arter hastalığı olan bireylerle yapılan çalışmalar incelendiğinde bireylerin yaşlarına göre uyku kalitelerinin değiştiği ve yaş arttıkça bireylerin uyku kalitelerinin daha da arttığı bulunmuştur (Andrechuk ve Ceolim, 2015; Gökçe ve Mert, 2015).

Bekar hastaların, anksiyete ve depresyon puanları anlamlı düzeyde daha yüksek bulunmuştur. Aynı zamanda, bekarların, SBTÖ alt boyutlarından Çaresiz Suçlayıcı Yaklaşım puanları anlamlı derece daha yüksek bulunurken, Sosyal Destek Arama ve İyimser Yaklaşım puanları daha düşük bulunmuştur. Evli olan hastaların eşlerinden ve ailelerinden aldıkları duygusal, sosyal ve ekonomik desteğin stresle daha etkin baş etmelerine katkı sağladığı düşünülmektedir. Bu nedenle, bekar hastaların sahip oldukları bu baş etme yöntemlerinin daha fazla anksiyete ve depresyon yaşamalarına yol açabilmektedir. Aynı zamanda bekar hastaların büyük bir kısmının eş kaybı olduğu ve buna bağlı sosyal desteğin azalması, yalnızlık ve kayıpla ilgili duyguların anksiyete ve depresyon düzeylerinin artmasına neden olduğu düşünülmektedir. Literatürdeki çalışmalar

değerlendirildiğinde, bekar olan ve stresle baş etmede güçlük yaşayan hastaların depresyon düzeyini daha yüksek olduğu görülmektedir (Çam ve Nehir, 2011; Erşan ve ark., 2013). Medeni duruma göre hastaların RCUÖ uyku kalitesi toplam puanlarının farklılaşmadığı bulunmuş ve literatürde MI tanılı hastalarla yapılan çalışmalar incelendiğinde medeni duruma göre uyku kalitesi puanının farklılaşmadığını göstermektedir (Andrechuk ve Ceolim, 2015; Gökçe ve Mert, 2015; Çevik ve Sarıtaş Çıtlık, 2020). Ancak, çalışma bulgularının aksine, koroner kalp hastalığı olan hastalarla yapılan çalışmalarda evli hastaların uyku kalitelerinin daha iyi olduğu bulunmuştur (Tenekeci ve Kara, 2016; Sakman, 2019).

Eğitim düzeyi düşük olan hastaların depresyon puanları anlamlı düzeyde daha yüksek, SBTÖ alt boyutlarından Kendine Güvenli Yaklaşım puanları daha düşük ve Boyun Eğici Yaklaşım puanları ise daha yüksek olduğu bulunmuştur. Bu sonuçların, eğitim düzeyi arttıkça birey kendini daha iyi tanıyıp ve etkili baş etme davranışlarının daha fazla kullanmasından kaynaklandığı düşünülmektedir. Eğitim düzeyinin artmasıyla bireyler kullanabileceği duygusal, ruhsal, fiziksel ve toplumsal destek kaynaklarını tanıyıp depresyon ve stres gibi etkenlerle daha etkili mücadele edebilmektedir. Kardiyoloji yoğun bakım ünitesinde yatan ve MI geçiren hastalarla yapılan çalışmalar incelendiğinde eğitim düzeyi düşük olan hastaların daha fazla etkisiz ve pasif baş etme yöntemleri kullandıkları bulunurken depresyon puanlarının daha yüksek olduğu bulunmuştur (Çam ve Nehir, 2011; Kutlu ve ark., 2016; Son ve ark., 2016). Bu çalışmada, hastaların eğitim düzeyine göre RCUÖ toplam uyku kalitesi puanlarının farklılaşmadığı bulunmuş, literatürde MI geçiren ve kalp yetmezliği olan hastalarla yapılan çalışmalarda hastaların eğitim düzeyine göre uyku kalitesi puanlarının farklılaşmadığı yer almaktadır (Gökçe ve Mert, 2016; Çevik ve Sarıtaş Çıtlık, 2020). Ancak, Sakman (2019) koroner arter hastalığı olan hastalarla yaptığı çalışmada eğitim düzeyi düşük olan hastaların uyku kalitesinin daha kötü olduğunu bulmuştur.

Geliri giderinden az olan hastaların anksiyete puanı geliri giderine eşit olanlara, geliri giderinden az olan hastaların geliri giderine eşit olanlara göre ve geliri giderine eşit olan hastaların ise geliri giderinden fazla olan hastalara göre depresyon puanları anlamlı düzeyde yüksek olduğu bulunmuştur. SBTÖ alt boyutlarından Çaresiz Suçlayıcı Yaklaşım puanı geliri giderinden az olan hastaların diğer gelir durumlarına göre istatistiksel olarak anlamlı düzeyde yüksek bulunurken, Boyun Eğici Yaklaşım puanı ise geliri giderine eşit olan hastaların geliri giderinden yüksek olan hastalara kıyasla istatistiksel olarak anlamlı derecede yüksektir. Gelir durumunun az olması kişinin eğitim düzeyi ile ilişkili olduğu düşünüldüğünde kullanacağı bireysel, sosyal ve toplumsal destek kaynakları hakkında bilgi eksikliğinin olmasına, aynı zamanda gelir durumundaki yetersizlik hastaların maddi kaygılar yaşamasına ve hastalığın oluşturduğu fiziksel yetersizliğe bağlı çalışmama durumunun hastaların anksiyete ve depresyon düzeyinin artması yönünde

etkileyebilmektedir. MI geçiren hastaların çoğunluğunun orta yaş erkeklerden oluştuğunu düşünüldüğünde hastaların bakmakla yükümlü aile bireylerinin olması ve hastalık sonrası çalışma yaşamı ile ilgili belirsizlik hastaların anksiyete ve depresyon düzeyini etkilemektedir. Akkaya ve ark. (2018) koroner anjiyografi laboratuvarına sevk edilen hastalarla yaptıkları çalışmada gelir düzeyi düşük olan hastaların anksiyete ve depresyon puanının daha yüksek olduğunu bulmuşlardır. Aynı zamanda, hastaların kullandıkları baş etme yöntemlerinin anksiyete ve depresyon düzeyleri üzerinde etkisi olmaktadır. Özer Canlı ve ark. (2009) MI geçiren hastalarda yaptıkları çalışmada da yine gelir durumu düşük olan hastaların hastalıkla etkin baş edemediği ve depresyon puanlarının yüksek olduğu bulmuşlardır. Hastaların gelir durumlarına göre, RCUÖ uyku kalitesi toplam puanının farklılaşmadığı bulunmuştur. Çalışma bulgularına benzer şekilde, Gökçe ve Mert (2015) kalp yetmezliği olan hastalarla yaptıkları çalışmada hastaların gelir durumlarına göre uyku kalitelerinin farklılaşmadığını bulmuşlardır. Ancak, Sakman (2019) koroner kalp hastaları ile yaptığı çalışmada, geliri giderine eşit olan hastaların geliri giderinden az olanlara göre uyku kalitesinin daha iyi olduğunu bulmuştur.

Kronik hastalığı olduğunu belirten hastaların depresyon ve SBTÖ alt boyutlarından Çaresiz Suçlayıcı Yaklaşım puanları kronik hastalığı olmayanlara göre anlamlı düzeyde yüksek bulunmuştur. Kronik hastalık tanısına sahip olmak bireylerin biyopsikososyal olarak etkilenmesine, yaşam kalitesinde azalmaya, kendini suçlama, pişmanlık ve öfke gibi birçok uyum bozucu tepkilere ve uzun dönemli tedaviye bağımlı olma zorunluluğunu getirmektedir. Bu durum, birçok psikososyal sorunlara neden olabilmektedir. Bayrak ve ark. (2019) yaptıkları çalışmada, koroner kalp hastalığının yanında hastaların kronik ek hastalıklarının olmasının hastaların stres düzeyini artırdığını bulmuşlardır. Bu durum şüphesiz hastaların ruhsal durumları üzerinde etkili olmaktadır. Ancak, literatürde MI geçiren ve farklı hastalıklara sahip hastalarla yapılan çalışmalarda başka bir kronik hastalığın varlığına göre hastaların depresyon, anksiyete ve baş etme tarzlarının değişmediğini gösteren çalışma sonuçları yer almaktadır (Deveci ve ark. 2012; Akkaya ve ark., 2018; Funuyet-Salas ve ark. 2021). Bu çalışmada, RCUÖ uyku kalitesi toplam puanının ise kronik hastalığı olmayan bireylerde anlamlı düzeyde daha yüksek olduğu bulunmuştur. Literatürde çalışma bulgusunu destekler şekilde MI tanılı ya da farklı hastalıklarda ek kronik hastalığa sahip olmanın bireylerin uyku kalitesini kötü etkilediği bulunmuştur (Bahar ve Taşdemir, 2008; Andrechuk ve Ceolim, 2015). Ancak, Gökçe ve Mert (2015), kalp yetmezliği olan hastalarla yaptıkları çalışmada ek kronik hastalığa sahip olma durumuna göre hastaların uyku kalitesinin değişmediğini bulmuşlardır.

Daha öncesinde hastane yatış öyküsü olan hastaların anksiyete ve depresyon puanları anlamlı düzeyde daha yüksek bulunmuştur. Hastaneye tekrarlı yatışların olması

bireyin hastalıkla baş etme motivasyonunun ve umudun azalmasına, hastalığın sürekli tekrarlamasının hastaların işlevselliğinde azalmaya ve uzun süreli tedavi ve bakıma bağımlı olmaya dolayısıyla anksiyete ve depresyon düzeyinde artışa sebep olabilmektedir. Bahar ve Taşdemir (2008) dahiliye ve cerrahi kliniklerinde yatmakta olan hastalarla yaptığı çalışmada daha öncesinde hastaneye yatma deneyimi olan hastaların anksiyete düzeyini daha yüksek bulmuşlardır. SBTÖ alt boyutlarından İyimser Yaklaşım puanlarının ise hastane yatış öyküsü olmayanlarda anlamlı düzeyde yüksek bulunmuştur. RCUÖ toplam puan ortalamasının hastane yatış öyküsüne göre farklılaşmadığı bulunmuştur. Araştırma bulgularına paralellik olarak. Karagözlü ve ark. (2007) hastanede yatan yetişkin hastalarla yaptıkları çalışmada daha önce hastaneye yatma deneyiminin uyku kalitesinde değişmeye yol açmadığını bulmuşlardır.

Günlük 6 saatten az uyuyanların hastaların anksiyete puanları diğer gruplara göre daha yüksek olduğu bulunurken, uyku süresinin yetersiz olduğunu bildiren hastaların anksiyete ve depresyon puanları anlamlı düzeyde yüksek bulunmuştur. Vücut gereksiniminden az veya fazla uyumak birtakım ruhsal sorunların semptomu olarak ortaya çıkabilmektedir. Özellikle ölümcül bir hastalık tanısı almak, korku ve stres, yoğun bakım ortamında bulunmak, yoğun bakım ortamlarında bulunan araç, gereç ve personelin hastaya aşırı duyuşsal uyaran oluşturması ve diğer hastaların tedavi süreçleri hastaların anksiyete düzeyini artırarak uyku kalitelerini ve sürelerini etkileyebilmektedir. Bu semptomlar, özellikle anksiyetenin yüksek olduğu dönemlerde ve depresyon gibi kronik ruhsal bozukluklarda ortaya çıkabilmekte ve hastaların yaşam kalitesini ciddi düzeyde etkileyebilmektedir. Literatür incelendiğinde hastaların uyku kalitesi ve sürecinde meydana gelen bozulmalar anksiyete ve depresyon düzeyini artırarak yaşam kalitesini olumsuz olarak etkileyebilmektedir (Karagözoğlu ve ark., 2007; Keskin ve ark., 2011; Emre, 2019). SBTÖ alt boyutlarından İyimser Yaklaşım ve Sosyal Destek Arama Yaklaşım puanlarının 6 saatten az uyuyanların diğer gruplara göre anlamlı düzeyde düşük olduğu, Çaresiz Suçlayıcı Yaklaşım puanı günlük uyku süresini yetersiz olarak bildiren hastalarda daha yüksek olarak bulunurken, günlük uyku süresinin yeterli olduğunu bildiren hastaların İyimser Yaklaşım puanları anlamlı düzeyde daha yüksek bulunmuştur. Johanson ve ark. (2007) koroner kalp hastaları ile yaptıkları çalışmada uykularının yeterli olduğunu ve dinlendiklerini bildiren hastaların günlük ve çalışma yaşamında, aile ve sosyal ilişkilerinde karşılaştıkları sorunları daha iyi yönettiklerini belirtmişlerdir. Literatürde farklı örneklem grupları ile yapılan araştırmalarda bireylerin uyku kalitesinde meydana gelen sorunların stresle baş etme becerileri üzerinde olumsuz etkileri olduğu ve uyku kalitesi bozuldukça daha fazla stres yaşadıkları ve baş etme becerilerinin yetersiz kaldığı bulunmuştur (Pınar ve ark., 2014; Güneşer ve Atalay, 2020). Günlük yaşamda 6 saatten az uyuyanların diğer gruplara göre RCUÖ toplam

puanlarının anlamlı düzeyde daha düşük olduğu bulunurken, günlük uyku süresini yeterli olarak bildiren hastaların ise RCUÖ toplam puanlarının daha yüksek bulunmuştur. Günlük yaşamda var olan uyku sorunları hayatı tehdit eden bir hastalık varlığında ve çevresel birçok stresör içeren hastane ortamında sıklıkla ortaya çıkabilmektedir. Bu nedenle, günlük yaşamda var olan sorununun zorlayıcı ve stres dolu bir ortamda daha da yaygın hale gelmesi kaçınılmazdır. Literatürde, kalp hastalığı olan hastalarla yapılan çalışmalarda hastaların yarıya yakınında uyku kalitesinin oldukça kötü olduğu yer almaktadır (Matsuda ve ark., 2017; Cheng ve ark., 2021). SBTÖ alt boyutlarından Kendine Güvenli Yaklaşım. İyimser Yaklaşım ve Sosyal Destek Arama ile HADÖ alt boyutlarından Anksiyete ve Depresyon arasında ise negatif yönde ilişki tespit edilmiştir. SBTÖ alt boyutlarından Çaresiz Suçlayıcı Yaklaşım ve Boyun Eğici Yaklaşım ile anksiyete ve depresyon düzeyleri arasında pozitif yönde ilişki olduğu belirlenmiştir. Olumlu baş etme tarzlarının kullanımı arttıkça hastaların anksiyete ve depresyon düzeyinin azaldığı görülürken, olumsuz baş etme tarzlarının kullanımı arttıkça hastaların anksiyete ve depresyon düzeylerinin arttığı görülmektedir. Literatürde hem kalp hastaları hem de farklı örneklem grupları ile yapılan çalışmalar incelendiğinde stres düzeylerini yüksek olan ve etkili baş etme becerilerine sahip olmayan kişilerin anksiyete ve depresyon düzeylerini yüksek bulunmuştur (Erşan ve ark., 2013; Dağlar ve Nur, 2014). RCUÖ uyku kalitesi ile anksiyete, depresyon ve SBTÖ alt boyutlarından Çaresiz Suçlayıcı Yaklaşım ile arasında negatif yönde ilişki olduğu bulunurken, İyimser Yaklaşım ve Kendine Güvenli Yaklaşım ile aralarında pozitif yönde ilişki olduğu tespit edilmiştir. Anksiyete, depresyon ve etkisiz baş etme becerileri yüksek olan hastaların uykuya dalma, sürdürme, uyku-uyanıklık döngüsü ve uyku kalitesinde çeşitli sorunlar yaşanabilmektedir. Literatürde MI geçiren hastalarla yapılan çalışmalar incelendiğinde uyku sorunu yaşayan hastaların anksiyete, depresyon ve stres düzeyi yüksek bulunmuştur (Johanson ve ark. 2010; Pınar ve ark., 2014; Güneşer ve Atalay, 2020).

### 5. Sonuç

Araştırmada elde edilen bulgular sonucunda MI bağılı olarak koroner yoğun bakım ünitesinde yatan hastaların anksiyete ve depresyon puanları sınırda ve uyku kaliteleri de kötü bulunmuştur. Hastaların kullandıkları baş etme yöntemleri ile hastaların ruhsal durumları ve uyku kaliteleri arasında anlamlı bir ilişki görülmektedir. Elde edilen bu bulgu, koroner yoğun bakım ünitelerinde yatan hastaların yaşayabileceği ruhsal ve psikososyal sorunların önlenmesinde ve uyku kalitelerinin artırılmasında hastalara yönelik uygulanması gereken psikososyal terapötik müdahalelerin önemi ortaya koymaktadır. Hastalara uygulanacak psikososyal terapötik müdahaleler ile hastalara etkili baş etme becerilerinin kazandırılması yaşanabilecek fiziksel, ruhsal, sosyal ve diğer psikososyal sorunların önlenmesi adına önemlidir.

## Sınırlılıklar

Bu araştırmanın, çeşitli sınırlılıkları bulunmaktadır. İlk sınırlılık olarak, araştırma, sadece bir hastanenin koroner yoğun bakım ünitesinde yatan hastalarla gerçekleştirilmiştir. Bu nedenle gelecek çalışmaların farklı örneklem grupları ile yapılması önerilmektedir. İkinci olarak, araştırma örnekleme, MI sonrası ilk birkaç gün yoğun bakım ünitesinde yatan hastalar dahil olmuştur ve hastaların anksiyete, depresyon, baş etme stilleri ve uyku kalitesi hastalığın akut döneminde değerlendirilmiştir. Bundan sonra yapılacak çalışmalarda MI sonrası uzun dönemli hastaların ruhsal durumlarının ve uyku kalitelerinin değerlendirilmesi önerilmektedir. Son sınırlılık ise, araştırma, tanımlayıcı ve ilişki arayıcı boyutta gerçekleşmiş ve kullanılan ölçeklere katılımcıların verdikleri yanıtlar esas alınmıştır. Gelecek çalışmalarda, hastaların anksiyete, depresyon, stres ve uyku problemlerini azaltmaya yönelik psikoeğitim ve girişimsel çalışmaların yapılması önerilmektedir.

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## PATELLOFEMORAL AĞRI SENDROMU TEDAVİSİNDE SON BEŞ YILDA KANITA DAYALI YENİ FİZYOTERAPİ YAKLAŞIMLARI

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**Özet:** Patellofemoral ağrı sendromu (PFAS), fleksiyon ve ekstansiyon sırasında dize aşırı yüklenme nedeniyle çömelme, koşma, tırmanma ve merdiven inip çıkma gibi ekleme yük binen aktiviteler sırasında ki ön diz ağrısı olarak tanımlanır. Klinik teşhiste altın bir standart yoktur. Olabilecek diğer problemler elimine edilerek tanı konulur. Konservatif tedavide nonsteroid anti-inflamatuvar ilaçlar, dizlik, bantlama, germe ve kuvvetlendirme egzersizleri uygulanmaktadır. Egzersiz programı olarak, PFAS'li hastalarda en etkin yöntemin, kuadriseps ve proksimal kalça egzersizlerinin birleştirilmesi yönünde olduğu belirtilmektedir. PFAS'de kullanılan yeni tedavi yöntemlerini belirlemek amacıyla PubMed, Google Scholar ve Science Direct veri tabanında "patellofemoral pain syndrome", "patellofemoral pain syndrome treatment", "intervention for patellofemoral pain syndrome" ve "patellofemoral ağrı sendromu", "patellofemoral ağrı sendromu tedavisi", "patellofemoral ağrı sendromu için müdahale" yazılarak İngilizce ve Türkçe dillerinde tarama yapılmıştır. Tarama başlangıç tarihi 2016 olup, belirlenen veri tabanlarında 30 Kasım 2021 tarihine kadar yer alan konuyla ilgili tüm araştırmalar incelenmiştir. Bu araştırmada PFAS'de kullanılan tedaviler ve tedavi yöntemlerindeki yeni yaklaşımlar üzerinde durulmuştur. Yeni çalışmalar, rehberler PFAS'de etkili olabilecek yeni yaklaşımların kullanılabilmesini göstermektedir. 5. Uluslararası Patellofemoral Ağrı tedavisi araştırma konsensüs kararlarında yürümenin tekrar eğitimi ve kan akımı kısıtlanmalı egzersizlerin PFAS'de yeni tedavi seçenekleri olarak kullanılabilmesinden bahsedilmiştir. Ayrıca son yıllarda yapılan çalışmalarda dizle ilgili vakum ve elastometrik bresler ve teknoloji destekli theraband, vücut vibrasyon eğitiminin kullanılabilmesi belirtilmiştir.

**Anahtar kelimeler:** Patellofemoral sendrom, Ön diz ağrısı sendromu, Kan akışı kısıtlama eğitimi, Tüm vücut vibrasyon eğitimi

### New Evidence-Based Physiotherapy Approaches in the Treatment of Patellofemoral Pain Syndrome in the Last Five Years

**Abstract:** Patellofemoral pain syndrome (PFPS) is defined as anterior knee pain during activities that are loaded with joint loads such as crouching, running, climbing, up and down stairs due to knee overload during flexion and extension. There is no gold standard in clinical diagnosis. Other possible problems are eliminated and diagnosis is made. In conservative treatment nonsteroidal anti-inflammatory drugs, knee brace, taping, stretching and strengthening applications are performed. As an exercise program, the most effective method in patients with PFAS is to combine quadriceps and proximal hip exercises. In order to determine new treatments used in PFPS, "patellofemoral pain syndrome", "patellofemoral pain syndrome treatment", "intervention for patellofemoral pain syndrome" were written and screened in PubMed, Google Scholar and Science Direct database. The scanning start date is 2016, and all the researches on the subject up to 30 November 2021 in the determined databases were examined. In this research, the treatments used in PFPS and new approaches in treatment are emphasized. New studies, guidelines show that new approaches that can be effective in PFPS can be used. 5. In the international patellofemoral pain treatment consensus decisions, it was mentioned that gait retrain and blood flow restricted exercises could be used as new treatment options in PFPS. In addition, in recent studies, it has been stated that vacuum and elastometric knee braces and technology supported theraband, body vibration training can be used.

**Keywords:** Patellofemoral syndrome, Anterior knee pain syndrome, Blood flow restriction training, Whole body vibration

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### 1. Giriş

Patellofemoral ağrı sendromu (PFAS), fleksiyon ve ekstansiyon sırasında dize aşırı yüklenme nedeniyle patella çevresinde ortaya çıkan dizin en sık görülen ağrı sendromudur. Doğası gereği travmatik olmayan, çömelme, koşma, tırmanma ve merdiven inme gibi ekleme

yük binen aktiviteler sırasında oluşan ağrı ön diz ağrısı olarak tanımlanmaktadır (Smith ve ark., 2018). PFAS 10-55 yaş aralığındaki bireylerde en yaygın görülen diz patolojisidir (Winters ve ark., 2020). PFAS genel popülasyonda özellikle adölesanlarda, genç aktif yetişkinlerde, elit sporcularda, askeri görevlilerde daha



yüksek insidanda olmakla birlikte en sık olarak kadınlarda ortaya çıkmaktadır (Smith ve ark., 2018; Winters ve ark., 2020). Prevalansı %15-45 arasındadır (Winters ve ark., 2020). PFAS tüm yaş gruplarının %85' ini etkilemekle birlikte ve hasta bireylerin %90'ına varan oranda tekrarlayabilmektedir. İlerleyen zamanlarda patellofemoral osteoartrite yol açabilmektedir. Yüksek prevalans ve ortalama 20 yıl süren yakınmalardan dolayı, ülkeler için tıbbi harcamalar konusunda çok büyük ekonomik yük oluşturmaktadır (Marra, 2020).

### 1.1. Patellofemoral Eklem Anatomi ve Biyomekanisi

Patellofemoral eklem kuadriseps kasına mekanik desteklik sağlar. Diz ekstansiyon kuvvetini %50 artırır. Anatomik olarak lateraldeki yapılar medialdeki yapılardan daha güçlüdür. Bu nedenle kuvvetler patellayı laterale hareket ettirir. Ayrıca Kuadriseps kasının, Vastus Medialis Obliquus (VMO) parçası, Vastus Lateralise (VL) göre daha küçük ve daha yavaş kasılan liflere sahip olduğu bilinmektedir. VMO son 20-30 drc patellanın primer stabilizörüdür. Bu açı aynı zamanda patellofemoral ağrının en fazla meydana geldiği açıdır. Patellofemoral eklem, yürüme sırasında vücut ağırlığının yarısı, merdiven inip-çıkma sırasında 3-4 katı, çömelme esnasında 7-8 katı yük biner (Kuru ve Yalman, 2012). Ayrıca obezite ve vücut postür bozuklukları diz eklemine olan yükü artırmakta, dize binen yük artışında patellar bölgede ağrıya neden olmaktadır.

### 1.2. Patellanın Laterale Hareketi

Yapılan çalışmalarda PFAS'de patellanın lateralizasyonun önemli rol oynadığına rastlanmıştır. Draper ve ark. (2012) dinamik MRI squat sırasında patellanın lateralizasyonunu ve laterale tiltini göstermiştir. Witvrouw ve ark. (2000) hiper mobil patellanın PFAS insidansı ile kayda değer ilişki olduğunu belirtmiştir. Wilson ve ark. (2009) PFAS'li hastalarda patellar kaymayı incelemek için deri üzerine elektrotlar ve optik elektronik hareket yakalayıcıları kullanmışlardır. Yaptıkları çalışmada PFAS'li hastaların patellasının sağlıklı gruba kıyasla artmış lateral kayma (maltracking), patellar spin ve lateral tilt eğiliminde olduğunu belirtmişlerdir. Patellanın laterale hareketi ise bireylerde ön diz ağrısı olarak ortaya çıkmaktadır. Ağrı, hareketi ve fonksiyonelliği kısıtlamaktadır.

PFAS önemli yapısal değişiklikler olmaksızın ön diz ağrısının en yaygın nedenidir. Klinik teşhiste altın bir standart yoktur. Olabilecek diğer problemler elimine edilerek tanı konulur. Bu nedenle bir dışlanma kriteri tanısıdır. Tanıda patellofemoral kompresyon testi, dirençli diz ekstansiyonda ve patellanın palpasyonunda ağrı gibi subjektif ve objektif yöntemler detaylı olarak incelenir (Smith ve ark., 2018). PFAS dizin ön kısmında retropatellar ve peripatellar bölgede ağrı ile karakterizedir (Marra, 2020). PFAS diz hareketleri sırasında patellar dizilimdeki kuvvet dengesizliğinden dolayı kaynaklanmaktadır (Emamvirdi ve ark., 2019). PFAS semptomlarının çeşitliliği nedeniyle geniş şekilde tartışılan bir terminolojiye sahiptir. Bu durum aynı zamanda koşucu dizi, patellar ağrı, patellar kondropati, patellar aşırı yük sendromu olarak da bilinmektedir

(Karakaşlı ve ark., 2014).

Patellofemoral ağrı sendromunda risk faktörleri arasında fonksiyonel testlerde zayıflık, gastroknemius, hamstring, kuadriseps ve iliotibial bant gerginliği, genel bağ laksitesi, hamstring, kuadriseps ve kalça kasları zayıflığı, aşırı kuadriseps (Q) açısı, patellar kompresyon veya tilti ve anormal VMO/VL refleksi yer almaktadır. PFAS'de etkin tedavinin ortaya çıkarılabilmesi için, sendroma neden olabilecek birincil nedenler üzerinde durulmalıdır (Hu ve ark., 2019). PFAS nedenleri çok faktörlü olup, hastalığa neden olabilecek asıl etkilerin belirlenmesi zordur. Bu bağlamda PFAS biyomekaniksel açıdan düşünüldüğünde, ayak bileği, diz ve kalça eklemi arasında güçlü bir ilişki olduğu görülmektedir (Carlson ve ark., 2017).

Koşma, çömelme ve squat aktiviteleri sırasında PFAS'li kadınlarda anormal kalça biyomekanikliği olduğu bildirilmiştir. Bu hareketler aşırı kontralateral pelvik drop, kalça adduksiyonu ve kalça iç rotasyonunun neden olmaktadır. Bu bağlamda dizde Q açısı artmakta ve patellofemoral eklem lateral eklem stresini artırarak ağrıya neden olmaktadır (Noehren ve ark., 2012).

### 1.3. Tedavide Genel Yaklaşım

PFAS'de çoğu tedavi konservatiftir. Cerrahi müdahaleler çok azdır. Bu genellikle çeşitli formlarda egzersiz, nonsteroid anti-inflamatuar ilaçları, dizlik, bantlama, germe, esneklik ve kuvvetlendirme egzersizlerini, propriyosepsiyon, endurans, fonksiyonel eğitimi, bantlamayı, ayak ortezini ve spora kademeli bir dönüşü içerir (Willy ve ark., 2019). Egzersiz programı, PFAS tedavileri içerisinde en etkin yöntemdir (Evcik ve ark., 2010).

Konservatif tedavi uygulandığında özellikle kuvvetlendirme egzersizleri, egzersiz programlarının önemli bir parçası olarak kabul edilir. Geleneksel olarak kuadriseps kuvvetlendirme, PFAS'li hastalarda fonksiyonel yeniden eğitim için kullanılmaktadır (Willy ve ark., 2019). Gluteus maksimus ve gluteus medius frontal ve transvers düzlemde kalçanın primer stabilizörleridir. PFAS'li hastalarda bu kaslar zayıf olduğu için, PFAS tedavisinde kalça kaslarının kuvvetlendirilmesi önerilmektedir. Ayrıca ağrıyı azaltma ve gelişmiş fonksiyonel beceriler açısından daha iyi sonuçlar elde etmek için PFAS'li hastalarda kuadriseps, proksimal kalça egzersizlerinin birleştirilmesi önemle tavsiye edilmektedir (Collins ve ark., 2018; Corum ve ark., 2018). PFAS ile ilgili bir kohort çalışmasında, kalça kaslarının kuvvetlendirilmesinin kısa sürede ağrının azaltılmasında etkili olduğu belirtilmiştir (Dolak ve ark., 2011). Marra ve ark. (2020) patellofemoral ağrıyla ilgili rehberde ağrının azaltılması ve fonksiyonla gelişiminin artması için birincil tedavi olarak posterior kalça ve kuadriseps egzersizlerin yapılması gerektiğini belirtmiştir (Marra, 2020).

Genel olarak çok yönlü bir tedavi yapılmasına rağmen, PFAS tekrarlama oran %91' lerin üzerindedir. Tedavi edilen bireylerin %55'inin üç ayda ve %40'ının ise on iki ayda şikayetlerinin devam ettiği görülmektedir. Olguların %57' sinin ise beş ile sekiz yılda tamamen iyileşemediği belirtilmektedir (de Souza Júnior ve ark., 2021).

Semptomların geri dönüşü hem hasta, hem de tedavi sağlayıcılar için hayal kırıklığı oluşturmaktadır. Yüksek tekrarlama oranı nedeniyle daha etkin ve yeni tedavi seçeneklerinin üzerinde odaklanılması gerekmektedir.

### 2. Materyal ve Yöntem

PFAS' de kullanılan yeni tedavi yöntemlerini belirlemek amacıyla PubMed, Science Direct ve Google Scholar veritabanlarında "ön diz ağrısı", "patellofemoral ağrı sendromu", "patellofemoral ağrı sendromu tedavi", "patellofemoral ağrı sendromu için müdahale veya yeni tedavi", "Anterior knee pain", "Patellofemoral pain syndrome", "Patellofemoral pain syndrome treatment", "reat or new treatment for patellofemoral pain syndrome" kelimeleri kullanılarak tarama yapılmıştır. Tarama başlangıç tarihi 2016 olup (son beş yıl), belirlenen veri tabanlarında 30 Kasım 2021 tarihine kadar yer alan konuyla ilgili tüm araştırmalar incelenmiştir. "Patellofemoral pain syndrome" yazılarak arama yapıldığında Pubmed veritabanında 562, Science direct 1054, Google Scholar veritabanında gelişmiş aramalarda sadece başlıklar seçilerek 377 araştırma bulunmuştur. Bu sonuçlar ayrıntılı bir şekilde incelenmiştir. Bu araştırmalarda PFAS' de kullanılan tedavi yöntemleri ve tedavideki yeni yaklaşımlar üzerinde durulmuştur. Bu yaklaşımlar belirlenirken PFAS ile ilgili rehberlerden de faydalanılmıştır. İncelemeler sonrasında PFAS kullanılabilir 5 yaklaşım belirlenmiştir. Sonrasında bu yaklaşımlar "Patellofemoral pain Gait Retraining", "Patellofemoral Pain Blood Flow Restriction Training", "Patellofemoral Pain Blood Whole Body Vibration", "Patellofemoral Pain Elastomeric Knee Braces", "Patellofemoral Pain Technology Assisted Exercise Band (Bandcizer)" anahtar kelimeleri yazılarak tekrar değerlendirilmiştir. Bulunan makaleler dahil edilmiştir. Tedavi yaklaşımlarının karşılaştırmalı sonuçları incelenmiştir. İleri ki çalışmalar için yol göstereceği düşünülmektedir.

Bu çalışma için etik kurul onayı gerekmemekte olup temin edilmemiştir.

### 3. Patellofemoral Ağrı Sendromunda Yeni Tedavi Yöntemleri

PFAS tanısında geleneksel tedavi olarak egzersizin çeşitli formları, splint, bantlama ve ayak ortezleri yaygınlıkla kullanılmaktadır. Fakat bu yaklaşımlarında semptomları başarılı bir şekilde çözemediği görülmüştür. Standart yaklaşımların başarılı olamamasından ve yüksek tekrarlama oranlarından dolayı, sorunun altta yatan sebebi iyice araştırılmalıdır (Davis ve ark., 2020). PFAS ile ilgili yeni çalışmalar, PFAS yönetiminde etkili olabilecek yeni yaklaşımların kullanılabilirliği göstermektedir. 5.Uluslararası Patellofemoral Ağrı Tedavisi araştırma (2018) konsensus kararlarında, yürümenin tekrar eğitimi ve kan akımı kısıtlayıcı egzersizlerin PFAS tanılı vakalarda yeni tedavi seçenekleri olarak kullanılabilirliği belirtilmiştir (Collins ve ark., 2018). Ayrıca elastrometrik

breyler ve teknoloji destekli elastik dirençli bant yöntemleri de mevcuttur (Rathleff ve ark., 2016; Uboldi ve ark., 2018). Yapılan yeni çalışmalarda tüm vücut vibrasyon eğitiminde de kullanılabilirliği belirtilmiştir (Corum ve ark., 2018; Yañez-Álvarez ve ark., 2020; Rasti ve ark., 2020).

#### 3.1. Yürümenin Tekrar Eğitimi

Yürümenin Tekrar Eğitimi (YTE), nörolojiksel teknikler veya yoğun egzersizler ile yürüyüşün rehabilitasyonuna odaklanan, non-invazif bir tekniktir (van Gelder ve ark., 2018). YTE tedavisi hastanın koşu bandında, ayna veya bir görüntü karşısında yürümedeki bozuklukların fizyoterapist veya yazılım programı sayesinde azaltılmasına dayanmaktadır. Hastadan bu anormal hareketleri, sesli ikaz ve yazılım programı yardımıyla düzeltilmesi istenmektedir. Bu yeni yürüyüş paternine, uyum sırasında en yaygın yaklaşım normal hareket paternlerini kontrol altına almak ve kasları kuvvetlendirmektir. Tedavi ortalama 4-6 hafta kadar sürmekte, 2-3 ayda ise alışkanlık haline gelmesi gerekmektedir. Devam eden dönemde ise aktiviteler kademeli olarak artırılmalıdır (Davis ve ark., 2020).

Willy ve Davis (2011) yaptığı çalışmada 40 bireyi, kalça kuvvetlendirme deney grubu ve kontrol grubunu randomize etmiştir. Kalça abduktör ve dış rotatörler kaslarına yönelik 6 haftalık kuvvetlendirme programı uygulamıştır. Bu kasların kuvvetinde artış olmasına rağmen kalça adduksiyonu, iç rotasyonunda, kontralateral pelvik düşmede (drop) azalma (bu parametreler PFAS'da görülen yaygın bozukluklardır) gözlemlenmiştir. Willy ve Davis (2011) bu sonuçlar nedeniyle tek başına kuvvetlendirme programının hareket şeklini değiştirmediğini öne sürmüştür. Kuvvetlendirme farklı hareket etme kapasitesi sağlayabilir, fakat kişinin hareket etme şeklini değiştirmek için hareketin yeniden eğitimi yoluyla motor modelin yeniden programlanmasının gerekli olduğu belirtilmiştir (Davis ve ark., 2020). Yürümenin tekrar eğitimi uzman görüşü olarak tavsiye edilmektedir (Barton ve ark., 2015).

Çalışmalar yeniden yürüyüş eğitiminin PFAS yönetiminde etkili bir tedavi sağladığını göstermektedir (Dos Santos ve ark., 2019; Davis ve ark., 2020). Noehren ve ark. (2011) PFAS'lı hastalarda yaptıkları çalışmada, YTE tedavisi ile kalça mekaniklerinden önemli gelişmeye bağlı olarak ağrı azalma ve fonksiyonel düzeyde artma sağlamışlardır. Roper ve ark. (2016) yaptıkları PFAS' lı hastalarında yürümenin tekrar eğitimi tedavisinde diz ağrısının önemli derece azaldığını, bu azalmanın kalça abduksiyon açılarındaki değişiklik ve ayağın ilk teması sırasında diz fleksiyon açılarındaki artış nedeniyle olduğunu belirtmişlerdir. Willy ve ark. (2012) PFAS'lı kadın koşuculara tam boy aynası kullanarak yaptıkları araştırmada, YTE'nin koşu sırasında anormal mekaniklerin ağrı azaltılmasında ve fonksiyonel becerilerin artırılmasında anlamlı değişiklikler olduğunu saptamıştır. Futrell ve ark. (2020), Willy ve ark. (2016) yaptıkları çalışmalarda vertikal yükü azaltmada, dize binen yükü azaltmada en etkili yolun ön ayak vuruş

modeline geçiş olduğu belirtilmiştir.

PFAS'li hastalarda YTE ile ilgili son 5 yıldaki çalışmalar Tablo-1' de özetlenmiştir. Bu çalışmaların çoğu koşuculara yapılmıştır. Koşma esnasında kalça adduksiyonunu azaltmaya, öne eğilmeyi arttırmaya, ön ayak vuruşuna geçmeye ve kadansı arttırmaya yöneliktir. Bir dizi araştırmada ise yürüme, çömelme, merdiven inme-çıkma, sandalyeden kalkmaya odaklanılmıştır. Son 5 yıldaki çalışmaların hepsinde ağrı ve fonksiyonellikle ilgili gelişmeler olduğunu bildirilmiştir. Çalışmalarda motor kontrol prensibine bağlı olarak hastalara geri bildirim sağlanmasında yeterli dozun önemli olduğu görülmüştür. Zaman için en büyük ağrı azalması ve kalıcı değişiklikler haftada 3-4 seans olan, toplamda 8-18 seansı içeren çalışmalarla kaydedilmiştir. Bunun aksine tedavi

sırasında geri bildirim bulunmadığı veya ara vermeden sürekli yapılan tedaviler şeklinde olan çalışmalarda ağrı azalmasının en az olduğu saptanmıştır (Corum ve ark., 2018; Yañez-Álvarez ve ark., 2020).

YTE klinikte koşu bandı ve görsel feedback olarak ayna karşısında fizyoterapist eşliğinde kolaylıkla yapılabilecek bir tedavidir. Tedavi süresi ortalama 2-4 hafta arasında değişmekte olup, etkinliğin artırılması için uzun süreli takipler gerekmektedir. Tedavide önemli olan hastanın YTE' ye iyi düzeyde katılması, fizyoterapist tarafından yürüme bozuklukları ilgili geri bildirimleri düzeltmeye çalışmasıdır. Çalışmalarda sesli geri bildirim için telefon üzerinden uygulamalar, hastanın hareketlerin daha iyi belirlenmesi için biyomekanik analizler de kullanılmıştır.

**Tablo 1.** Patelofemoral ağrısı sendromunda yeni yaklaşımlar

Yazarlar	Yayın tarihi	Çalışma tipi	Örneklem grubu	n	Tedavi Grubu	Veri toplama aracı	Tedavi Süresi	İstatiksel sonuç	Sonuç
Santos A.	2019	RCT	DG1,2,3	18	YTE	AKPS, AEFS, biyomekani k analiz	2hf,8s	P<0,001 eb=0,19	3 farklı YTE' de de ağrı azaldı ve fonksiyonellikte anlamlı derecede arttı.
Banocci J.	2017	RCT	DG1=YTE DG2=AOG	16	YTE	AKPS, VAS	6hf,12s	P<0,05	YTE ile AOG grubuna kıyasla daha fazla oranda ağrı azaldı ve fonksiyonellik anlamlı derecede arttı.
Roper j.	2016	RCT	DG=YTE KG	16	YTE	VAS, ÜBHA	2hf,8s	P<0,05; eb=0,02	Diz ağrısı anlamlı derecede azaldı. Üç grupta da ağrı anlamlı derece azaldı.
Esculier J.F.	2020	RCT	DG1=Eği DG2=Egz DG3=YTE	68	YTE	VAS, GYUIDT	2 hf,5s	P<0,001	Sadece Egzersiz ve YTE' de fonksiyonellik arttı. Semtomlar azaldı.
Junior J,R,S.	2021	RCT	DG1=YTE+S DG2=YTE-S KG	21	YTE	VAS, PFHS, Kinematik analiz	2hf,8s	P<0,05	Ağrı anlamlı DG1' de anlamlı derece azaldı.
Korakakis V.	2017	RCT	DG=KAKT+ DDE KG=DDE	40	KAKT	NAS, FT	8hf	P<0,001 eb:0,56	DG ağrı anlamlı azaldı. Gruplar arasında anlamlı fark yoktu.
Giles L.	2017	RCT	DG=KAKT+ KK KG=KK	69	KAKT	VAS, KPFS	8hf, 24s	P<0,001	Her iki grupta ağrı ve GYA anlamlı azaldı.
Antonis C.	2020	RCT ,AP	DG=KAKT+D KE KG=DKE DG=	76	KAKT	VAS, KPFS, TKÖ, FT	8hf,12s	-----	-----
Rasti E.	2020	RCT	TVVE+Egz KG=Egz DG= TVVE+ Egz	24	TVVE	NAS, FT	4hf.12s	P<0,001 eb:0,2	Her iki grupta da ağrı anlamlı azaldı. Esneklik DG anlamlı olarak arttı.
Yanez-Alvarez A.	2020	RCT	DG= TVVE+ KG= Egz	50	TVVE	VAS, FT, KPFS AEFS	4hf.12s	P<0,001 eb:0,43	DG ağrı anlamlı azaldı. Fonksiyonellik arttı.
Çorum M.	2018	RCT	DG= TVVE+ EvEgz KG= EvEgz	40	TVVE	VAS, KPFS, SF-36	8f,24 s	P<0,005	Her iki grupta da ağrı anlamlı azaldı, diz ektansör kuvvet arttı.

Randomize kontrollü (RCT), Araştırma Protokolü (AP), Deney grubu (DG), Kontrol Grubu (KG), Ayak Ortez Grubu (AOG), Yürümenin tekrar eğitimi (YTE), Kan Akışı Kısıtlama Teapisi (KAKT), Tüm vücut vibrasyonu eğitimi (TVVE), Düşük Direçli Eğitim (DDE), Kuadriseps Kuvvetlendirme (KK), Süpervizörlü (+S), Süpervizörsüz (-S), Egzersiz (Egz), Diz Kalça Egzersizi (DKE), Ev Egzersizi ( EvEgz) Eğitim (Eği) Egzersiz, Anterior Diz Ağrı Skalası: (AKPS), Kujula Patellofemoral skor (KPFS). Tamp Kinezyofobi Ölçeği(TKÖ), Alt Ekstremitte Fonsiyonel Skala (AEFS), Vizüel Anolog Skala (VAS), Günlük Yaşam Uğraşlarına İlişkin Diz Testi (GYUIDT), Günlük Yaşam Aktivitesi (GYA), Short Form-36 (SF-36) Üç Boyutlu Hareket Analizi (ÜBHA), Patello femoral hastalık skalası (PFHS), Fonsiyonel testler (FT), Numerik Ağrı Skalası (NAS). Hafta (hf), Seans (s), Etki Büyüklüğü (eb).

### 3.2. Kan Akımı Kısıtlama Terapisi

Kan akışı kısıtlama terapisi (KAKT), ilk olarak Japonya' da 1970' lerin sonunda KAATSU eğitimi olarak adlandırılan yerde geliştirilmiştir. Bu terapi ile metabolik ve mekanik

stres kombine edilerek kas kuvveti, hipertrofi ve anjiyogenesizi uyarmak amaçlanmıştır. Kan akımı kısıtlamalı egzersiz; turnike, manşon veya elastik bir bandaj vasıtasıyla hedef kasın proksimalinden kan

akımını eksternal basınçla kısıtlama yöntemine dayanan bir egzersiz protokolüdür (Vopat ve ark., 2020). Arterial akış devam ederken, venöz kan akışına metabolik stres uygulanır. Bu stres, proksimal üst veya alt ekstremitede bir turnike kullanımıyla vasküler tıkanma yoluyla oluşur. Arterial akış devam ederken venöz çıkışı tıkayarak anaerobik metabolizmayı hareket geçiren hipoksik bir ortam oluşturulur (Minniti ve ark., 2020; Cuyul-Vásquez ve ark., 2020). Oluşan bu hipoksik ortamda egzersizin etkilerinin arttığı, dolayısıyla kas kuvveti ve kütlelerinde artma sağlanmaktadır.

Mekanik stres maksimum tekrarın %20 kadar düşük yüklerle dirençli egzersiz yoluyla oluşur (Barber-Westin ve Noyes 2019). KAKT' nin avantajı maksimum kuvvetin %30' larında yapılan egzersizlerde maksimum kuvvetin %80' lerinde fazla etki oluşturmasıdır. Bu tedavi yöntemi yaralı veya postoperatif hastaların yanı sıra, yüksek dirençli eğitimi tolere edemeyen hastalarda kullanılabilir. Son yıllarda sporcular üzerindeki kas-iskelet stresini azaltmak için geleneksel antrenman rutinlerine ek olarak, birçok profesyonel organizasyonda da dahil olmak üzere atletik performans eğitiminde popüler hale gelmiştir (Vopat ve ark., 2020). Birçok araştırmada, sağlıklı katılımcılar ve sporcular ile yaşlı bireylerde KAKT' nin pozitif etkileri gösterilmiştir (Barber-Westin and Noyes 2019). Araştırmalarda PFAS' lı hastalarda 1 set 30 tekrar veya 3 set 15 tekrar olarak yapılan kuvvetlendirme programlarının etkin olduğu görülmüştür (Giles ve ark., 2017).

PFAS semptomlarını iyileştirmede kuadriseps kuvvetlendirme önemli tedavi yaklaşımıdır, ancak diz ağrısını arttırabilecek ağır direnç gerektirir. KAKT, egzersiz sırasında kan akışını sınırlandırmak için kasın proksimaline pnömatik bir manşet yerleştirmeyi içerir ve geleneksel kuvvetlendirme programlarından daha düşük yüklerde kas kuvvetini artırabilir. Giles ve ark. (2017) yaptığı çalışmada KAKT, PFAS' lı kişilerde kuadriseps kuvvetini artırmak için düşük yüklü bir alternatif tedavi seçeneği belirtilmiştir (Giles ve ark. 2017). Tek başına düşük düzeyde dirençli eğitiminin kas gelişimini desteklediği gösterilmemiş olsa da, KAKT ile birleştirildiğinde olumlu etkiler olduğu bildirilmiştir (Vopat ve ark., 2020). Hughes ve ark. (2017) 20 çalışmayı araştıran bir meta-analizde, KAKT' nin tek başına düşük yüklenmelerle eğitiminin, tek başına terapi programına kıyasla, kas kuvvetini artırmada daha etkili olduğunu belirlemiştir. Fakat düşük yüklenmelerle KAKT tedavisi ile yüksek dirençli eğitimi ile kıyaslandığında yüksek dirençli eğitimin daha iyi kuvvet kazanımları oluşturduğu belirtilmiştir (Hughes ve ark., 2017). Tablo 1'de KAKT ile ilgili son beş yıldaki çalışmalar özetlenmiştir.

KAKT yöntem olarak yeni bir metot olmamasına rağmen, PFAS kullanım açısından yeni bir tedavi seçeneğidir (Constantinou, 2020). Giles ve ark. (2017) yaptıkları çalışmada ağrının azaltılmasında etkin olduğunu belirtmişlerdir. PFAS' lı hastalarda düşük yüklenme ile yapılan, KAKT ile birlikte kuadriseps kuvvetlendirme, sadece yapılan standart kuvvetlendirmeye göre ağrı

azaltılmasında ve fonksiyonel artmasında daha etkilidir. Bu nedenle KAKT ağrı nedeniyle ağır dirençli egzersize zayıf toleransı olan hastalar için bir alternatif olabilir.

Herhangi bir egzersiz yönteminin reçetesinde olduğu gibi, doktorlar ve fizyoterapistler bu konularda eğitilmeli ve hastaya özel optimal bir KAKT eğitimin rejimini oluşturmak için fizik tedavi ekibi ile iş birliği içinde çalışmalıdır. Gelecekte belki de KAKT tedavisi dünya çapında ortopedik rehabilitasyon merkezleri tarafından benimsenebilir. KAKT tedavisinin PFAS kullanımı için daha fazla çalışmaya ihtiyaç vardır. Ayrıca bu gelecekteki araştırmalar KAKT' in yöntem tekniğinin, dozajı ve parametreleri dahil olmak üzere spesifik rehabilitasyon kılavuzlarını oluşturmaya odaklanmalıdır (Vopat ve ark., 2020).

### 3.3. Tüm Vücut Vibrasyon Eğitimi

Tüm vücut vibrasyonu eğitimi (TVVE) klinikte nöromusküler aktiviteleri geliştirmek, egzersizlerin etkisini yükseltmek, kemik yoğunluğunu artırmak ve esnekliği sağlamak amacıyla alternatif bir yöntem olarak kullanılmaktadır (Türkmen ve Köse, 2016). TVVE fizyoterapi, profesyonel spor, fitness gibi birçok alanda uygulanmaktadır.

TVVE, bir kişinin ayakta kaldığı süreçte, kişiye platform titreşim sağlanarak bu titreşimin kişiyi etkilemesidir (Corum ve ark., 2018). Cihazların ürettiği titreşimin genliği 0,7 ile 14 mm arasında, salınım frekansı 0,5 ile 80 Hz arasında değişmektedir. TVVE, özellikle ağrı hissini azaltması, kan akışının artması, kas gerginliğinin azalması, esnekliğin artırılmasında, ağrı yoğunluğunun azalması ve alt ekstremitelerde işlevselliğini artırma üzerinde olumlu etkileri vardır. Çalışmalarda (hafta 3 kez) 4 hafta boyunca yapılan egzersizin TVVE üzerinde etkili olduğu bildirilmiştir (Yañez-Álvarez ve ark., 2020).

TVVE sonrasında ağrı şiddetinin azaldığı çalışmalarda bildirilmiştir. Fakat etki mekanizmasını açıklamada birkaç mekanizma vardır (Dong ve ark., 2019). Genel titreşim analjezinin etkisinin açıklamak için kapı kontrol teorisi ve titreşime bağlı uyarılar spinotalamik saha nöronlarının önleyici etkisi gibi birkaç teori ile açıklamaya çalışılmıştır. Vibrasyon platformu, kas içciklerinde Ia-afferenler ile ilişkili tonik vibrasyon refleksi olarak adlandırılan, kas kontraksiyonu yoluyla sinüzoidal titreşimler üretir. Vibrasyon etkisi tonik aracılığıyla pozitif analjezik etki oluştu. Kas içcikliklerin uyarılabilirliği motor ünitlerin alımı ve senkronizasyonu sayesinde nöromusküler fasilasyonu artar (Yañez-Álvarez ve ark., 2020). TVVE sonrasında ağrının azalması cildin mekanoreseptörlerinden gelen duyuşal girdilerdeki artışın, eklem ve kas yanıtlarının artışına neden olmaktadır. Titreşim ayrıca PFAS'lı hastalarda fiziksel aktivitenin neden olduğu ağrı seviyesinde bir azalmayı destekleyebilir, hatta kuadriseps artrojenik kas inhibisyonunu iyileştir. Her durumda, PFAS'da altta yatan ağrı mekanizmalarının daha iyi anlaşılması, yeterli tedaviyi uygulamak için önemlidir.

Çalışmalar, sağlıklı yaşlılar ve voleybolcularda kuvvet antrenmanına, TVVE eklendiğinde titreşim uyarıcıları ile

kuvvet, güç ve sıçrama performansının arttığını göstermektedir. Etkili TVVE için titreşim frekansının ve süresinin belirlenmesini içeren optimum tedavi protokolü oluşturulması gerektiği belirtilmiştir (Corum ve ark., 2018).

Rasti ve ark. (2020) PFAS' lı sporcularda yaptığı çalışmada, egzersiz tedavisine TVVE' nin eklenmesinin, tek başına egzersiz terapisine göre esneklikte daha büyük bir iyileşmeye yol açabileceğini belirtmişlerdir. TVVE, sporcularda geleneksel egzersiz terapisinin etkinliğini artırmak için PFAS' lı sporcular için rehabilitasyon programlarında uygulanabileceğini göstermektedir.

Corum ve ark. (2018) PFAS'li kadınlarda yaptığı çalışmada sekiz haftalık TVVE artı ev egzersiz programının, ev egzersiz programından diz ekstansör enduransı artırmada daha etkili olduğunu bildirilmiştir. TVVE PFAS'li hastaların yönetiminde uygun ve etkili bir tedavi olabileceği belirtilmiştir.

Çalışmalar, TVVE'nin egzersiz tedavisine ek olarak uygulandığında kas kuvveti, güç, esnekliği, kasın kesitini ve kemik mineral yoğunluğunu önemli ölçüde artırdığını ve ayrıca abdominal yağın azaldığını göstermektedir (Rasti ve ark., 2020). Osawa ve ark. (2013) tarafından gerçekleştirilen meta-analiz çalışmasında, rutin egzersizlere TVVE'ye eklenmesinin, hem genç hem de yaşlı erişkinlerde TVVE' siz aynı egzersizlere kıyasla diz ekstansör gücünde ve karşı hareket atlama yüksekliğinde önemli ölçüde daha fazla iyileşmeye yol açtığını saptamıştır.

Çalışmalar, TVVE diz osteoartritli bireylerde diz ağrısını, diz fonksiyonunu ve kas performansını iyileştirdiğini göstermiştir. Bu durum, TVVE' nin PFAS için bir eğitim tekniği olarak etkili ve alternatif bir seçenek olabileceğini düşündürmektedir. Son 5 yılda yapılan çalışmalar incelendiğinde kuvvet, endurans, denge, fonksiyonelliği iyileştirme veya ağrıyı azaltma üzerindeki güçlü olumlu etkileri nedeniyle TVVE'nin etkili bir yöntem olarak kullanılabilirliği görülmektedir (Tablo 1).

Sonuç olarak, bir titreşimli platformda kalça, diz ve karın egzersizlerinin bir eğitim protokolünün gerçekleştirilmesi, PFP'li hastaların ağrı seviyesi ve fonksiyonel kapasitesi üzerinde olumlu etkiler yaratır ve PFP' li hastalarda ağrı ve işlevi iyileştirmede tek başına egzersizden daha etkili olduğu görülmüştür (Yañez-Álvarez ve ark., 2020). Bu nedenle PFAS' lı hastalarda yeni tedavi seçeneği olarak kullanılabilir.

Ayrıca çalışmalarda eğitilmiş kas sistemi üzerindeki potansiyel adaptasyonlar üzerine kanıtlar mevcut değildir. Çalışmalar da daha çok kadınlar üzerine yapılmıştır. Gelecek planda yapılacak çalışmaların daha büyük örneklem büyüklüğüne sahip olması ve daha uzun takip sürelerinde gerçekleştirilmesi, cinsiyet olarak erkeklerin de dahil edilmesi gerektiği belirtilmiştir.

#### 4. Elastomerik Diz Breysleri (Dizlikler)

Patellar breysler non-operatif ve teknik olarak PFAS'de kullanılmaktadır. Patellofemoral ağrı için dizliklerin amacı bu biyomekanik anormallikleri düzeltmek ve uygun

mekanik desteklemektir. Patellofemoral eklem breysleri ile desteklenmesi ağrı, yürüme ve çömelme gibi fonksiyonel aktivitelerde kısa süreli olarak etkili olduğunu göstermektedir (Uboldi ve ark., 2018).

Mevcut breysler patellayı troklear oluk içerisinde doğru çekerek patellofemoral temas alanını artırmak ve patello femoral basıncı azaltmak amacıyla tasarlanmıştır. Piyasada geleneksel olarak bulunan dizlikler çoğunlukla, teoride patellanın lateralizasyonuna yol açma eğilimine karşı koyan, medial olarak yönlendirilmiş bir kuvvet uygulamak üzere tasarlanmış ve üretilmiştir (Sisk ve Fredericson, 2020).

Ayrıca yeni breys olarak atletler için tasarlanmış elastomerik breysel mevcuttur. Elastomerik dizlik ile patellanın dikey hareketini kontrol etmenin yanı sıra sporla ilgili spesifik fleksiyon hareketinde biriken kinetik enerjinin dönüşümünü sağlayan ve böylece darbe kuvvetlerini azalmasını sağlayan yeni nesil bir breystir. Elastik bir dış iskeleti olan ve uzayabilir bileşenlerin uzamasıyla eklem üzerindeki etki kuvvetlerini azaltan ve böylece eklem hareketi boyunca propriyoseptif temasını korunmasını sağlayan elastomerik bantlardan oluşan ön kısmı ağ benzeri yapıdan oluşan splintlerdir. Ağ benzeri yapının sağlıklı deneklerde sporla ilgili farklı motor görevler sırasında diz stabilitesini iyileştirdiği gösterilmiştir. Ayrıca ağ benzeri yapının patellofemoral eklem ve ekstansör mekanizmaya uygulanan kuvvetleri eşit dağıtmaktadır (Uboldi ve ark., 2018) (Şekil 1).



**Şekil 1.** Elastomerik breys (Reaksiyon dizlik) (<https://www.djoglobal.com/products/donjoy/reaction-web-knee-brace>).

Uboldi ve ark. (2018) yaptığı çalışmada patellofemoral ağrı sendromunda elastomerik diz breyslerinin kişilerin diz ağrısını azaltmada ve spora dönüşü hızlandırmada etkili bir yardımcı olabileceği gösterilmiştir (Uboldi ve ark., 2018).

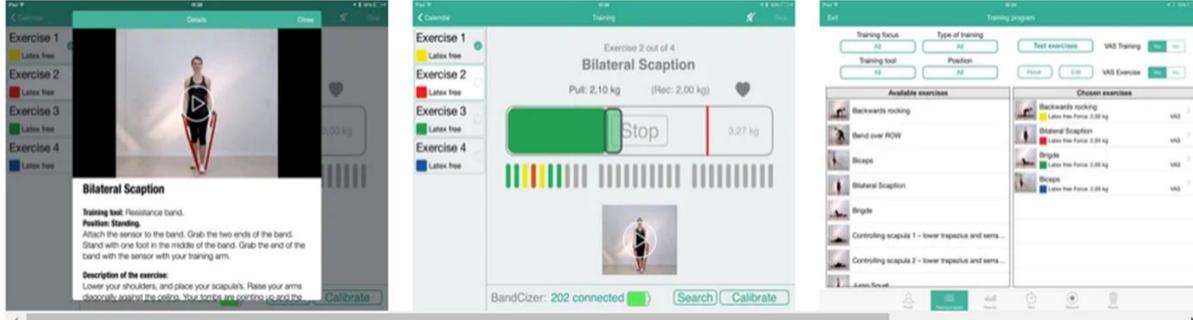
Bu tür cihazların etkinliğinin altında yatan mekanizmaları ve rehabilitasyondaki rollerini daha derinlemesine araştırmak için daha fazla biyomekanik ve klinik çalışmaya ihtiyaç vardır.

#### 5. Teknoloji Destekli Egzersiz Bandı (BandCizer)

Bandcizer, direnç bantları Danimarka'da icat edilmiş patentli bir aktivite sensörlü banttır. Elastik bant, bir

BandCizer ve BandCizer uygulamasına sahip bir ipadten meydana gelir. Ev tabanlı elastik dirençli bant egzersizlerinin kalitesi hakkında canlı geri bildirim sağlamak amacıyla, BandCizer adlı bir sensör kullanılmaktadır (Riel ve ark., 2016). BandCizer, her iki tarafa monte edilen ve dahili miknatıslarla bir arada tutulan iki parçadan oluşur. Verileri BandCizer uygulamasıyla bir iPad'e iletir. Elastik dirençli banttaki bir sensör yardımıyla, gerilim ve set sayısını ölçüp kişiye yönelik egzersiz vermektedir. Uygulama, kullanıcıya gerilim ve çekme kuvveti hakkında canlı geri bildirim sağlar. Egzersizler sırasında canlı geri bildirim, hastaların egzersizi ön

görüldüğü şekilde yapmalarına yardımcı olur ve egzersize uyumu artırır, böylece ön görülen egzersiz dozunun elde edilmesi sağlanacaktır. Bu egzersize entegre sistem ile egzersizlerin talimatlara göre gerçekleştirilmelerine yardımcı olacağı öngörülmektedir. Her egzersiz için 10-12 tekrar, hafta 3 kez, 6 hafta önerilmektedir. Egzersiz doğru yapıldığında uygulanan çekme kuvveti, BandCizer tarafından ölçülecek ve kaydedilecektir. Egzersizleri yaparken, canlı görsel ve işitsel geri bildirim ve BandCizer uygulamasında olacaktır (Riel ve ark., 2016; Rathleff ve ark., 2017) (Şekil 2).



Şekil 2. İpad 'ten bluetooth yoluyla elastik dirençli banta bağlantısının sağlanması (Riel ve ark., 2016).

Bandın kalınlığını ölçerek kasılma süresini, gerçekleştirilen tekrar sayısını ve elastik bantı germek için kullanılan kuvveti ölçülebilen geçerli bir yöntemdir. Riel ve ark. (2016) PFAS'li hastalarda yaptıkları çalışmada Bandcizer ile egzersizlerin adolesanlar için uygun olduğu bildirilmiştir. Bu yeni sistemin, klinisyenler ve araştırmacılar için ev egzersizlerinde tekrar ve set sayısı, egzersizin yoğunluğunun tespiti ve tedavisi amaçlı önemli bir kullanım aracı olabileceği görülmüştür.

## 6. Sonuç ve Öneriler

PFAS de son yıllardaki çalışmalara bakıldığında birçok farklı yeni yöntemin kullanıldığı görülmektedir. Bu yöntemlerle ilgili çalışmaların da genel olarak ağrıyı azalttığı ve fonksiyonelliği artırdığı görülmektedir. Bu da yüksek tekrarlama oranı olan PFAS' de etkin bir tedavinin ortaya çıkmasında umut vericidir. Bu yöntemlerin uzun dönem sonuçlarıyla ilgili çok az sayıda çalışma mevcuttur. Yeni çalışmalar uzun dönem etkinlikleri üzerine odaklanabilir.

### Katkı Oranı Beyanı

Konsept: M.Ç. (%50) ve İ.Ç.K. (%50), Tasarım: M.Ç. (%50) ve İ.Ç.K. (%50), Denetim: M.Ç. (%50) ve İ.Ç.K. (%50), Veri toplama ve/veya işleme: M.Ç. (%50) ve İ.Ç.K. (%50), Veri analizi ve/veya yorumlama: M.Ç. (%50) ve İ.Ç.K. (%50), Kaynak taraması: M.Ç. (%50) ve İ.Ç.K. (%50), Yazma: M.Ç. (%50) ve İ.Ç.K. (%50), Eleştirel inceleme: M.Ç. (%50) ve İ.Ç.K. (%50), Gönderim ve revizyon: M.Ç. (%50) ve İ.Ç.K. (%50). Tüm yazarlar makalenin son halini incelemiş ve onaylamıştır.

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## VASKÜLER CERRAHİYE GENEL BAKIŞ

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**Özet:** Bu çalışmada vasküler cerrahi konulu literatürün incelenmesi amaçlandı. Çalışmada doküman araştırma yöntemlerinden bibliyometrik analiz metodu kullanıldı. Bibliyometrik veri tabanlarından olan Web of Science (WOS) veri tabanı anahtar kelimeler kullanılarak değerlendirme yapıldı. Arama dili olarak İngilizce tercih edildi. Arama çubuğu kısmında 'vascular surgery' yazılarak yayınlara ulaşıldı. Sadece araştırma makaleleri değerlendirildi. Yayınlar yıllara göre dağılım, ülke, kurum, yayımlandıkları dergi, finansal destek sağlayan kuruluşlara göre ayrıntılı olarak değerlendirildi. 67166 yayına ulaşıldı. Sadece araştırma makaleleri araştırmanın örneklemini oluşturduğundan 55508'i araştırma makalesi ayrıntılı olarak incelendi. İlk yayın 1970 yılında yayınlanmıştı. 1990 yılı öncesi yıllık 1000 makaleden az yayın tespit edilirken, 1991 yılında artış gözlenmiş, 1998 yılından itibaren yıllık 1000 makalenin üstünde yayın sayısına rastlanmıştır. Yayınların hâkim yazı dili İngilizce idi (%92,828). 19,995 tanesi (%36) açık erişim (open access) olarak yayınlanmıştı. En fazla yayın Harvard Üniversitesi'nden yayınlanmıştı (n=1556, %2,8002). 171 ülkeden makale olup, en fazla yayın Amerika Birleşik Devletleri (n=16612, %29,9) menşeyli yazarlar tarafından yayınlanmıştı. Almanya, Japonya, Çin, İngiltere, İtalya, Fransa, Kanada, Hollanda ve Türkiye ise en fazla yayımı bulunan diğer 9 ülke idi. Amerika Birleşik Devletleri (ABD) Sağlık Bakanlığı İnsan Hizmetleri (n=2949, % 5,311) en fazla finansal destek sağlayan kurumdu. Dünya genelinde kardiyovasküler cerrahide en önemli konu başlıklarından olan vasküler cerrahi konusundaki araştırmaların global olarak özellikle gelişmekte olan ülkelerde artırılması gerekmektedir.

**Anahtar kelimeler:** Vasküler cerrahi, Bibliyometrik analiz, Web of Science

### Overview on Vascular Surgery

**Abstract:** In this study, it was aimed to examine the literature on vascular surgery. In the study, bibliometric analysis method, one of the document research methods, was used. The Web of Science (WOS) database, which is one of the bibliometric databases, was evaluated using key words. English was chosen as the search language. The publications were found by typing 'vascular surgery' in the search bar section. Only research articles were evaluated. The publications were evaluated in detail according to their distribution by years, countries, institutions, journals in which they were published, and institutions providing financial support. 67,166 publications were reached. Since only research articles constituted a sample of the research, 55508 research articles were examined in detail. The first publication was published in 1970. While fewer than 1000 articles were published annually before 1990, an increase was observed in 1991, and since 1998, the number of publications has been above 1000 articles per year. The dominant language of the publications was English (92,828%). 19,995 of them (36%) were published as open access. The most publications were from Harvard University (n = 1556, 2.8002%). Germany, Japan, China, England, Italy, France, Canada, the Netherlands, and Türkiye were the other 9 countries with the highest number of publications. The United States (USA) Department of Health and Human Services (n = 2949, 5.311) was the institution that provided the most financial support. Research on vascular surgery, which is one of the most important topics in cardiovascular surgery worldwide, needs to be increased globally, especially in developing countries.

**Keywords:** Vascular surgery, bibliometric analysis, Web of Science.

**Keywords:** Vascular surgery, Bibliometric analysis, Web of Science

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### 1. Giriş

Vasküler cerrahinin bağımsız bir cerrahi uzmanlık olarak tanınması kaçınılmazdır, ancak tam özerkliğe giden yol belirsizliğini korumaktadır. Vasküler cerrahi, 1950'lerin ortalarında sentetik greftler ve mikrovasküler tekniklerin ortaya çıkmasıyla genel cerrahiden doğmuş bir daldır. 1980'lerin başında, çoğu büyük akademik tıp merkezlerinde, Lisansüstü Tıp Eğitimi için Akreditasyon Konseyi onaylı burslar kuruldu. Amerikan Cerrahi Kurulu (ACK), bu ek uzmanlık eğitimini mezunlarına, onları genel

cerrahlardan ayıran bir Özel Nitelikler Sertifikası (Vasküler cerrahi mezunları) vererek tanıdı. Endovasküler cerrahinin ortaya çıkışı, vasküler cerrahinin çehresini, genel cerrahi alt uzmanlığından, giderek artan minimal invaziv araçlar dizisiyle benzersiz bir cerrahi uzmanlığa dönüştürdü. Vasküler cerrahide birincil sertifikanın oluşturulması ve ardından entegre uzmanlıkların geliştirilmesi ile vasküler cerrahi, bağımsız bir cerrahi uzmanlık alanı olarak tanınmaya daha da yaklaşmıştır. Ancak son 50 yılda gözlemlenen kayda değer



ilerlemelere rağmen, o dönemde vasküler cerrahi branşı henüz resmi olarak ayrı bir branş olarak tanımlanmamıştır (Eidt, 2019; Ozaki ve ark., 2019). Amerikan Cerrahi Kurulu (ACK), Lisansüstü Tıp Eğitimi Akreditasyon Konseyi tarafından onaylanmış cerrahi eğitim programlarının mezunlarının sertifikalandırılmasına 80 yıldan fazla bir süredir dahil olmuştur. Böylece ABD cerrahi eğitimine hem doğrudan hem de dolaylı olarak destek vermiştir. En son olarak da 1998'de 'Vasküler Cerrahi Kurulu' kurulmuştur. Böylece, bunu takip eden iki yılda vasküler hastalıkların değerlendirilmesi ve tedavisi, vasküler ve endovasküler cerrahların eğitimi için paydaş kuruluşlarla ortaklıklar sağlanmıştır (Ozaki ve ark., 2019). Sonuç olarak, bu çalışmada, ilk temelleri ABD'de atılan ve bağımsız bir cerrahi branş olarak tanınan vasküler cerrahi konusundaki literatürünün incelenmesi ve bu konudaki bilimsel gelişimin değerlendirilmesi amaçlandı.

## 2. Materyal ve Yöntem

Çalışmada doküman inceleme yöntemlerinden bibliyometrik analiz yöntemi kullanıldı. Bibliyometrik analizler için, Web of Science (WOS) veri tabanı tercih edildi. Bu veri tabanı anahtar kelimeler kullanılarak

değerlendirme yapıldı. Arama dili olarak İngilizce tercih edildi. Arama çubuğu kısmında 'vascular surgery' yazılarak yayınlara ulaşıldı. Sadece araştırma makaleleri değerlendirildi. Yayınlar yıllara göre dağılım, ülke, kurum, yayımlandıkları dergi, finansal destek sağlayan kuruluşlara göre ayrıntılı olarak değerlendirildi.

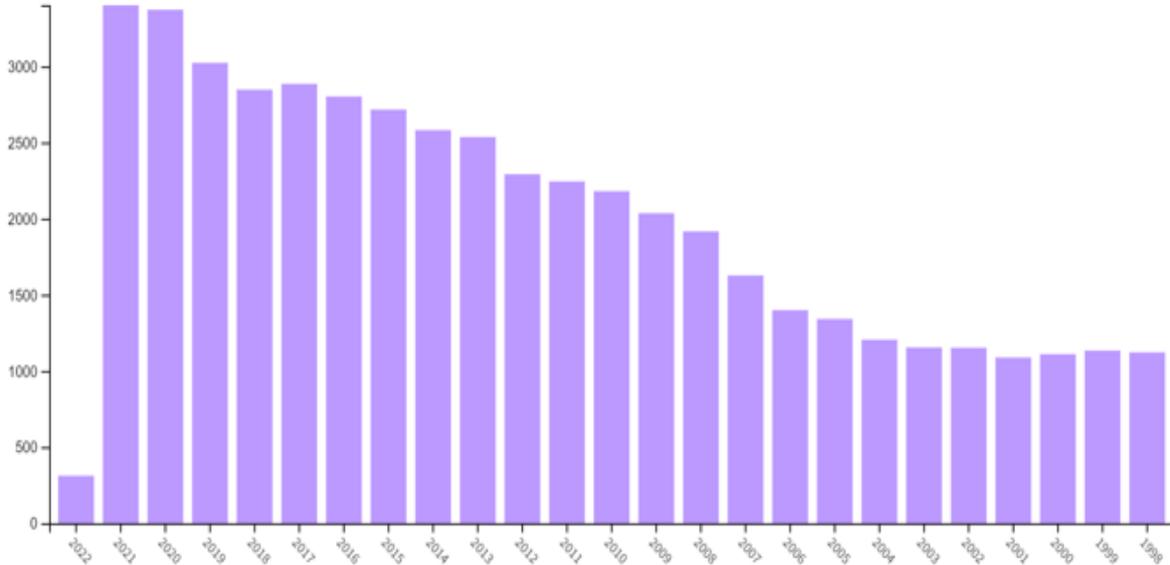
Çalışmada 15 Şubat 2022 tarihine kadar yayınlanmış tüm yayınlar incelendi. Çalışılan veri tabanı günlük eklenen makale sayısı ile güncellendiği için, tek günde veri taraması yapıldı.

### 2.1. İstatistiksel Analiz

Tanımlayıcı veriler yüzde ve frekans değerleri açısından analiz edildi.

## 3. Bulgular

Anahtar kelimelerle yapılan araştırma sonucunda 67166 yayına ulaşıldı. Sadece araştırma makaleleri araştırmanın örneklemini oluşturduğundan, 55508'i araştırma makalesi ayrıntılı olarak incelendi. İlk yayın 1970 yılında yayınlanmıştı. 1990 yılı öncesi yıllık 1000 makaleden az yayın tespit edilirken, 1991 yılında artış gözlenmiş, 1998 yılından itibaren yıllık 1000 makalenin üstünde yayın sayısına rastlanmıştır (Şekil 1).



Şekil 1. Yıllara göre yayın sayısı (1998-2022).

Yayınlara hâkim yazı dili İngilizce idi (n=51,541, %92,828). 19,995 tanesi (%36) açık erişim olarak yayınlanmıştı. Araştırmada yayınlar, WOS indeksinde taranan alt kategorilere göre incelendiğinde, en fazla oranda Science Citation Index Expanded (SCI-Expanded) (%89,832) dergilerde makale yayınlanmış olduğu saptandı (Tablo 1). Hollanda'dan Don Poldermans vasküler cerrahi konusunda en fazla makale yayınlayan çalışmacı idi (Tablo 2). En fazla yayın Harvard Üniversitesi'nden yayınlanmıştı (n=1556, %2,8002) (Tablo 3). European Journal of Vascular and Endovascular Surgery dergisi en fazla sayıda makaleyi yayınlayan dergi idi (Tablo 4).

Çalışmamız sonucunda 171 ülkeden makale olduğu, en fazla yayının Amerika Birleşik Devletleri (ABD) (n=16612, %29,9) menşeyli yazarlar tarafından yayınlandığı saptandı (Tablo 5). En fazla yayını bulunan diğer 9 ülke ise, Almanya, Japonya, Çin, İngiltere, İtalya, Fransa, Kanada, Hollanda ve Türkiye idi. Ülkemiz 10. sırada yer almaktaydı. ABD Sağlık Bakanlığı İnsan Hizmetleri (n=2949, %5,311), Ulusal Sağlık Enstitüleri ABD (n=2822, %5,083) ve Çin Ulusal Doğa Bilimleri Vakfı (n=1121, %2,019) yayınlara en fazla finansal destek sağlayan kurumlardı.

**Tablo 1.** WOS indeksinde taranan alt kategorilere göre makalelerin dağılımı

Web of Science Index	Sayı	Yüzde
Arts&Humanities Citation Index (A&HCI)	4	0.007
Book Citation Index – Social Sciences & Humanities (BKCI-SSH)	4	0.007
Book Citation Index – Science (BKCI-S)	373	0.672
Emerging Sources Citation Index (ESCI)	5233	9.427
Index Chemicus (IC)	3	0.005
Conference Proceedings Citation Index – Social Science & Humanities (CPCI-SSH)	12	0.022
Conference Proceedings Citation Index – Science (CPCI-S)	4160	7.494
Science Citation Index Expanded (SCI-EXPANDED)	49864	89.832
Social Sciences Citation Index (SSCI)	719	1.295

**Tablo 2.** İlk 10 sırada yer alan yazar

Yazar	Makale sayısı	%
Poldermans D	130	0.234
Wang Y	130	0.234
Zhang Y	126	0.227
Li J	124	0.223
Moll FL	120	0.216
Goodney PP	110	0.198
Schermerhorn ML	105	0.189
Bax JJ	97	0.175
Wang L	93	0.167
Bjorck M	91	0.164

**Tablo 3.** En fazla yayını olan ilk 10 kurum

Kurum	Makale sayısı	%
Harvard Üniversitesi	1556	2.802
Kaliforniya Üniversitesi	1410	2.539
Assistance Paris Publique Hastanesi	976	1.758
Teksaş Üniversitesi	737	1.327
Mayo Klinik	721	1.299
Amerikan Gazi Hastanesi	706	1.272
Amerikan Gaziler Sağlık İdaresi	699	1.259
Pennsylvania Eyalet Yüksek Öğrenim Sistemi (PASSHE)	697	1.255
Londra Üniversitesi	670	1.207
Johns Hopkins Üniversitesi	649	1.169

**Tablo 4.** Vasküler cerrahi konusunda en fazla sayıda makale yayınlayan 10 dergi

Dergi	Makale sayısı	%
European Journal of Vascular and Endovascular Surgery	2314	4.168
Journal of Vascular Surgery	2078	3.743
Annals of Vascular Surgery	993	1.788
Journal of Neurosurgery	669	1.205
Annals of Thoracic Surgery	534	0.962
European Journal of Cardio Thoracic Surgery	413	0.744
Journal of Cardiovascular Surgery	399	0.719
World Neurosurgery	383	0.690
Neurosurgery	360	0.648
Gefasschirurgie	331	0.596

**Tablo 5.** Vasküler cerrahi konusunda en fazla sayıda makale yayınlayan ilk 20 ülke

Ülke	Yayın sayısı	%
ABD	16612	29.919
Almanya	4852	8.739
Japonya	4154	7.482
Çin	3922	7.064
İngiltere	3717	6.695
İtalya	3552	6.397
Fransa	3049	5.491
Kanada	1901	3.424
Hollanda	1835	3.305
Türkiye	1806	3.253
İspanya	1558	2.806
Avustralya	1271	2.289
Güney Kore	1257	2.264
Hindistan	1206	2.172
İsviçre	1194	2.150
İsveç	1113	2.005
Brezilya	931	1.677
Belçika	766	1.380
Avusturya	742	1.336
Tayvan	666	1.200

#### 4. Tartışma

Bibliyometrik analizler bir konudaki literatüre bütüncül bakış açısı katmaya yardımcı olan doküman inceleme çalışmalarıdır. Ülkemizde son zamanlarda tıp alanında da sıkça kullanılmaya başlanmıştır (Alkan ve ark., 2021; Alkan Çeviker ve ark., 2021; Dindar Demiray ve ark., 2021; Dindar Demiray ve ark., 2021; Küçük ve ark., 2021;

Mızrakçı ve ark., 2021; Öntürk ve ark., 2021; Özlü, 2021; Özlü, 2022; Özlü, 2021; Öztürk, 2022; Yıldız, 2022). Kalp damar cerrahisi alanında yayınlanmış sınırlı sayıda bibliyometrik analiz mevcuttur (Antoniou ve ark., 2015; Chau ve ark., 2021). Bu çalışmada dünyada kalp damar cerrahisi bilim dalına ait olan vasküler cerrahi konulu literatürün bibliyometrik analizi gerçekleştirildi. Bu çalışmanın konu açısından benzerine gerek ülkemizde gerekse de ulaşılabilen literatürde ulaşılamadı.

Bu bibliyometrik çalışmaların çoğunda Scopus ve WOS gibi hazır veritabanları kullanılmış olsa da bazen çalışmacıların oluşturdukları veritabanları veya tezler, kitaplar gibi materyallerin incelenmesi yolu ile de bu analizler gerçekleştirilebilir (Akyüz ve ark., 2022; Alkan ve ark., 2021; Alkan Çeviker ve ark., 2021; Dindar Demiray ve ark., 2021; Küçük ve ark., 2021; Özlü, 2021; Özlü, 2022; Özlü, 2021; Yıldız, 2022). Bu çalışmada Dünya'nın en prestijli veritabanlarından olan WOS veritabanının incelenmesi yolu ile analizler yapıldı. Çalışmamız sonucunda çoğu benzer çalışmada olduğu gibi ABD vasküler cerrahi konusunda hakim ülke idi. Yayın sayıları 1998'den sonra hızla artmış olarak saptandı. Bu durum Amerikan Cerrahi Kurulu'nun damar cerrahisi uzmanlığını birincil uzmanlık alanı olarak kabul gördüğü ve Vasküler Cerrahi Kurulu'nun 1998'de kurulmuş olmasına bağlı olabilir (Ozaki ve ark., 2019). İlk 9 sırada yer alan ülkeler gelişmiş ülkeler olup, ülkemizin 10. sırada yer alması da ülkemiz adına yüz güldürücüdür. 171 ülkeden de yayın olması, konunun global önemini göstermektedir.

WOS indeksinde taranan alt kategorilere göre incelemede, en fazla oranda Science Citation Index Expanded (SCI-Expanded) (%89,832) dergilerde makale yayınlanmış olması, vasküler cerrahi konusunun bilimsel saygın bir alan olmasına bağlı olabilir. Yayın diline bakıldığında çoğu global bibliyometrik çalışmalarla benzer şekilde olup, İngilizce hakimdir. Bu da bu dilin global özelliğine bağlı olabilir. En fazla sayıda makale yayınlayan dergi European Journal of Vascular and Endovascular Surgery dergisi idi. Bu dergi endovasküler yöntemleri ve bunların kritik değerlendirmelerini açıklayan makaleler yayınlayan aylık hakemli bir dergidir. Journal Citation Reports'a göre derginin 2019 etki faktörü 5,328'dir (URL 1). Bu derginin bu kadar fazla sayıda makaleyi yayınlaması konuya özgü bir dergi olması ve aylık olmasına bağlı olabilir.

Finansal destek sağlayan kuruluşlara ve yayın sayılarının en fazla olduğu kuruluşlara bakıldığında yine bu kurum ve kuruluşların ABD ağırlıklı olduğu saptanmıştır. Bu da ABD'nin vasküler cerrahiye verdiği önemi destekler niteliktedir.

### Çalışmanın Kısıtlılıkları

Çalışmada tek veri tabanı kullanıldı. Bu nedenle tüm bilimsel literatürü yansıtmayabilir. Çalışmamızda veri görselleştirme ve atf analizi yapılmamıştır.

### Katkı Oranı Beyanı

Tüm işlemler S.Ş. (100%) tarafından yapılmıştır; Konsept, Tasarım, Denetim, Veri toplama ve/veya işleme, Veri analizi ve/veya yorumlama, Kaynak taraması, Yazma, Eleştirel inceleme, Gönderim ve revizyon. Yazar, makalenin son halini incelemiş ve onaylamıştır.

### Çatışma Beyanı

Yazarlar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

### Etik Onay/Hasta Onamı

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## ENCEPHALOCELE: RETROSPECTIVE ANALYSIS AND OUR CLINICAL EXPERIENCE

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**Abstract:** Encephalocele is defined as extracranial herniation of the CSF, meninges, or cerebral tissue through a midline fusion defect in the cranium. The aim of this article is to present the clinical experience of the authors on encephalocele management. A total of 19 patients who underwent surgery for encephalocele in our hospital between 2015 and 2021 were included in the study. We reached 7 cases who were diagnosed with encephalocele and underwent pregnancy termination between 2018 and 2020 in our hospital. The patients' demographics, neurological examinations, procedure and anaesthesia data, and postoperative follow-up were all evaluated. 15 of 19 patients were female. 2 mothers used folic acid supplementation, but it was not effective. 7 patients were diagnosed prenatally, whereas the others were not followed up during pregnancy. 9 of the patients had parenchyma inside the sac, while the rest had none. 5 patients required shunts. All of the patients were followed up by the departments of neurosurgery, pediatrics, pediatric neurology, neonatal, pediatric gastroenterology, and genetics for their needs. It was demonstrated that folic acid supplementation before conception greatly reduces the incidence of encephalocele. It would be appropriate to inform the families of babies diagnosed with encephalocele in detail at prenatal follow-up about what problems they can expect in the future. Follow-up of encephalocele patients must be done with a multidisciplinary approach to ensure a quality life throughout their life.

**Keywords:** Encephalocele, Hydrocephalus, Seizure, Sac content, Anesthesia

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### 1. Introduction

Encephalocele occurs as a result of a midline fusion defect in the skull bone (Greenberg, 2019). This defect allows the herniation of the cerebral tissue or meninges (Ghatan, 2011). It has a prevalence of 0.8-4 per 1000 births (Ugras et al, 2016). Encephalocele occurs as a result of defective neural tube closure or a defect in post-neurulation (Rolo et al, 2019). It has also been reported that folic acid intake significantly reduces the incidence of all neural tube defects, including encephalocele (Copp et al., 2013). It is frequently located in the midline and occipital region and is accompanied by other malformations and chromosomal anomalies (Chen et al., 2000; Stoll et al., 2007). The presence of parenchyma within the sac, the development of hydrocephalus, and seizures often indicate a poor prognosis, mostly occurring in occipital encephaloceles (Bui et al., 2007). The purpose of encephalocele surgery is to place the herniated functional structures back into the calvarial component (Drake and MacFarlane, 2001). Congenital anomalies that occur with an encephalocele, the size of the sac diameter, hydrocephalus, and hemodynamic disturbances that may develop during surgery complicate anaesthetic management. These patients may have perioperative complications such as electrolyte imbalance (due to CSF drainage), hypothermia, and blood

loss (Mahajan et al., 2011; Singh et al., 2012). Hemodynamic changes caused by blood loss can necessitate a blood transfusion (Mahajan et al., 2011). In addition, during the opening of the encephalocele, rapid drainage of cerebrospinal fluid may lead to hemodynamic disturbances that may cause bradycardia or even cardiac arrest (Mahajan et al., 2011; Singh et al., 2012). Therefore, these patients should be followed up with a multidisciplinary approach.

### 2. Materials and Methods

Encephalocele patients operated between 2015-2021 (2011-KAEK-25 with 2020/12-12 clinical research and ethics committee decision number) were scanned retrospectively. Since the data of 2 of 21 patients who were operated on were not available, they were not included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

In our hospital, 7 cases underwent pregnancy termination upon the diagnosis of encephalocele between 2018 and 2020. We utilized patient files, anaesthesia forms, outpatient follow-up observations,



radiological examinations, and we contacted any families we could contact for the study. We scanned patients' surgical data, length of hospital stay, and other findings that may affect their quality of life. The data we screened were as follows: birth weight, birth head circumference, mother's gravity-parity, gestational week of delivery, prenatal folic acid supplementation, time of prenatal diagnosis, prenatal medication use, type of delivery, infant's APGAR score, microcephaly/ macrocephaly of development, neurological examinations, follow-up period, size of the sac, presence of parenchyma in the sac content, shunt requirement, history of seizure, presence of nutritional problems and growth retardation, operation time, perioperative and postoperative surgery and anaesthesia complications, preoperative and postoperative electrolyte and hemoglobin values, presence of intraoperative blood transfusion, length of ICU and hospital stay, duration of intubation and discharge-ex status. Verbal consent was obtained from all families who could be reached.

### 2.1. Statistical Analysis

Within the scope of the study, 19 patients were compared with 33 different clinical parameters. All analyzes were performed using IBM Statistics SPSS 25 and GraphPad Prizm 8 programs. The quantitative data obtained as a result of the measurements were first subjected to the normality test. Parametric One-Way ANOVA test was applied to the data found to be suitable for normal distribution. The Kruskal-Wallis test was used when comparing clinical data that did not show normal distribution. Chi-square test was used when comparing categorical variables among themselves. In the light of the findings obtained, Spearman r correlation analysis was performed in the analysis of the relationship between clinical data with a statistically significant difference. In the analyses, 95% confidence interval and statistical significance were accepted as  $P < 0.05$  (Önder, 2018).

### 3. Results

The patient data are given in Table 1. Birth weights varied between 2575 and 4000 grams, with no low birth weight infants. The patients' head circumference at birth was between 25 and 36 cm.

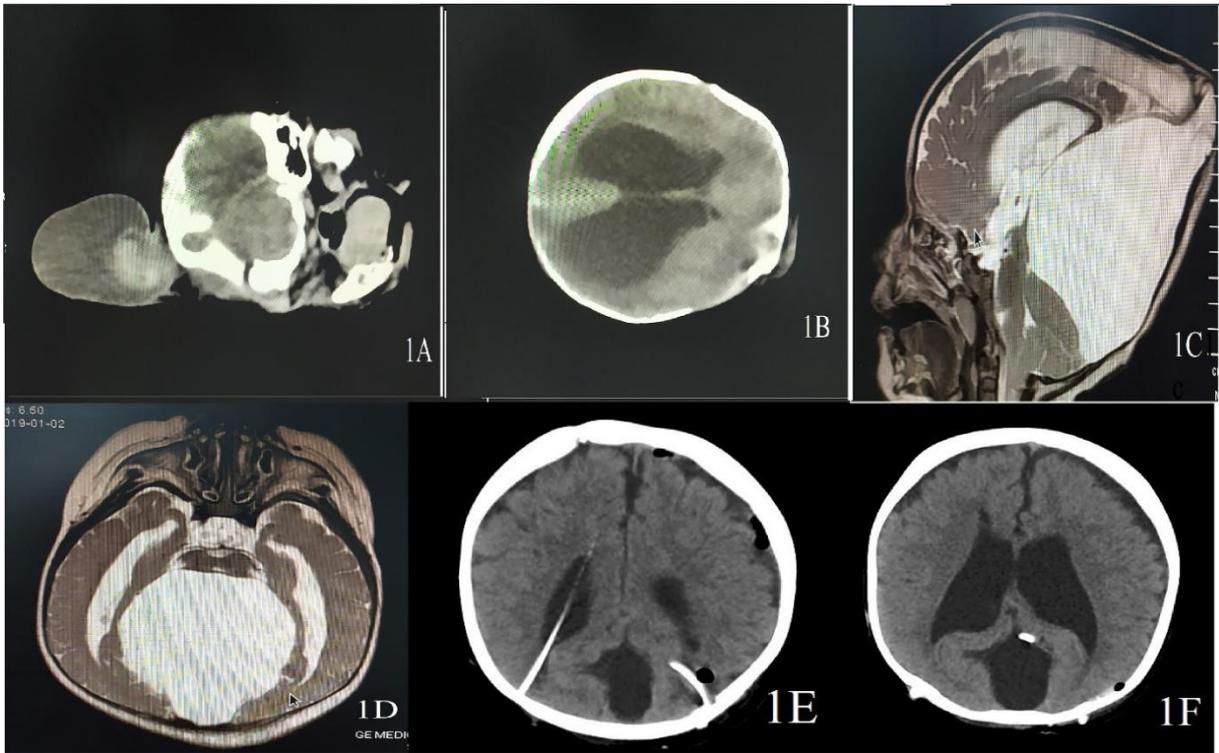
The patients were born at 36 and 39 weeks of gestation. The APGAR scores were reported as 9-10 in 15 patients, 8-9 in 1 patient, and 4-8 in 3 patients. The length of a patients' stay in the newborn intensive care unit is influenced by their Apgar scores at birth. A patient with an Apgar score of 4-8 required 14 days of newborn intensive care unit follow-up. Neurological examinations of 16 of 19 patients were normal, the first of the remaining 3 patients had genu recurvatum deformity, the second was hypoactive and had a dysmorphic facial appearance, with a broad nasal bridge and proptosis-like appearance in the eyes on physical examination, whereas the third patient was hypoactive and had accessory fingers in both hands (Figure 1). One of the patients had

an omphalocele accompanying encephalocele (Figure 2 and Figure 3). 3 patients were found to have microcephaly during follow-up, while the others' head circumferences were within the normal percentile (Figure 4). The size of the sac also varied from 1x1.5 cm to 10x10 cm. Parenchyma was observed within the sac in 9 patients, and only CSF content was present in the sac of 10 patients.

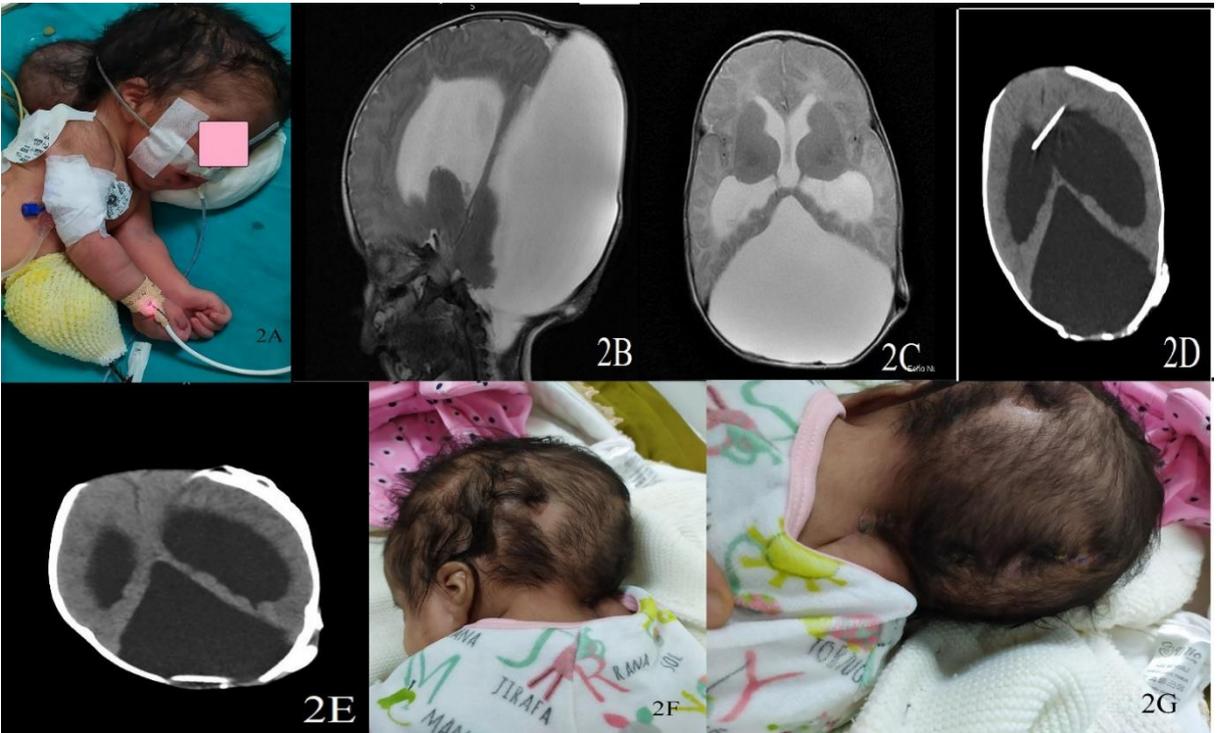
**Table 1.** Descriptive statistics of patients

Gender n (%)	
Female	15 (78.9)
Male	4 (21.1)
Weight (gr); med (min-max)	3128.68 (2575-4000)
Gestational age, week; med (min-max)	38 (36-39)
Apgar 1.minute n/%) $\leq 7$	3 (15.8 %)
Apgar 5.minutes n/%) $\leq 7$	0
Family story n (%)	
No	19 (100)
Head circumference, cm; med (min-max)	34.23 (25-36)
Paranchyma tissue in the sac n (%)	
No	10 (52.6)
Yes	9 (47.4)
Microcephaly vs macrocephaly n (%)	
No	16 (84.2)
Microcephaly	3 (15.8)
Additional anomalies n (%)	
Cardiac	1(33.3)
2 handheld accessory fingers	1 (33.3)
Omphalocele	1 (33.3)

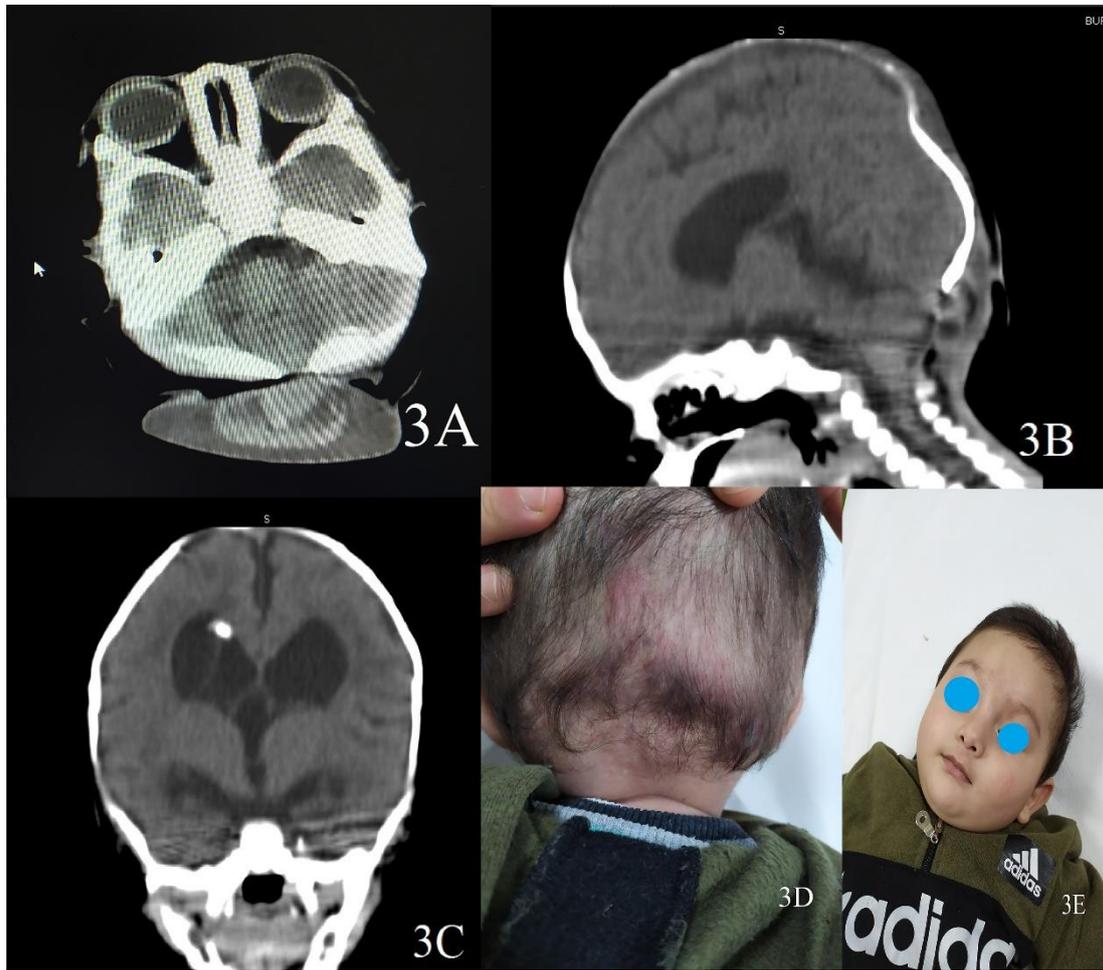
The data of the mothers are given in Table 2. 15 of 19 patients were female and 4 were male. The mean age of the mother was 27 (Range of age group: 21 to 45 years). Two of the mothers had preeclampsia and 1 had DM-HT. No history of prenatal medication use was reported among the mothers. Of 19, 16 mothers never used folic acid. 12 mothers had no pregnancy follow-up. 2 mothers used folic acid supplementation, but the first one started to use it after the 10th week of pregnancy, while the second mother used folic acid in the first 3 months of pregnancy and then stopped. The first was diagnosed at 12 weeks, the second at 16 weeks, the third at 8 months, the fourth at 37 weeks, and the fifth at 12 weeks, according to the statements of five mothers who were followed up by an obstetrician (2 mothers were diagnosed at which week could not be reached). Termination was recommended to those who did not exceed the termination period, but they did not accept it. One patient who was diagnosed at 12 weeks underwent a karyotype analysis and was reported as normal. No diagnosis of midline defect anomaly was present in the family history of any patient.



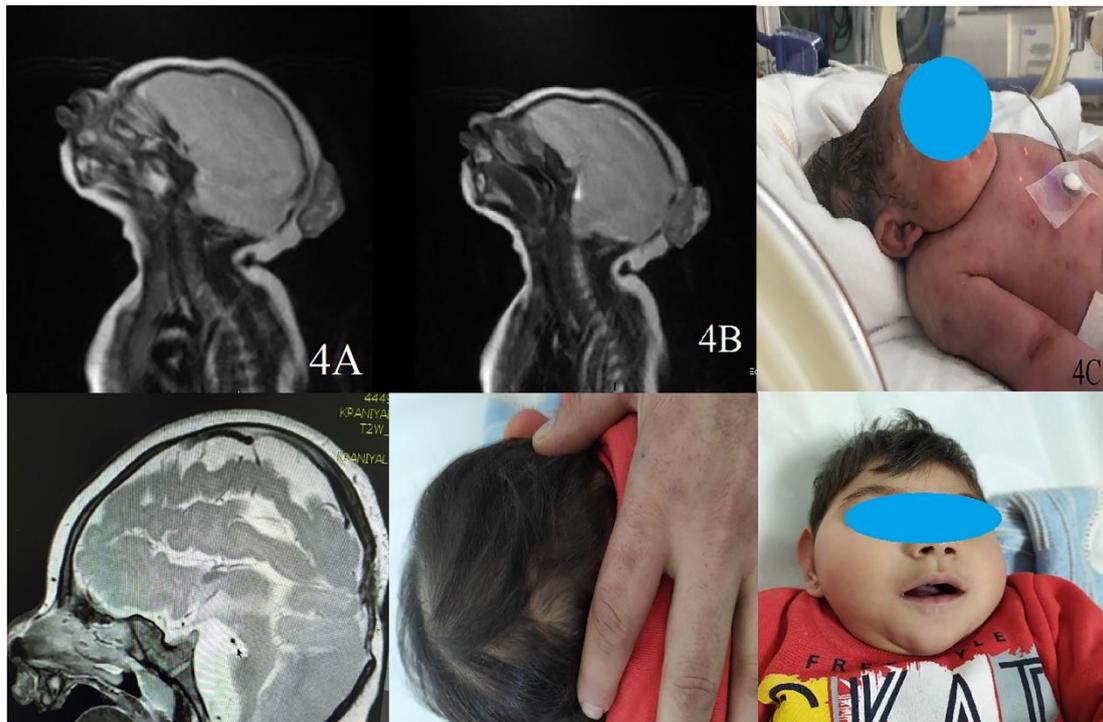
**Figure 1.** 1A: Preoperative cranial CT 1B: Postoperative hydrocephalus developed. 1C-1D: There was a large cystic appearance in the suprasellar area. 1E-1F: VP shunt was inserted in the right occipital and supracerebellar region.



**Figure 2.** 2A: Preoperative view of an encephalocele case with omphalocele association. 2B-2C: Postoperative MR image 2D-E: Control cranial CT after VP shunt from the left frontal and then a VP shunt from the left occipital to the posterior fossa. 2F-G: 5-month outpatient control view.



**Figure 3.** 3A: Preoperative cranial CT view 3B: Postoperative cranial CT image 3C: Control cranial CT after VP shunt surgery. 3D-E: 11-month outpatient control view.



**Figure 4.** 4A-B: Preoperative MR image 4C: Preoperative view of the patient 4D: Postoperative MR image 4E-F: 1 year and 5 months outpatient control view.

**Table 2.** Maternal data

Age, years; med (min-max)	27 (21-45)
Comorbidity of mother n (%)	
DM + HT	1 (5.3)
Preeclampsia	2 (10.5)
No	16 (84.2)
Gravity; med (min-max)	1.89 (1-3)
Parity; med (min-max)	1.73 (1-3)
Use of folic acid during pregnancy n (%)	
No	16 (84.2)
Yes	2 (10.5)
Unfollowed	1 (5.3)
Prenatal diagnosis (%)	
Unfollowed	12 (63.2)
Yes	7 (36.8)
Drug used in pregnancy n (%)	
No	18 (94.7)
Unfollowed	1 (5.3)

DM= Diabetes mellitus, HT= Hypertension.

One of the patients was born by vaginal delivery while the others were delivered by cesarean section under spinal anaesthesia.

Patients' operative and postoperative data are given in Table 3. The operation time varied between 0-720 days after birth. 9 patients were admitted as intubated from the preoperative neonatal unit to the operating room, while the other 10 patients were intubated in the operating room. No difficult intubation was observed in patients operated under general anaesthesia. The duration of operation varied between 45-150 minutes. While 7 patients were taken to the clinic after postoperative extubation (there was no need for newborn intensive care unit), the other 11 patients were taken to the neonatal unit as intubated and 1 patient as extubated. All patients who were extubated were over 1 month old. In this regard, it is important that patients who do not require emergency surgery are included in elective surgery. Our patients did not experience any complications related to perioperative anaesthesia or surgery. None of the patients needed perioperative blood transfusion. 17 patients were extubated on the first postoperative day. One of the other two patients was extubated after 2 days and the other after 4 days. The replacement was not required since there was no serious decrease in the preoperative and postoperative sodium, potassium, and hemoglobin values. Patients admitted to the newborn intensive care unit were admitted to the hospital for 1 to 24 days. 2 patients had prolonged newborn intensive care unit stay. The first patient, who had an Apgar score of 4-8, required 14 days of newborn intensive care unit. The second one was the patient who had omphalocele accompanying encephalocele. The patient who was operated on the same session due to encephalocele and omphalocele developed subsequent hisrodephagia, thereby requiring an EVD replacement. A 3-week EVD follow-up was required for the abdomen to be ready for ventriculoperitoneal shunt placement after

the omphalocele surgery. Therefore, a 24-day newborn intensive care unit stay was required. The patient was taken to the service without any problem following shunt surgery. The length of stay in the hospital also varied between 2-31 days. In the end, all the patients were discharged with full recovery. The follow-up period ranged from 1 month (due to the recently operated patients) to 52 months.

**Table 3.** Operation and after data

Operation time, minute; med (min-max)	81.31 (45-150)
Operation day; med (min-max)	88.73 (0-720)
Intubated when arrives, n (%)	
Yes	9 (47.4)
No	10 (52.6)
Intubated when out of operation n (%)	
Yes	11 (57.9)
No	8 (42.1)
Need for shunt n (%)	
Yes	5 (26.3)
No	14 (73.7)
Facial asymmetry n (%)	
Yes	1 (5.3)
No	18 (94.7)
Seizure n (%)	
Yes	3 (15.8)
No	16 (84.2)
Nutrition and growth retardation n (%)	
Yes	5 (26.3)
No	14 (73.7)
Length of stay in the hospital, day; med (min-max)	12 (2-31)
Follow up time, month; med (min-max)	19 (1-52)
Result n (%)	
Discharge	19 (100)

Only 5 patients required shunts. Parenchyma was present in the sac in 2 of the patients who needed a shunt, whereas the other had no parenchyma. The seizure occurred in 3 patients while there was no occurrence of seizures in the others. 5 of the patients were followed up by the department of pediatric gastroenterology due to malnutrition and growth retardation. One patient was admitted to the clinic due to a wound infection 3 months later and died due to aspiration while receiving antibiotic treatment. The others are still alive.

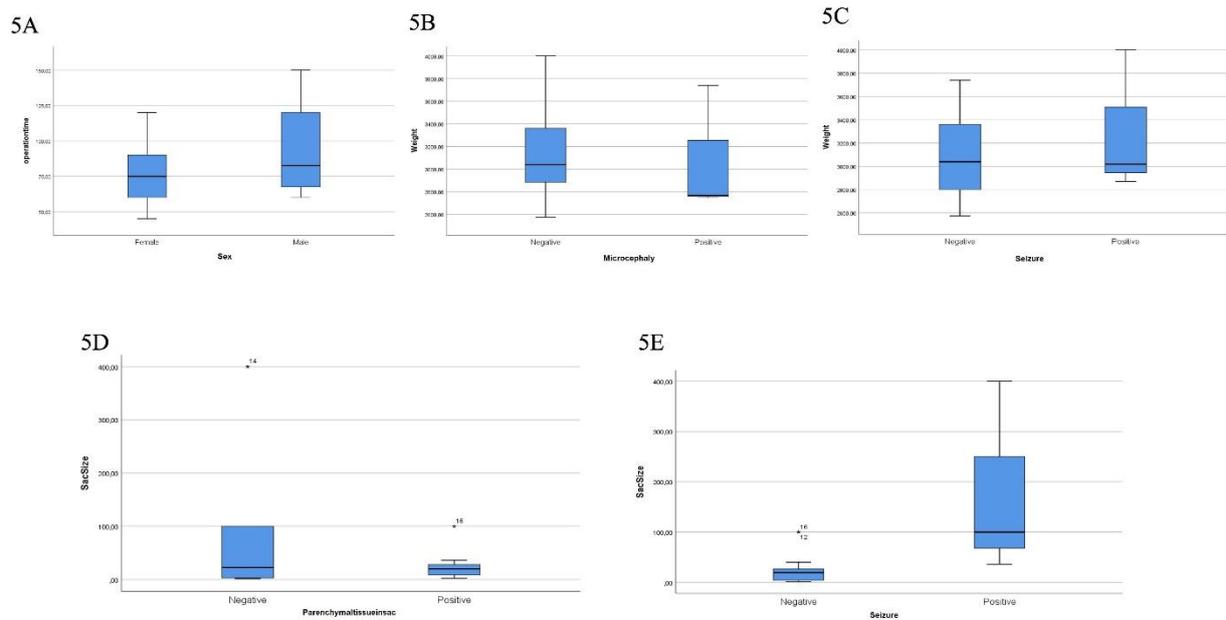
In conclusion, the mean weight of our 19 cases was 3128, the mean age of the mothers was 27, the mean gravity/parity was 1.89/1.73, the mean gestational age was 38 weeks, the infant 1-min/5-min APGAR score was 8/9 mins, taking into account the recently operated cases, the mean follow-up period was 19 months, the mean length of stay in newborn intensive care unit was 8,5 days (7 patients did not need newborn intensive care

unit), the mean head circumference was 34 cm, the duration of operation was minimum 45 and maximum 150 minutes, with a mean of 81 minutes, and the mean operation time was 88 days. According to the statistical comparisons; the operation times were found to be significantly shorter in female patients than in male patients (Figure 5), the incidence of microcephaly increased in low-weight patients (Figure 5), and the chance of seizures increased as the patients' weight increased (Figure 5). Significant changes were found in all parameters with maternal age. As maternal age increases, the frequency of pathological neurological examination increases, pregnancy without follow-up increases, microcephaly increases, the frequency of seizures increases, the parenchyma tissue in the sac increases, and the frequency of nutrition and growth

retardation increases (Table 4).

As the gestational age increased, the duration of postoperative extubation became shorter, and the incidence of pathological neurological examination increased. In addition, we found that patients with pathological neurological examination had lower head circumference and longer operation times.

We found a correlation between the APGAR scores of the patients and some data. We found that APGAR scores were low in microcephalic cases, cases with parenchyma tissue in the sac, cases with seizures, and cases who were intubated on arrival (Table 5). In addition, we found that the size of the sac was higher in those without parenchyma tissue in the sac (Figure 5), and the risk of seizures was higher in those with a larger sac size (Figure 5).



**Figure 5.** The statistical significance of the analyzed parameters. 5A: Operation time and gender, 5B: weight and microcephaly, 5C: weight and seizure status, 1D: The size of the sac diameter and presence of parenchyma in the sac content, 1E: The size of the sac diameter and seizure status.

**Table 4.** The parameters that were found to be statistically significant with maternal age

Maternal age vs. Pathological neurological examination	226.8	Yes	*	0,0121
Maternal age vs. Microcephaly	379.5	Yes	****	<0.0001
Maternal age vs. The parenchyma tissue in the sac	329.3	Yes	****	<0.0001
Maternal age vs. Need for shunt	362.7	Yes	****	<0.0001
Maternal age vs. Seizure status	379.5	Yes	****	<0.0001
Maternal age vs. Nutrition and growth retardation	362.7	Yes	****	<0.0001
Maternal age vs. Additional anomaly	367.8	Yes	****	<0.0001
Maternal age vs. Arrived intubated	329.3	Yes	****	<0.0001
Maternal age vs. Postoperative extubation time	334.6	Yes	****	<0.0001

**Table 5.** The statistical significance of the analyzed parameters

Baby apgar score 1 min vs. Microcephaly	317.9	Yes	****	<0.0001
Baby apgar score 1 min vs. The parenchyma tissue in the sac	267.7	Yes	***	0,0003
Baby apgar score 1 min vs. Need for shunt	301.2	Yes	****	<0.0001
Baby apgar score 1 min vs. Seizure status	317.9	Yes	****	<0.0001
Baby apgar score 1 min vs. Nutrition and growth retardation	301.2	Yes	****	<0.0001
Baby apgar score 1 min vs. Additional anomaly	306.3	Yes	****	<0.0001
Baby apgar score 1 min vs. Arrived intubated	267.7	Yes	***	0,0003
Baby apgar score 1 min vs. Postoperative extubation time	273.1	Yes	***	0,0002
Baby apgar score 5 min vs. Microcephaly	334.7	Yes	****	<0.0001
Baby apgar score 5 min vs. The parenchyma tissue in the sac	284.5	Yes	****	<0.0001
Baby apgar score 5 min vs. Need for shunt	318	Yes	****	<0.0001
Baby apgar score 5 min vs. Seizure status	334.7	Yes	****	<0.0001
Baby apgar score 5 min vs. Nutrition and growth retardation	318	Yes	****	<0.0001
Baby apgar score 5 min vs. Additional anomaly	323.1	Yes	****	<0.0001
Baby apgar score 5 min vs. Arrived intubated	284.5	Yes	****	<0.0001
Baby apgar score 5 min vs. Postoperative extubation time	289.9	Yes	****	<0.0001

#### 4. Discussion

Encephalocele occurs as a result of a midline fusion defect in the skull bone (Greenberg, 2019). This defect allows the herniation of the cerebral tissue or meninges (Ghatan, 2011). The most accepted theory for the origin of a congenital encephalocele is the incomplete separation of the surface ectoderm from the neuroectoderm after the closure of the neural folds (Matos Cruz and De Jesus, 2022). Genetic and environmental factors also play a role in the etiology of encephalocele. Encephalocele has been linked to TORCH diseases, consanguineous relationships, genetic predisposition, and more than 30 syndromes (Yucetas and Uçler, 2017). None of these additional pathologies was encountered in the history of our patients. Although encephalocele is a post neurulation defect, the use of folic acid has been reported to significantly reduce the incidence of all neural tube defects, including encephalocele (Copp et al., 2013). While the mothers of 16 of the 19 patients presented were not taking folic acid, the mother of the other 3 patients was not found to be using it ideally.

The incidence of congenital encephalocele is estimated to be 0.8-2.0 per 10000 live births (Cavalheiro et al., 2020). However, its actual incidence is estimated to be higher as termination is recommended when the diagnosis is made during pregnancy (Matos Cruz and De Jesus, 2022). Encephalocele is diagnosed during pregnancy follow-up in the first trimester (Engels et al., 2016). In our hospital, a total of 42593 deliveries were realized with 18260 C/S and 24333 vaginal deliveries between 2018 and 2020. The obstetrics department conducted 325 terminations in patients who were followed up on during pregnancy, with 7 of them being diagnosed with encephalocele (The data between 2016 and 2018 were not available). We operated 8 encephalocele cases between 2018-2020 and 19 encephalocele cases between 2015-2021 (In our

hospital, a total of 67832 deliveries were realized with 26643 C/S and 41189 vaginal deliveries between 2015-2021. 3.09 out of 10000 live births were operated on with the diagnosis of encephalocele.). 2.1% of the terminations performed between 2018 and 2020 were due to encephalocele, and 1.4 out of 10000 live births were operated on with the diagnosis of encephalocele.

As with all neural tube defects, female gender predominance is seen in encephaloceles. Female patients are more likely to have an occipital encephalocele compared to an anterior encephalocele (1.9/1) (Rehman et al., 2018). Of our 19 cases, 15 were girls and 4 were boys, all of whom were classified as posterior encephalocele, which is frequently located in the midline and occipital region. Approximately, 70-90% of them are located at the occipital region (Matos Cruz and De Jesus, 2022).

The presence of parenchymal tissue within the sac, the development of hydrocephalus, and seizures often indicate a poor prognosis, mostly occurring in occipital encephaloceles (Bui et al., 2007). In our case series, only 6 patients needed a shunt.

In radiological examinations, USG is used to show the content of the sac, CT to expose bone structures, and MRI to reveal the relationship of the sac with the venous sinus and vascular structures (Ozek and Hicdonmez, 2014). Preoperative cranial CT examination was performed in all cases. It provided great guidance for us as it revealed the sac content, any bone defects, and the presence of hydrocephalic appearance (Figure 1). Encephalocele surgery is performed in the prone position under general anaesthesia. The purpose of the operation is to excise the gliotic tissue and the ischemic neural contents in the sac, taking into account the sinus which may be passing through (Murthy et al., 2019). Given that there is only CSF content present in the sac and the sac neck is not wide, then the pedicle of the sac is exposed and the

remaining sac is excised, leaving enough part for dural repair. However, if there is unfunctional neural tissue in the sac, it is coagulated with bipolar and removed, and the dura and skin are closed, and the operation is terminated. If the neural tissue is thought to be functional and cannot be included in the intracalvarial area, the bony exposure is enlarged sufficiently covering the neural tissue with dura and skin, and the operation is terminated (Partington and Petronio, 2001). There was no need for calvarial reshaping in our cases. Additionally, congenital malformations that may accompany encephalocele, hydrocephalus, enlarged sac, and hemodynamic disorders that may develop during the perioperative period make anaesthesia management difficult. These patients may have perioperative complications such as electrolyte imbalance (due to CSF drainage), hypothermia, and blood loss (Mahajan et al., 2011; Singh et al., 2012). A blood transfusion may be required due to blood loss and related hemodynamic changes. In addition, during the opening of the encephalocele, rapid drainage of cerebrospinal fluid may lead to hemodynamic disturbances that may cause bradycardia or even cardiac arrest (Mahajan et al., 2011; Singh et al., 2012).

There was no severe electrolyte imbalance, low hb, and blood transfusion requirement in any of our cases. It is vital for these patients to be followed up with a multidisciplinary approach. Although postoperative newborn intensive care unit follow-up is very important in encephalocele cases, the absence of prolonged intubation and newborn intensive care unit requirement is more ideal for these patients. In this regard, elective surgery eliminates the need for newborn intensive care unit, except for cases with ruptured sac and cases with very thin skin at risk of rupture. 7 of our 19 cases did not need newborn intensive care unit, while 1 case was taken to newborn intensive care unit after extubation. All of these 5 patients were over 1 month old. The other 14 patients were taken into operation at 2-13 days old depending on the patient's condition, due to the need for urgent surgery. Except for the patient with a low Apgar score and the patient with accompanying omphalocele, other patients were extubated on the same day. Since the inclusion of cases in elective surgery eliminates the need for newborn intensive care unit and shortens the duration of intubation, we believe that the cases should be operated on electively unless it is very urgent. (Operated electively except for the cases with a high risk of rupture with ruptured sac or very thin skin). There was no serious electrolyte imbalance and blood transfusion requirement in the perioperative period. Classically, children with encephalocele develop significant rates of spastic paraparesis (11%), moderate to severe developmental delay (7%), and hydrocephalus (20%-65%) (Gandhoke et al., 2017). Posterior encephaloceles exhibit a worse prognosis than anterior encephaloceles due to the higher incidence of hydrocephalus development and seizures and being

neurologically worse in the presence of functional cerebral tissue, and they also lead to greater physical, emotional and cognitive delay (Bui et al., 2007). All of our cases were classified as posterior encephalocele and we did not have any patients with physical and cognitive impairment, except for the case who was born hypoactive with a dysmorphic facial appearance. The seizure occurred in only 3 patients while there was no occurrence of seizures in the others. 5 of the patients were followed up by the department of pediatric gastroenterology due to malnutrition and growth retardation. Parenchyma was observed within the sac in 9 patients, and only CSF content was present in the sac of 10 patients. Meningocele have a better prognosis than encephaloceles. While the mortality due to postoperative infection and shunt complications is 14% in meningocele, it is 52% in encephaloceles (French et al., 1990; Partington et al., 2001). Motor and mental retardation is found in 83% of all encephaloceles (French, 1990). Of our 19 cases, 9 were classified as encephalocele (48%), and 10 as meningocele (52%).

### 5. Conclusion

Encephalocele cases should be followed up multi disciplinarily before and after surgery because of the risk of concomitant additional malformations, feeding problems, and seizures.

The presence of parenchyma in the sac and its functionality, its relationship with vascular structures, and the presence of hydrocephalus are significant surgical factors, whereas CSF fistula formation, shunt requirement or shunt-related complications, and seizure development are significant postoperative factors.

Additionally, planning elective surgery for encephalocele cases that do not have an indication for emergency surgery also eliminates the need for postoperative newborn intensive care unit. For these reasons, encephalocele cases should be treated with care, taking into account the timing of surgery as well as any potential preoperative and postoperative complications. And most importantly, we hope that the incidence of encephalocele will decrease with greater encouragement of folic acid supplementation and more strict pregnancy follow-up in the future.

### Author Contributions

Concept: E.B.G (%50) and N.K. (50%), Design: E.B.G (%50) and N.K. (50%), Supervision: E.B.G (%50) and N.K. (50%), Data collection and/or processing: E.B.G (%50) and N.K. (50%), Data analysis and/or interpretation: E.B.G (%50) and N.K. (50%), Literature search: E.B.G (%50) and N.K. (50%), Writing: E.B.G (%50) and N.K. (50%), Critical review: E.B.G (%50) and N.K. (50%), Submission and revision E.B.G (%50) and N.K. (50%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest.

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## Ethical Approval/Informed Consent

The study was initiated after obtaining approval from the Bursa Health Sciences University ethics committee (Decision number and date: 011-KAEK-25 2020/11-12 / 25.11.2022). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants in the study.

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## INVESTIGATION OF GLOBAL TRENDS IN PUBLICATIONS ON SYPHILIS WITH BIBLIOMETRICS

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**Abstract:** Syphilis is a primarily sexually transmitted disease that has gained importance again due to the increasing number of cases worldwide. This study aimed to investigate at how scientific output on Syphilis has changed since 1970 globally. This bibliometric study was performed in the Clarivate Analytics' Web of Science (Wos) database by searching the 'Treponema pallidum' or 'Treponema pallidum subsp. pallidum' or 'Syphilis' keywords. The research only included documents categorized as 'journal article' in the Wos database; reviews, letters, and editorials were excluded. Analysis was performed on articles published between 1970-2021. We compared the total global output relating to syphilis. We then looked at the contributions of countries, organizations, authors to the global output. Based on the search method utilized in this study, the findings revealed that 6747 articles on syphilis were indexed in the Wos database between 1970 and 2021. This articles were 96790 times cited (14.35 times average per item), the H-Index was 101. 57.329% of them were published after 2000s. Since 2015, the number of articles has never dropped below 200. The top cited articles were published in recent 20 years. The USA (35.230%) published most of the articles on syphilis. The People's Republic of China, England, the United Socialist Soviet Republic, Brazil, France, Australia, Canada, and Germany were also 10 ranked countries. The articles were from 181 countries globally. Publications and organizations providing financial support were from developed countries. However, researchers in developing countries should be supported to reduce the spread and mortality/morbidity of syphilis.

**Keywords:** Syphilis, Publications, Bibliometrics

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### 1. Introduction

Syphilis, an important public health problem caused by *Treponema pallidum subspecies pallidum*, is known as a great mimicer. It is an infectious disease that can progress with complications if not treated appropriately. It is transmitted sexually, by laboratory accident, contact with active cutaneous lesions, blood transfusion, or transplacental (Oğrum et al., 2019; URL 1).

Although it has been known since ancient times, it is a disease whose epidemiological data is followed globally, which is still up-to-date. According to the data of the American Center for Disease Prevention (CDC), 129,813 cases of syphilis in all stages were reported in 2019. Since reaching a historic low in 2000 and 2001, the rate of syphilis has increased almost every year. The number of cases is increasing, especially in the heterosexual group, with an increase of 30.0% in the 2018-2019 period and 178.6% in the 2015-2019 period (Newman et al., 2015; URL 1). Venereal syphilis, in particular, continues to be a global public health problem. Every year, around 5.6 million people become infected for the first time (Mattei et al., 2012). The prevalence of primary and secondary syphilis has risen in the last decade,

necessitating a greater focus on the disease's detection and treatment. Men who have intercourse with other men are most vulnerable; nevertheless, rises in infection rates have been observed in women of all ages and races. Furthermore, new findings reveal that the prevalence of syphilis is rising in many countries, particularly among people infected with the human immunodeficiency virus (HIV) (Oğrum et al., 2019; Köksal et al., 2020; Alkan et al., 2022). High-risk individuals must be carefully screened by doctors. The surge in congenital syphilis necessitates special attention and highlights the importance of continuing early prenatal care and syphilis screening for all pregnant women (Köksal et al., 2020).

This study aimed to investigate at how scientific output on Syphilis has changed since 1970 globally.

### 2. Materials and Methods

The information was obtained from the Clarivate Analytics' Web of Science (Wos) database, which offers a highly comprehensive and detailed search engine. We also searched the Wos database based on the article title. These phrases were then utilized to conduct a thorough search using the MeSH tree. Only documents that have



these MeSH phrases identified as important subjects will be considered (URL 2). The research only included documents categorized as 'journal article' in the Wos database; reviews, letters, and editorials were excluded. Analysis was performed on articles published since 1970 period. We first compared the total global output relating to syphilis. We then looked at the contributions of countries, organisations, authors to the global output. Two independent reviewers conducted the screening. We used the following search strategy:

- i. Title: *Treponema pallidum* or *Treponema pallidum subsp. pallidum* or Syphilis
- ii. Document Types: Article
- iii. Timespan: 1970–2021.
- iv. Indexes: Web of Science Core Collection Editions: All

On April 1, 2022, all electronic searches were completed, and the year 2022 was excluded from the study because complete data for that year was unavailable. The citation analysis and co-authorship analysis were done by using the free web app Dimension AI. (<https://www.dimensions.ai/>).

### 3. Results

Based on the search method utilized in this study, the findings revealed that 6747 articles on syphilis were

indexed in the Wos database between 1970 and 2021. This articles were 96790 times cited (14.35 times average per item) the H-Index was 101. 57.329% of them were published after 2000s. Since 2015, the number of articles has never dropped below 200. The top cited articles were published in recent 20 years (Figure 1). 2,364 (35.038%) of them published as open access. English (82.303%) was the most preferred writing language. 87.995% of the articles were published in Science Citation Index Expanded (SCI-EXPANDED) journals. The most of the articles were from Infectious Diseases (37.720%) field (Table 1). The Centers for Disease Control and Prevention (USA) was the most productive affiliation on syphilis (Table 2).

The vast majority of the articles (6.551%) on syphilis were published in the journal Sexually Transmitted Diseases (Table 3). The vast majority (12.835%) of the articles on syphilis was funded by the United States Department of Health Human Services (Table 4). The USA (35.230%) published most of the articles on syphilis. The People's Republic of China, England, the United Socialist Soviet Republic, Brazil, France, Australia, Canada, Germany were also 10 ranked countries. The articles were from 181 countries globally (Table 5). The list of top cited articles were given in Table 6. The citation analysis and co- authorship analysis were given in Figure 2 and Figure 3.

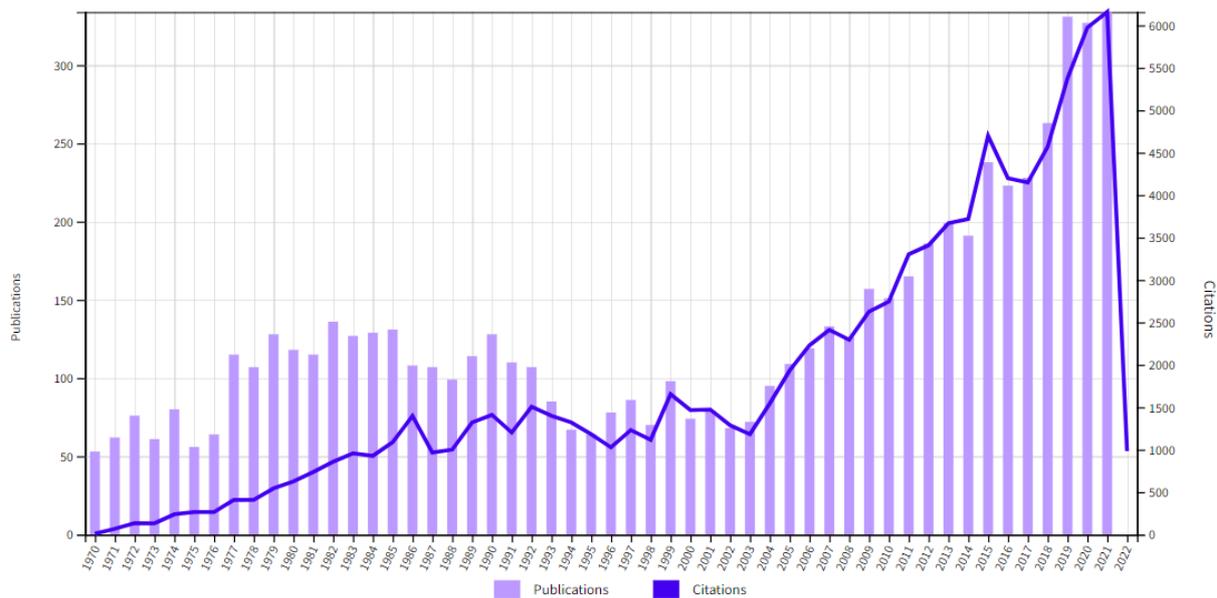


Figure 1. The number of published articles and citations on syphilis.

**Table 1.** The articles according to Web of Science (Wos) categories\*

Wos Categories	Record Count	% of 6.747
Infectious Diseases	2545	37.720
Dermatology	1145	16.971
Immunology	975	14.451
Public Environmental	862	12.776
Occupational Health		
Medicine General	839	12.435
Internal		
Microbiology	648	9.604
Obstetrics	230	3.409
Gynecology		
Pediatrics	194	2.875
Multidisciplinary	163	2.416
Sciences		
Tropical Medicine	162	2.401

\*Showing 10 out of 147 entries; 2 record(s) (0.030%) do not contain data in the field being analyzed.

**Table 2.** The top ranked affiliations on syphilis\*

Affiliations	Record Count	% of 6.747
Centers For Disease Control Prevention USA	403	5.973
University of California System	277	4.106
University of Texas System	219	3.246
University of Washington	187	2.772
University of Washington Seattle	186	2.757
University of London	185	2.742
University of California Los Angeles	158	2.342
University of North Carolina	143	2.119
University of North Carolina Chapel Hill	136	2.016
State University of New York Suny System	118	1.749

\*Showing 10 out of 5.210 entries; 288 record(s) (4.269%) do not contain data in the field being analyzed.

**Table 3.** Top ranked journal list\*

Publication Titles	Record Count	% of 6.747
Sexually Transmitted Diseases	442	6.551
Vestnik Dermatologii I Venerologii	423	6.269
International Journal of STD AIDS	255	3.779
British Journal of Venereal Diseases	200	2.964
Infection and Immunity	190	2.816
Sexually Transmitted Infections	188	2.786
Journal of Clinical Microbiology	125	1.853
Plos One	108	1.601
Genitourinary Medicine	91	1.349
Clinical Infectious Diseases	87	1.289
BMC Infectious Diseases	84	1.245
Journal of Infectious Diseases	59	0.874
Journal of Bacteriology	43	0.637
Hautarzt	41	0.608
Acta Dermato Venereologica	40	0.593
Annales de Dermatologie et de Venereologie	38	0.563
Journal of immunology	37	0.548
Plos Neglected Tropical Diseases	35	0.519
BMC Public Health	33	0.489
American Journal of Public Health	31	0.459
Archives of Dermatology	31	0.459
Sexual Health	30	0.445
Cutis	29	0.430
South African Medical Journal	29	0.430
Diagnostic Microbiology and Infectious Disease	27	0.400

\*Showing 25 out of 1.449 entries.

**Table 4.** Top ranked funding agencies\*

Funding Agencies	Record Count	% of 6.747
United States Department of Health Human Services	866	12.835
National Institutes of Health	752	11.146
National Institute of Allergy Infectious Diseases	565	8.374
National Natural Science Foundation of China	145	2.149
Fogarty International Center	107	1.586
Centers For Disease Control Prevention USA	90	1.334
European Commission	76	1.126
National Institute of Mental Health	72	1.067
United States Public Health Service	54	0.800
Eunice Kennedy Shriver NICHD	49	0.726

\*Showing 10 out of 1.670 entries; 4.929 record(s) (73.055%) do not contain data in the field being analyzed. NICHD= national institute of child health human development

**Table 5.** The top ranked countries on syphilis\*

Countries/Regions	Record Count	% of 6.747
USA	2377	35.230
PRC	514	7.618
England	490	7.262
USSR	366	5.425
Brazil	313	4.639
France	253	3.750
Australia	221	3.276
Canada	211	3.127
Germany	183	2.712
Switzerland	146	2.164
Italy	145	2.149
Spain	144	2.134
India	139	2.060
Netherlands	130	1.927
South Africa	128	1.897
Japan	124	1.838
Germany	81	1.201
Türkiye	78	1.156
Belgium	74	1.097
Denmark	74	1.097
South Korea	62	0.919
The Czech Republic	61	0.904
Poland	61	0.904
Austria	59	0.874
Peru	58	0.860

\*Showing 25 out of 181 entries; 279 record(s) (4.135%) do not contain data in the field being analyzed. PRC= The People's Republic of China, USSR= The United Socialist Soviet Republic

**Table 6.** The top 10 cited articles on syphilis

Info	Article name	Journal	APY	Total
Fraser et al.,1998	Complete genome sequence of <i>Treponema pallidum</i> , the syphilis spirochete	Science	30.96	774
Thomas et al.,1991	The Tuskegee-Syphilis-Study, 1932 To 1972- Implications For HIV Education And AIDS Risk Education-Programs In The Black-Community	American Journal of Public Health	13.44	430
Rowley et al., 2019	Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates	Bulletin of The World Health Organization	106.25	425
Freimuth et al., 2001	African Americans' views on research and the Tuskegee Syphilis Study	Social Science and Medicine	18.18	400
Lukehart et al.,1988	Invasion of the central nervous-system by <i>Treponema-pallidum</i> - implications for diagnosis and treatment	Annals of Internal Medicine	11.29	395
Tobian et al., 2009	Male circumcision for the prevention of HSV-2 and HPV infections and syphilis	The New England Journal of Medicine	23.79	333
Rolfs et al.,1997	A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection	The New England Journal of Medicine	12.81	333
Berry et al.,1987	Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with hiv-infection	The New England Journal of Medicine	8.08	291
Buchacz et al., 2004	Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections	National HIV Prevention Conference	15.16	288
Marra et al., 2004	Cerebrospinal fluid abnormalities in patients with syphilis: Association with clinical and laboratory features	the Journal of Infectious Diseases	14.68	279

APT= average per year

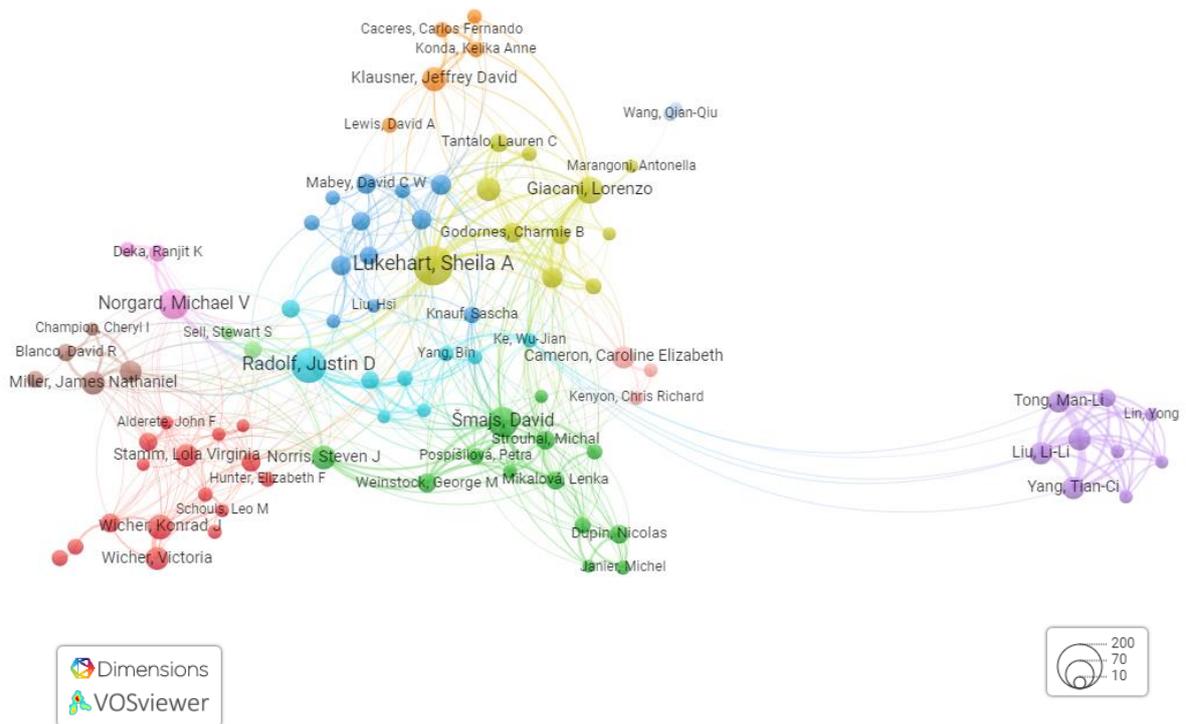


Figure 2. The citation analysis.

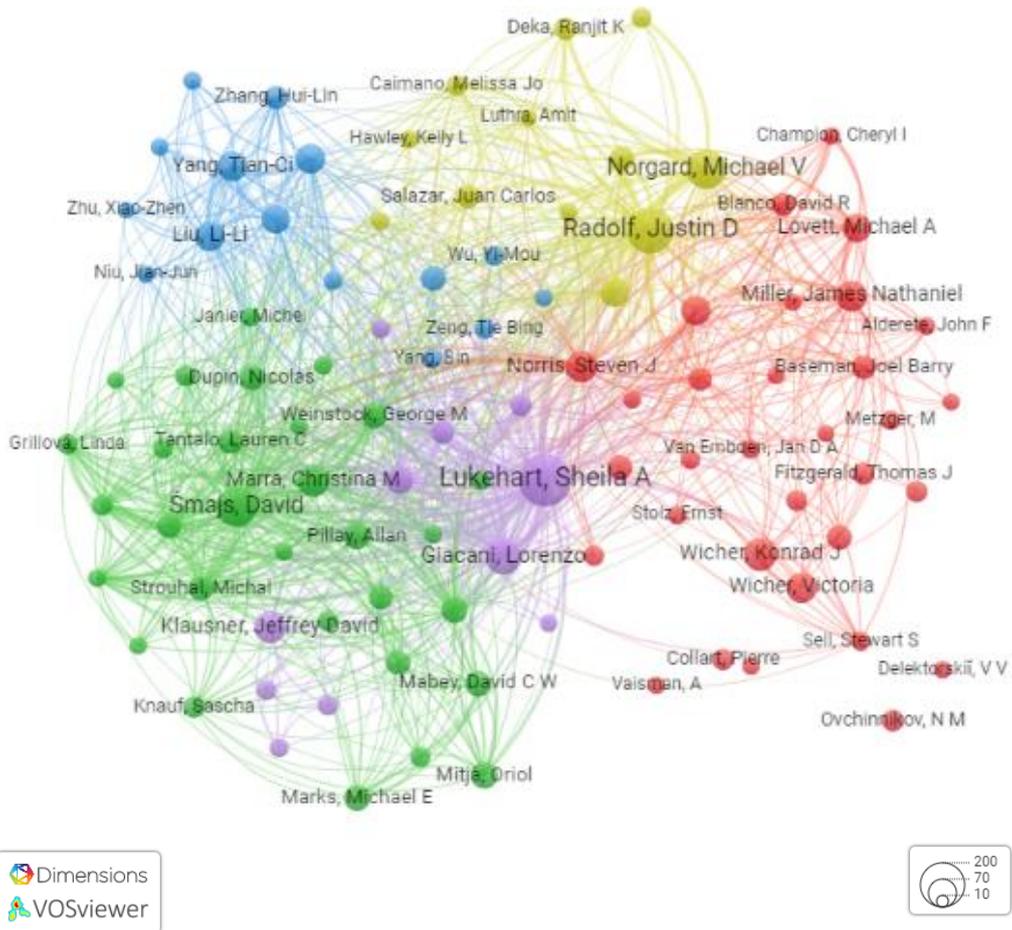


Figure 3. The co- authorship analysis.

#### 4. Discussion

This study aimed to provide a bibliometric summary of the literature on "syphilis" between the years 1970 and 2021. A common and thorough approach for examining and interpreting vast amounts of scientific data is named bibliometric analysis. It allows us to examine the evolutionary subtleties of a particular discipline while also offering light on developing topics in a field. Scholars utilize bibliometric analysis for a number of purposes, including identifying developing trends in article and journal performance, cooperation patterns, and research elements, as well as investigating the intellectual structure of a certain topic in the existing literature. The number of bibliometric analysis studies in medicine has been rising in recent years. Although there are bibliometric analyzes published in many different disciplines (Kahraman and Yıldırım, 2020; Alkan-Çeviker et al., 2021; Alkan Çeviker et al., 2021; Çeviker et al., 2021; Dindar Demiray et al., 2021; Gürler et al., 2021; Köylüoğlu et al., 2021; Özlü, A. 2021; Özlü, 2021; Zengin and Baldemir, 2021; Akyüz et al., 2022; Durgun et al., 2022; Özlü, 2022), no similar studies have been found on syphilis.

Eugene Garfield created the Science Citation Index in 1955, bringing in the current era of bibliometrics (Garfield, 1955). There are two types of bibliometric analysis techniques: (1) performance analysis and (2) scientific mapping. In essence, performance analysis accounts for research constituent contributions, whereas science mapping focuses on the links between research constituents (Donthu et al., 2021). In this study, mapping, network visualization and content analysis were not done. Each article's bibliometric parameters were examined: publication title, citation count, citation density (the average number of citations per year), publication year, authorship, country and institution of origin, and topic of interest.

Although syphilis concerns different fields of medicine (such as dermatology, newborns, ophthalmology, and public health), it is primarily followed by infectious diseases specialists.

Especially syphilis cases apply the dermatology outpatients' clinics (Karaosmanoğlu et al., 2019). This is in line with our study, in which it was determined that the highest number of publications were published in the field of infectious diseases. In this case, it may be due to the coexistence of other STDs in these patients or to the fact that this branch is more effective in complex patient management.

According to our results, the majority of the articles were published from the USA. The People's Republic of China, England, the United Socialist Soviet Republic, Brazil, France, Australia, Canada, and Germany were also among the top ten listed nations. The articles came from 181 different nations throughout the world. This significant contribution from the USA might be attributed to the presence of a big population of active researchers as well as a diversity of funding agencies.

Since this infection was nearly totally eliminated in the nation 50 years ago, China has seen a dramatic upsurge in the incidence and prevalence of syphilis, particularly in recent years (Tucker and Cohen, 2011). The results of our study may reflect the remarkable increase in the incidence of this disease. China was the second leading country in our study. According to World Health Organization (WHO, 2019) data, in 2019, 1% or more of prenatal care attendance tested positive for syphilis in 38 of the 78 reporting countries. An average of 3.2 percent (range: 1.1 percent to 10.9 percent) of prenatal care attendance tested positive for syphilis in these 78 reporting countries. Pregnancy-related syphilis is the second greatest cause of stillbirth worldwide, and it also causes preterm, low birthweight, neonatal mortality, and infections in neonates (URL 3). In our study, we found that the articles were from 181 countries globally and this reflects the global impact of this topic.

In 2019, 11 of the 25 reporting nations stated that 5% or more of MSM were diagnosed with active syphilis, while 7 countries reported that 10% or more of MSM were diagnosed with active syphilis. In 2019, an average of 11.8 percent (range: 5.2 percent to 19.6 percent) of MSM in these 25 reporting nations are infected with syphilis. There have been indications of rising tendencies in various nations (URL 3). According to a previous report from France, overall, 96 % of syphilis cases were in men with an average age of 36.5 years, and 70% were born in France. The proportion of syphilis patients with HIV co-infection fell with time, from 60% in 2000 to 33% in 2003. The Ile-de-France region, particularly the city of Paris, has been the most hit by the syphilis epidemic (Couturier et al., 2004). In 2019, syphilis infected more than 5% of sex workers in 11 of the 32 reporting nations, and more than 10% in four. An average of 10.8 percent (range 5.8 percent to 30.3 percent) of sex workers tested in these 32 reporting countries in 2019 were diagnosed with active syphilis. Sex workers are female, male, and transgender adults and youth who accept money or items in return for sexual services on a regular or sporadic basis. Many sex workers are especially vulnerable to HIV and other sexually transmitted illnesses (such as syphilis) due to a combination of variables, including a large number of sex partners, risky working circumstances, and the inability to negotiate continuous condom usage (URL 3). In our study, it was determined that especially the most cited articles were from the hot topics such as MSM, HIV and neonatal syphilis. In addition, the complexity of the disease in these cases and the difficulty of its management may have been effective in the increase in the number of publications over the years.

Untreated syphilis can cause major consequences in 25% of infected people who do not obtain diagnosis and treatment. Complications can be severe, even fatal, and increase the risk of HIV acquisition and transmission (Alkan et al., 2021; URL 3).

## 5. Conclusion

This report gives historical insights on syphilis research patterns. Over the previous 20 years, the number of published articles has grown dramatically, as has the general trend of publications. The findings of our study might be valuable to syphilis researchers, funding agencies, and health management.

## Limitations

This is the first bibliometric analysis of syphilis research trends from the WOS database in recent years. Furthermore, there are several limitations to this bibliometric analysis. The electronic database is confined to the WOS database, and other electronic databases, such as, PubMed, Scopus, etc., were not searched and evaluated. Non-English papers were also disqualified. In this study, the majority of included papers are written in English; nonetheless, this limitation may result in a publishing bias. The last constraint is that influential articles were not mentioned with a high citation frequency since some potentially significant papers were released lately and may not be cited often. In addition, mapping, network visualization and content analysis were not done. Only citation analysis and co-authorship analysis were done.

## Author Contributions

Concept: E.K.D.D. (34%), S.A. (33%) and C.Y (33%), Design: E.K.D.D. (34%), S.A. (33%) and C.Y (33%), Supervision: E.K.D.D. (34%), S.A. (33%) and C.Y (33%), Data collection and/or processing: E.K.D.D. (34%), S.A. (33%) and C.Y (33%), Data analysis and/or interpretation: E.K.D.D. (34%), S.A. (33%) and C.Y (33%), Literature search: E.K.D.D. (34%), S.A. (33%) and C.Y (33%), Writing: E.K.D.D. (34%), S.A. (33%) and C.Y (33%), Critical review: E.K.D.D. (34%), S.A. (33%) and C.Y (33%), Submission and revision E.K.D.D. (34%), S.A. (33%) and C.Y (33%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest.

## Ethical Approval/Informed Consent

The study complied with the Helsinki Declaration, which was revised in 2013. Ethics committee approval was not required for this study because of there is no animal or human research.

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## EVALUATION OF CORNEAL AND LENS DENSITOMETRY WITH SCHEIMPFLUG IMAGING IN YOUNG BETA THALASSEMIA PATIENTS

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**Abstract:** The aim of this study is to compare corneal and lens density of children with Beta ( $\beta$ ) thalassemia and healthy controls using Pentacam HR. This is a case-control and cross-sectional study. Anterior segment parameters, corneal, and lens densitometry of patients with  $\beta$ -thalassemia and healthy controls were evaluated with Scheimpflug corneal topography. For corneal densitometry analysis, the 12 mm diameter area of the cornea was divided into four concentric radial zones and anterior, central, and posterior layers according to corneal depth. The mean densitometry value for the crystalline lens was calculated in three regions around the center of the pupil. Non-contact specular microscopy was used to examine the morphology of the corneal endothelium. The study group consisted of 32  $\beta$ -thalassemia major patients and the control group consisted of 31 healthy volunteers. The mean age of the study group was 12.12 $\pm$ 3.94 years (range: 5-19 years) and 10.90 $\pm$ 3.84 years (range: 5-19 years) in the control group ( $P>0.05$ ). Corneal light backscattering in the posterior layer was significantly lower in the patient group than in the control group. Corneal endothelial cell density was determined as 3053.55 $\pm$ 189.71 in the patient group and 3214 $\pm$ 195.12 in the control group ( $P=0.094$ ). Lens densitometry values did not differ between the two groups ( $P>0.05$ ). We detected changes in corneal densitometry examination without any clinical findings in patients with  $\beta$ -thalassemia major. Pentacam may be a suitable screening technique for early detection of  $\beta$ -thalassemia ocular signs in children. Prospective studies with a large number of cases are needed to support these findings.

**Keywords:** Beta thalassemia, Corneal densitometry, Lens densitometry, Corneal endothelium

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### 1. Introduction

Beta ( $\beta$ ) thalassemia syndromes, one of the most common inherited blood disorders, are prevalent in Mediterranean countries, the Middle East, Central and Far East Asia, India, Southern China, and South America (Kadhim et al., 2017). The World Health Organization reported that thalassemia is common in 60 countries and affects the lives of approximately 10,000 people per year (Taneja et al., 2010). Hypochromic microcytic anemia occurs because of the defect in the synthesis of the beta globulin chain in the adult hemoglobin a structure (Demosthenous et al., 2019). In individuals with thalassemia major, they are diagnosed in the first years of life because of severe anemia and hepatosplenomegaly. With regular transfusion program and chelation therapies that reduce transfusion-induced iron overload, normal growth and development can be monitored and overall prognosis can be improved (Origa, 1993).

Regular blood transfusions are performed to treat

chronic anemia in thalassemia patients. Continuous transfusion can cause iron overload in tissues, leading to organ dysfunction. Desferrioxamine, deferasirox, and deferi-prone are used as iron chelating agents to prevent excessive iron accumulation in tissues (Jafari et al., 2015). Beta thalassemia major has systemic and ocular effects due to chronic anemia, iron accumulation in tissues as a result of erythrocyte destruction, use of chelation agents and blood transfusion (Taneja et al., 2010).

Ocular anomalies in thalassemia patients have been reported between 10.5% and 74%. This difference is due to the variable age in the patient groups, different treatment modalities, and the type of chelation drugs used. The most frequently reported ocular disorders are visual acuity loss, visual field defect, cataracts, retinal pigment epithelial degenerations, vascular tortuosity, and dry eye findings (Heydarian et al., 2020). In a study in iron-overloaded rats, hemosiderin accumulation was observed in interstitial tissue macrophages of ocular



tissues and lacrimal gland (Repanti et al., 2008).

Scheimpflug imaging system is used for morphological visualization of anterior segment parameters and measurement of ocular density of ocular tissues such as cornea and lens (Consejo et al., 2020). With this system, it is possible to evaluate changes in the lens before the development of clinically detected cataract.

A clear corneal tissue, which is necessary for a healthy visual acuity, depends on the regular collagen arrangement and the presence of healthy keratocytes. Corneal tissue is affected by many systemic diseases (e.g., endocrine disorders, inflammatory, infectious, and metabolic diseases) (Shah et al., 2021). In this study, it was aimed to compare corneal and lens density of young  $\beta$ -thalassemia patients and healthy controls using Pentacam HR device and to detect ocular disorders before clinical findings appear. To the best of our knowledge, this is the first study in the literature to evaluate lens and corneal density in patients with  $\beta$ -thalassemia.

## 2. Material and Methods

This case-control and cross-sectional study was performed from May 2021 to July 2021 at the department of ophthalmology and the department of paediatric haematology of a tertiary center. After explaining the purpose and content of the study to the children and their parents, written informed consent was obtained to participate in the study.

We included patients aged 5-19 years, who were diagnosed with  $\beta$ -thalassemia and regularly followed up and treated in the pediatric hematology clinic of the hospital. Hematological and electrophoretic tests were performed to diagnose  $\beta$ -thalassemia. In the hematological tests of the patients, it was observed that the hematocrit, erythrocyte count, and erythrocyte indices were low, and the HbA synthesis decreased (10-20%) and the HbF synthesis increased (80-90%) in the hemoglobin electrophoresis. All patients were receiving monthly blood transfusions and were using deferasirox and deferiprone as chelating agents. Patients' age at diagnosis, duration of disease, duration of chelating agent use, blood hemoglobin (Hb; g/dL) and ferritin (ng/mL) levels were recorded.

Patients were excluded from the study in the presence of the criteria listed below. 1) History of previous ocular surgery and trauma, 2) Best corrected visual acuity (BCVA) level less than 20/20, 3) Presence of ocular disease (e.g., cataract, glaucoma, ocular surface disorder), 4) Patients with spherical refractive error of more than three diopters, cylindrical refractive error of more than two diopters, 5) History of systemic or topical steroid use, 6) History of systemic disease other than  $\beta$ -thalassemia, 7) Patients unable to adapt for Scheimpflug imaging.

The control group consisted of age- and sex-matched healthy children who were consulted to the ophthalmology clinic for routine eye examination from

the pediatric clinic. Complete ophthalmologic examinations of all patients were performed, including refractive measurement (RK-F2, Canon, Japan), best corrected visual acuity (BCVA), biomicroscopic examination, intraocular pressure (IOP) measurement (CT.1P, Topcon, Japan) and fundus examination. Non-contact specular microscopy (NSP-9900, Konan, Japan) was used to examine the morphology of the corneal endothelium. Three measurements were taken from the center of the cornea in each patient. At least 100 adjacent cells were analyzed by the automatic program. Specular microscopy automatically assessed endothelial cell density (ECD), the coefficient of variation (CoV), and percent cell hexagonality (Hex).

### 2.1. Scheimpflug Imaging of the Cornea and Lens

All participants underwent topographic and densitometric analyses through a rotating Scheimpflug camera (Pentacam HR, Oculus Optikgeräte GmbH). Measurements were performed by a single experienced user in the same clinical evaluation room. A black shield designed by the company was used to provide ambient darkness. All measurements were performed at the same time interval of day (between 12 and 13) to minimize the effect of diurnal changes in corneal hydration. Patients were instructed to blink twice just before measurement and then to keep their eyes open during measurement. Automatically triggered Scheimpflug scans (25 images in 2 sec) were performed for analysis. Acquisitions that the device's software quality control rated "OK" were used. The highest quality measurement data from the right eye of the participants were recorded. After the first Scheimpflug imaging, two drops of 1% tropicamide were instilled at five-minute intervals for pupil dilation. The second imaging was taken 45 minutes after the second drop of tropicamide for crystalline lens densitometry measurements.

Corneal densitometry with backscattering of corneal light on the standard Scheimpflug densitometry scale, it is expressed in grayscale units (GSUs). The measurements ranged from 0 (minimum dispersion and maximum transparency) to 100 (maximum dispersion and minimum transparency). The entire corneal area was divided into 4 zones. Zone 1 is the area with a diameter of 2 mm from the center of the cornea. Zone 2, 2-6 mm diameter annular area around zone 1. Zone 3, 6-10 mm diameter annular area around zone 2. Zone 4, 10-12 mm diameter annular area around Zone 3. Densitometry analyzes in all zones were performed at 3 different depths of the cornea. The anterior layer was 120 microns deep from the corneal surface, the posterior layer was at 60 microns of the inner most cornea, and the central layer was the area between the two layers (Figure 1).

Three-dimensional scanning modes were used for crystalline lens density measurement. The mean densitometry value for the crystalline lens was calculated in three regions around the center of the pupil. Pentacam Densitometry of Zone 1 (PDZ1), 2.0 mm around. Pentacam Densitometry of Zone 2 (PDZ2) 4.0 mm

around. Pentacam Densitometry of Zone 3 (PDZ3) 6.0 mm around.

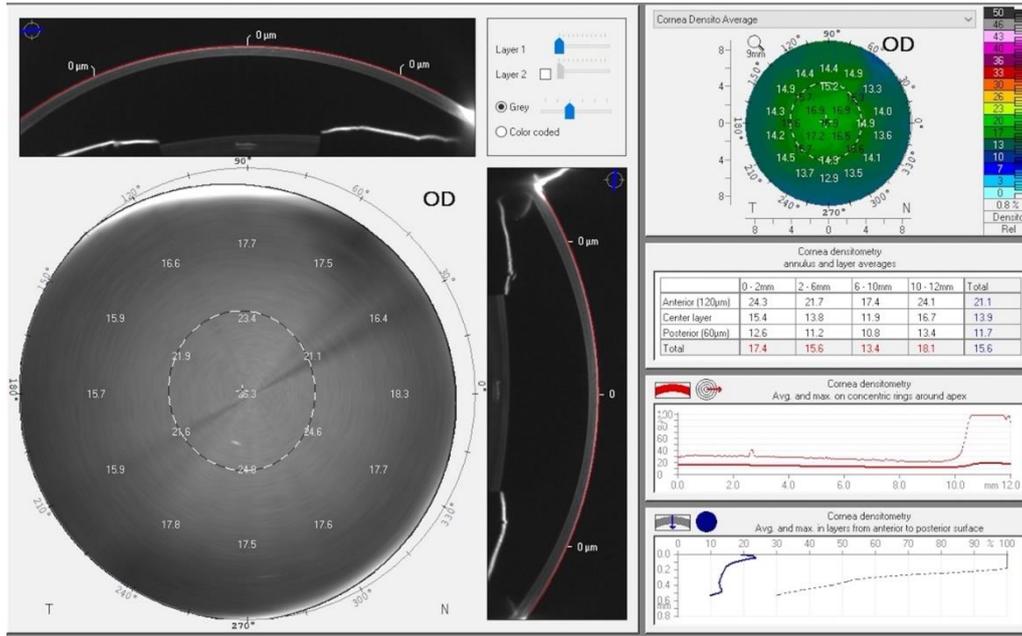


Figure 1. Scheimpflug tomography images and corneal densitometry values.

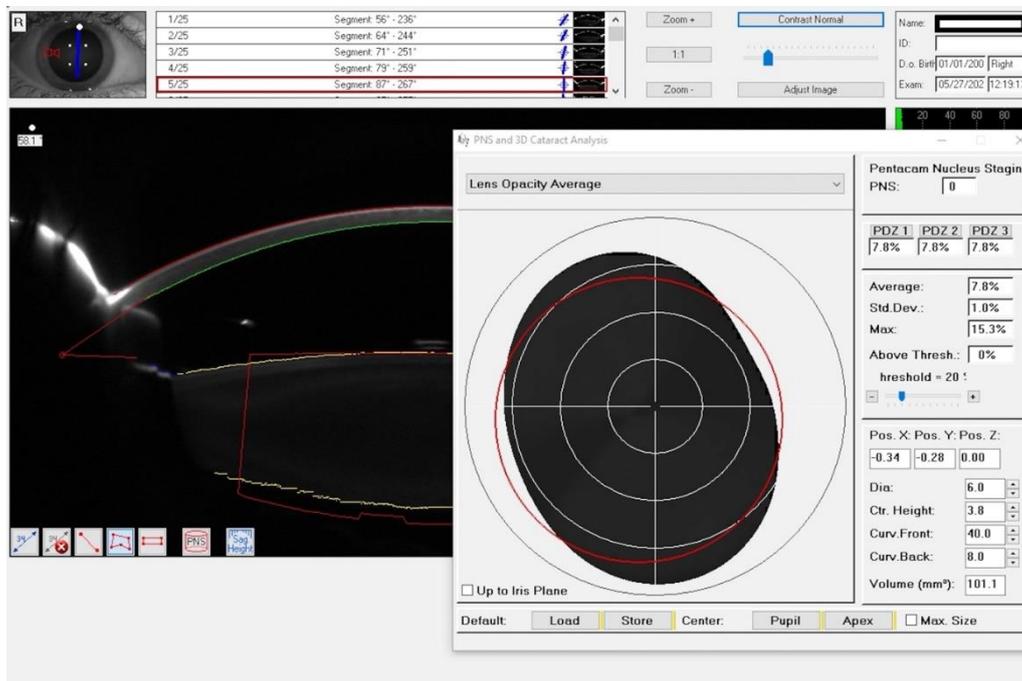


Figure 2. The crystalline lens densitometry measurements of patients.

Pentacam nucleus (PNS) staging (0–5), average lens density (ALD), maximum (Max) and lens thickness (LT) values were automatically determined in the device software (Figure 2). The following data have been analyzed from the acquisition prior to pupillary dilation. 1) Flat keratometry (K1) and steep keratometry (K2) for the central 3.0 mm of the cornea, maximum keratometry (Kmax), the central, apical, and thinnest corneal thickness (CCT, ACT, and TCT respectively) 2) Corneal volume (CV), chamber volume (ChV), anterior chamber depth (ACD), horizontal white to white (HWTW) and

iridocorneal angle (ICA) 3) Corneal densitometry (CD) values were recorded separately in all zones in the anterior, center, and posterior layers. Crystalline lens density data obtained from measurements made after pupillary dilatation were recorded (PDZ1, PDZ2, PDZ3, PNS staging, ALD, Max, and LT).

## 2.2. Statistical Analysis

The data was examined by the Shapiro Wilk test whether or not it presents normal distribution. The results were presented as mean ± standard deviation or frequency and percentage. Normally distributed data were

compared with independent samples t-test. Categorical variables were compared using Pearson's Chi-square test between groups. Correlations between variables were tested using Pearson correlation coefficient.  $P < 0.05$  was considered as significance levels. Statistical analyses were performed with IBM SPSS ver.23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

### 3. Results

For the study, 34 beta thalassemia patients were examined. Two of the patients were excluded from the study due to lens opacity and corneal scarring. The study group consisted of 32  $\beta$ -thalassemia major patients and the control group consisted of 31 healthy volunteers. Of the 32 patients in the study group, 15 were female and

17 were male. In the control group, 21 were female and 10 were male. The mean age of the study group was  $12.12 \pm 3.94$  years (range: 5-19 years) and  $10.90 \pm 3.84$  years (range: 5-19 years) in the control group. There was no statistically significant difference between age and gender in both groups ( $P > 0.05$ ). Demographic data of the study and control groups, mean age at diagnosis (months), duration of diagnosis (years), blood hemoglobin and ferritin levels of patients with  $\beta$ -thalassemia major are summarized in Table 1.

Among the corneal topographic parameters, CCT ( $544.25 \pm 30.45$  vs.  $562.23 \pm 30.95$ ;  $P = 0.025$ ) and CV ( $59.97 \pm 3.26$  vs.  $62.60 \pm 3.54$ ;  $P = 0.004$ ) were found to be significantly lower in the study group. All data are shown in Table 2.

**Table 1.** Demographic features

	Study Group (n=32)	Control Group (n=31)	P value
Age (years)	$12.12 \pm 3.94$ (5 - 19)	$10.9 \pm 3.84$ (5 - 19)	0.218*
Gender			0,094‡
Female	15 (46.9 %)	21 (67.7 %)	
Male	17 (53.1 %)	10 (32.3 %)	
Age at Diagnosis (months)	$11.07 \pm 5.76$ (2 - 36)		
Duration of diagnosis (years)	$11.10 \pm 4.14$ (4 - 19)		
Hemoglobin (g/dL)	$8.98 \pm 1.02$ (6.1 - 10.8)	$13.07 \pm 0.58$ (11.90 -14.1)	<0.0001*
Ferritin (nmol/L)	$1692.59 \pm 1199.7$ (334 - 6092)	$53.72 \pm 23.09$ (30-75)	<0.0001*

Descriptive statistics were given for continuous variables as mean  $\pm$  standard deviation (SD) with minimum and maximum values and frequency and percentage for categorical variables. \*= Independent samples t test, ‡= Chi-square test.

**Table 2.** Comparison of corneal topographic parameters data between study and control groups

	Study Group (n = 47)	Control Group (n = 47)	P value*
K1 (D)	$42.86 \pm 1.30$ (39.2-46.80)	$43.39 \pm 1.36$ (40.70-46.60)	0.123
K2 (D)	$43.80 \pm 1.54$ (40.0-47.90)	$44.29 \pm 1.48$ (42.00-48.40)	0.209
CCT ( $\mu$ m)	$544.25 \pm 30.45$ (459-593)	$562.23 \pm 30.95$ (499-617)	0.025
ACT ( $\mu$ m)	$546.34 \pm 30.76$ (461-593)	$563.13 \pm 30.88$ (498-618)	0.036
TCT ( $\mu$ m)	$541.50 \pm 30.66$ (457-589)	$559.27 \pm 30.79$ (497-615)	0.026
Kmax Front (D)	$44.38 \pm 1.61$ (40.50-48.60)	$44.74 \pm 1.51$ (42.30-48.80)	0.379
CV ( $\text{mm}^3$ )	$59.97 \pm 3.26$ (51.10-64.30)	$62.60 \pm 3.54$ (57.0-70.20)	0.004
ChV	$178.41 \pm 31.93$ (128-251)	$180.13 \pm 23.81$ (131-241)	0.809
ACD	$3.08 \pm 0.2$ (2.14-3.70)	$3.02 \pm 0.3$ (2.32-3.60)	0.362
HWTW	$11.88 \pm 0.41$ (11.10-13.00)	$11.68 \pm 0.41$ (10.70-12.40)	0.059
ICA ( $^{\circ}$ )	$36.90 \pm 5.30$ (27.60-45.20)	$36.94 \pm 4.55$ (26.10-43.50)	0.975

Descriptive statistics were given for continuous variables as mean  $\pm$  standard deviation (SD) with minimum and maximum values and frequency for categorical variables. K1= flat keratometry; K2= steep keratometry; D= diopter; CCT= central corneal thickness; ACT= apical corneal thickness; TCT= thinnest corneal thickness; Kmax= maximum keratometry; CV= corneal volume; ChV= chamber volume;

ACD= anterior chamber depth; HWTW= horizontal white to white; ICA= irido-corneal angle.

Only in the posterior layer corneal light backscattering was significantly lower in the patient group than in the normal group. There was no significant difference in corneal densitometry values in all other layers. All data are shown in Table 3.

Endothelial cell density counted by specular microscopy was determined as 3053.55±189.71 in the patient group and 3214±195.12 in the control group. The difference in ECD between the two groups was not statistically significant (P=0.094). The CoV and hex values were found to be similar in both groups.

The lens densitometry values did not differ between the two groups in all zones (P>0.05). All data are shown in Table 4.

Correlations between age, Hb, ferritin levels, disease duration, and ocular changes were evaluated. Only ferritin levels were found to be correlated with corneal densitometry. Corneal density of anterior layer (r=-0.453, P=0.014) and corneal density of central layer (r=-0.467, P=0.011) were negatively correlated with ferritin.

**Table 3.** Comparison of Corneal densitometry measurements

	Study Group (n = 32)	Control Group (n = 31)	P value*
<b>Anterior Layer</b>			
0-2 mm	25.03 ± 2.42	25.08 ± 1.17	0.921
2-6 mm	22.02 ± 2.23	22.36 ± 1.04	0.452
6-10 mm	19.24 ± 3.61	19.93 ± 2.75	0.405
10-12 mm	25.69 ± 6.14	27.94 ± 7.22	0.191
Total	22.23 ± 3.02	22.87 ± 2.02	0.335
<b>Central Layer</b>			
0-2 mm	15.25 ± 1.53	15.44 ± 0.86	0.546
2-6 mm	13.38 ± 1.31	13.67 ± 0.77	0.283
6-10 mm	11.93 ± 1.75	12.66 ± 1.43	0.079
10-12 mm	15.78 ± 3.31	15.25 ± 3.83	0.170
Total	13.58 ± 1.63	14.33 ± 1.17	0.043
<b>Posterior Layer</b>			
0-2 mm	12.51 ± 1.17	12.98 ± 0.98	0.094
2-6 mm	11.32 ± 1.01	11.85 ± 0.84	0.029
6-10 mm	10.92 ± 1.30	11.98 ± 1.31	0.002
10-12 mm	12.90 ± 2.41	15.25 ± 3.83	0.005
Total	11.64 ± 1.14	12.54 ± 1.05	0.002
<b>Total Layer</b>			
0-2 mm	17.43 ± 1.86	17.84 ± 0.81	0.268
2-6 mm	15.43 ± 1.60	15.95 ± 0.76	0.105
6-10 mm	13.97 ± 2.22	14.86 ± 1.78	0.088
10-12 mm	18.07 ± 3.80	20.40 ± 4.64	0.034
Total	15.71 ± 2.00	16.58 ± 1.33	0.051

Descriptive statistics were given for continuous variables as mean ± standard deviation (SD). \*=Student's t-test were used.

**Table 4.** Comparison of lens densitometry measurements

	Study Group	Control Group	P value*
PDZ 1	7.95 ± 0.27	7.92 ± 0.20	0.556
PDZ 2	7.93 ± 0.25	7.95 ± 0.22	0.713
PDZ 3	7.97 ± 0.22	8.02 ± 0.27	0.399
ALD	7.96 ± 0.25	8.00 ± 0.22	0.446
SD	1.13 ± 0.46	1.27 ± 0.25	0.147
MAX	22.17 ± 10.11	19.08 ± 3.63	0.123
Lens thickness	3.63 ± 0.18	3.61 ± 0.21	0.773

Descriptive statistics were given for continuous variables as mean ± standard deviation. PDZ= pentacam densitometry of zone, ALD= average lens density, SD= standard deviation, Max= maximum, \*=Student's t-test were used.

#### 4. Discussion

In this study, non-invasive Pentacam imaging was performed to detect corneal, and lens changes early in β-thalassemia major patients without any ocular signs or

symptoms. The cornea and lens density values of healthy children and patients with β-thalassemia major were compared in different layers and zones. We aimed to detect disease-related ocular complications early before

symptoms develop. Corneal densitometry is an indicator of corneal transparency. The cornea maintains its clarity through the regular lattice arrangement of collagen fibrils in the stroma. The main sources of light scattering are the corneal epithelium and corneal endothelial layer (Smith et al., 1990). Nerves and cell nuclei in the corneal tissue are the structures with the highest backscattering indices of light (Otri et al., 2012). In the current study, corneal densitometry values were found to be lower in the thalassemia group than in the control group only in the posterior 60-micron layer of the cornea. Although the endothelial cell density value was found to be higher in the healthy group ( $3214 \pm 195.129$ ) than thalassemia group ( $3053.55 \pm 189.71$ ) in specular microscopic evaluation, the difference was not statistically significant ( $P=0.094$ ).

Patients with thalassemia are exposed to chronic hypoxia due to anemia. It is known that chronic hypoxia has negative effects on the corneal endothelium. In the study of Coskun et al. (2015) in patients with sickle cell anemia, it was shown that corneal endothelial cells and CCT decreased, and it was observed that chronic anemia and hypoxia caused morphological changes in the structure of the cornea. In our study, ECD was lower in the patient group, but we could not statistically prove corneal endothelial cell loss. We hypothesize that the decrease in densitometry detected in the posterior corneal layer is due to changes in the structural properties of the cornea endothelium. In a study conducted in high myopic eyes, the corneal posterior layer density was found to be lower than the control. It has been suggested that the density of endothelial cells, which are part of the luminescent corneal tissue, is reduced in high myopic eyes (Dong et al., 2018).

Previous studies on biometric parameters and refractive errors in thalassemia patients found a shorter axial length and ACD, a steeper cornea, and a thicker lens compared to normal subjects. It has been suggested that this is to compensate for growth retardation due to growth hormone deficiency and orbital bone changes (Nowroozzadeh et al., 2011; Elkitkat et al., 2018). In this study, no difference was found between the patient and control groups in terms of corneal curvature, ACD, and lens thickness. Corneal thickness measurements and corneal volume were statistically significant lower in the thalassemia group. There are many factors that can cause ocular disorders due to thalassemia, such as chronic anemia, iron overload, chelation drugs used and growth and development retardation. However, we suggest that the reason for the lower corneal thickness measurement and volume is due to growth retardation. In animal studies, it has been shown that growth hormone, Insulin like growth factor 1 (IGF-1) and recombinant growth factor therapy cause extracellular matrix synthesis and stimulate the development of ocular tissues (Burren et al., 1996). In addition, Dereli and Kara (2019) observed a mild to moderate positive correlation between IGF-1 values and ACT and CV values.

The biometric and refractive characteristics of the thalassemia major patients have previously been investigated (Heydarian et al., 2016; Elkitkat et al., 2018). Patients with thalassemia major have been shown to have a lower axial length compared to controls. It is due to the bone structure of the orbit, which is due to skeletal disorders as a result of bone marrow enlargement. In the study of Heydarian et al. (2016) in adult thalassemia patients, the mean axial length was significantly lower in thalassemia patients than in the normal group, and the flattest meridian of the cornea was significantly steeper in thalassemia patients. They argue that this is because there may be steeper corneal curvatures that overcome the refractive disadvantage of shorter axis lengths. In our study, we did not evaluate the axial length of the patients. Unlike the other study, we did not detect a significant difference in the radius of corneal curvature, since pediatric patients who did not complete the emmetropization process were included in the study and the compensation mechanisms that would develop in the cornea and lens would not have been completed yet.

Previous studies have shown an increase in LT in thalassemia patients (Nowroozzadeh et al., 2011; Elkitkat et al., 2018; El-Haddad, 2020). The reason for this has not been fully explained. It has been discussed that the precipitation of iron in the lens material may be due to the chelating agents used. One of the mechanisms proposed is that the cornea becomes steeper, and the lens becomes thicker to compensate for the shorter axial length in thalassemia patients (Heydarian et al., 2016). In the current study, we did not detect a significant difference between the control group and thalassemia patients in terms of lens thickness. Unlike other studies, lens thickness measurement was evaluated with Pentacam for the first time, not ultrasonic method. Other differences are that the mean age of the patients included in the study was lower than in other studies, and patients with cataract were excluded from the study. In different studies, the prevalence of cataracts in patients with  $\beta$ -thalassemia ranged from 6.3% to 45.7% (Heydarian et al., 2020). It is argued that the factor contributing to the development of cataract in patients with  $\beta$ -thalassemia may be due to free radical damage due to iron overload, chelating agents used, and nutritional deficiencies (Popescu et al., 1998; Athanasiadis et al., 2007; Taneja et al., 2010). Jafari et al. (2015) detected cataracts in 10.2% of thalassemia patients aged 14-42 years. They reported that the prevalence of cataract was higher in patients using deferiprone. Taneja et al. (2010) found lens opacity in 40% of thalassemia patients aged 6 months to 21 years. They found that the prevalence of cataracts was higher in patients receiving desferrioxamine treatment than in patients receiving deferiprone.

Although the cause of cataract in thalassemia patients is not clear, it has been proven in many studies that its prevalence increases. Based on the literature, we aimed to evaluate the lens densitometry with a Pentacam device and to follow up the patients with high lens densitometry

values to detect the signs of cataract before it develops clinically in thalassemia patients. In this study, lens densitometry in all zones showed similar results in thalassemia and control groups. Although only the maximum lens density was found to be high in the thalassemia group, no statistically significant difference was observed.

## 5. Conclusion

In conclusion, we found a change in corneal densitometry without any clinical findings in patients with  $\beta$ -thalassemia major. Although no significant difference was detected in the lens density of our patients, changes in the Max value may be a new hope for Pentacam, which is a non-invasive and fast method, especially in early indication of lens opacities. This finding should be supported by prospective studies with a large number of cases.

To our knowledge, this study is the first to evaluate anterior segment structures in children with  $\beta$ -thalassemia using Pentacam. Another strength of the study is the prospective patient recruitment and the inclusion of patients with no ocular pathology in the eye examination. However, the small sample size is an important limitation due to the poor cooperation of younger age groups with the device during examination in the pediatric group. Since there is no study with Pentacam in the literature, it was not possible to compare the data. Prospective evaluation with larger numbers of patients is needed to determine whether Pentacam will be an appropriate screening technique for early detection of  $\beta$ -thalassemia ocular findings in children.

## Author Contributions

Concept: H.G.U. (%50) and E.G.K. (50%), Design: H.G.U. (%50) and E.G.K. (50%), Supervision: H.G.U. (%50) and E.G.K. (50%), Data collection and/or processing: H.G.U. (%50) and E.G.K. (50%), Data analysis and/or interpretation: H.G.U. (%50) and E.G.K. (50%), Literature search: H.G.U. (%50) and E.G.K. (50%), Writing: H.G.U. (%50) and E.G.K. (50%), Critical review: H.G.U. (%50) and E.G.K. (50%), Submission and revision H.G.U. (%50) and E.G.K. (50%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest.

## Ethical Approval/Informed Consent

The study protocol was approved by the Bursa University of Health Sciences local ethics committee (2011- KAEK-25 2021/04-30) in accordance with the principles of the Helsinki declaration. Written informed consent was obtained from the children and their parents before participating in the study.

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## THE IMPACT OF ENDEMIC *IRIS TAOCHIA* ETHANOLIC EXTRACTS ON HUMAN LUNG ADENOCARCINOMA CELLS

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**Abstract:** *Iris taochia* is an elegant endemic plant in Türkiye and it has limited distribution. In this study, cytotoxic effects of ethanolic extracts from different parts and concentrations extracted from *I. taochia* collected from the surroundings of Tortum (Erzurum), on A549 human lung adenocarcinoma cell line were investigated. Cytotoxicity of extracts were evaluated by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) method. Apoptotic activity of IC<sub>50</sub> values of extracts were evaluated with Annexin V and Caspase 3/7 assays. Ultrastructural changes of IC<sub>50</sub> doses treated cells were investigated by transmission electron microscopy. As a result, it was determined that ethanol extract of *I. taochia* showed significant cytotoxic activity on A549 cells after 24 hours the extract a dose-dependent reduction in cell viability. IC<sub>50</sub> values of above and below ground parts ethanolic extracts were determined as 7 µg/ml and 20 µg/ml respectively. Specifically, apoptosis inducing effect was increased at 7 and 20 µg/ml concentrations by 24 hours. We found that *I. taochia* ethanol extracts had antiproliferative and apoptotic effects on the human lung adenocarcinoma cells A549. However, further studies at molecular level are required to support our findings and to elucidate chemopreventive and chemotherapeutic effects of *I. taochia* on lung cancer.

**Keywords:** *Iris taochia*, Endemic, Biological activity, Lung cancer, Apoptosis

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### 1. Introduction

Türkiye, with its different climatic and ecological conditions is one of the richest countries of the world in terms of plant species. Many plant species consumed for medical purposes are members of this rich flora (Bayram et al., 2010). A good number these plants are reported to have anticancer, antiulcer, antimicrobial, antioxidant and antifungal effects (Rigona et al., 2007; Conforti et al., 2009; Ertürk et al., 2010; Bhalodia and Shukla, 2011; Hacibekiroglu and Kolak, 2011; Kandemir et al., 2022). The resistance towards chemotherapeutics that has developed in recent years rapidly has caused a pursuit of new active substances and the discovery of new and more effective active pharmeochemical ingredients from plants has gained importance.

*Iris* L. genus has wide distribution in the Northern Hemisphere. In Türkiye, it is one of the richest genera in terms of number of species. *Iris* genus is represented

with 50 taxa in Türkiye (Güner et al., 2012). The species of this genus, among flowering plants are mainly used as ornamental plants due to their colorful, showy and pleasant fragrant flowers (Kandemir and Yakupoğlu, 2016). *Iris* taxa contains many biologically active substances as alkaloids, saponins, tannins, steroids, isoflavonoids, flavanoids, flavones, iridal type triterpenoids and their glycosides, benzoquinones, flavones, c-glycosylxanthenes, glycosylflavones, phenolics, stilbene glycosides and cardiac glycosides (Wang et al., 2003; Nighat et al., 2008; Ma et al., 2012; Tantry et al., 2013; Kassak, 2014; Kukula-Koch et al., 2015). Isoflavonoids, flavanoids, quinones and xanthenes of these are common substances in *Iris* species (Orhan et al., 2003; Asghar et al., 2010; Kassak, 2012). While the isoflavonoids are found in the rhizomes, c-glycosylxanthenes, xanthone glycosides and flavonoid aglycones are found in the leaves and flowers of *Iris* taxa

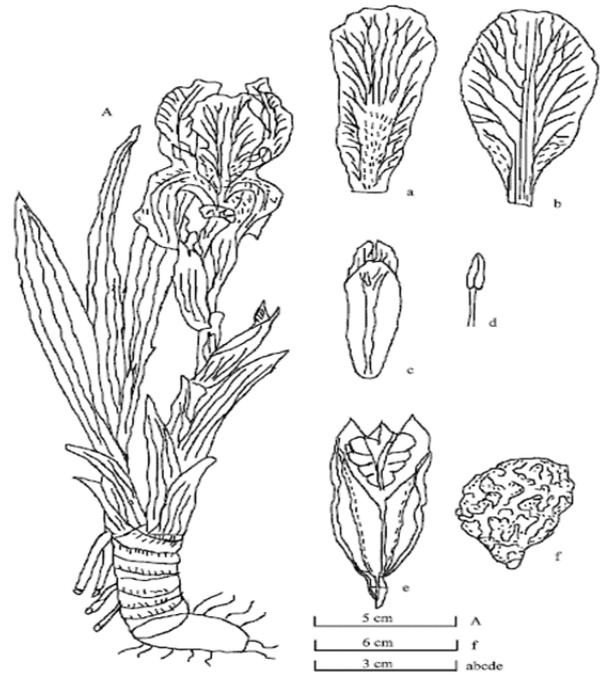


(Kassak, 2012). *Iris* taxa have been used as medicine (in the treatment of cancer, inflammation, bacterial and viral infections and venereal disease) (Wollenweber et al., 2003; Fang et al., 2008; Conforti et al., 2009; Sabrin et al., 2012; Xie et al., 2013; Bozyel et al., 2019; Yazgan et al., 2022) and as economic plants (in perfumes and cosmetics) since the very early years due to the piscicidal, antineoplastic, antioxidant, antitumor, antiplasmodial, antiulcer, molluscicidal, estrogenic, hypolipidemic and anti-tuberculosis properties (Bonfils et al., 2001; Wang et al., 2003; Orhan et al., 2003; Rigano et al., 2009; Fang et al., 2008; Conforti et al., 2009; Huwaitat et al., 2013) of isolated secondary metabolites.

Cancer, as a major health problem, is defined as uncontrolled cell proliferation and spread. Depending on the stages of cancerous cells, surgical interventions, radiotherapy, chemotherapy, immunotherapy or hormone replacement therapies are among the options. In general, chemotherapeutic drugs affect apoptotic cell death and have a cytotoxicity effect on cancerous cells (Fang et al., 2008; Yazgan et al., 2022). For this reason, finding anti-cancer agents that are more effective on cancer cells as soon as possible increases its importance day by day. On the other hand, apoptosis is programmed cell death, an important molecular mechanism that removes abnormal and damaged cells. Studies have reported that it is necessary to develop innovative methods for cancer treatment and to recognize molecular targets in apoptotic cell death pathways (Huang et al., 2012). In this regard, the use of herbal drugs for therapeutic purposes is increasing day by day. It has been reported that there are 160 plant taxa and 17 multi-herbal formulas used in cancer treatment in Turkish traditional medicine today (Bozyel et al., 2019).

*Iris taochia* Woronow ex Grossh. belongs to subgenus *Iris* of *Iris* genus. This subgenus is represented by 8 taxa in Türkiye Flora 4 of which (*I. juaonia* Schott & Kotschy ex Schott, *I. taochia*, *I. schachtii* Markgraf and *I. purpureobracteata* B. Mathew & T. Baytop) are endemic to Türkiye. *I. taochia*, endemic Irano-Turanien element, is distributed only in the North East Anatolia (Erzurum-Tortum) in Türkiye. It is a rhizomatous and perennial plant and its length is 18.5-30 cm (Figure 1). This species has yellow and purple colored, sweet-smelling and showy 2-5 flowers (Mathew, 1984; Kandemir, 2006). *I. taochia* is used as a decorative plant because of the above mentioned characteristics and is called "Tortum suseni" in Türkiye. It contains iridals and essential oils in the rhizomes. According to International Union for Conservation of Nature (IUCN) endangered categories, this taxa are in the VU (Vulnerable) category in Türkiye (Ekim et al., 2000).

Based on the fact that there has been no recorded study on this endemic species, here it is aimed to investigate the impact of ethanolic *I. taochia* extracts on human lung adenocarcinoma (A549) cells mainly focusing on potent cytotoxic, antiproliferative and apoptosis triggering activities.

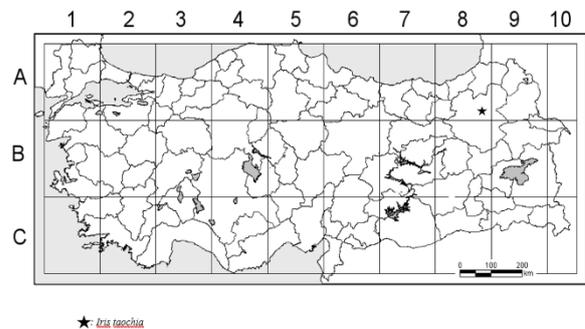


**Figure 1.** General appearance of *Iris taochia*. A= Plant, a=Outer tepal, b=Inner tepal, c=Style, d=Stamen, e=Capsule, f=Seed (illustrated by N. Kandemir from the living specimen flowered).

## 2. Materials and Methods

### 2.1. Preparation of Plant Materials

The samples of *I. taochia* were collected from vicinity of Tortum (Erzurum) during the flowering period in July 2018 (Figure 2). Taxonomic description of the species was made according to Mathew (1984). The locality of collected plant samples is given below; A8 Erzurum: Between Tortum and Oltu (2 km from Tortum), rocky areas, 1650 m., 20 July 2018, Kandemir, 867. A8 Erzurum: Near Tortum, rocky areas, 1500 m., 20 July 2018, Kandemir, 869.



**Figure 2.** The distribution areas of *Iris taochia* in Türkiye

### 2.2. Preparation of Ethanolic Extracts from Plant Materials

The below-ground (rhizome and root) and above-ground parts (scape, leaf, flower, fruit and seed) of plant samples were cleaned, cut into pieces and dried on the benches at room temperature and in shadow in laboratory

conditions. They were often stuffed to prevent molding. Then, dried samples were grinded in the mill with sieve 2 mm and speed 500 rpm. Dried plant samples were stored in cloth bags. Plant powder was extracted with ethanol by maceration. Plant powder and ethanol (1:20 m/V) were continuously stirred at room temperature in dark for 72 hours (Trusheva et al., 2007). Then, extracts were filtered through 0.22 µm pore size membrane filter and stored at 4°C. Ethanol was evaporated in room temperature for measuring crude weight of extracts.

### 2.3. Evaluating the Cytotoxicity of the Extracts by MTT Assay

Different concentrations (ranging from 1.56-100 µg/ml) of the ethanolic extracts were prepared by dilution method in 96-well plates with fresh prepared growth medium. A549, human lung adenocarcinoma cells were seeded 2x10<sup>3</sup> cells per well in the 96-well plate containing the above given concentrations. Cells were incubated for 24 hours at 37°C in a humidified atmosphere of 5% CO<sub>2</sub> in air. After the incubation period 20 µl of MTT solution (5 mg/ml) was added per well and allowed to incubations in the same conditions for 2 hours. At the end of incubation period the growth media were changed with 200 µl/well of dimethyl sulphoxide and samples were kept at room temperature for 5 minutes. Samples were prepared in triplicates and absorbances were read on an ELISA reader at a wavelength of 570 nm (n = 3) (Mosmann, 1983). Then IC<sub>50</sub> concentrations were determined from the obtained viability percentages calculated with the following equation 1 (Edmondson et al., 1988).

$$\text{Cell proliferation} = [\text{OD sample}] \times 100 / [\text{OD control}] \quad (1)$$

Where; OD is optical density

### 2.4. Annexin-V Analysis

The apoptosis triggering action of *I. taochia* extract on A549 cells was evaluated by Annexin-V FITC/propidium iodide (PI) staining. For this manner, the cells were incubated with the IC<sub>50</sub> value of plant extracts for 24 hours. At the end of incubation period, 100 ml of untreated and treated cells were transferred to separate tubes. 100 µl of Annexin-V reagent was added to each tube and allowed to incubation in dark, for 20 minutes at room temperature. After the incubation period, samples were analyzed on Muse™ Cell Analyzer (Merck, Millipore, Hayward, California, USA). All the samples were prepared in triplicate according to the user manual of Muse® Annexin-V and Dead Cell Assay Kit.

### 2.5. Caspase 3/7 Analysis

A549 cells treated with IC<sub>50</sub> value of plant extract for 24 hours and untreated A549 cells were prepared for incubation by adding 5 µl Muse® Caspase 3/7 working solution (1:8 in 1 X PBS) to 50 µl of the cells. After the incubation period, 150 µl of 7-AAD working solution (2µl of 7-AAD to 148 µl of 1X assay buffer) was added. At the end of the incubation all samples were analyzed on

Muse™ Cell Analyzer (Merck, Millipore, Hayward, California, USA). All the samples were prepared in triplicate according to the user manual of Muse® Caspase 3/7 Assay Kit.

### 2.6. Transmission Electron Microscopy for Analyzing the Ultrastructural Changes

The test cells treated with IC<sub>50</sub> concentration of the *I. taochia* extracts for 24 hours were fixed in glutaraldehyde and post was fixed in osmium tetroxide. Following the fixation, the cells were dehydrated in graded ethyl alcohol and embedded in Epon 812 epoxy. Obtained blocks were sectioned on ultramicrotome. Thin sections were prepared by using a glass knife of a maximum thickness of 100 nm and stained in lead citrate and uranyl acetate. Stained samples were observed under a TEM (FEI Tecnai BioTWIN, Limmen, The Nederland) (Vejselova and Kutlu, 2015).

### 2.7. Statistical Analysis

Statistical comparison of the samples was carried out by one-way analysis of variance for multiple comparisons using Graphpad Prism 7.0 for Windows. The data was expressed as means ± SDs.

## 3. Results

### 3.1. MTT Assay Results

Cytotoxicity activity of *I. taochia* below and above ground parts ethanolic extracts were carried out against A549 cell line at different concentrations to determine the IC<sub>50</sub> (50% growth inhibition) by MTT assay. MTT assay of *I. taochia* showed significant effect on A549 in concentration range between 1,56 to 100 µg/ml compared with control. IC<sub>50</sub> value of below ground parts were detected to be 20 µg/ml for 24 hours (Figure 3). IC<sub>50</sub> value of above ground parts were detected to be 7 µg/ml for 24 hours (Figure 4).

### 3.2. Annexin V Staining Results

To evaluate the apoptosis level, annexin-V antibody was used. Annexin V staining results of untreated A549 cells (Figure 5A) showed 90.40% live, 1.25% early apoptotic and 1.30% late apoptotic cells. In A549 cells treated with IC<sub>50</sub> value of ethanolic extract of *I. taochia* above ground parts for 24 hours (Figure 5B) percentage of live cells were detected to be 86.10; whereas, 6.70% of these cells were in early apoptotic and 1.75% in late apoptotic stage. Live cell percentages in A549 cells treated with IC<sub>50</sub> value of ethanolic extract of *I. taochia* below ground parts (Figure 5C) for 24 hours were 7.10 and 0.25 in early apoptosis and 10.20 in late apoptosis.

### 3.3. Caspase 3/7 Analysis Results

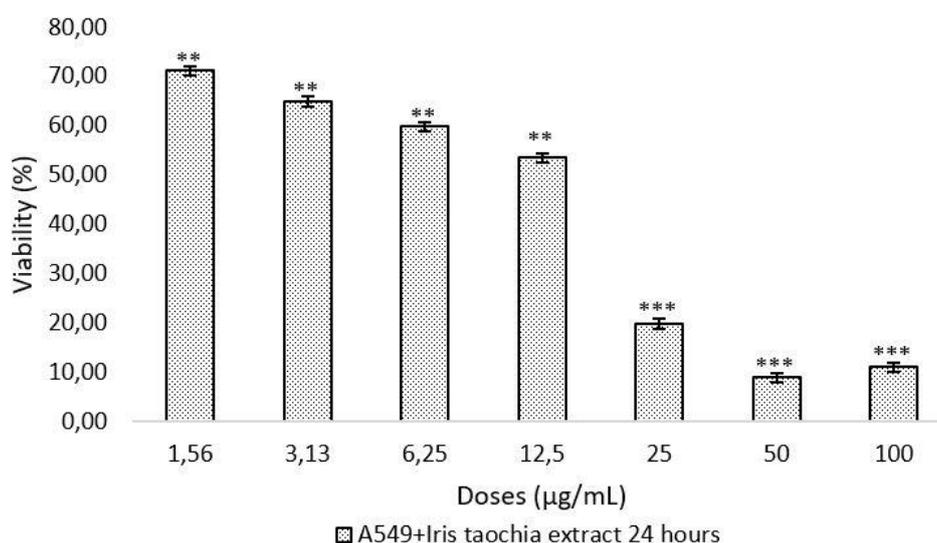
In apoptosis profile of untreated A549 cells (Figure 6A) percentages of live cells detected to be 98.61%. Apoptotic/dead cells were 1.20% in the same group and 0.14% of cells were apoptotic. Only 0.05% of the control A549 cells were dead. In A549 cells treated with IC<sub>50</sub> concentration of *I. taochia* below ground parts ethanolic extract for 24 hours (Figure 6B) the percentage of live cells was 79.64%. The percentage of apoptotic/dead cells in this group was 18.84%, 0.97% were apoptotic and

0.55% were dead. In the A549 cells treated with IC<sub>50</sub> concentration of *I. taochia* below ground parts ethanolic extract (Figure 6C) for 24 hours' percentage of live cells was detected to be 28.59. Of these cells 1.48% were dead and 69.21% apoptotic/dead and 0.72% apoptotic.

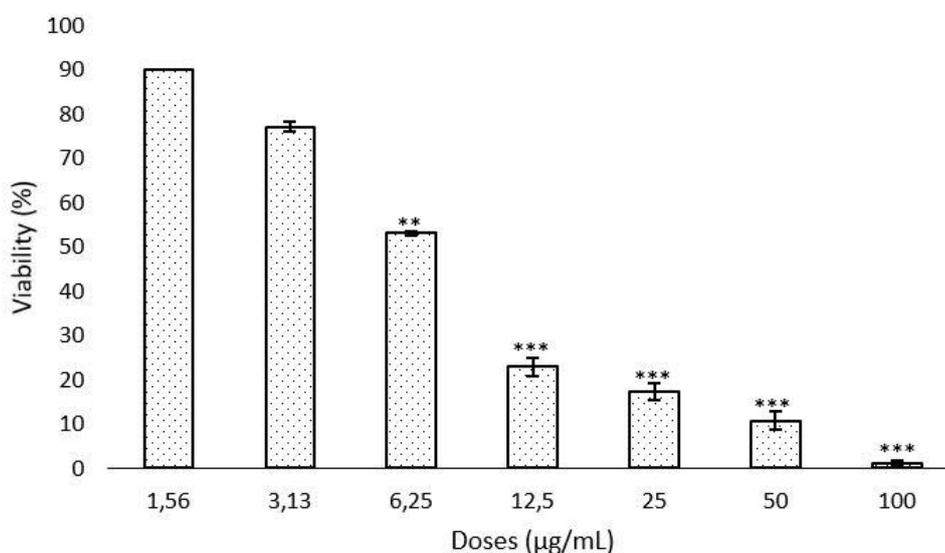
### 3.4. Ultrastructural Changes Detected by Transmission Electron Microscopy

In order to determine whether the growth inhibition by plant extracts were associated with apoptosis, we further examined the morphological changes A549 cancer cell lines under transmission electron microscope. The control cells demonstrated fusiform cell shape and contact cell membrane. While A549 cells that were treated with the IC<sub>50</sub> value of *I. taochia* above ground parts ethanolic

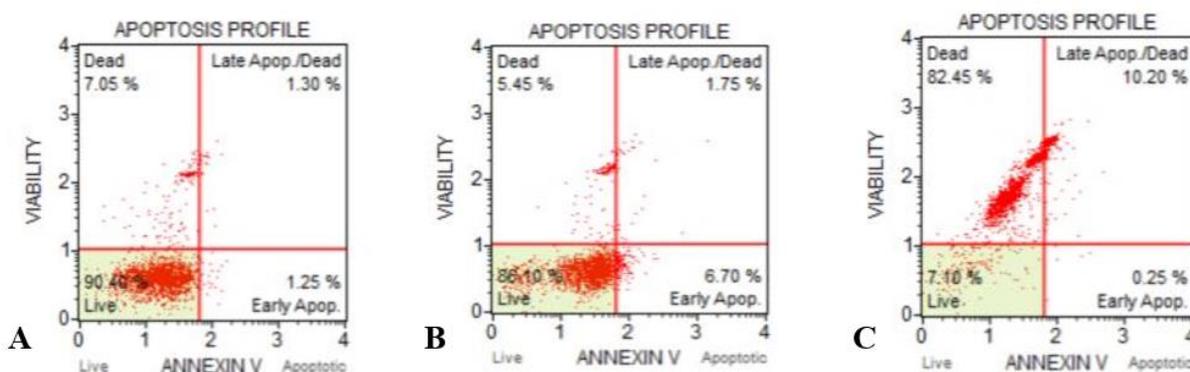
extract for 24 hours were displaying a circular cell shape, chromatin condensation, nuclear membrane disintegration, holes on the cytoskeleton, swelling in the endoplasmic reticulum tubes, loss of mitochondrial cristae and swelling of mitochondria and ondulation in nuclear membrane (Figures 7A, B, C and D); IC<sub>50</sub> value of *I. taochia* below ground parts ethanolic extract in the same incubation time displayed in addition to the circular cell shape and chromatin condensation, fragmentation of nucleus, blebbings on cell membrane, disintegration of nuclear membrane and loss of mitochondria were significantly determined at the micrographs (Figures 7E and F).



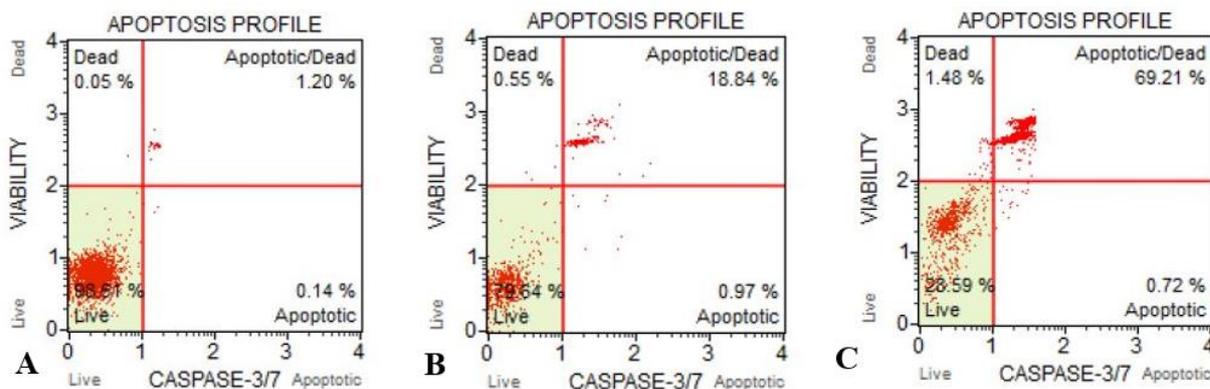
**Figure 3.** Viability percentages of A549 cells treated with ethanolic extract of *Iris taochia* below ground parts for 24 hours. \*\* P<0.01; \*\*\* P<0.05



**Figure 4.** Viability percentages of A549 cells treated with ethanolic extract of *Iris taochia* above ground parts for 24 hours. \*\* P<0.01; \*\*\* P<0.05



**Figure 5.** Percentages of apoptotic A549 cells treated with IC<sub>50</sub> values of *Iris taochia* extracts for 24 hours. A= Untreated A549 cells, B= IC<sub>50</sub> values of *Iris taochia* above ground parts, C= IC<sub>50</sub> values of *Iris taochia* below ground parts.



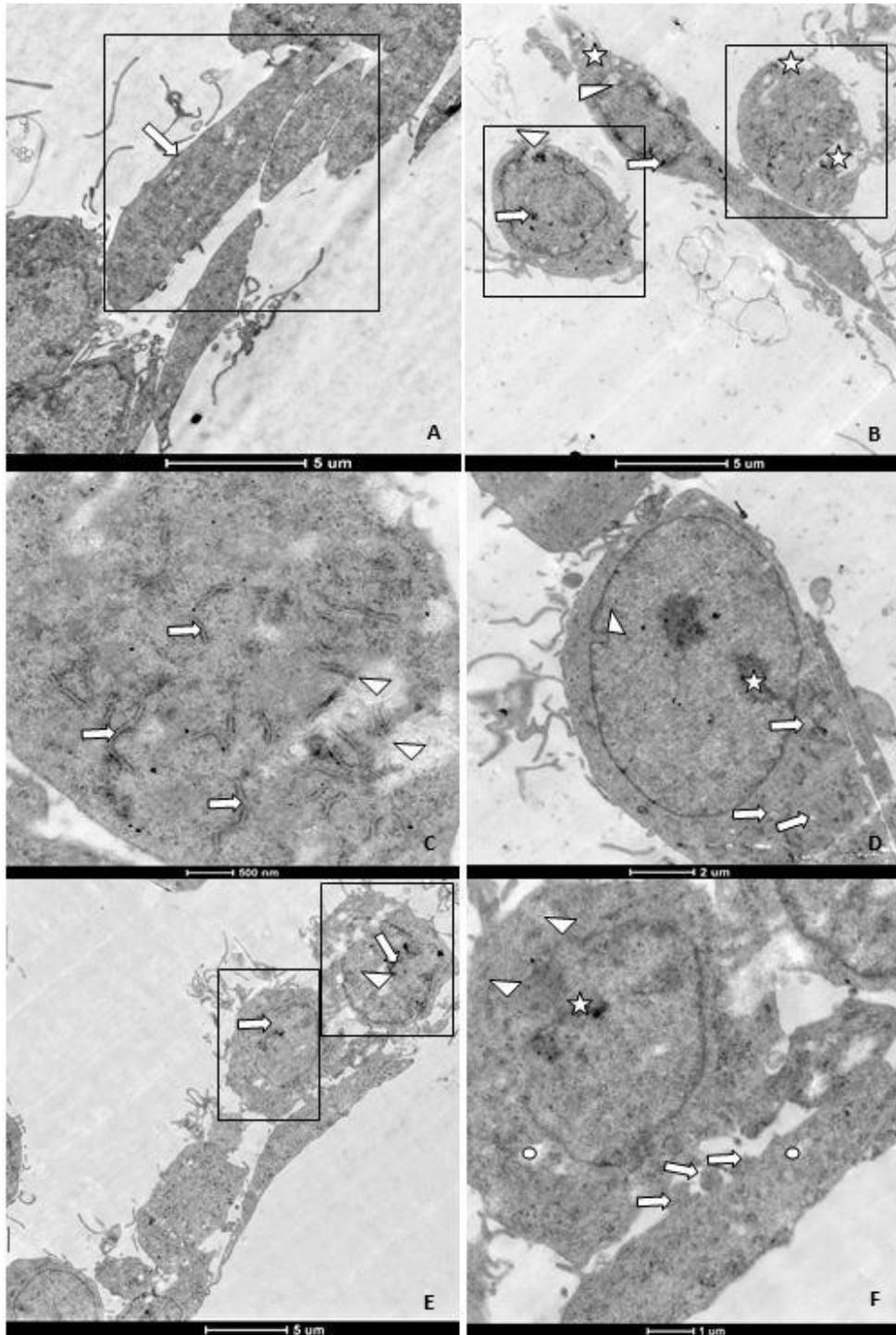
**Figure 6.** Apoptosis profiles of untreated A549 cells and A549 cells treated with IC<sub>50</sub> values of *Iris taochia* extracts for 24 hours. A= Untreated A549 cells, B= IC<sub>50</sub> values of *Iris taochia* above ground parts, C= IC<sub>50</sub> values of *Iris taochia* below ground parts.

#### 4. Discussion

Lung cancer has become one of the common diseases worldwide that in terms of the cause of death of the patients (Duan and Zhang, 2006). Chemotherapy is an effective approach to cancer therapy including lung cancer, but it is limited since the developing resistance towards current chemotherapeutics like vinblastine and paclitaxel has been reported frequently (Spitz et al., 2009; Hsieh et al., 2010; Obradovic et al., 2013). This fact indicates a need for novel chemotherapy agents that are effective in low concentrations and short time application. Recently, plant-derived drugs have been made and become a good alternative in cancer therapy (Balunas and Kinghorn, 2005). Consequently, this research is focused on the investigation of anticancer activity of *I. taochia*, which belongs to the largest genus in the Iridaceae family, extracts on the A549, human lung adenocarcinoma cell line.

Our MTT assay findings (Figures 3 and 4) showed that ethanolic extract of *I. taochia* below ground parts remarkably decreased the viability of the A549 cells in concentration-dependent manner in short term application of 24 hours. The determined IC<sub>50</sub> value of the extract was to be 20 µg/ml. Viability percentages

determined from the A549 cells treated with ethanolic extract of *I. taochia* above ground parts (Figure 3) significantly decreased with the increase of the concentration of the applied extract in the same incubation period. The IC<sub>50</sub> value for this extract was detected to be 7 µg/ml. These values can be interpreted as effective in the inhibition of the proliferation of A549 cells at low doses and in short-time application, both for the extracts from above and below and ground parts of *I. taochia*. Similarly, in a research the anticancer activity of an Iridaceae family member *Romulea tempskyana* extract on hepatoma G2 and H1299 cell lines is showed. In 24 hours of application of IC<sub>50</sub> value of the extract for G2 cells was reported as 94.79 µg/ml, whereas; it was 76.15 µg/ml for H1299 cells in the same time of incubation (Ozkan and Erdogan, 2012). Additionally, growth of 25.2% of the treated large lung carcinoma cells was reported to be inhibited in 48 hours' application of *Iris pseudopumila* Tineo extracts obtained from the flowers of the species at the highest concentration, 100 µg/ml.



**Figure 7.** Ultrastructure of the untreated A549 cells. A (6000 $\times$ )=  $\square$  fusiform cell shape,  $\Rightarrow$  compact cell membrane. A549 cells treated with the IC<sub>50</sub> value of *Iris taochia* above ground parts ethanolic extract for 24 hours, B (6000 $\times$ )=  $\square$  circular cell shape,  $\Rightarrow$  chromatin condensation,  $\nabla$  nuclear membrane disintegration,  $\star$  holes on the cytoskeleton, C (11,500 $\times$ )= swelling in the endoplasmic reticulum tubes,  $\nabla$  loss of mitochondrial cristae and swelling of mitochondria, D (8200 $\times$ )= chromatin condensation,  $\Rightarrow$  loss of mitochondrial integrity,  $\nabla$  ondulation in nuclear membrane. A549 cells exposed to IC<sub>50</sub> concentration of *Iris taochia* below ground parts ethanolic extract for 24 hours, E (6000 $\times$ )=  $\square$  circular cell shape,  $\Rightarrow$  chromatin condensation,  $\nabla$  fragmentation of nucleus, F (8200 $\times$ )=  $\Rightarrow$  blebblings on cell membrane,  $\star$  chromatin condensation,  $\nabla$  disintegration of nuclear membrane,  $\circ$  loss of mitochondria.

The percentage of inhibited cells at *I. pseudopumila* extract obtained from the rhizomes of the species was detected to be 31.5 (Conforti et al., 2009). Our results were found to be very low when compared to the above

mentioned findings. This might be attributed to the difference of the used plant species, consequently, the content of the extracts as well as the type of the exposed cell lines. In previous pharmacological studies it was

reported that pharmacological activity of *Iris* species is mainly attributed to their flavonoids ingredients (Fang et al., 2008). Consequently, this might be occurred in the antiproliferative action of the *I. taochia* extracts in our study but this fact needs to be further investigated to be confirmed. Additionally, since the active ingredients of many drugs used in cancer treatment today are obtained from medicinal plants, anticancer activities of medicinal plants should be screened for further use (Bozyel et al., 2019). On the other hand, when the anticancer properties of medicinal plants were examined, it was determined that the active substances in medicinal plants were effective on different types of cancer such as prostate, colon, stomach breast and leukemia (Padmaharish and Lakshmi, 2017).

Apoptosis is one of the main regulatory pathways in proliferation and death of cells. This programmed cell death occurs as a response to initiating intracellular and/or extracellular signals. Characteristic physiological changes of apoptosis were well described of which externalization of phosphatidylserine to the cell surface can be showed by annexin-V that is a calcium-dependent phospholipid-binding protein that binds the externalized phosphatidylserine during apoptosis. Also it may refer to the membrane disintegration in early apoptotic cells (Kerr et al., 1972; Wyllie et al., 1980; Wyllie, 1993; Majno and Joris, 1995; Rudin and Thompson, 1997). The induction of apoptosis in cancer cells has been a common investigation issue, recently (Ghobrial et al., 2005). As it is shown in our annexin V staining results, in A549 cells treated with IC<sub>50</sub> value of ethanolic extract of *I. taochia* above ground parts for 24 hours (Figure 5B); the percentage of live total apoptotic cells (8.45%) was low when compared to that of ethanolic extract of *I. taochia* below ground parts (10.45%) (Figure 5C). Extract of these species below ground parts can be considered as more effective in activation of apoptotic cell death but the difference between the action of extracts is very slight. Yazgan et al. (2022) examined how *I. taochia* extracts affect apoptotic activity on MCF7 cells and research results showed that MeOH extract of *Iris taochia* on MCF7 cells could be a regulator of cell death proteins, growth factors and cell repair mechanisms.

Proapoptotic signals trigger apoptotic cell death by activating specific cysteine proteases so called caspases. Some of these enzymes are initiators of intracellular event cascade and the others act further to direct cellular breakdown through cleavage of structural proteins. The latter group of caspases are caspase-3 and caspase-7 (Riedl and Shi, 2004; Benetti and Roizman, 2007). Activation of these caspases is a hallmark of apoptosis. In this study, activation of these caspases are measured in untreated A549 cells and cells treated with the *I. taochia* extracts. In untreated A549 cells (Figure 6A) percentages of live cells were detected to be 98.61%. That means caspases are not activated. In A549 cells treated with IC<sub>50</sub> concentration of *I. taochia* above ground parts extract for 24 hours (Figure 6B) the percentage of total apoptotic

cells was 19.81%. In the A549 cells treated with IC<sub>50</sub> concentration of below ground parts extract of the plant (Figure 4C) 69.93% were apoptotic. Activation of caspases 3/7 was determined more than that of above ground parts extract applied cells. This may be as a result of the differences in the ingredients of the extracts.

Physiological changes that occur during apoptotic cell death can be used in evaluating the type of cell death. Many of these changes can be showed by transmission electron microscopic evaluation that is taken as 'gold standard' in determined the ultrastructural changes of cells. Cleavage and degradation of specific cellular proteins, fragmentation of nuclear chromatin, and loss of membrane integrity as well as the integrity of organelles mainly mitochondria can be observed (Kerr et al., 1972). In a research by Özkan and Erdoğan (2013), the effects of the natural agents' eugenol, eucalyptol, terpinen-4-ol, and camphor on cell membrane and DNA damage were investigated in human lung cancer cell lines and they were reported to damage cell membrane and the DNA. Similarly, in our study the natural ethanolic extracts of *I. taochia* ground parts and above parts were investigated to understand their effect on the A549 cell ultrastructure in respect of finding the type of cell death. Ultrastructural changes determined on the A549 cell treated with the IC<sub>50</sub> concentration of *I. taochia* above ground parts extract for 24 hours were found to be circular cell shape, chromatin condensation, nuclear membrane disintegration, holes on the cytoskeleton, swelling in the endoplasmic reticulum tubes, loss of mitochondrial cristae and swelling of mitochondria and on dilation in nuclear membrane (Figures 7B, C and D). All TEM findings can be considered as significant signs of apoptosis. Especially loss of mitochondrial cristae and nuclear membrane disintegration indicate apoptotic cell death that further mechanism needs to be cleared with additional experiments. Comparatively, in A549 cells exposed to IC<sub>50</sub> value of *I. taochia* below ground parts extract for the same incubation time in addition to the circular cell shape and chromatin condensation, fragmentation of nucleus, blebblings on cell membrane, disintegration of nuclear membrane and loss of mitochondria were significantly determined at the micrographs (Figure. 7E and F). Blebbing of the cell membrane and fragmentation of the nuclei are direct indicators of programmed cell death. This might be resulted from the higher IC<sub>50</sub> concentration determined than that of above ground parts extract for 24 hours. This finding is supported with our annexin V findings.

Taken all together, our results suggest that *I. taochia* ethanolic extracts both that from the above ground parts and below ground parts of the plant exhibit their cytotoxicity as well as anticancer and apoptosis triggering activity at lower concentrations on the investigated human lung adenocarcinoma cells. These findings might be encouraging for sequential investigations in this field. Further research is required to unravel the deeper molecular mechanisms of action of

the above investigated extracts including with identification of the active compounds and their separate molecular targets for their effective usage in drug development processes for cancer therapy.

## 5. Conclusion

In conclusion, our experimental results can be considered as *I. taochia* ethanolic extracts are both obtained from the above and below ground parts of the plant showed growth-inhibiting, cytotoxic and apoptotic effects in the A549 human lung adenocarcinoma cell line.

## Author Contributions

Concept: C.V.S. (%50) and H.M.K. (%50), Design: C.V.S. (%50) and H.M.K. (%50), Supervision: C.V.S. (%50) and H.M.K. (%50), Data collection and/or processing: E.Ç. (%50) and U.Ç. (50%), Data analysis and/or interpretation: C.V.S. (%50) and H.M.K. (%50), Literature search: C.V.S. (%25), H.M.K. (%25), N.K. (%25) and Ö.İ. (%25), Writing: C.V.S. (%25), H.M.K. (%25), N.K. (%25) and Ö.İ. (%25), Critical review: N.K. (%100), Submission and revision C.V.S. (%50) and H.M.K. (%50). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest.

## Ethical Approval/Informed Consent

Ethics committee approval was not required for this study because of there is no animal or human study. In this research, since artificial cell cultures were used, no ethical statement was needed.

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## GLOBAL TRENDS IN HEMOPHILIA RESEARCH

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**Abstract:** The hemophilias are the most common X-linked inherited bleeding disorders, and if not managed properly, they can lead to chronic disease and lifelong disabilities. The hemophilias remains a hot topic in the field of hematology. This bibliometric study aimed to investigate the current status of publications on haemophilia. The goal of this study was to retrieve data from journals that were indexed in the Web of Science (WoS; Thomson Reuters, New York, NY, USA) database. Keywords related to "Hemophilia" were used. The time span was set from 1970 to 2021. Data pertaining to growth of publications, the most active countries and institutions, the most cited journals, and mapping of publications and keywords were analyzed. Retrieved data were analyzed to present various bibliometric indicators while maps were visualized using the VOS viewer technique. The Hirsch (H) index and the impact factor (IF) of the publishing journal were used as indicators of impact of publications. A total of 7.736 articles were retrieved with an average of 22.06 and total of 170.624 citations. H index was found as 149. Study searches the publications in the period between 1970 and 2020 first article was in the year 1970. The leading country on journal number is the United States of America (USA) with (n=2474; 31.98%), followed by England (11.69%), Germany (9.76%), Italy (8.59%), Canada (6.81%), France (6.67%). Most of the retrieved articles were from research areas of Hematology (n=4706; 60.83%), Cardiovascular System/Cardiology (11.46%), General Internal Medicine (10.12%), Pediatrics (4.52%), Genetics Heredity (n4.25%). The number of publications from the development countries should be increased and research on hemophilia should be supported. The landscape of this illness is changing continuously, and bibliometric studies like the one presented are a useful tool for highlighting developments inside this field.

**Keywords:** Bibliometric analysis, Citation analysis, Hemophilia

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### 1. Introduction

Plasma deficits of coagulation proteins are of enormous concern to the hematologist, entailing a lifelong bleeding tendency with significant morbidity and death if not effectively treated, among the more than 6000 human disorders caused by single gene defects (Jackson, et al., 2018). According to the standards used in the United States (less than 200000 instances countrywide) and Europe, inherited coagulation deficits are rare disorders (less than 5 cases per 10,000 persons in the general population) (Khosla et al., 2018).

Haemophilia A and B are X-linked congenital illnesses caused by a loss or shortage of clotting factor VIII (FVIII) or IX (FIX). The severity of the condition is dictated by the amount of FVIII or FIX that is reduced, which is determined by the sort of causal mutation in the genes that encode the factors (F8 and F9, respectively). Bleeding (spontaneous or after trauma) into major joints such as ankles, knees, and elbows is a defining clinical feature, especially in untreated severe forms, and can lead to the development of arthropathy. Intracranial hemorrhage, as well as bleeds into internal organs, can be fatal (Berntorp et al., 2021). According to a recent report on the global distribution of hemophilias, the

disease is more common than previously thought: 17.1 cases per 100,000 males with HA for all degrees of FVIII deficit, 3.8 cases per 100000 of HB, and a prevalence of 6 cases per 100000 for HA and 1.1 cases per 100000 for HB of individuals with total plasma factor insufficiency, indicating a more severe clinical phenotype (Iorio et al, 2019).

Hemophilia treatment became a success story in the 1970s, when plasma-derived concentrates of coagulation factor VIII (FVIII) and factor IX (FIX) became available for the treatment of bleeding in patients with hemophilia A and B. When the first recombinant coagulation factors were developed in the 1990s, this optimistic scenario was solidified in terms of increased safety and availability. This meant that prophylactic regimens might be used to avoid bleeding instead of only treating it when it happened. Prophylaxis became the evidence-based standard of care after its superiority was demonstrated in two randomized clinical trials. These advancements have resulted in a patient's life expectancy approaching that of the general male population in high-income countries (Mannucci, 2020).

This bibliometric study aimed to investigate the current status of publications on hemophilia.



## 2. Material and Methods

The goal of this study was to retrieve data from journals that were indexed in the Web of Science (WoS; Thomson Reuters, New York, NY, USA) database. The WOS Core Collection was used to retrieve comprehensive bibliometric data and the SCI-EXPANDED, SSCI, A & HCl, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI indexes database, which has previously been regarded the optimal database for bibliometrics (Alkan et al., 2021; Öntürk et al., 2021; Özlü, 2022).

Keywords related to “Hemophilia” were used in a search query in the WOS search engine. For more accurate results “United Kingdom English and United States English words used. The time span was set from 1970 to 2021. Data pertaining to growth of publications, the most active countries and institutions, the most cited journals, and mapping of publications and keywords were analyzed.

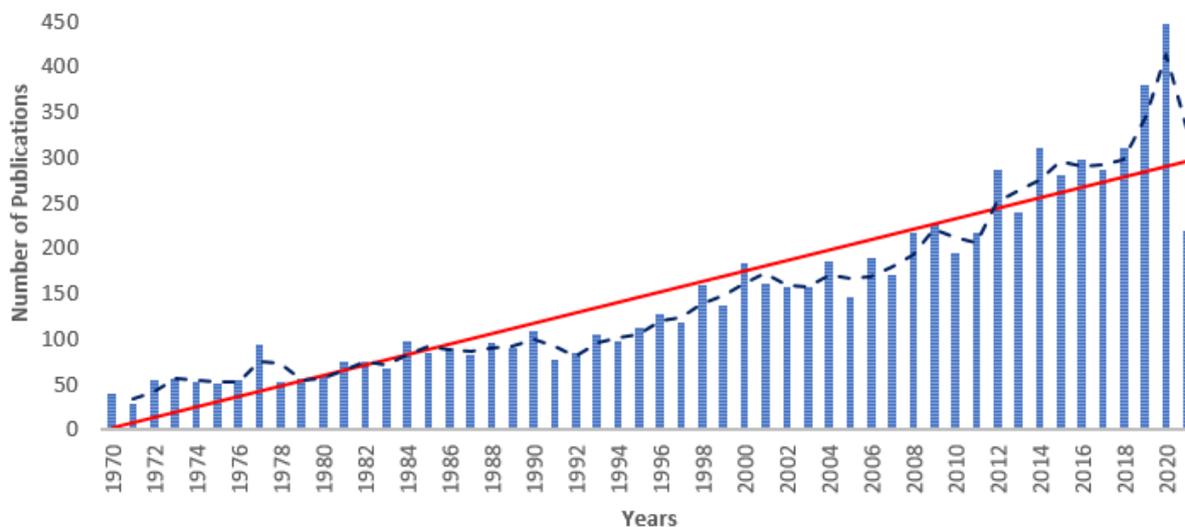
This study was carried out to retrieve data about the journals with dataset as in the title “dataset: TI=(hemophilia)” in the WOS search engine searched

between 1970 and 2021. In this study, the selected keywords to be used in the WOS search engine were those related to the “hemophilia”. We used the search query and got 20645 different type of results and analyzed according to documents types and year they published. After we deducted from 20645 entries to only the journal articles 7736. Retrieved data were analyzed to present various bibliometric indicators while maps were visualized using the VOS viewer technique. The Hirsch (H) index and the impact factor (IF) of the publishing journal were used as indicators of impact of publications.

## 3. Results

### 3.1. General Information

A total of 20645 publications were retrieved, and 37.472% of them articles. Search the publications in the period between 1970 and 2020 first article was in the year 1970. Distribution of publication showed in Figure 1.



**Figure 1.** Graphics of publication frequency by years between 1970 and 2021. Black dashed line express the moving median. Red line express the trend line.

### 3.2. Detailed Information

#### 3.2.1. Detailed analysis of the articles

A total of 7736 articles were retrieved with an average of 22.06 and total of 170624 citations. H index was found as 149. Study searches the publications in the period between 1970 and 2020 first article was in the year 1970. 39 Article was published in 1970 (Figure 2).

Most of the retrieved articles were from research areas of Hematology (n=4706; 60.83%), followed by Cardiovascular System/Cardiology (n=887; 11.46%), General Internal Medicine (n=783; 10.12%), Pediatrics (n=350; 4.52%), Genetics Heredity (n=329; 4.25%) and the rest was various areas (Table 1).

#### 3.2.2. Active countries and organizations

The leading country on journal number is the United States of America (USA) with (n=2474; 31.98%), followed by England (n=905; 11.69%), Germany (n=755;

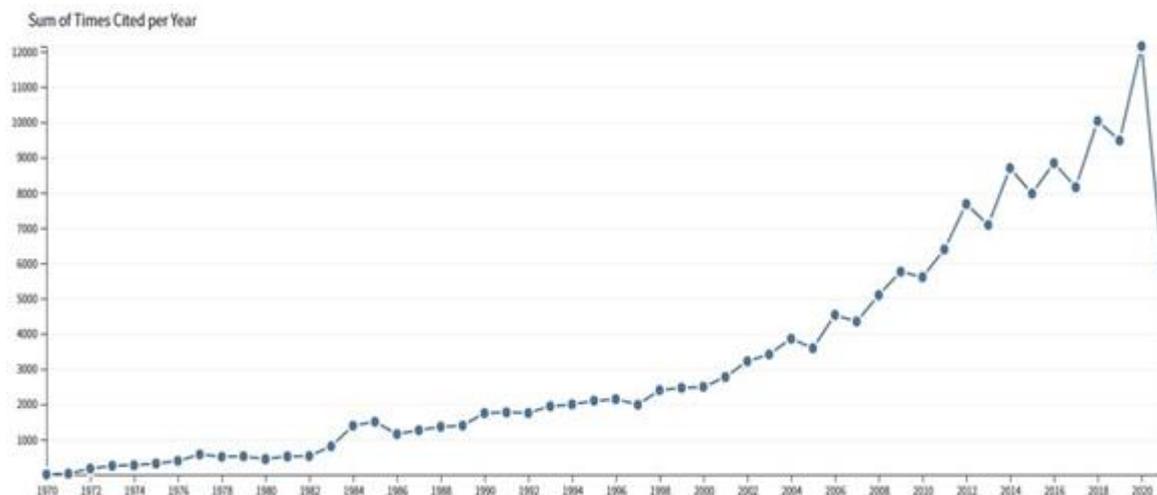
9.76%), Italy (n=665; 8.59%), Canada (n=527; 6.81%), France (n=516; 6.67%). Other 113 countries which around the globe were (n=5385; 69.61%) (Table 2).

The University of London was the leader organisation on hemophilia research (Table 3).

#### 3.2.3. Citing analysis and international collaborations

The list of active countries includes countries from all over the world, including North and South America, Europe, Asia, and Africa.

Papers co-authored by authors from multiple countries were designated as "international collaborations." The map depicts the international collaborative network (Figure 3) Using the VOSviewer approach, an investigation of international cooperation for active nations with at least one document revealed that there were clusters of international collaboration (Figure 3).



**Figure 2.** Graphics of citation by years between 1996 and 2021. Line express the cite number.

**Table 1.** The top 10 research areas of the articles

Research Areas	Frequency	% of 7736
Hematology	4706	60.832
Cardiovascular System/ Cardiology	887	11.466
General Internal Medicine	783	10.122
Pediatrics	350	4.524
Genetics Heredity	329	4.253
Research Experimental Medicine	301	3.891
Surgery	199	2.572
Health Care Sciences Services	166	2.146
Immunology	150	1.939
Oncology	141	1.823

**Table 2.** The ranked countries on hemophilia research

SCR	Country	Frequency	Percentage of total publications (n=7736)
1 <sup>st</sup>	USA	2474	31.98
2 <sup>nd</sup>	England	905	11.699
3 <sup>rd</sup>	Germany	755	9.76
4 <sup>th</sup>	Italy	665	8.596
5 <sup>th</sup>	Canada	527	6.812
6 <sup>th</sup>	France	516	6.67
7 <sup>th</sup>	Netherlands	483	6.244
8 <sup>th</sup>	Japan	400	5.171
9 <sup>th</sup>	Sweden	392	5.067
10 <sup>th</sup>	Spain	319	4.124

SCR= Standard Competition Ranking. Equal countries were given the same ranking number.

The total number of citations for the articles that were found was 170.624, with an average of 22.06 citations per article. The Hirsch index of the articles that were found was 149. The number of citations increased with time, and annual citation growth of "haemophilia" and "hemophilia" was modest until 2012, then increased in the last decade. The annual increase of the terms "haemophilia" and "hemophilia" is depicted in the graph. The year with the most citations was 2020, with a total of 12154 citations (Figure 2). The United States of America was the most frequently mentioned country (Table 4 and Figure 4).

### 3.2.4. Journals

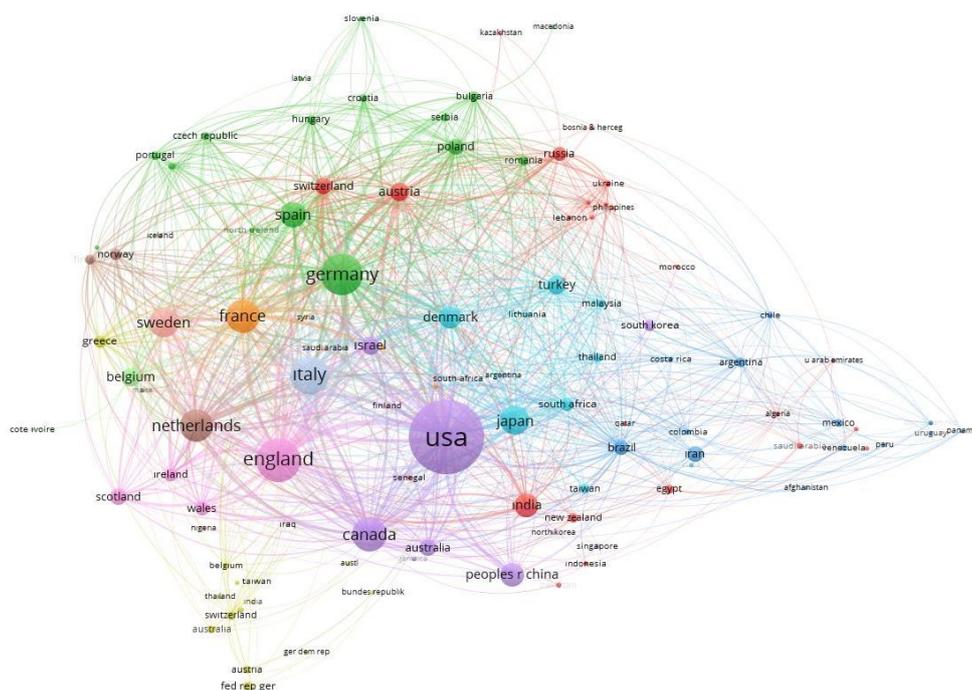
The articles from the journal of New England Journal of Medicine were cited mostly. The detailed information on top 20 of the most cited articles and journals were given in Table 5.

## 4. Discussion and Conclusion

The hemophilias are the most common X-linked inherited bleeding disorders, and if not managed properly, they can lead to chronic disease and lifelong disabilities. Children encounter challenges and issues that are distinct from those faced by older children and adults.

**Table 3.** The top ranked organizations on hemophilia research

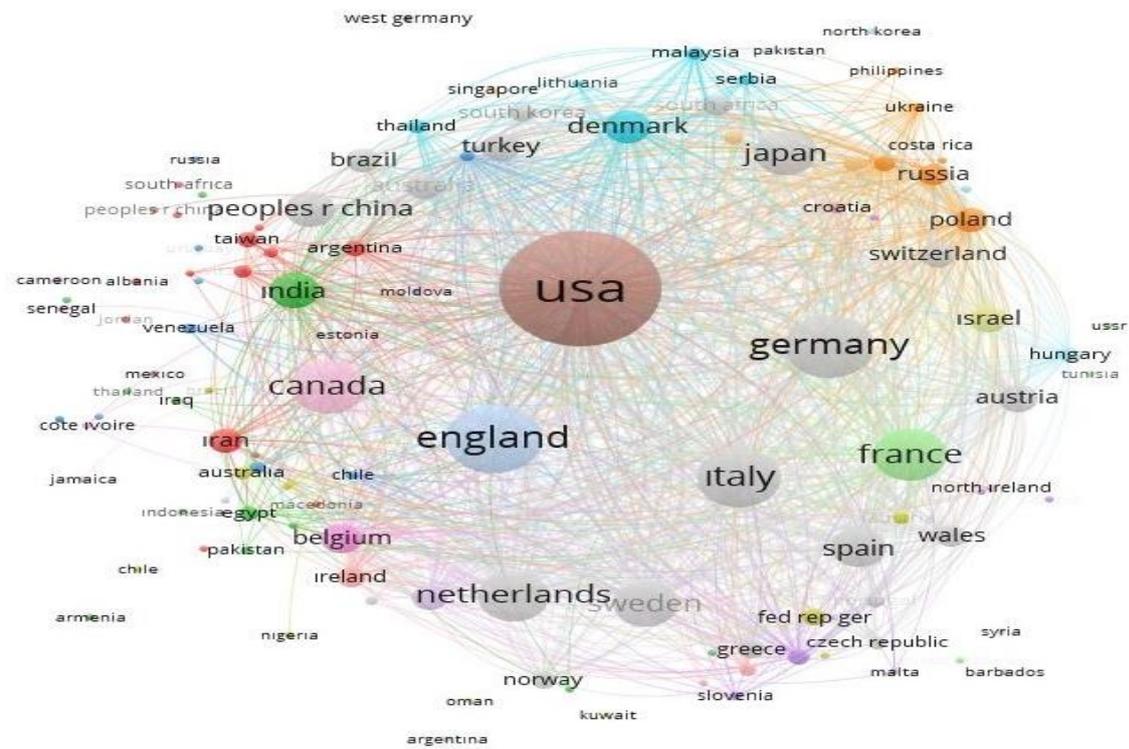
Organizations-Enhanced	Frequency	% of 7737
University of London	382	4.937
University College London	293	3.787
Lund University	275	3.554
Utrecht University	263	3.399
Irccs Ca Granda Ospedale Maggiore Policlinico	246	Mar.18
University of North Carolina	242	3.128
University of North Carolina Chapel Hill	232	2.999
Utrecht University Medical Center	227	2.934
University of Bonn	216	2.792
Skane University Hospital	207	2.675
University of Pennsylvania	200	2.585
Assistance Publique Hopitaux Paris	196	2.533
Novo Nordisk	191	2.469
Mcmaster University	178	2.301
University of Toronto	178	2.301
University of Milan	177	2.288
University of California System	166	2.146



**Figure 3.** Co-authorship network visualization map across nations with at least one publication on "hemophilia" and "haemophilia." Collaboration is indicated with lines connecting countries. Stronger cooperation are indicated by thicker lines. Countries with a larger circle or text size had a higher level of international collaboration.

**Table 4.** Top 10 countries according to citations

Country	Number of documents	Number of citations
USA	2358	80390
England	832	30263
Germany	732	19879
Italy	644	18828
Netherlands	464	17352
Sweden	373	14681
Canada	513	14557
France	480	14053
Spain	288	6913
Japan	363	6760



**Figure 4.** Countries having at least one publication on "haemophilia" are represented by a network visualization map of citations. Collaboration is indicated with lines connecting countries. Stronger cooperation are indicated by thicker lines. Countries with a larger circle or text size had a higher level of international collaboration.

**Table 5.** Top 20 of most cited articles and journals

Source Title	Article Title	Times Cited
Nature Medicine	Successful transduction of liver in hemophilia by AAV-factor IX and limitations imposed by the host immune response	1308
New England J Medicine	Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia	1238
New England J Medicine	Adenovirus-Associated Virus Vector-Mediated Gene Transfer in Hemophilia B	1111
Haemophilia	Guidelines for the management of hemophilia	1076
New England J Medicine	An Improved Method For Prenatal-Diagnosis Of Genetic-Diseases By Analysis Of Amplified Dna-Sequences - Application To Hemophilia-A	781
Nature Genetics	Evidence for gene transfer and expression of factor IX in haemophilia B patients treated with an AAV vector	777
J Clinical Investigation	Immunologic Differentiation Of Classic Hemophilia (Factor-Viii Deficiency) And Von-Willebrands Disease - With Observations On Combined Deficiencies Of Antihemophilic Factor And Proaccelerin (Factor V) And On An Acquired Circulating Anticoagulant Against Antihemophilic Factor	765
J Internal Medicine	25 years experience of prophylactic treatment in severe hemophilia-a and hemophilia-b	741
New England J Medicine	Long-Term Safety And Efficacy Of Factor Ix Gene Therapy In Hemophilia B	669
Nature Genetics	Inversions Disrupting The Factor-Viii Gene Are A Common-Cause Of Severe Hemophilia-A	648
Nature	Hemophilia-a resulting from denovo insertion of I1 sequences represents a novel mechanism for mutation in man	642
New England J Medicine	A Prospective-Study Of Human Immunodeficiency Virus Type-1 Infection And The Development Of Aids In Subjects With Hemophilia	547
Blood	AAV-mediated factor IX gene transfer to skeletal muscle in patients with severe hemophilia B	526
Lancet	1-deamino-8-d-arginine vasopressin - new pharmacological approach to management of hemophilia and von-willebrands disease	516
Haemophilia	The epidemiology of inhibitors in haemophilia A: a systematic review	475
Nature Medicine	Long-term correction of canine hemophilia B by gene transfer of blood coagulation factor IX mediated by adeno-associated viral vector	439
New England J Medicine	Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy	434
New England J Medicine	Recombinant Factor-Viii For The Treatment Of Previously Untreated Patients With Hemophilia-A - Safety, Efficacy, And Development Of Inhibitors	418
New England J Medicine	Emicizumab Prophylaxis in Hemophilia A with Inhibitors	395
Blood	Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation	384

Bleeding episodes are still the most prevalent diagnostic trigger in children, but bleeding sites vary by age. Intracranial hemorrhage (ICH), circumcision, and venipuncture bleeding are prevalent in newborns, whereas joint disease and head trauma are common in older children and adolescents. In order to institute effective care and adopt preventative efforts, it is critical to be aware of clinical symptoms and therapeutic problems. The most difficult consequences are now inhibitors and ICH, and prophylaxis is emerging as the best preventive management technique (Kulkarni and Soucie, 2011). Until the 1960s, the median life expectancy was 30 years, but improved understanding of the disorder and the development of effective therapy based on prophylactic replacement of the missing factor resulted in a paradigm shift, and today, people with haemophilia can expect a nearly normal life expectancy and quality of life. Nonetheless, in a significant proportion of patients, the formation of inhibitory antibodies to infused factor remains a significant challenge to overcome. Finally, gene therapy for both types of haemophilia has made significant progress and is on the verge of becoming a reality (Berntorp et al., 2021). This study sought to give a bibliometric perspective of literature on haemophilia between the years 1970 - 2021. To accomplish this, we used the well-known WOS database, which has been used in previously published bibliometric studies (Alkan et al., 2021; Alkan-Çeviker et al., 2021; Köse et al., 2021; Öntürk et al., 2021; Mızrakçı, 2022; Özlü, 2022; Yıldız, 2022).

In the area of hematology, similar bibliometric studies were also conducted (Latif et al., 2018; Okoroiwu et al., 2020; Seo et al., 2020; Chen et al., 2021). However, there was no relevant study on haemophilia in the literature available.

Bibliometric analysis has recently been used to identify field frontiers and evaluate the achievements of publications, organisations, and nations. In the bibliometric analysis method, internet databases are frequently utilised. It can also provide details on research clusters, current topics of interest, and emerging topic trends. Visualization techniques can be used to analyse and map a variety of databases (Dindar Demiray et al., 2021; Gürler et al., 2021; Köylüoğlu et al., 2021; Küçük et al., 2021; Mızrakçı et al., 2021; Özlü, 2021; Akyüz et al., 2022; Durgun et al., 2022). In this study both visualization techniques and data analyses were done.

Although this disease has been known since since the 1800s, as the main developments in medicine are in recent years, publications after 1970s were analyzed in this study. Our study showed that publications "haemophilia" have been increasing and growing rapidly in the past decade and in the past ten years, over two-thirds of all documents have been published.

Although the University of London was the leader organisation on hemophilia research, the USA was the most cited and most productive country on hemophila research. This may be due to the excess of institutions

and economic support in the USA. In addition, there were no development countries in the list of top 10 ranked countries.

An article's overall impact to the clinical world is measured by the number of citations it receives (Chen et al., 2021; Latif, et al., 2018). This study showed that the articles on haemophilia had increasing number of citations. This shows that this topic is an important research area.

In conclusion, the number of publications from the development countries should be increased and research on hemophilia should be supported. The landscape of this illness is changing continuously, and bibliometric studies like the one presented are a useful tool for highlighting developments inside this field.

### Limitations

This bibliometric analysis has a lot of disadvantages. PubMed, Embase, Scopus, and the Cochrane Library are among the electronic databases that are not searched or evaluated. Articles written in languages other than English were also excluded. Despite the fact that the majority of the research in this study are written in English, this limitation may lead to a publishing bias. Finally, because several potentially influential articles were published recently and could not be mentioned frequently, influential publications were not referred to frequently enough.

### Author Contributions

Concept: C.Ö. (50%) and G.C. (50%), Design: C.Ö. (50%) and G.C. (50%), Supervision: C.Ö. (50%) and G.C. (50%), Data collection and/or processing: C.Ö. (50%) and G.C. (50%), Data analysis and/or interpretation: C.Ö. (50%) and G.C. (50%), Literature search: C.Ö. (50%) and G.C. (50%), Writing: C.Ö. (50%) and G.C. (50%), Critical review: C.Ö. (50%) and G.C. (50%), Submission and revision C.Ö. (50%) and G.C. (50%). All authors reviewed and approved final version of the manuscript.

### Conflict of Interest

The authors declared that there is no conflict of interest.

### Ethical Approval/Informed Consent

The study complied with the Helsinki Declaration, which was revised in 2013. Ethics committee approval is not required as there is no human or animal research.

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## TIME-DEPENDENT RECEIVER OPERATING CHARACTERISTIC ANALYSIS AND APPLICATIONS IN THE FIELD OF MEDICINE

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**Abstract:** When there is a time-dependency between the biomarker and the event of interest (death, disease, relapse etc.), classical receiver operating characteristic (ROC) analysis may not be able to estimate the true performance of the biomarker. For such cases, time-dependent ROC, an extended version of the standard ROC, is developed. In this study, the aim is to demonstrate applications of this modified ROC method on medical datasets and find out if it should be preferred over classical ROC for time-dependent situations. Comparison between classical ROC and Kaplan-Meier (KM) estimator, which is one of the two time-dependent ROC estimators, has been made using datasets in this study. Nearest Neighbor Estimator (NNE), the alternative of KM estimator, is also applied on all datasets. Then the findings of these two approaches are compared. It is concluded that time-dependent ROC method is superior to the standard ROC analysis. In general, the closer to the event time, the higher performance is observed. Especially, biomarkers measured at last 12 or 6 months before the event are determined to be better at classification than the earlier measurements. Though in all applications KM and NNE yielded very similar results, the latter is considered to be more appropriate to evaluate the performance of a biomarker when a time dependent data is also censored. Results of this study show that time-dependent ROC analysis performs more accurately when there is a time dependency between the biomarker and the event of interest; therefore, it is recommended.

**Keywords:** Time-dependent ROC, Diagnostic tests, Biomarker, Kaplan-Meier, Nearest neighbor estimator

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### 1. Introduction

Purpose of a diagnostic test is to detect and sometimes predict a certain disease. For example, biomarkers such as PSA or CA-125 concentration in blood serum provides diagnosis for cancer before its clinical onset. Time between the diagnosis and the clinical onset of the disease is called "lead time". The earlier the diagnosis, the better are the chances for the patient (Pepe, 1997).

Receiver operating characteristic (ROC) analysis is a graphical approach for comparison of two empirical distributions (Ünal, 2018). It is also commonly used for evaluating the accuracy of a continuous diagnostic test or a biomarker (Ünal, 2010). Standard ROC analysis considers only the present status of the individual (healthy or diseased). However, the simple two-class status might not always be the case. In some prospective cohort studies, status of the individual may shift from one class to another during follow-up. Or disease may not occur at the same time as the biomarker measurement (Zheng et al., 2006). Such characteristics of dataset indicate a time-dependency between the biomarker and the event of interest. At this point, a potential problem arises since the classical ROC approach might be insufficient for time-dependent cases.

Addressing the need for an analysis method for

forementioned conditions, Etzioni et al. (1999) proposed time-dependent ROC analysis. Based on their paper, other researchers continued working on this area. Especially in recent years, popularity of time-dependent ROC has increased. In order not to leave out this time-dependent nature of the disease onset, "time-dependent" sensitivity, specificity and ROC curve concepts are put forward and have taken place in several studies (Zheng and Heagerty, 2004; Antolini et al., 2005; Heagerty and Zheng, 2005; Zheng and Heagerty, 2007).

Time-dependent ROC analysis is suitable for both longitudinal and survival data. In this paper, the main focus is to demonstrate applications of this modified ROC method on survival data while providing a brief information about its theory, and find out if it should be preferred over classical ROC for time-dependent situations.

### 2. Materials and Methods

Event of interest in survival data is usually death or recurrence of a disease. Leisenring et al. (1997) and Balasubramanian and Lagakos (2001) defined time-dependent sensitivity using the "incident cases and long-term controls" approach for selection of cases and controls in survival data. Test result is measured at a



baseline ( $t = 0$ ) and test's capacity of predicting the event happening on a time  $t$  in the future is investigated. In other words, the question is how well the test predicts people that *will* have the disease in a certain  $[0, t]$  follow-up interval.

There are two time-dependent ROC curve estimators in the literature: Kaplan-Meier (KM) estimator and Nearest-Neighbor estimator (NNE). A brief information on the theory of these two methods is provided in the following section.

**2.1. Kaplan-Meier Estimator (KM)**

Sensitivity and specificity are expressed using Bayes' theorem as Equation 1:

$$P\{X > c | D(t) = 1\} = \frac{\{1 - S(t|X > c)\}P\{X > c\}}{\{1 - S(t)\}} \tag{1}$$

$$P\{X \leq c | D(t) = 0\} = \frac{S(t|X \leq c)P\{X \leq c\}}{S(t)}$$

where  $S(t) = P(T > t)$  is the survival function and  $S(t | X > c)$  is the conditional form of  $S(t)$ .

KM estimator is a commonly used nonparametric estimator of  $S(t)$ , proposed by Kaplan and Meier (1958) and expressed as given in Equation 2:

$$\hat{S}_{KM}(t) = \prod_{s \in T_n, s \leq t} \left\{ 1 - \frac{\sum_j 1(Z_j = s)\delta_j}{\sum_j 1(Z_j \geq s)} \right\} \tag{2}$$

where  $T_n$  be defined as unique values of  $Z_i$  when  $\delta_i = 1$  ( $\delta_i$  being the censoring indicator).

In order to estimate the survival function, KM estimator uses all the information in the data, including censored observations. A simple estimator for sensitivity and specificity at time  $t$  may be calculated as below (Equations 3 and 4), by combining empirical distribution function of biomarker  $X$  and KM estimator (where  $\hat{F}_X(c) = \sum 1(X_i \leq c)/n$ ):

$$\hat{P}_{KM}\{X > c | D(t) = 1\} = \frac{\{1 - \hat{S}_{KM}(t|X > c)\}\{1 - \hat{F}_X(c)\}}{\{1 - \hat{S}_{KM}(t)\}} \tag{3}$$

$$\hat{P}_{KM}\{X \leq c | D(t) = 0\} = \frac{\hat{S}_{KM}(t|X \leq c)\hat{F}_X(c)}{\hat{S}_{KM}(t)} \tag{4}$$

One complication of this estimator is that it does not assure the monotonicity of the TPR and FPR; and therefore the ROC curve. More specifically, although in definition  $P\{X > c | D(t) = 1\} \geq P\{X > c' | D(t) = 1\}$  when  $c' > c$ ; the monotonicity might be distorted by the nature of Bayes theorem and KM method. In addition, the conditional KM estimator  $\hat{S}_{KM}(t|X > c)$  assumes that the censoring process is independent of biomarker, which is another complication of the ROC estimation based on KM method (Heagerty et al., 2000).

**2.2. Nearest Neighbor Estimator (NNE)**

An ROC curve estimator is obtained using the binary distribution function  $F(c, t) = P(X \leq c, T \leq t)$  of Akritas (1994), or its equivalent  $S(c, t) = P(X > c, T > t)$  as cited in Heagerty et al (2000). This estimator depends on the expression  $S(c, t) = \int_c^\infty S(t|X = s)dF_X(s)$  and calculated as given in Equation 5:

$$\hat{S}_{\lambda_n}(c, t) = \frac{1}{n} \sum_i \hat{S}_{\lambda_n}(t|X = X_i)1(X_i > c) \tag{5}$$

where  $F_X(s)$  is the distribution function of  $X$  and  $\hat{S}_{\lambda_n}(t|X = X_i)$  is an estimator for the conditional survival function specified by a smoothing parameter  $\lambda_n$ .

When  $X$  is not a categorical variable and there is not sufficient number of observations contained in each  $X_i$ , smoothing becomes necessary for the estimation of  $\hat{S}_{\lambda_n}(t|X = X_i)$ . It is performed by the means of a kernel function  $K_{\lambda_n}(X_j, X_i)$  depending on  $\lambda_n$  and after weighting of the KM estimator,  $\hat{S}_{\lambda_n}(t|X = X_i)$  is attained as given in Equation 6:

$$\hat{S}_{\lambda_n}(t|X = X_i) = \prod_{s \in T_n, s \leq t} \left\{ 1 - \frac{\sum_j K_{\lambda_n}(X_j, X_i)1(Z_j = s)\delta_j}{\sum_j K_{\lambda_n}(X_j, X_i)1(Z_j \geq s)} \right\} \tag{6}$$

Akritas (1994) prefers  $K_{\lambda_n}(X_j, X_i) = 1\{-\lambda_n < \hat{F}_X(X_i) - \hat{F}_X(X_j) < \lambda_n\}$  as a kernel function, the nearest neighbor to point  $(0,1)$ . The percentage of observations contained in each neighborhood is represented by  $2\lambda_n \in (0,1)$ . Even if the selection of other kernels is not unorthodox, using the nearest neighbor would prevent the ROC estimations from the effect of monotone transformations on the biomarker.

Sensitivity and specificity calculated (Equation 7) with the NNE approach is as follows (where  $\hat{S}_{\lambda_n}(t) = \hat{S}_{\lambda_n}(-\infty, t)$ ):

$$\hat{P}_{\lambda_n}\{X > c | D(t) = 1\} = \frac{1 - \hat{F}_X(c) - \hat{S}_{\lambda_n}(c, t)}{1 - \hat{S}_{\lambda_n}(t)} \tag{7}$$

$$\hat{P}_{\lambda_n}\{X \leq c | D(t) = 0\} = 1 - \frac{\hat{S}_{\lambda_n}(c, t)}{\hat{S}_{\lambda_n}(t)}$$

As opposed to KM estimator, the equations above fulfill the condition that the ROC curve is monotone increasing. Additionally, that NNE allows a censoring process dependent on the biomarker  $X$  is another advantage of the method.

**2.3. Data and Software**

Two methods (KM, NNE) considering the time effect when evaluating the performance of diagnostic tests are examined in this study. Regarding results are compared to the ones obtained using classical ROC analysis which is independent of time. Additionally, a more specific comparison between KM and NNE methods is performed.

Datasets used in the applications are as follows and all contain a biomarker, a survival time and a censoring variable:

- Open datasets named “Melano” and “Paquid” from the “timeROC” package found in R program (Blanche et al., 2013).
- A part of Hodgkin Lymphoma data from a multicenter study conducted by Paydas et al. (2021) in Oncology Department in Cukurova University, Adana, Türkiye.

### 2.3.1. Melano dataset

This dataset contains information obtained from 205 malignant melanoma patients who had radical surgery in 1962-1977 in University of Odense, Denmark. Considering survival time after the operation, death is the event of interest and tumor thickness (1/100 mm) is the biomarker. All patients were followed until the end of 1977, and 134 survived while 71 died, 14 of which is not cancer related (which are excluded from the study). Applications are carried on the remaining 191 patients.

### 2.3.2. Paquid dataset

This dataset consists of the records belonging to 2561 patients participated in a prospective cohort study in southwestern France in 1988. There are two different time covariates as “time until the onset of Alzheimer’s” and “time until death before the onset of Alzheimer’s”. Since the event of interest in the applications is the onset of Alzheimer’s disease, those who died without it are removed from the data. Analyses are performed on the remaining 1927 participants, out of which 449 had the disease at the end. Time after registration until the onset of the disease is considered as the time covariate. Two test scores are credited as biomarkers: DSST (Digit Symbol Substitution Score Test) and MMSE (Mini Mental State Examination). Due to the fact that lower values of DSST and MMSE indicate disease existence, reciprocal values of the scores are used so as to obtain ROC curves in the upper diagonal.

### 2.3.3. Hodgkin lymphoma (HL) dataset

Out of 364 HL patients that this data contains, 88 had died from HL while 276 survived. A score with seven factors (age, sex, stage, hemoglobin, albumin, lymphocyte count and white cell count) developed for diagnosis of HL is called IPS7 (IPS: International Prognostic Score). A reduced version of IPS with 3 factors (IPS3) alternative to IPS7 was later proposed (Diefenbach et al., 2015). Both IPS3 and IPS7 are evaluated as biomarker in the applications of this paper. Event of interest is death, and the survival time is the time covariate.

The applications in this study are carried out using R 3.2.2 (Vienna, Austria, 2015) and SPSS v20 (Armonk, New York U.S.A, 2011). R libraries are: “survivalROC” (Heagerty and Saha-Chaudhuri, 2013) for plotting the time-dependent ROC curves and comparison of KM and NNE approaches; “timeROC” (Blanche et al., 2013) for the standard error calculations regarding the ROC curves at specific time points.

## 3. Results

### 3.1. Time-Dependent ROC vs Classical ROC

#### 3.1.1. Melano dataset

Data consist of 191 malignant melanoma patients. Tumor thickness along with the post-operation survival statuses and times of the patients are recorded in 15 years. Diagnostic performance of tumor thickness is of interest. Since a period of 15 years is too long for diagnostic purposes, data of the last 6 years to event (death) are used in time-dependent ROC analysis applications of this study (Table 1).

**Table 1.** Area under the curve (AUC), standard errors (SE) and 95% CIs obtained from Melano dataset

Time to Event	AUC	SE	95% CI
6 years	0.73	0.05	0.63 - 0.81
Classical ROC	0.75	0.04	0.68 - 0.82
5 years	0.77	0.04	0.67 - 0.84
4 years	0.80	0.04	0.73 - 0.88
3 years	0.81	0.04	0.73 - 0.89
2 years	0.88	0.03	0.82 - 0.95
1 year	0.91	0.03	0.85 - 0.97

Findings in Table 1 show that prediction of mortality annually improved as getting closer to the event. Especially in the last two years’ results are in favor of that time-dependent ROC analysis foresees death 17% (2 years to the event) and 21% (1 year to the event) more accurately than the classical ROC approach.

#### 3.1.2. Paquid dataset

There are two test scores used as the biomarkers for Alzheimer’s diagnosis in this dataset: DSST (Digit Symbol Substitution Score Test) and MMSE (Mini Mental State Examination). The event of interest is the onset of Alzheimer’s and follow-up time is 12 years. Even 10 years before the event, time dependent AUC estimations still perform more than 10% better, when compared to the AUC estimation of the classical ROC for both DSST and MMSE (Table 2). Their ability to predict the event has increased at each time point, reaching the highest level in the end. Although they seem to behave similarly along the way, DSST has higher AUC estimations at all measurement times; and therefore it is found more successful than MMSE at classification (Table 2).

#### 3.1.3. Hodgkin lymphoma (HL) dataset

Characteristics and measurements of 364 HL patients were recorded in this dataset, with an almost 19-year follow-up which is a very long time for a biomarker to predict the disease. Thus, only the last 6 years have been taken into account in this study. Diagnostic performance of IPS7 and IPS3 in estimating mortality is examined at each time point. Area under the curve (AUC) of the classical ROC and time-dependent AUCs are presented in Table 3.

**Table 2.** Area under the curve (AUC), standard errors (SE) and 95% CIs obtained from two biomarkers of Paquid dataset

Time to Event	DSST			MMSE		
	AUC	SE	95% CI	AUC	SE	95% CI
Classical ROC	0.69	0.01	0.66 - 0.71	0.63	0.02	0.60 - 0.66
12 years	0.74	0.02	0.71 - 0.77	0.66	0.02	0.63 - 0.69
11 years	0.77	0.02	0.72 - 0.78	0.69	0.02	0.65 - 0.72
10 years	0.79	0.02	0.74 - 0.80	0.71	0.02	0.67 - 0.74
9 years	0.79	0.02	0.75 - 0.81	0.71	0.02	0.66 - 0.73
8 years	0.79	0.02	0.74 - 0.81	0.71	0.02	0.67 - 0.74
7 years	0.80	0.02	0.75 - 0.82	0.73	0.02	0.68 - 0.76
6 years	0.81	0.02	0.76 - 0.84	0.75	0.02	0.70 - 0.79
5 years	0.81	0.02	0.77 - 0.84	0.74	0.02	0.69 - 0.79
4 years	0.83	0.02	0.77 - 0.86	0.74	0.03	0.69 - 0.80
3 years	0.83	0.02	0.77 - 0.87	0.77	0.03	0.70 - 0.82
2 years	0.88	0.03	0.81 - 0.93	0.82	0.04	0.75 - 0.89
1 year	0.91	0.04	0.83 - 0.98	0.82	0.07	0.68 - 0.97

**Table 3.** Area under the curve (AUC), standard errors (SE) and 95% CIs obtained from two biomarkers of HL dataset

Time to Event	IPS7			IPS3		
	AUC	SE	95% CI	AUC	SE	95% CI
Classical ROC	0.62	0.04	0.54 - 0.69	0.65	0.04	0.58 - 0.72
6 years	0.62	0.04	0.54 - 0.70	0.64	0.04	0.57 - 0.71
5 years	0.61	0.04	0.55 - 0.70	0.65	0.04	0.58 - 0.72
4 years	0.62	0.04	0.56 - 0.72	0.67	0.04	0.60 - 0.74
3 years	0.64	0.04	0.56 - 0.73	0.69	0.04	0.62 - 0.77
2 years	0.64	0.05	0.56 - 0.74	0.70	0.04	0.63 - 0.78
1.5 years	0.67	0.05	0.58 - 0.77	0.74	0.04	0.66 - 0.82
1 year	0.66	0.05	0.56 - 0.77	0.72	0.05	0.63 - 0.81
6 months	0.75	0.06	0.63 - 0.87	0.81	0.05	0.71 - 0.91

For both IPS7 and IPS3, AUCs of earlier time points are found to be similar or close to the classical ROC value, while a general increase can be mentioned when getting closer to event of death. Maximum AUC value is 0.75 for IPS7 whereas IPS3 reaches 0.81 level, 6 months before the event. Only the last 6 months' measurements have been significantly different from the rest of the time points as well as the classical ROC for both biomarkers. In other words, IPS7 and IPS3 at 6 months to the event predict mortality, respectively 21% and 24% better than classical ROC.

**3.2. Kaplan-Meier Estimator (KM) vs Nearest Neighbor Estimator (NNE)**

After establishing time-dependent ROC analysis is a better way when there is a time dependency between the biomarker and event of interest, two time-dependent AUC estimators KM and NNE are compared to find out if one is superior to the other.

In Table 4, KM and NNE AUCs again fall into one another's 95% confidence intervals, though KM values are obtained higher than NNE values.

Table 5 demonstrates that KM yielded higher values than NNE for both DSST and MMSE biomarkers. An additional interpretation of this table is that DSST is a better biomarker than MMSE when the two is compared in each method.

Table 6 presents that very similar results are obtained from KM and NNE methods for IPS7 and IPS3 at all-time points. In addition, when the two biomarkers are compared using KM and NNE approaches, it can be concluded that one score is not better than the other; in fact, they are statistically the same.

**Table 4.** Comparison of KM and NNE methods using Melano dataset

Time to Event	KM-AUC (95% CI)	NNE-AUC (95% CI)
6 years	0.73 (0.63 - 0.81)	0.69 (0.62 - 0.79)
5 years	0.77 (0.67 - 0.84)	0.72 (0.65 - 0.82)
4 years	0.80 (0.73 - 0.88)	0.77 (0.71 - 0.87)
3 years	0.81 (0.73 - 0.89)	0.77 (0.68 - 0.87)
2 years	0.88 (0.82 - 0.95)	0.86 (0.78 - 0.94)
1 year	0.90 (0.85 - 0.97)	0.90 (0.83 - 0.98)

KM= Kaplan-Meier estimator, NNE= Nearest Neighbor estimator, AUC= area under the curve

**Table 5.** Comparison of KM and NNE methods using two biomarkers of Paquid dataset

Time to Event	DSST		MMSE	
	KM-AUC (95% CI)	NNE-AUC (95% CI)	KM-AUC (95% CI)	NNE-AUC (95% CI)
12 years	0.74 (0.71 - 0.77)	0.71 (0.71 - 0.74)	0.66 (0.63 - 0.69)	0.64 (0.61 - 0.68)
11 years	0.77 (0.72 - 0.78)	0.73 (0.70 - 0.76)	0.69 (0.65 - 0.72)	0.67 (0.64 - 0.71)
10 years	0.79 (0.74 - 0.80)	0.75 (0.72 - 0.78)	0.71 (0.67 - 0.74)	0.69 (0.65 - 0.72)
9 years	0.79 (0.75 - 0.81)	0.75 (0.72 - 0.79)	0.71 (0.66 - 0.73)	0.69 (0.65 - 0.72)
8 years	0.79 (0.74 - 0.81)	0.76 (0.72 - 0.79)	0.71 (0.67 - 0.74)	0.69 (0.65 - 0.73)
7 years	0.80 (0.75 - 0.82)	0.77 (0.73 - 0.80)	0.73 (0.68 - 0.76)	0.71 (0.67 - 0.75)
6 years	0.81 (0.76 - 0.84)	0.78 (0.74 - 0.81)	0.75 (0.70 - 0.79)	0.73 (0.69 - 0.78)
5 years	0.81 (0.77 - 0.84)	0.78 (0.75 - 0.82)	0.74 (0.69 - 0.79)	0.73 (0.68 - 0.78)
4 years	0.83 (0.77 - 0.86)	0.79 (0.74 - 0.84)	0.74 (0.69 - 0.80)	0.73 (0.68 - 0.79)
3 years	0.83 (0.77 - 0.87)	0.80 (0.74 - 0.85)	0.77 (0.70 - 0.82)	0.75 (0.69 - 0.82)
2 years	0.88 (0.81 - 0.93)	0.86 (0.79 - 0.92)	0.82 (0.75 - 0.89)	0.81 (0.73 - 0.88)
1 year	0.91 (0.83 - 0.98)	0.91 (0.87 - 0.98)	0.82 (0.68 - 0.97)	0.81 (0.66 - 0.98)

KM= Kaplan-Meier estimator, NNE= Nearest Neighbor estimator, AUC= area under the curve

**Table 6.** Comparison of KM and NNE methods using two biomarkers of HL dataset

Time to Event	IPS7		IPS3	
	KM-AUC (95% CI)	NNE-AUC (95% CI)	KM-AUC (95% CI)	NNE-AUC (95% CI)
6 years	0.61 (0.54 - 0.70)	0.61 (0.53 - 0.68)	0.64 (0.57 - 0.71)	0.64 (0.55 - 0.71)
5 years	0.61 (0.55 - 0.70)	0.60 (0.52 - 0.68)	0.65 (0.58 - 0.72)	0.65 (0.56 - 0.72)
4 years	0.62 (0.56 - 0.72)	0.62 (0.54 - 0.70)	0.67 (0.60 - 0.74)	0.67 (0.57 - 0.74)
3 years	0.64 (0.56 - 0.73)	0.64 (0.55 - 0.72)	0.69 (0.62 - 0.77)	0.69 (0.59 - 0.77)
2 years	0.64 (0.56 - 0.74)	0.64 (0.54 - 0.73)	0.70 (0.63 - 0.78)	0.70 (0.60 - 0.77)
1.5 years	0.67 (0.58 - 0.77)	0.66 (0.56 - 0.75)	0.74 (0.66 - 0.82)	0.74 (0.64 - 0.82)
1 year	0.66 (0.56 - 0.77)	0.66 (0.55 - 0.76)	0.72 (0.63 - 0.81)	0.72 (0.61 - 0.81)
6 months	0.75 (0.63 - 0.87)	0.75 (0.62 - 0.86)	0.81 (0.71 - 0.91)	0.81 (0.68 - 0.92)

KM= Kaplan-Meier estimator, NNE= Nearest Neighbor estimator, AUC= area under the curve

#### 4. Discussion

In this study, the most common time-dependent ROC methods (KM, NNE) are examined in theory and application. Their performances are compared both to each other and to classical ROC analysis. When biomarkers measured at different time-points are compared, (except for some situations) AUC estimations are found to show monotone increase similar to the literature. In the real-data application detailed in Martinez-Camblor et al. (2016), AUC estimations corresponding to biomarker values obtained in the beginning of the follow-up descended for a while, and

then started to escalate as the time of failure became closer. This fluctuation might be due to the loss of diagnostic ability of a biomarker in long follow-up periods.

Though not sufficient number of studies comparing classical and time-dependent ROC exist in the literature, paper of Chambless and Diao (2006) is one of the few in this regard. Writers explained that AUC values obtained from these two ROC methods cannot be the same. Results of this study have turned out to be supportive to their claim. When KM and NNE methods are compared to each other at time t, in all datasets they yielded similar results

parallel to Blanche et al. (2013). Although KM method results in higher estimations indicating higher performance, it has a limitation that does not allow the censoring process to be dependent on the biomarker. On the other hand, NNE method does not possess such restrictions. Even if its AUC estimations are lower, the smoother curves are obtained with NNE; and thus the well-known feature of the ROC curve being a monotone increasing function is satisfied. Hence, when deciding which to prefer, choosing NNE option would be more advantageous.

## 5. Conclusion

The insufficiency of standard ROC analysis, when time is a parameter that cannot be set aside, is proven with examples in this study. Time-dependent ROC analysis for time-dependent situations is recommended as a substitution. KM and NNE as time-dependent estimators gave mostly similar results; yet, one must consider the limitations of KM while choosing between the two.

## Author Contributions

Concept: C.E.S. (50%) and İ.Ü. (50%), Design: C.E.S. (50%) and İ.Ü. (50%), Supervision: C.E.S. (50%) and İ.Ü. (50%), Data collection and/or processing: C.E.S. (50%) and İ.Ü. (50%), Data analysis and/or interpretation: C.E.S. (80%) and İ.Ü. (20%), Literature search: C.E.S. (50%) and İ.Ü. (50%), Writing: C.E.S. (50%) and İ.Ü. (50%), Critical review: C.E.S. (50%) and İ.Ü. (50%), Submission and revision C.E.S. (50%) and İ.Ü. (50%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest.

## Ethical Approval/Informed Consent

Ethics committee approval is not required for this study because used data are open for public usage.

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## THE RELATION BETWEEN THE URIC ACID LEVELS AND THE RECANALIZATION TIMES IN PATIENTS WITH CEREBRAL VENOUS THROMBOSIS

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**Abstract:** Recanalization times in cerebral venous thrombosis (CVT) patients are generally around six months, but do vary from patient to patient. The reasons for the variation in the recanalization times between the CVT patients are still a matter of debate. Thus, in this study, the relation between the uric acid (UA) level, which has been shown to have antioxidant properties in ischemic stroke, and the recanalization time in CVT patients was investigated. In this context, the CVT patients, who were followed up between January 2015 and May 2020, were analyzed retrospectively. Of the 78 patients, who met the eligibility criteria to be included in the research, 76.9 % were female and 23.1 % were male. It was determined that headache was the most common (73.1 %) symptom, and that the gynecological reasons were the most common (38.5 %) etiological reasons. A weakly significant negative correlation was found between the UA levels and the recanalization times in the study group ( $P = 0.003$ ,  $r = -0.327$ ). There was a weakly negative correlation between the UA levels and the recanalization times in female patients ( $P = 0.046$ ,  $r = -0.259$ ). The UA levels of male patients were also found to be negatively correlated with the recanalization times, albeit not statistically significantly. The finding that the recanalization times were shortened as UA levels were increased in female CVT patients was interpreted as that there is a gender-specific relationship between the UA levels and the recanalization times in CVT patients.

**Keywords:** Cerebral venous thrombosis, Uric acid, Recanalization, Gender, Prognosis

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### 1. Introduction

Cerebral venous thrombosis (CVT) is one of the rare causes of stroke, accounting for 0.5% to 1% of all strokes (Saposnik et al., 2011). CVT has been known to be typically more difficult to diagnose as compared to the diagnoses of ischemic and hemorrhagic strokes, yet its diagnosis has become relatively easier thanks to the widespread use of magnetic resonance imaging (MRI) and increased clinical awareness. Its prevalence in women is three times more than in men (Ferro et al., 2004; Coutinho et al., 2009). The reason for this disparity has been attributed to the increased risk of CVT with pregnancy, puerperal and oral contraceptive use (Stam, 2005). CVT is most commonly seen in individuals of younger ages, as opposed to arterial stroke, which is most commonly seen in individuals over the age of 65. Only 8% of the patients with CVT were reported to be over 65 years of age (Ferro et al., 2005). Low molecular weight heparin (LMWH) treatment has been reported as an effective and safe method for the treatment of CVT. Venous infarction, hemorrhagic venous infarction or isolated subarachnoid hemorrhage do not act as a contraindication in respect of the use of anticoagulant

therapy in patients with CVT. The recanalization times in CVT patients commonly range between 3 to 6 months, which sometimes extend to 12 months, but very rarely extend to longer than 12 months. High recanalization rates have been reported in many studies previously conducted (Baumgartner et al., 2003; Stolz et al., 2004; Sidhom et al., 2014; Herweh et al., 2016;).

Uric acid (UA) is an important blood antioxidant in humans. The plasma concentration of UA is ten times higher than other antioxidants. UA is responsible for two-thirds of all free radical scavenging capacity (Becker, 1993). In an experimental study, it was shown that UA treatment significantly suppressed oxidative stress, alleviated neuronal damage and reduced infarct volume in rats with transient focal cerebral ischemia/reperfusion (Ya et al., 2018). It was also demonstrated in several studies that UA has a neuroprotective effect when administered exogenously (Onetti et al., 2015; Justicia et al., 2017). Despite the controversy over the factors associated with CVT, there is only a handful of studies available in the literature that addressed the relation between CVT and the antioxidant system. In one of these few studies, it was shown that there was a decrease in



the antioxidant system level in the acute period of CVT (Tiwari et al., 2016).

In view of the foregoing, it is aimed in this study to investigate the relation between the UA levels and the recanalization times in CVT patients.

### 2. Material and Method

The files of 101 patients over the age of 18 who were diagnosed with CVT by means of magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) between January 2015 and May 2020, were reviewed retrospectively. The patients that were followed up for at least three months and whose follow-up MRVs were taken every three months for the first year were included in the study. Accordingly, 12 CVT patients, whose follow-up MRI and MRV were not available, and 11 patients, whose imaging data did not indicate recanalization, were excluded from the study. Consequentially, the study group consisted of 78 CVT patients. Demographic characteristics, neurological and radiological findings, etiological risk factors and treatment details of these patients were recorded. Etiological risk factors that may be associated with CVT; namely infections (systemic or focal infections; otitis media, mastoiditis, sinusitis, etc.), gynecological causes (pregnancy, puerperium, use of oral contraceptives), malignancies, hematological causes (thrombocytosis, anemia, etc.), rheumatological or connective tissue diseases, causes of thrombophilia (antithrombin III, protein C-S deficiency, hyperhomocysteinemia, factor V Leiden mutation, prothrombin II mutation) were recorded. The patency of the veins in the patients included in the study was categorized as either partial or complete recanalization. Normal blood flow in previously occluded cerebral veins was defined as complete recanalization, whereas presence of residual thrombus and of blood flow disruption was defined as partial recanalization. The follow-up MRVs, which were taken every 3 months for a year, of the patients who were followed up with partial recanalization were examined in terms of complete recanalization during the said term, and the recanalization times were recorded as the time to the observation of the first partial recanalization for the patients who did not develop complete recanalization. MRIs were not repeated in patients who developed complete recanalization in the first 3 months. Neurological outcomes of the patients were categorized using the Modified Rankin Scale (mRS) as either good (mRS: 0-1) or poor (mRS: 2-6) based on the clinical status of the patients at the time of first admission and six months later. The serum UA levels measured in the blood samples taken from the patients within the first 24 hours after admission were recorded. Patients with hepatic and renal dysfunction and those with a history of heart attack were not included in the study.

The research data were analyzed using the SPSS 20 (IBM Statistical Package for Social Sciences version 20) software package. Kolmogorov-Smirnov test was used to

check whether the research data conformed to the normal distribution or not. Categorical data were expressed in terms of n (%) values, whereas the numerical data were expressed in terms of median (minimum-maximum) values as they did not conform to normal distribution. Mann-Whitney U test and Kruskal Wallis tests were used in the analysis of numerical data that did not conform to normal distribution. Chi-square test was used to analyze the categorical data. Yates correction and Fisher's exact tests were applied taking the expected values in the chi-square test into consideration. Spearman's correlation analysis was used to assess the relationship between any two non-normally distributed numerical data. Probability (p) values of <0.05 were considered to indicate statistical significance.

### 3. Results

The median age of the patients was 33 years (min. 18 and max. 76 years). Of the 78 CVT patients included in the study, 60 (76.9%) were female and 18 (23.1%) were male. There was a significant difference between genders in terms of age distribution ( $P < 0.001$ ). It was determined that headache was the most common (73.1%) symptom, and that the gynecological reasons were the most common (38.5%) etiological reasons. Multiple venous involvement was present in 65.4% ( $n=51$ ) of the patients and the most frequently involved vein/sinus was transverse sinus (89.7%). The most common (21.8%) accompanying MRI finding was hemorrhagic infarction, and the most frequently (20.5%) affected area was the temporal lobe. It was determined that LMWH treatment was used in 83.3% ( $n=65$ ) of the patients and that warfarin sodium treatment was used in 16.7% ( $n=13$ ) of the patients. The incidence of epileptic seizures was 20.5% ( $n=16$ ). Parenchymal lesions were observed in 14.1% ( $n=11$ ) of the patients with epileptic seizures. No parenchymal lesions were observed in 6.4% ( $n=5$ ) of the patients with epileptic seizures. There was a statistically significant correlation between status of having parenchymal lesion and epileptic seizure ( $P = 0.025$ ). The most commonly affected vein/sinus in patients with epileptic seizures was transverse sinus. It was determined that superior sagittal sinus and transverse sinus were affected in 6 patients, that transverse sinus was affected in 6 patients, that superior sagittal sinus was affected in 3 patients, and that deep veins were affected in 1 patient. Clinical and demographic data and the radiological findings pertaining to the patients included in the study are shown in Table 1 and Table 2, respectively. Of the 7 CVT patients with vasculitis due to etiological reasons, 4 patients had Behçet's Disease, 1 patient had systemic lupus erythematosus, 1 patient had systemic lupus erythematosus and Sjögren's syndrome, and another 1 patient had Wegener's granulomatosis. The most common causes of infection were focal infections (65%) such as mastoiditis and otitis.

**Table 1.** Clinical and demographic data of patients

	n
Age (year), median (min-max)	33 (18-76)
Sex (%)	
Female	60 (76.9)
Male	18 (23.1)
Etiology (%)	
Gynecological reasons (Pregnancy, postpartum, OCS)	30 (38.5)
Thrombophilia	
Vasculitis	9 (11.5)
Infection	7 (9)
Anemia	19 (24.4)
Multiple causes	3 (3.8)
Idiopathic	5 (6.4)
Uric acid (mg/dL), Median (min-max)	4 (1-11.8)
Recanalization time (months), Median (min- max)	6 (3-24)
Recanalization (%)	
Partial	17 (21.8)
Full	61 (78.2)
High homocysteine (%)	13 (16.7)
Drug used (%)	
LMWH	65 (83.3)
Warfarin sodium	13 (16.7)
Symptoms (%)	
Headache	57 (73.1)
Unconsciousness	3 (3.8)
Aphasia	5 (6.4)
Motor deficit	13 (16.7)
Epileptic seizure (%)	16 (20.5)
mRS hospitalization (%)	
Good result (0-1)	36 (46.2)
Poor result (2-6)	42 (53.8)
mRS after discharge 6.month (%)	
Good result (0-1)	75 (96.2)
Poor result (2-6)	3 (3.8)

**Table 2.** Radiological findings of the patients

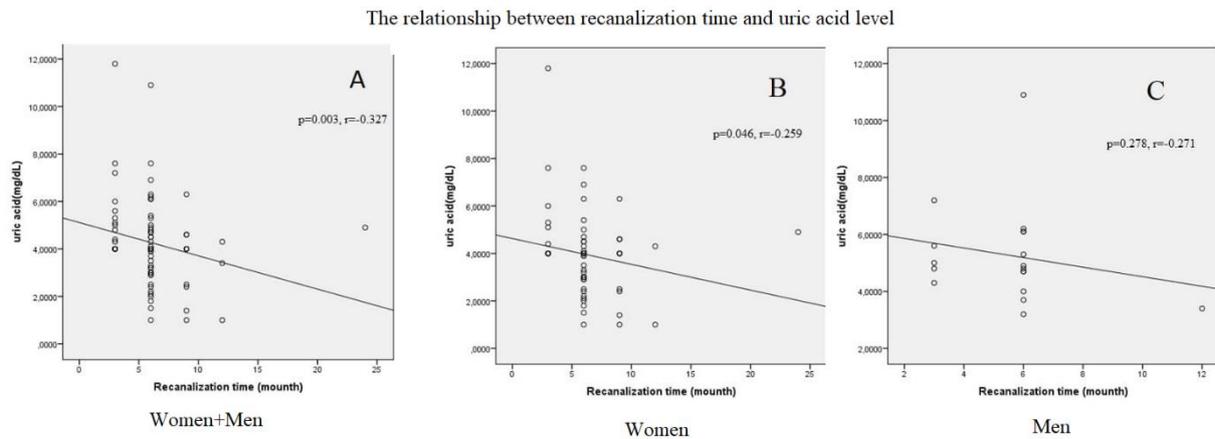
	n (%)
MRI finding	
No parenchymal lesion	42 (53.8)
Infarct	15 (19.2)
Hemorrhage	4 (5.1)
Hemorrhagic infarct	17 (21.8)
MRI lesion localization	
Temporal	16 (20.5)
Frontal	7 (9)
Parietal	11 (14.1)
Occipital	2 (2.6)
Involved vein/sinus	
Superior sagittal sinus	32 (41)
Left transverse	39 (50)
Left sigmoid sinus	26 (33.3)
Right transverse	31 (39.7)
Right sigmoid sinus	19 (24.4)
Jugular vein	20 (25.6)
Deep veins	6 (7.7)
Multiple venous involvement	51 (65.4)

Two of the 5 patients with multiple risk factors in etiology had a gynecological cause and Behçet's disease, 2 had a gynecological cause and factor V Leiden mutation, and 1 had a malignancy (breast cancer) and anemia. UA levels were statistically significantly higher in males than in females ( $P = 0.001$ ). There was no significant relationship between age and UA level both in male and

female patient groups ( $P = 0.515$ ,  $r=0.086$ ; and  $P = 0.864$ ,  $r=-0.044$ , respectively). Median UA level was 4 (min.1 and max. 11.8) mg/dL and the range taken as reference was 2.6 mg/dL to 6 mg/dL. It was determined that 11.5% of the patients had hyperuricemia. The median recanalization time was 6 months (min. 3 months and max. 24 months). The patient with the longest

recanalization time (24 months) was the patient with Wegener's granulomatosis. Complete recanalization was observed in 78.2% (n=61) of the patients, whereas partial recanalization was observed in 21.8% (n=17) of the patients. It was determined that 20.5% (n=16), 61.5% (n=48), 12.8% (n=10), 3.8% (n=3) and 1.3% (n=1) of the patients had either complete or partial recanalization at 3, 6, 9, 12 and 24 months, respectively. There was no significant difference in terms of recanalization times between the patient groups categorized according to gender and etiology (P = 0.146 and P = 0.301, respectively). There was no significant correlation between the recanalization times and the etiology within the female patient group (P = 0.366). Additionally, no significant difference was found between the number of involved veins and the recanalization times (P = 0.795) and between the extent of recanalization and the clinical outcome (P = 0.473). A weakly significant negative correlation was found between the UA levels and the recanalization times in the study group (P = 0.003, r=-0.327) (Figure 1A). There was a weakly negative correlation between the UA levels and the recanalization times in female patients (P = 0.046, r=-

0.259) (Figure 1B). The UA levels of male patients were also found to be negatively correlated with the recanalization times, albeit not statistically significantly (P = 0.278, r=-0.271) (Figure 1C). There was no significant difference between the UA levels and the recanalization times of patients with or without parenchymal lesions (P = 0.932, P = 0.804). A significant correlation was observed between the mRS score and the status of having parenchymal lesion at admission (P < 0.001), which turned into a non-significant correlation at 6-months' time (P = 0.094). There was no significant difference between the UA levels of the patients, in whom either partial or complete recanalization was observed (P = 0.799). Analysis of the mRS scores of the CVT patients at admission revealed that 46.2% (n=36) of the patients had good and 53.8% (n=42) of the patients had poor neurological outcomes, whereas the analysis of the mRS scores of the CVT patients at 6-months' time revealed that 96.2% (n=75) of the patients had good and 3.8% (n=3) of the patients had poor neurological outcomes. There was no mortality in the patient group included in this study.



**Figure 1.** Correlation plot of serum uric acid level and recanalization time. The x-axis represents the recanalization time in months, and the y-axis represents the serum uric acid level in mg/dL. Each dot on the graph represents a patient. There was a significantly negative correlation between the recanalization times and the serum uric acid levels in the study group (Figure 1A). There was a significant negative correlation between the recanalization times and the uric acid levels in the female patient group (Figure 1B). There was also a negative however not a significant correlation between the recanalization times and the uric acid levels in the male patient group (Figure 1C).

#### 4. Discussion

Similar to the demographic and clinical characteristics of the CVT patient groups investigated in the previously conducted studies available in the literature, majority of the CVT patients included in this study were female (76.9%) and gynecological reasons were the most commonly observed etiological reason (38.5%). Complete recanalization was observed in 78.2% (n=61) of the patients, whereas partial recanalization was observed in 21.8% (n=17) of the patients. There are studies in which a better functional outcome was reported in patients with complete recanalization (Arauz et al., 2016), yet there are also other studies in

which no difference was found between the scope of recanalization and the clinical outcome, similar to the finding of this study (José et al., 2004; Herweh et al., 2016). In paralel with the results of the previously conducted studies available in the literature (Putala et al., 2010; Hiltunen et al., 2016), 96.2% of the patients included in this study were found to have clinically good outcomes with a good prognosis of CVT, at 6-months' time after being discharged.

Gazioğlu et al. (2017) reported that recanalization rates were lower in patients with thrombosis in more than one sinus. In comparison, in this study, no significant difference was found between the recanalization times in

terms of number of involved veins. A significant correlation was observed between the mRS score and the status of having parenchymal lesion at admission ( $P < 0.001$ ), which turned into a non-significant correlation at 6-months' time ( $P = 0.094$ ). This finding is supported by the finding of Singh et al., who reported that the presence of parenchymal lesion was not a factor in the clinical outcome (Singh et al., 2020). Etiological causes are considered among the important factors affecting the recanalization time. Accordingly, anticoagulation treatment is recommended for the treatment of CVT for a duration of 3 to 6 months, 6 to 12 months or longer depending on whether CVT is caused by a temporary risk factor, an idiopathic cause or a history of thrombophilia or recurrent thrombosis, respectively (Saposnik et al., 2011). However, no significant difference was found in this study in terms of recanalization times between the patient groups categorized according to gender and etiology ( $P = 0.146$  and  $P = 0.301$ , respectively). Although it does not have an explicit effect on the recanalization time, it is important to find the etiologic cause in order to determine the conditions that require long-term treatment such as thrombophilia and perform the necessary treatments. The fact that recanalization takes place on or around 6 months in the vast majority of the CVT patients, that this situation persists for long periods in patients with partial recanalization, and that there is no correlation between the extent of recanalization and prognosis suggests that repeating MRIs every 3 months is unnecessary in most of the patients. On the other hand, considering that the rate of patients, in whom recanalization was observed in the first three months, was not very low (20.5% in this study), MRI can be repeated every three months for the first six-month period in these patients in order to prevent the unnecessary use of medication.

There are studies available in the literature in which UA was shown to increase inflammatory cytokines such as C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) suggesting that it may be associated with vascular diseases such as coronary artery disease, ischemic stroke and hypertension (Kanellis and Kang, 2005). To give an example, Talebi et al. (2020) found that patients with high serum UA levels had an increased risk of ischemic stroke, whereas Saadat et al. (2018) did not find any significant relationship between serum UA levels and stroke risk factors such as hypertension, ischemic heart disease and hyperlipidemia. The rate of hyperuricemia reported in the literature in patients with ischemic stroke varies between 13% and 30% (Iranmanesh et al., 2012; Serdarevic et al., 2020). There are studies, in which UA levels were found to have increased in ischemic stroke patients compared to healthy control subjects (Lamani and Vishwanath, 2013; Serdarevic et al., 2020), yet there are also studies in which no significant difference was found between the patient and control groups in terms of UA levels (Varga et al., 2011). The findings on the UA levels in ischemic

stroke patients as to whether it is a vascular risk factor remain to be controversial. In an experimental study, it was demonstrated that UA significantly suppressed oxidative stress, reduced neuronal damage, and decreased infarct volume in rats with ischemia/reperfusion, due to its antioxidant effect (Ya et al., 2018). In comparison, in this study, no significant difference was found between the male and female patient groups in terms of recanalization times. Yet, there was a weakly significant negative correlation between the UA levels and the recanalization times in the study group ( $P = 0.003$ ,  $r = -0.327$ ). In terms of gender, there was a weakly negative correlation between the UA levels and the recanalization times in female patients ( $P = 0.046$ ,  $r = -0.259$ ), and a negative correlation between the UA levels and the recanalization times also in male patients, which was however not statistically significant ( $P = 0.278$ ,  $r = -0.271$ ). The fact that UA levels were found to have increased as the recanalization times have decreased in both female and male patient groups suggests that the UA level has a positive effect on the prognosis in CVT patients. Despite the controversy over the factors associated with CVT, there is only a handful of studies available in the literature that addressed the relation between CVT and the antioxidant system, and UA levels in particular. The results of this study, one of the said few studies, support that high serum UA levels in CVT patients are associated with prognosis based on gender and are an indicator of good prognosis in female gender. These results are in line with the results of another study, one of the few such studies available in the literature (Song et al., 2018).

There were some limitations to this study. First, it was carried out as a retrospective study; secondly, number of male patients included in the study was relatively low; and thirdly, the serum UA levels of patients were not re-measured during the follow-up period.

In conclusion, the shortening of the recanalization times as the UA levels increase and the finding of a weak correlation between the said two parameters were interpreted as that high UA level has a positive effect on prognosis in CVT patients. In addition, the fact that a significant relationship was found between the UA levels and recanalization times in female patient group was interpreted as that the UA level is more effective on the prognosis of female CVT patients than the male CVT patients. In other words, the results of this study indicate that there is a gender-specific relationship between the UA levels and the recanalization times. The decrease in the antioxidant system level in the acute period in CVT and the shorter recanalization time in patients with high UA levels suggest that UA, which has antioxidant properties, can be used as an effective therapeutic agent. However, further studies with larger patient groups are needed to support the results of this study.

**Author Contributions**

All task made by single author and the author reviewed and approved the manuscript.

**Conflict of Interest**

The author declared that there is no conflict of interest.

**Ethical Approval/Informed Consent**

The research was conducted in line with the declaration of Helsinki and good clinical practice. The study protocol was approved by the Ataturk University, Faculty of Medicine local ethics committee (02/8/25.03.2021). Written informed consent was obtained from all individual participants and their parents before participating in the study.

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## YETİŞKİN BİREYLERDE ÖLÜM ALGISININ MANEVİ İYİ OLUŞ ÜZERİNE ETKİSİ

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**Özet:** Küreselleşen dünyada insanlığın iç huzura ve özün değerine duyduğu ihtiyaç, manevi iyi oluş kavramının önemini artırmıştır. Tanımlayıcı tipte yapılan bu araştırma ile ölüme verilen anlamın manevi iyi oluşa etkisini incelemek amaçlanmıştır ve 523 yetişkin birey araştırmaya katılmıştır. Veriler Sosyodemografik Veri Formu, Ölümün Kişisel Anlamları Ölçeği ve Manevi İyi Oluş Ölçeği ile çevirim içi olarak toplanmıştır. Yapılan lojistik regresyon analizinde manevi iyi oluş puanının yordanmasında Yok Olma faktörü puanındaki bir puanlık artış 0,91 kat, Ölüm Sonrası Hayat faktörü puanındaki bir puanlık artış 1,38 kat, yaştaki bir birimlik artış 1,06 kat artış sağlamaktadır. Ayrıca çalışanlarda çalışmayanlara göre manevi iyi oluş 1,66 kat artmaktadır. Araştırma sonuçlarına göre ölümden sonra hayatın varlığına inanmanın, ileri yaşın ve çalışmanın manevi iyi oluşu artırdığı, ölümü yok olma olarak algılamamanın manevi iyi oluşu azalttığı söylenebilir.

**Anahtar kelimeler:** Manevi iyi oluş, Ölüm, Ölüm algısı, Yetişkin bireyler

### The Effect of Perception of Death on Spiritual Well-Being in Adults

**Abstract:** In the globalizing world, humanity's need for inner peace and the value of the self has increased the importance of the concept of spiritual well-being. In this descriptive study, it was aimed to examine the effect of the meaning given to death on spiritual well-being and 523 adult individuals participated in the research. Data were collected online using the Sociodemographic Data Form, the Personal Meanings of Death Scale, and the Spiritual Well-Being Scale. In the logistic regression analysis, a one-point increase in the Extinction factor score was 0.91 times, a one-point increase in the Life After Death factor score was 1.38 times, a one-point increase in the spiritual well-being score unit increase provides an increase of 1.06 times. In addition, moral well-being increases 1.66 times in employees compared on on-workers. According to the results of the research, it can be said that believing in the existence of life after death, advanced age and working increase spiritual well-being, and perceiving death as extinction reduces spiritual well-being.

**Keywords:** Spiritual well-being, Death, Perception of death, Adult individuals

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### 1. Giriş

Ölümü anlamlandırma ve yaşam amacını bulma maneviyat kavramı içinde yer alan önemli değerlendirmelerdir. Maneviyat, insanın daha genel bir yaşam amacı olmasını, evrenin anlamını ve kainattaki yerini bilmesini, yaşamın anlamına yönelik eylemlerini ve inançlarını kapsamaktadır (Bannink, 2017). Küreselleşme ile birlikte hızla değişen ve dönüşüm yaşayan dünyaya uyum sağlayamayan ve ruhsal boşluğa düşen insanlığın, iç huzura ve özün değerine duyduğu ihtiyaç manevi iyi oluş kavramının önemini artırmıştır (Acar, 2014). Manevi iyi oluş, üstün bir güce inanıp o güce bağlanmayı, yaşamda bir anlama ve güçlü bir değer sistemine sahip olmayı, bu doğrultuda ilişkiler kurmayı içerir (Mahdian ve Ghaffari, 2016). Manevi iyi oluşu zayıf olan bireylerin umutsuzluk, anlamsızlık ile birlikte madde kötüye kullanımı (Doğan, 2019), depresyon ve kaygı bozuklukları gibi ruhsal sorunlar yaşadığı, karşılaştıkları sorunlarla etkili baş

etmede yetersiz kaldığı, intihara kadar gidebilen sonuçları olduğu bildirilmektedir (Gaskin-Wasson ve ark., 2018). Manevi iyi oluşu yüksek bireylerin ise yaşamda anlam bulma, umutlu olma, kendine güvenme, yaşamından memnun olma, kriz yaratan ya da travmatik olaylarla daha güçlü mücadele etmeleri nedeniyle psikolojik ve ruhsal yönden daha sağlıklı oldukları vurgulanmıştır (Halil ve Kardeş, 2017). Manevi iyi oluşu yüksek bireyler üstün bir gücün varlığına inandığında başlarına gelen zorlu durumları yapıcı bir deneye dönüşürme eğilimi içinde olurlar, bu durumun da baş etmelerine ve iyi hissetmelerine katkı sağladığı belirtilmiştir (Uğurluoğlu ve Erdem, 2019).

Maneviyat içinde yer alan bir diğer kavram ise ölüme atfedilen anlamdır. Yaşamın kaçınılmaz bir parçası olan ölüm, her insanın başına gelen eşitlikçi gerçeği ve bilinmeyene duyulan korkuyu temsil eder. Varoluş halinin nitelik ve nicelik olarak biçim değiştirmesi şeklinde tanımlanan ölüm göreceli bir algı olup, bireylerin ölüme



yükledikleri anlamlar doğrultusunda duygu ve davranışlarını etkiler (Badur, 2010). Bazı bireyler için ölüm acı duyma, bedenini kaybetme, yok olma, yalnız kalma gibi bir sonu çağrıştırırken, bazıları için ölümden sonra hayatın varlığı ile bir başlangıcı ifade edebilir (Erdoğan ve Özkan, 2007). Bireyler ölümün başka bir hayata geçiş olduğuna inansın ya da inanmasın, ölüm evrensel bir gerçektir ve bireyler için kaygı veren bir bilinmezliktir. Ölümün karşısında bir kavram gibi duran “yaşam” ise ölümden önceki mücadeleyi barındıran süreci kapsar. Bireylerin nasıl yaşadığı ve nasıl öldüğü birbiri ile bağlantılı olmakta, bir ömrün nasıl yaşandığı sorusuna verilen cevap, ölüme hazır olma yönünden değer kazanmaktadır (Seki Öz ve Kargın, 2020). Bu bakış açısı ile anlamlı bir yaşam, başarılı ve rahat bir ölüme katkı sağlamaktadır.

Salgınlar ve doğal afetler gibi büyük kitleleri etkileyen travmatik yaşam olayları doğası gereği beklenmedik ölümlerin yaşanması ve etki gücüyle ölümün varlığını hatırlatır, ölümün kaçınılmazlığı ile yüzleşmeyi zorunlu kılar. COVID-19 pandemisi ile dünya yeni bir küresel salgınla mücadele etmek zorunda kalmış, bu salgın iki yıllık süreçte 6.099.380 insanın ölümüne yol açmıştır (WHO, 2022). Bu durum ölümü güncel bir konu haline getirmiş, salgının etkisiyle her gün bildirilen ölüm olguları, yakınlarını kaybetme gibi deneyimler ile ölümün varlığı daha görünür bir hal almıştır. İnsanlık ölümle ilgili bilinmezlikle ölüme yönelik düşüncelerini bilinçaltına bastırarak (Yalom, 2020) ve ölümü başkalarının başına gelen bir olgu olarak kabul ederek baş edebiliyorken (Gashi, 2021), pandemiyle birlikte ölümün her an gerçekleşebileceği gerçeği ile karşı karşıya kalmıştır. Bu beklenmedik sürecin getirdiği belirsizlik bireylerin yaşadığı ruhsal sorunları artırarak maneviyat, manevi iyi oluş ve manevi bakım gibi kavramlarını ön plana çıkarmıştır.

Literatür incelendiğinde manevi iyi oluş ve ölüm algısına yönelik çalışmaların olduğu, ancak bu çalışmaların sıklıkla manevi bakım bağlamında hasta bireyler ile yapıldığı dikkat çekmektedir (Amirmohamadi ve ark., 2017; Gültekin, 2018; Kavalalı-Erdoğan, 2019; Öner, 2021). Koruyucu ve geliştirici ruh sağlığı girişimlerinin planlamasında herhangi bir hastalığa sahip olmayan bireylerin de incelenmesi ve bu doğrultuda durumun tanımlanması Kovid-19 pandemisiyle birlikte önem kazanmıştır. Bu nedenle bu çalışmada yetişkinlerin ölüm algısının manevi iyi oluş üzerindeki etkisini incelemek amaçlanmıştır. Bu sayede özellikle sağlık ve sosyal hizmet alanlarında yardım sunan meslekler için bu iki soyut kavramın birbirine olan etkisi ortaya konarak, uygun yaklaşımların geliştirilmesine fırsat sunulacaktır.

## 2. Materyal ve Yöntem

### 2.1. Araştırma Tasarımı

Kesitsel türde tanımlayıcı olarak gerçekleştirilen bu araştırmanın örneklemini 18-65 yaş arası kişiler oluşturmaktadır. Örneklem hesaplaması G\* Power programı kullanılarak yapılmıştır. Cohen (1988)

regresyon analizi için etki büyüklüğünü değerlerini  $0,02 \leq f^2 < 0,15$  değeri için küçük etki,  $0,15 \leq f^2 < 0,35$  değeri için orta etki,  $0,35 \leq f^2$  değeri için ise geniş etki şeklinde ifade etmiştir. Cohen değerleri referans alınarak lojistik regresyon için örneklem büyüklüğü hesaplaması yapılmıştır. Orta etki büyüklüğü değeri 0,25 alınarak tip I hata 0,05, tip II hata 0,20 (%80 güç) ile örneklem sayısı 488 olarak bulunmuştur. Araştırmaya dahil olma kriterleri olarak, 18-65 yaş aralığında olmak, Türkçe okuyup anlama ve araştırmaya katılmaya gönüllü olmak belirlenmiştir. Bu kapsamda oluşturulan çevrim içi bir anket linki ile olasılıksız örnekleme yapılarak, Haziran-Ekim 2021 tarihleri arasında toplamda 532 kişiye ulaşılmıştır. Veri temizliği yapılarak yaş grubuna uymayan ve ölçek maddelerine mükerrer giriş yapan kişilerin verileri silinerek 523 kişi araştırmaya dahil edilmiştir.

### 2.2. Veri Toplama Araçları

#### 2.2.1. Sosyo-demografik veri formu

Araştırmacılar tarafından oluşturulan bu form yaş, cinsiyet, eğitim düzeyi, medeni durumu, çalışma durumu, yaşadığı yer ve Kovid-19 geçirme durumunu vb. inceleyen 8 sorudan oluşmaktadır.

#### 2.2.2. Ölümün kişisel anlamları ölçeği (ÖKAÖ)

Cicirelli (1998) tarafından ölüme atfedilen anlamları yani ölüm algısını ölçmek amacıyla geliştirilmiş bir ölçektir. Ölçeğin Türkçe geçerlilik ve güvenilirlik çalışması 2005 yılında Koçanoğlu (2005) tarafından yapılmıştır. Ölümün Kişisel Anlamları Ölçeği “Yok Olma”, “Ölüm Sonrası Hayat” ve “Motivasyon/Geride Anlamlı Şeyler Bırakmak” olmak üzere 3 alt boyut ile 15 maddeden oluşan 5’li Likert tipi cevaplama seçeneği içeren bir ölçektir. Alt boyutlardan elde edilen yüksek puan, bireylerin ölüme verdiği anlamı ifade etmektedir. Koçanoğlu’nun (2005) çalışmasında Ölümün Kişisel Anlamları Ölçeği’nin, Yok Olma alt boyutu Cronbach Alpha güvenilirlik katsayısı 0,78, Motivasyon/Geride Anlamlı Şeyler Bırakma Cronbach Alpha güvenilirlik katsayısı 0,72, Ölüm Sonrası Hayat Cronbach Alpha güvenilirlik katsayısı 0,82 olarak bulunmuştur.

#### 2.2.3. Manevi iyi oluş ölçeği (MİÖÖ)

Ekşi ve Karadağ tarafından 2017 yılında geliştirilen ölçek 5’li Likert tipte cevaplama seçeneği içeren 29 maddeden oluşmaktadır. Ölçek 3 boyut üzerinden değerlendirilebileceği gibi toplam puan üzerinden de değerlendirilebilmektedir. Ölçekten alınan puan arttıkça manevi iyi oluşun arttığı söylenebilir. Geliştirme çalışmasında ölçeğin Cronbach Alpha iç tutarlık kat sayısı 0.886 olarak bulunmuştur.

### 2.3. İstatistik Analizi

Bu araştırma verilerinin analizi SPSS 23.0 programı ile yapılmıştır. Öncelikle kategorik olan demografik verilerin sayı yüzde dağılımları, sürekli değişkenlerin ise minimum-maksimum değerleri ile ortalamaları ve standart sapmaları hesaplanmıştır. Verilerin normal dağılıma uygunluğu Kolmogorov-smirnov testi ile değerlendirilmiştir. Ölçeklerin iç tutarlık kat sayıları Cronbach Alpha ile değerlendirilmiş olup, toplam puanlar arası ilişkiler de korelasyon katsayılarıyla incelenmiştir.

Katılımcıların manevi iyi oluş düzeylerinin yordanması için ise lojistik regresyon analizine başvurulmuştur.

### 3. Bulgular

Katılımcıların sosyo-demografik özelliklerine bakıldığında; %65,8'inin kadın, %57,2'sinin evli, %54,7'sinin üniversite mezunu, %70,2'sinin gelir durumunun orta olduğu görülmektedir. Ayrıca katılımcıların %53,9'u il merkezinde yaşamakta, %59,8' i gelir getiren bir işte çalışmaktadır. Katılımcıların %24'ünün ise KOVİD-19 enfeksiyonu geçirdiği görülmektedir (Tablo 1).

Kullanılan ölçeklerin Cronbach Alpha iç tutarlık katsayıları Yok Olma faktörü için 0,843, Ölüm Sonrası Hayat faktörü için 0,760, Motivasyon/Geride Anamlı Şeyler Bırakmak faktörü için, 0,832, Manevi İyi Oluş Ölçeği için ise 0,885 olarak bulunmuştur. Sürekli değişkenlerin ortalama puanları ise Yok Olma faktörü için 17,34±5,06, Ölüm Sonrası Hayat faktörü için 11,45±2,79, Motivasyon/Geride Anamlı Şeyler Bırakmak faktörü için, 23,80±6,01, Manevi İyi Oluş Ölçeği için 120,41±14,67 ve yaş değişkeni için ise 34,36±12,16 olarak bulunmuştur (Tablo 2). Toplam puanlar arasında yapılan çoklu korelasyon analizi sonuçları incelendiğinde kat sayıların

0,015 ile 0,406 arasında değiştiği görülmektedir (Tablo 2). Manevi İyi Oluş Ölçeği ortalama puanı esas alınarak ortalama puanın altı düşük, üstü yüksek olmak üzere iki kategori oluşturulmuş, sonra da manevi iyi oluş durumu çoklu lojistik regresyon analizi ile yordanmıştır. Nicel sürekli bağımsız değişkenler olarak Ölümün Kişisel Anlamları Ölçeği faktör puanları ve yaş, kategorik bağımsız değişkenler olarak da cinsiyet, eğitim durumu, medeni durum, gelir durumu, gelir getiren bir işte çalışma ve KOVİD-19 enfeksiyonu geçirme durumu değişkenleri alınarak Wald İleriye Doğru (Forward Wald) yöntemiyle çoklu lojistik regresyon modeline eklenmiştir. Yapılan analiz sonucunda modele, Yok Olma ve Ölümünden Sonra Hayat faktörü, yaş ve çalışma durumu girerken diğer değişkenler model dışında kalmıştır. Sonuçlara göre model-veri uyumunu değerlendiren Hosmer ve Lemeshow testine göre model uyumlu çıkmıştır ( $\chi^2$  HL (8)=3,654; P=0,887). Nagelkerke sözde (Nagelkerke pseudo) R<sup>2</sup> değerine göre oluşturulan model toplam varyansın %30,9'unu açıklamaktadır. Şans eseri doğru sınıflandırmanın orantılı yüzdesine (%56,1) oranla artış %16,5'dir. Bu artış oranıyla genel isabet oranı %72,6 olarak belirlenmiştir. Manevi iyi oluşu düşük olan grup için %65,1, yüksek olan grup için %78,5 doğru tahmin oranları bulunmuştur.

**Tablo 1.** Sosyodemografik değişkenlerin dağılımları

Değişkenler	Gruplar	n	%
Cinsiyet	Erkek	179	34,2
	Kadın	344	65,8
Medeni durum	Bekar	224	42,8
	Evli	299	57,2
	İlkokul- Orta Okul	38	7,3
Eğitim durumu	Lise	135	25,8
	Üniversite	286	54,7
	Lisansüstü	64	12,2
Yaşanılan yer	İl	282	53,9
	İlçe	241	46,1
	Düşük	65	12,4
Gelir durumu	Orta	367	70,2
	İyi	91	17,4
Gelir getiren bir işte çalışma durumu	Çalışan	313	59,8
	Çalışmayan	210	40,2
KOVİD-19 enfeksiyonu geçirme durumu	Evet	136	24,0
	Hayır	387	76,0
Toplam		523	100,0

**Tablo 2.** Ölçeklerin betimleyici istatistikleri, iç tutarlık ve korelasyon katsayıları

	Alfa	Min-Maks	Ort.	SS	1	2	3	4	5
1. ÖKAÖ-Yok olma	0,843	5-25	17,34	5,06					
2. ÖKAÖ-Ölüm sonrası hayat	0,760	3-15	11,45	2,79	0,065				
3. ÖKAÖ-Motivasyon/ Geride Anamlı şeyler bırakmak	0,832	7-35	23,80	6,01	0,300**	0,567**			
4. Yaş	-	18-67	34,36	12,16	0,133**	0,009	-0,072		
5. Çalışma durumu	-	-	-	-	-0,015	0,089*	0,089*	-0,406**	
6. Manevi iyi oluş ölçeği	0,885	39-145	120,41	14,67	-0,078	0,398**	0,153**	0,326**	-0,198**

**Tablo 3.** Manevi iyi oluş gruplarının yordanması için çoklu lojistik regresyon analizi sonucu

	B	s.h.	Wald	s.d.	P	Exp(B)	%95 G. A. Exp(B)
Yok olma	-0,098	0,02	20,16	1	0,000	0,91	0,869-0,946
Ölüm sonrası hayat	0,324	0,04	58,54	1	0,000	1,38	1,272-1,502
Yaş	0,05	0,01	35,41	1	0,000	1,06	1,040-1,080
Çalışma durumu	0,50	0,23	4,95	1	0,026	1,66	1,062-2,588
Sabit	-3,98	0,64	38,49	1	0,000	0,02	
Nagelkerke sözde R <sup>2</sup>	0,309						

Wald testi, bağımsız değişkenler olarak Yok Olma faktörü puanının ( $\chi^2$  Wald (1)=20,16; P<0,001), Ölüm Sonrası Hayat faktörü puanının ( $\chi^2$  Wald (1)=58,54; P<0,001), yaşın ( $\chi^2$  Wald (1)=35,41; P<0,001) ve çalışma durumunun ( $\chi^2$  Wald (1)=4,95; P<0,001) manevi iyi oluş düşük ve yüksek gruplarından birine düşmenin istatistiksel olarak anlamlı yordayıcıları olduğunu göstermiştir (Tablo 3).

#### 4. Tartışma

Bu çalışmada manevi iyi oluşun yordayıcıları olarak sosyodemografik değişkenler ve ölüm algısının ölçümleri alınmıştır. Böylece çalışmaya katılan kişilerin manevi iyi oluşunun ölüme verilen anlamlardan hangileriyle yordandığının belirlenmesi amaçlanmıştır. Ölüm algısının yanı sıra yaş, cinsiyet, eğitim durumu, medeni durum, ekonomik durum ve çalışma durumu değişkenlerinin de manevi iyi oluşa etki edip etmediği incelenmiştir. Elde edilen sonuçlar çalışmaya alınan kişilerin, yordayıcı bağımsız değişkenler kümesinin manevi iyi oluş durumu düşük ve yüksek grupları %72,6 genel isabet oranıyla ayırdığını ve en baştaki tahmini sınıflandırma oranını %16,5 arttırdığı görülmüştür. Wald testi sonuçlarına göre manevi iyi oluş puanının yordanmasında bağımsız değişkenler olarak önem sırasına göre Yok Olma faktörü puanındaki bir puanlık artış 0,91 kat (%95 G.A. = 0,869-0,946), Ölüm Sonrası Hayat faktörü puanındaki bir puanlık artış 1,38 kat (%95 G.A. = 1,272-1,502), yaştaki bir birimlik artış 1,06 kat (%95 G.A. = 1,040-1,080) artış sağlamaktadır. Ayrıca çalışanlarda çalışmayanlara göre manevi iyi oluş 1,66 kat (%95 G.A. = (%95 G.A. = 1,062-2,588) artmaktadır.

Manevi iyi oluş kavramı insan yaşamında bir anlam bulmasıyla ve üstün bir güçle ilişki kurmasıyla ilişkili bir kavramdır. Araştırma bulgusu olan ölümden sonra hayata yönelik anlam arttığında, manevi iyi oluş artmakta; ölüme bir yok olma anlamı yüklemenin ise manevi iyi oluşu olumsuz etkilediği görülmüştür. Ölüm bilinmezlikleri ve kaygıyı içinde barındıran karmaşık bir olgudur, ölüme ve ölümden sonraki hayata yönelik en doyumsuz açıklamalar ise dinler tarafından sağlanmaktadır. Literatür incelendiğinde din değişkeninin ve dolayısıyla ölümden sonra hayatın varlığına inanmanın ölüm kaygısını hafifletmede etkili olduğunu gösteren araştırmalar olduğu görülmektedir (Richardson ve ark., 1983; Roff ve ark., 2002; Falkenhain ve Handal, 2003; Tanhan, 2007; Şahin, 2016). Manevi iyi oluşun dinsel iyilik ve varoluşsal iyilik

hali olarak iki alt boyutu tanımlanmıştır. Dinsel iyilik hali insanın üst varlıkla ilişkisinde manevi yaşamında hissettiği doyum, memnuniyet ve tatmin olarak açıklanmıştır (Acar, 2014). Dolayısıyla bir dini tercih eden bireyler hayatının anlamını oluşturup, hayata daha özgüvenli bakabilir, ölümden sonra yaşamın farklı boyutta olsa da devam edeceği düşüncesi, yaşamı daha anlamlı hale getirebilir ve bu bakış açısı bireylerin manevi iyi oluşlarını artırabilir. Ölümü yok olma durumu olarak değerlendiren bireyler için de benzer şekilde, ölüm sonrası süreci bir yokluk, bitiş, kaybolma gibi değerlendiren bakış açısı manevi iyi oluşu azaltabilir (Başar, 2013). Ayrıca, manevi iyi oluşun özellikle zorlu yaşam deneyimleri ve travmalarla baş etmede önemli katkılar sunduğu literatürde tanımlanmaktadır (Restrepo-Madero ve ark, 2016; Uğurluoğlu ve Erdem, 2019). Ölüm gibi henüz yaşanılmamış ama yaşanılması kaçınılmaz olan bir gerçeğin varlığıyla yaşamı sürdürmek zorunda olan bireyin, bu belirsizlikle de maneviyatını güçlü tutarak baş ettiği söylenebilir.

Araştırmada çalışma durumunun manevi iyi oluşu etkileyen bir değişken olduğu, bir işte çalışmanın manevi iyi oluşu artırdığı saptanmıştır. Amirmohamadi ve ark. (2017) kanser hastalarıyla yaptığı çalışmada, çalışan hastaların çalışmayan hastalara göre manevi iyi oluş düzeylerinin daha yüksek olduğu belirlenmiştir. Psikiyatrik bozukluğa sahip bireylerle yapılan başka bir çalışmada bireylerin çalışma hayatı içinde olmaları ile manevi iyi oluş düzeylerinin daha yüksek olduğu bulunmuştur (Gültekin, 2018). Cerrahi onkoloji hastaları ile yapılan çalışmada ise bir işte çalışan hastaların, çalışmayanlara göre manevi iyi oluşlarının daha yüksek olduğu saptanmıştır (Öner, 2021). Ata'nın (2018) onkoloji hastalarıyla gerçekleştirdiği çalışmada da bir işte aktif olarak çalışan hastaların manevi iyi oluş düzeyleri daha yüksek düzeyde bulunmuştur. Araştırma bulgusunun literatürle uyumlu olduğu görülmektedir. Manevi iyi oluşun bireylerin kendisiyle ve çevresiyle olan bir tür psikolojik ve zihinsel sağlık durumu olduğu düşünüldüğünde, bir işte çalışıyor olmanın hem kişisel doyum sağlaması hem de çevresiyle daha çok etkileşim halinde olmasını sağlayarak bireylerin manevi iyi oluş düzeylerine olumlu katkı sağladığı düşünülebilir. Manevi iyi oluşu yükseltmek için bazı gereksinimler tanımlanmıştır. Bu gereksinimler güven, doğruluk, umut, yaşamın anlamı ve amacını bulma arzusu, iyi ilişkiler kurma, konuşma, yaratıcılık, tecrübe kazanma, teselli,

ritüeller, dua etme ve ibadet etme olarak sıralanmaktadır (Arslan ve Konuk Şener, 2009). Manevi iyi oluşun yaşamın anlam ve amacına yönelik varoluşsal boyutu dini inanıştan bağımsız olarak değerlendirilebilir (Moberg ve Brusek, 1978). Çalışan bireylerde manevi iyi oluşun daha yüksek bulunmasının bireylerin meslek edinme sürecinden sonra bir işte çalışarak hem yaşamında anlam ve amaç edindiği hem de iyi ilişkiler kurma, konuşma, yaratıcılık, tecrübe kazanma gibi manevi ihtiyaçlarını karşılamada çalışma ortamının fırsatlar sunduğu söylenebilir.

Araştırmada yaş arttıkça manevi iyi oluşun da arttığı bulunmuştur. Tate ve Forchheimer'in (2002) çalışmasında ileri yaş grubundaki hastaların manevi iyi oluş puanının genç yaştaakilere göre daha yüksek olduğu ifade edilmiştir. Bir başka çalışmada benzer şekilde ileri yaştaki hastaların manevi iyi oluşlarının daha yüksek düzeyde olduğu bulunmuştur. (Peterman, ve ark., 2002). Yetişkin bireylerde yaş ilerledikçe yaşamın doğal akışı içinde gerçekleşen eşin ya da yakın arkadaşların ölümü, emekli olma, rol değişiklikleri, kronik ya da ölümcül hastalıkların tanısını alma gibi durumlar bireylerin stres düzeyini artırmakta ve bu durumlar anksiyete, depresyon gibi ruhsal sorunların yaşanmasına yol açabilmektedir (Klavuz ve Klavuz, 2016). Yaşlılık döneminde yaşanan kayıplarla baş etmede dini ve manevi eğilimler önemli bir yer tutar. Yetişkin bireylerin yaş ilerledikçe yaşadıkları kayıpların yerine duygusal ve manevi boyutta destek sağlamaları yaşama tutunmalarına yardımcı olabilmektedir (Gürsu ve Ay, 2018). Manevi doyumu sağlamak, yaşlılık döneminde oluşan bu değişimlerle ve ortaya çıkan stresle başa çıkmalarında önemli bir katkı sunmaktadır. Bu nedenle bireylerin bu döneme ait zorluklarla başa çıkmasında üstün bir güce sığınması, onunla iletişime geçerek yardım istemesi ve bu süreci atlama rehberlik beklemesi maneviyatın etkin bir biçimde kullanıldığını ve bu nedenle yaş ilerledikçe manevi iyi oluşun doğal olarak arttığını gösterebilir.

Ölümcül hastalıklar, stres, travmatik olaylar, kayıplar, afetler, salgınlar gibi yaşam olayları bireylerin manevi iyi oluşunu etkileyerek, manevi ihtiyaçlarını keşfetmesine ya da bu ihtiyaçlarının ortaya çıkmasına neden olabilir (Eğlence ve Şimşek, 2014). Manevi iyi oluşun sağlanmasının yollarından biri manevi bakımdır. Manevi bakım sadece hastaların değil aynı zamanda riskli grupların ve sağlıklı bireylerin anlam ve amaç bulmaları, içindeki buldukları zorlayıcı durumlar ile etkili biçimde baş edebilmelerini sağlayan varoluşsal ve inançlara ilişkin desteklerin sağlanmasıdır. Diğerleri ile etkileşime girme, başkasına yararlı olma, saygı duyma, şefkat gösterme ile oldukça ilgili olan bu kavram bir başkasının ruhuna dokunma/ulaşma çabasıdır (Baird, 2010; Ferrel ve Munevar, 2012; Erişen ve Sivrikaya, 2017). Sağlıklı bireylerin ölüm algısının manevi iyi oluşlarına etkisini değerlendiren bu çalışma ile sağlıklı bireylerin manevi bakım gereksinimlerinin tanımlanması ve sağlığın geliştirilmesine yönelik ruh sağlığı girişimleri içinde maneviyatın da ele alınmasının gerekliliği görülmektedir.

## 5. Sonuç

Manevi iyi oluş, yaşamı anlamlandırma, geleceğe umutla bakma, güçlükler karşısında dirayetli davranma ve kendine güvenme gibi konularda bireylerin iyi olma düzeylerini tanımlamaktadır. Çalışmada ölümden sonra hayatın varlığına inanmanın, ileri yaşta olmanın ve çalışmanın manevi iyi oluşu artırdığı, ölümü yok olma olarak algılamanın ise manevi iyi oluşu azalttığı saptanmıştır. Bu doğrultuda yetişkin bireylerin ruh sağlığını koruma ve geliştirmede önemli bir yeri olan manevi iyi oluşun ölüme atfedilen anlamlardan etkilendiği söylenebilir. Manevi iyi oluşu etkileyen değişkenlerinin tanımlanması ruhsal bakımın içerisine maneviyatın nasıl ekleneceği ve destekleneceğini göstermesi açısından önemlidir. Bununla birlikte manevi bakımla hedeflenen manevi iyi oluşun yükseltilmesi amacına ancak bu kavramı etkileyen durumların bilinmesi ile ulaşılabilir. Koruyucu ruh sağlığı hizmetlerinin ulaştığı grup olan sağlıklı bireylerin manevi iyi oluşlarının yükseltilmesi için bireylerin ölümü algılama ve yorumlama biçimleri üzerinde durulabilir. Ayrıca manevi iyi oluşu yükselten bazı uygulamaların deneysel çalışmalar ile ortaya konulması, konu ile ilgili boyutsal çalışmalar yapılması önerilebilir.

### Katkı Oranı Beyanı

Konsept: D.A. (%50) ve H.S.Ö. (%50), Tasarım: D.A. (%50) ve H.S.Ö. (%50), Denetim: D.A. (%50) ve H.S.Ö. (%50), Veri toplama ve/veya işleme: D.A. (%50) ve H.S.Ö. (%50), Veri analizi ve/veya yorumlama: D.A. (%50) ve H.S.Ö. (%50), Kaynak taraması: D.A. (%50) ve H.S.Ö. (%50), Yazma: D.A. (%50) ve H.S.Ö. (%50), Eleştirel inceleme: D.A. (%50) ve H.S.Ö. (%50), Gönderim ve revizyon: D.A. (%50) ve H.S.Ö. (%50). Tüm yazarlar makalenin son halini incelemiş ve onaylamıştır.

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## EFFECT OF APACHE-II AND THE AGE-ADJUSTED CHARLSON COMORBIDITY INDEX AT PREDICTING MORTALITY IN PATIENTS WITH COVID-19

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**Abstract:** The COVID-19 pandemic disproportionately affects patients with comorbidities. Comprehensive comorbidity assessment is important in establishing the risk stratification of patients with COVID-19 after hospital admission. In this study, our aim is to investigate the effectiveness of Acute Physiology and Chronic Health Assessment II (APACHE-II) and Age Adjusted Charlson Comorbidity Index (ACCI) in predicting mortality in COVID-19 patients admitted to the Intensive Care Unit (ICU). Patients aged >18 years who were admitted to the intensive care unit with the diagnosis of COVID-19 pneumonia in the Health Sciences University Bursa Yüksek İhtisas Training and Training Hospital between July 2021 and September 2021 were included in the study. The medical records of the patients were then scanned into the hospital automation system. Demographics, comorbidities, clinical features, laboratory parameters, APACHE-II score, treatments, and outcomes were recorded in a standard form. ACCI score was calculated from the data and recorded. The 276 patients analyzed were divided into two groups as surviving (n=129) and developing mortality (n=147). The mortality rate was 58.93%, mostly male (58%), median age 65 years, ACCI score 1 (IQR.3) and APACHE-II score 2 (IQR.8). There was no difference between the groups in terms of age, gender distribution and APACHE-II score (P= 0.519, P= 0.927, P= 0.364, respectively). The groups did not differ in terms of comorbidity except for chronic renal failure (CRF), and CRF was significantly higher in patients who developed mortality (P= 0.037). The ACCI score was found to be higher in patients who developed mortality (P= 0.034). Death risk; Those with an ACCI score of >2 were 2.26 times higher than those with an ACCI score of ≤2 (P= 0.021). The APACHE-II score did not differ between the groups in terms of mortality (P= 0.380). As a result, high ACCI score was found to be effective in predicting mortality. It could potentially be used to identify at-risk patients infected with COVID-19 and to predict their clinical status.

**Keywords:** COVID-19 pneumonia, Comorbidity, Index, APACHE-II score, Intensive care unit, Mortality

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### 1. Introduction

The coronavirus disease (COVID-19) that emerged in Wuhan, China in December 2019 spread rapidly due to its high contagiousness and was defined as a pandemic. Since then, total confirmed cases and deaths continue to rise worldwide. As of 25 April 2022, the World Health Organization (WHO, 2022) reported approximately 507,501,771 confirmed cases of COVID-19 globally, including 6,220,390 deaths (WHO, 2022).

In patients diagnosed with COVID-19; studies have been conducted to show the impact of clinical, demographic, laboratory, epidemiological and radiological characteristics on mortality (Li et al., 2020). Many descriptive observational studies have also found that patients with comorbidities are disproportionately affected by COVID-19 and are associated with poorer clinical outcomes (Christensen et al., 2020; Guan et al., 2020; Shanbhag et al., 2021). Therefore, comprehensive

assessment of comorbidities for risk stratification of hospitalized patients with COVID-19 and accurate prediction of prognosis are important for clinical management and outcomes.

The age-adjusted Charlson comorbidity index (ACCI) evaluates age and 19 medical comorbidities to calculate the total score with a specific score assigned to each comorbid condition. ACCI is a simple and easily applicable scoring system for estimating the risk of death from comorbid disease (Charlson et al., 1987; Bannay et al., 2016). In recent studies on COVID-19 patients; the ACCI score has been stated to have an independent prognostic value, confirming its use to predict adverse outcomes in terms of COVID-19 disease severity and mortality (Richards et al., 2011; Ferroni et al., 2020).

Acute Physiology and Chronic Health Assessment II (APACHE-II) is a widely used assessment to predict disease severity and in hospital mortality in critically ill



patients in the intensive care unit (ICU) (Richards et al., 2011; Sun et al., 2017). It is a scoring system that helps predict mortality within 24 hours of admission ICU, using the patient's findings, various laboratory values, and acute and chronic diseases. There are many studies evaluating various organ functions and predicting mortality in COVID-19 patients using the APACHE-II score (Zou et al., 2020; Cheng et al., 2021).

In this study, we evaluated the effectiveness of the APACHE-II score and the ACCI, which shows comorbid burden of disease, in predicting the risk of death in patients with COVID-19 infection admitted to the ICU.

## 2. Materials and Methods

Patients under 18 years of age and missing data were excluded from the study. The clinical records of the patients were scanned retrospectively by entering the hospital automation system. Demographic data, comorbidities, clinical features, laboratory parameters, APACHE-II score, treatments and results were collected and recorded in a standard form. ACCI score was calculated from the available information and recorded.

A Shapiro-Wilk test was used to assess whether the variables followed normal distribution. Variables were reported as median (interquartile range) values. According to the normality test results, Mann Whitney U test was used to compare the study groups. Categorical variables were compared by Chi-square test and Fisher's exact test. In order to estimate the sensitivity and specificity of ACCI and APACHE-II scores for predicting the presence of mortality, receiver operator characteristic (ROC) curve analysis was performed. Logistic regression analysis was performed to determine the risk factors affecting mortality. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used for performing statistical analysis and type I error was accepted as 5%.

## 3. Results

There were 284 patients admitted with the diagnosis of COVID-19 infection in the ICU between 15 July 2021 and 15 September 2021. Data for 8 patients were insufficient for this study. Variables were recorded for a total of 276 patients, and the patients were divided into two groups: those who survived (n=129) and those who developed mortality (n=147) (Figure 1). The patients were mostly male (58%), median age 65 (57-74.7) years, median ACCI score of 1 (IQR.3) and APACHE-II score of 20 (IQR.8).

In terms of comorbidities, 44.6% of patients had hypertension (HT), 27.5% had diabetes mellitus (DM), 21.4% had coronary artery disease (CAD), 15.6% had chronic obstructive pulmonary disease (COPD), 9.1% had heart failure (HF), 4.32% had chronic renal failure (CRF), and 3.6% had cerebrovascular disease (CVD). Eighty-eight (31.9%) of the patients came to the ICU intubated. 116 (42.03%) were intubated median 5(IQR.5) days after

admission to ICU. The median length of stay in the total ICU was 10 (IQR, 8) days (Table 1).

The mortality rate was 58.93%. There was no difference between the groups in terms of age and gender distribution. It was determined that the ACCI score was higher in patients who developed mortality (P= 0.034). The APACHI-II score did not differ between the groups (P= 0.364). There was no difference between the groups in the distribution of comorbid diseases shown in Table 1, except for CRF. Chronic renal failure was observed at a rate of 6.70% in patients who developed mortality, and this result was significantly higher (P= 0.037).

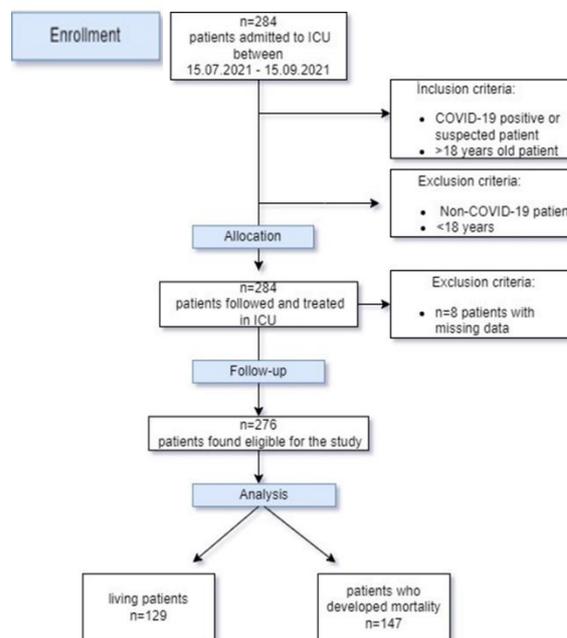


Figure 1. Flowchart of the study.

Coming to the intensive care unit intubated did not differ between patients who survived and those who developed mortality (P= 0.096). It was determined that among 116 patients who were intubated after coming to the ICU, the rates of intubation did not differ between patients who developed and survived mortality (P= 0.409). It was determined that 50 patients who were subsequently intubated in the mortality group were intubated on a median 4 (IQR,6) days when they came to the ICU and on a median 5 (IQR,4) days in the living group, and there was no difference between the groups in terms of the number of days of intubation in the ICU (P= 0.308). The length of stay in the ICU was longer in patients who developed mortality compared to those who survived (median 11 (IQR, 9.5) days, median 9 (IQR,6) days, P= 0.002, Table 1). The laboratory values of the patients who came to the ICU are shown in Table 1. There was no difference between the groups except for fibrinogen. Fibrinogen level was found to be significantly higher in patients with mortality (P= 0.019).

The distribution of treatments administered to patients in the ICU is shown in Table 2. Steroid treatment was used in 95.3% of the patients. There was no difference

between the groups in terms of all treatments used (P= 0.576, P= 0.109, P= 0.323, P= 0.458, P> 0.99, P= 0.358, "respectively). Vasopressor therapy, cytokine filter, Anakinra therapy, and dialysis application rates in the ICU were found to be significantly higher in patients who developed mortality than in patients who survived (P< 0.001, P= 0.008, P= 0.041, P= 0.014, respectively, Table 2).

Receiver operator characteristic (ROC) curve analysis was performed to estimate the sensitivity and specificity of ACCI for predicting the presence of mortality, and the cut-off point for ACCI was determined as >2. The area under the curve for ACCI was 0.58 (sensitivity 34.23%,

specificity 77.95%, P= 0.031), showing that a CCI> 2 was significantly related to an increased risk of the presence of mortality (Figure 2). In our study, the ACCI score of 79 patients was >2, and the ACCI score of 197 patients was ≤2. The incidence of mortality was 64.60% (n=51) and 49.70% (n=98), respectively, and the mortality rate was found to be higher in the patient group with ACCI score >2 in the Univariate logistic regression model (P= 0.027, Table 3). However, in our study, the cut-off point could not be determined to predict the presence of mortality for the APACHE-II score. As a result of ROC analysis, it was determined that the area under the curve was not significant (AUC=0.53, P= 0.368).

**Table 1.** Demographic characteristics and comorbidities of the patients<sup>s</sup>

	Total (n=276)	Ex (n=149)	Survival (n=127)	p
Age (years), n (%)				
<50	39(14.10)	23(15.40)	16(12.60)	
50-59	47(17)	26(17.40)	21(16.50)	
60-69	87(31.50)	41(27.50)	46(36.20)	0.519 <sup>a</sup>
70-79	63(22.80)	34(22.80)	29(22.80)	
≥80	40(14.50)	25(16.80)	15(11.80)	
Gender, n (%)				
Female	116(42)	63(42.30)	53(41.70)	0.927 <sup>a</sup>
Male	160(58)	86(57.70)	74(58.30)	
ACCI, median	1(3), 1.83(±2.09)	1(3), 2.10(±2.28)	1(2), 1.50(±1.77)	0.034 <sup>b</sup>
APACHE II, median	22(8)	22(8:39)	20(8:39)	0.364 <sup>b</sup>
Comorbidity, n (%)	188(68.1)	98(52,1)	90(47.9)	0.365 <sup>a</sup>
HT	123(44.60)	62(41.60)	61(48)	0.285 <sup>a</sup>
DM	76(27.50)	40(26.80)	36(28.30)	0.781 <sup>a</sup>
CAD	59(21.40)	33(22.10)	26(20.50)	0.735 <sup>a</sup>
CF	25(9.10)	15(10.10)	10(7.90)	0.527 <sup>a</sup>
COPD	43(15.60)	23(15.40)	20(15.70)	0.943 <sup>a</sup>
CVD	10(3.60)	5(3.40)	5(3.90)	>0.99 <sup>c</sup>
CRF	12(4.30)	10(6.70)	2(1.60)	0.037 <sup>a</sup>
Coming to ICU, n (%)				
Intubated	88(31.90)	55(62.50)	33(37.50)	0.052 <sup>a</sup>
Not intubated	188(68.10)	94(50.00)	94(50.00)	
number of days intubated, median*	1(0)	1(0)	1(0)	0.978 <sup>a</sup>
Intubation in ICU, n (%)	116(42,03)	66(44.30)	50(39.40)	0,409 <sup>a</sup>
Intubation day in ICU, **median	5(5)	4(6)	5(4)	0,308 <sup>b</sup>
Laboratory findings, median				
WBC	11.88(7.43)	12(7.53)	11.55(7.41)	0.820 <sup>a</sup>
Lymphocyte	0.70(0.53)	0.65(0.55)	0.75(0.59)	0.132 <sup>a</sup>
platelet	254(147)	241(165.50)	259(135)	0.225 <sup>a</sup>
CRP	121.50(122.30)	116(122.15)	126(123.20)	0.450 <sup>a</sup>
INR	1.08(0.34)	1.10(0.36)	1.08(0.33)	0.949 <sup>a</sup>
Fibrinogen	598.50(442.30)	628(457)	574(377)	0.019 <sup>a</sup>
D'Dimer	2.68(5)	2.57(5)	3(4)	0.618 <sup>a</sup>
Ferritin	860.50(933)	893(881)	795(1030)	0.706 <sup>a</sup>
LDH	561(401)	568(373)	561(433)	0.667 <sup>a</sup>
Number of days of hospitalization in ICU, median	10(8)	11(9.50)	9(6)	0.002 <sup>a</sup>

<sup>s</sup>Data were reported as median (interquartile range), mean (± standard deviation) or n (%).

\*It was calculated on n=88 patients who came to the ICU as intubated.

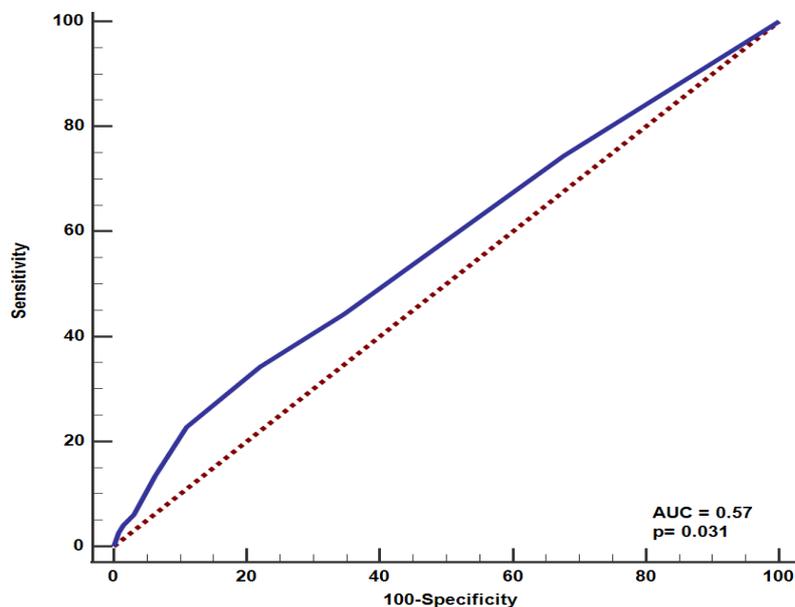
\*\*It was calculated on n=116 patients who were intubated after coming to the ICU. <sup>a</sup>Chi-square Test, <sup>b</sup>Mann-Whitney U Test, <sup>c</sup>Fisher's Exact Test

**Table 2.** Distribution of treatments applied to patients

n(%)	Total (n=276)	Ex (n=149)	Survival (n=127)	p
ICU hospitalization oxygen requirement				
Intubated	88(31.90)	55(36.90)	33(26.00)	
HFO	130(47.10)	65(43.60)	65(51.20)	
CPAP	32(11.60)	15(10.10)	17(13.40)	0.323 <sup>a</sup>
O <sub>2</sub> mask with reservoir	13(4.70)	8(5.40)	5(3.90)	
Nasal oxygen	13(4.70)	6(4.00)	7(5.50)	
Steroid use in the ICU				
Steroid Given in ICU	263(95.30)	141(94.60)	122(96.10)	0.576 <sup>a</sup>
Methylprednisolone	210(76.10)	106(71.10)	104(81.90)	
Dexamethasone	53(19.20)	35(23.50)	18(14.20)	0.109 <sup>a</sup>
None	13(4.70)	8(5.40)	5(3.90)	
Steroid Dose*				
1000 mg	27(10.30)	10(7.10)	17(13.90)	
500 mg	6(2.30)	4(2.80)	2(1.60)	
250 mg	104(39.50)	52(36.90)	52(42.60)	
120 mg	12(4.60)	5(3.50)	7(5.70)	
80 mg	49(18.60)	26(18.40)	23(18.90)	
40 mg	2(0.80)	1(0.70)	1(0.8)	
20 mg	8(3)	6(4.30)	2(1.60)	
8 mg	38(14.40)	26(18.40)	12(9.80)	
6 mg	14(5.30)	9(6.40)	5(4.10%)	
4 mg	3(1.10)	2(1.40)	1(0.80)	
ICU vasopressor therapy				
Cytokine filter	176(63.80)	130(87.2)	46(36.20)	<0.001
Immunoplasma therapy	8(2.90)	8(5.40)	0	0.008 <sup>c</sup>
Kaletra	7(2.54)	5(3.40)	2(1.60)	0.458 <sup>c</sup>
Ritonavir/ Lopinavir	7(2.54)	4(2.70)	3(2.40)	>0.99 <sup>c</sup>
Dialysis	9(3.26)	8(5.40)	1(0.80)	0.041 <sup>c</sup>
Dialysis	26(9.42)	20(13.40)	6(4.70)	0.014 <sup>a</sup>
Need for plasmapheresis	36(13.04)	22(14.80)	14(11.0)	0.358 <sup>a</sup>

<sup>§</sup>Data were reported as n (%). HFO= high flow oxygen, CPAP= continuous positive airway pressure.

\*It was calculated on n=263 patients given steroids. <sup>a</sup>Chi-square Test, <sup>c</sup>Fisher's Exact Test



**Figure 2.** Receiver-operator characteristic (ROC) curves for determining the presence of mortality. The area under the curve (AUC) for Charlson Comorbidity Index is 0.58 with P= 0.031.

Logistic regression analysis was performed to determine the factors affecting the development of mortality and the results are presented in Table 3. Variables were first tested with univariate logistic regression analysis and variables satisfying the  $P < 0.20$  condition were included in the multivariate logistic regression model. The regression model created as a result of the analysis was found to be significant ( $P < 0.001$ ) and it was determined that the data set was compatible with the regression model ( $P = 0.147$ ). When Table 3 is examined; It was

determined that the risk of mortality in patients with a CCI score of  $>2$  was 2.26 times higher than in the  $CCI \leq 2$  patient group. Again, it was determined that the risk of mortality in patients with a need for vasopressors was 12.48 times higher than in patients without a need for vasopressors. It was determined that the patient's length of stay in the ICU, the presence of CRF, the patient's intubated admission to the ICU, and the patient's dialysis did not affect mortality.

**Table 3.** Identification of risk factors affecting mortality development

	Univariate LRM			Multivariate LRM		
	Wald	OR(95%CI)	p	Wald	OR (95%CI)	p
Age (years)						
<50	0.12	0.86(0.37:2.03)	0.733			
50-59	1.50	0.62(0.29:1.33)	0.220			
60-69	0.25	0.82(0.36:1.83)	0.621			
70-79	0.10	1.16(0.47:2.86)	0.748			
ICU hospitalization period	8.28	1.06(1.02:1.10)	0.004	2.02	1.03(0.99:1.09)	0.156
HT (presence)	1.14	0.77(0.48:1.24)	0.285			
DM (presence)	0.08	0.93(0.55:1.58)	0.781			
CAH (presence)	0.11	1.11(0.62:1.98)	0.735			
KY (presence)	0.40	1.31(0.57:3.03)	0.528			
COPD & ASTHMA (presence)	0.01	0.98(0.51:1.88)	0.943			
SVO (presence)	0.07	0.85(0.24:2.99)	0.797			
CRY (presence)	3.67	0.22(0.05:1.04)	0.055	2.26	4.14(0.65:26.36)	0.132
Arrival in ICU (intubated)	2.75	1.56(0.92:2.65)	0.097	0.62	1.27(0.37:2.40)	0.472
lymphocyte	0.46	0.89(0.63:1.25)	0.496			
D-dimer	0.80	1.02(0.98:1.07)	0.370			
LDH	0.92	1(0.99:1.01)	0.337			
APACHE II	0.77	1.02(0.98:1.06)	0.380			
CCI (>2)	4.92	1.84(1.07:3.15)	0.027	5.29	2.26(1.13:4.53)	0.021
Steroid Use (Presence)	0.31	0.72(0.23:2.27)	0.577			
Need for vasopressors (Presence)	65.62	12.05(6.60:22)	<0.001	58.08	12.48(6.51:23.89)	<0.001
Cytokine Filter (Presence)	<0.1	-	>0.99			
Immunoplasma therapy (Presence)	0.84	2.17(0.41:11.38)	0.359			
Kaletra (Presence)	0.03	1.14(0.25:5.19)	0.865			
Dialysis (Presence)	5.59	0.32(0.12:0.82)	0.018	3.12	2.70(0.90:8.10)	0.077
Need for plasmapheresis (Presence)	0.84	1.40(0.68:2.86)	0.359			
Kaletra (Presence)	0.03	1.14(0.25:5.19)	0.865			

LRM= logistic regression model, OR= odds ratio, CI= confidence interval

#### 4. Discussion

The mortality rate was high in patients with COVID-19 infection admitted to the ICU. The ACCI total score was significantly higher in patients with mortality, and the risk of mortality in patients with ACCI score  $>2$  was 2.26 times higher than in the  $ACCI \leq 2$  patient group. The APACHI-II score did not differ between the groups with regard to mortality. The ACCI score was independently associated with mortality and outperformed the APACHE-II score in predicting hospital mortality in COVID-19 patients.

Mortality developed in 147 of 276 COVID-19 patients

admitted to the ICU in our study. Multiple risk factors associated with mortality and disease severity have been reported in the literature. Many studies have shown that age, male gender, and comorbidities are predictors of mortality (Imam et al., 2020; Abate et al., 2020; Fang et al., 2020; Pérez et al., 2020). Perez et al. associated with a higher risk of death age  $\geq 65$  years at patients COVID-19. In our study, patients admitted to the ICU were mostly male (58%). The age of the patients ranged from 25 to 92 years, the median age was 65 years. However, contrary to these studies, the mortality outcomes of the disease in our study were similar between age and gender.

Many studies have reported that patients with comorbidities are affected by COVID-19 at varying rates and are associated with worse clinical outcomes (Imam et al., 2020; Abate et al., 2020; Fang et al., 2020; Pérez et al., 2020; Zhou and Fan, 2021). Abate et al. in a systematic review and meta-analysis in which they evaluated ICU admission rate and outcomes among coronavirus patients; revealed that the rate of comorbidity was 66% in 12 studies and 59% in 10 studies. In our study, the comorbidity rate at ICU admission was 68.1%, and the most common were HT, DM, CHD, COPD, heart failure, CKD, and CVO. Our findings were consistent with studies in the literature. In our study, when the distribution of comorbid diseases according to the groups was examined, there was no difference between the groups except for CRF. Although the frequency of CRF was 4.32%, it was seen in 6.70% of patients who developed mortality and this result was significantly higher. Fang et al. In their systematic review and meta-analysis of COVID-19 patients, they stated that CRF mostly contributed to death, similar to our study, and that the cause was an immunological condition due to a weakened immune system in patients with CRF. Again in our study, the rate of dialysis application was significantly higher in patients with COVID-19 who developed mortality compared to those who survived. This situation also coincided with comorbidity.

Early detection of COVID-19 patients whose condition will progress to serious illness is of great importance. For this purpose, various scoring and evaluation systems have been used in many studies. Of these, the Charlson comorbidity index has been reported as an important prognostic marker (Bannay et al., 2016; Christensen et al., 2020; Imam et al., 2020; Shanbhag et al., 2021; Sabaz and Aşar, 2021). It is a simple and easy scoring system that evaluates the total comorbidity burden. ACCI, which was developed considering the effect of age on mortality, has been used to estimate mortality in patients with COVID-19 (Kim et al., 2021). Kim et al. found the median ACCI 2 for their nationwide cohort of COVID-19. In a multivariate Cox proportional analysis for mortality, they found a higher risk of mortality in patients with CCIS  $\geq 3$  (OR, 22.96 [95% CI 7.20-73.24]), and reported that ACCI was the best predictor for severe clinical outcome in COVID-19. Kuswardhani et al. (2020) in their systematic review and meta-analysis, a high CCI score was associated with increased mortality and disease severity in COVID-19 patients, and they reported a 16% increase in mortality for each increase in the CCI score. Varol et al. (2020) in their studies in which they investigated the effect of CCI on mortality in patients infected with SARS-CoV-2 virus; found a median CCI score of 1 (0-11) in the cohort and reported that patients with a CCI score  $>2.5$  (OR = 10.7; 95% CI 4.5-25.6) had a 10.7-fold higher risk of mortality than those with  $\leq 2.5$ . In our study, the median ACCI score was 1 (IQR,3). In the multivariate logistic regression analysis, we determined that the risk of mortality in patients with ACCI  $>2$  (OR=2.26; 95%CI

1.13:4.53, P= 0.021) was 2.26-fold higher than in the  $CCI \leq 2$  patient group. The low rate compared to other studies can be explained by the fact that the patient populations are much larger than in our study. In conclusion, the effect of ACCI on predicting mortality in our study was similar to the literature.

Another widely used evaluation system in the literature for COVID-19 patients is the APACHE-II scoring system (Zou et al., 2019; Cheng et al., 2021; Chen et al., 2021). Zou et al. (2019) in their study on the effect of 3 scoring systems (APACHE-II, SOFA and CURB65) on predicting mortality in patients with COVID-19, they showed that the APACHE-II score was independently associated with hospital mortality and was better in predicting mortality compared to the other two scoring systems. They reported that an APACHE-II score of  $\geq 17$  is an early warning indicator of mortality. Cheng et al. found a median APACHE-II score of 17 in their study, in which they evaluated the severity and mortality of COVID-19 pneumonia with different scores, and stated that the APACHE-II score was a strong predictor of COVID-19 pneumonia severity and mortality. Chen et al. evaluated the performance of CURB-65, PSI, and APACHE-II to predict COVID-19 pneumonia severity and mortality. Contrary to previous studies, they stated that the sensitivity of an APACHE-II score of  $\geq 11$  was low and should be used with caution. In our study, the median APACHE-II score was 22. However, there was no difference in mortality between the groups. Similar to the results of our study, Plotnikow et al. (2020) and Yang et al. (2020) reported in their study that the APACHE-II score failed to distinguish the severity of the patients, and they could not find any difference between patients who developed and survived mortality. The reason for the failure of the APACHE-II score to predict mortality; It may be that COVID-19 patients are accompanied by various comorbidities, but there is no scoring for comorbidities in the APACHE-II score.

Angiotensin converting enzyme (ACE) is an enzyme bound to the membranes of cells in the lungs, arteries, heart, kidneys, and intestines. It plays an important role in the regulation of blood pressure (Fang et al., 2020). ACE is also the binding site of the COVID-19 virus (Pérez et al., 2020). Excretion takes place via the kidneys. In our study, CRF was more common in patients who developed mortality. Again in the multivariate logistic regression model, it was determined that the risk of mortality in patients with a need for vasopressors was 12.48-fold higher than in patients without a need for vasopressors. The reason for this result may be the decreased excretion of ACE through the kidneys and the negative effects of common comorbidities such as HT, DM and HF on the vessels.

Sabaz and Aşar (2021) in their study evaluating the relationship between mortality and different scoring systems in COVID-19 patients in the ICU, they found that the duration of stay in the ICU was significantly longer in patients who survived than those who developed

mortality. Contrary to this study, in our study, the duration of stay in the ICU was found to be significantly longer in those who developed mortality compared to those who survived. However, in the logistic regression analysis performed to determine the factors affecting the development of mortality, the length of stay in the ICU, the presence of CRF, the patient's admission to the ICU as intubated, and the application of dialysis to the patient were not effective on mortality.

Our study had several limitations. This study was single-center, retrospective, and had a relatively small sample size. Therefore, there may be other unidentified independent predictors of mortality. Treatment protocols were not uniform, as they had been constantly evolving since the beginning of the pandemic. The effects of this condition on the prognosis of the patients were uncertain. Also, when calculating ACCI, the researchers were not blinded to the result because they had to access data from patients' medical records.

## 5. Conclusion

In conclusion, in this study, the authors showed that approximately one in two COVID-19 patients admitted to the ICU developed mortality. Their found an independent association between higher ACCI scores and the mortality rate. Because ACCI assesses total comorbidity burden and age at ICU admission, its potential use in identifying at-risk patients infected with COVID-19 and estimating their clinical status is recommended. It is thought that it can contribute to the intensive care planning and treatment of risky patients in clinical practice.

## Author Contributions

Concept: S.E. (50%) and S.E.O. (50%), Design: S.E. (50%) and S.E.O. (50%), Supervision: S.E. (50%) and S.E.O. (50%), Data collection and/or processing: S.E. (50%) and S.E.O. (50%), Data analysis and/or interpretation: S.E. (50%) and S.E.O. (50%), Literature search: S.E. (50%) and S.E.O. (50%), Writing: S.E. (50%) and S.E.O. (50%), Critical review: S.E. (50%) and S.E.O. (50%), Submission and revision S.E. (50%) and S.E.O. (50%). All authors reviewed and approved final version of the manuscript.

## Conflict of interest

The authors declared that there was no potential conflict of interest related to the research, authorship, and/or publication of this article.

## Ethical Approval/Informed Consent

This study was approved by the Department of Health COVID-19 Scientific Research Evaluation Board and the local Ethics Committee (2011-KAEK-25 2021/07-19). In accordance with the principles of the Declaration of Helsinki, it was conducted at University of Health Science Bursa Yuksek Ihtisas Training and Education hospital between July 2021 and September 2021. Patients admitted to the ICU and diagnosed with confirmed or

probable COVID-19 pneumonia according to the guidelines of the Ministry of Health Scientific Committee (2021) ([bilgi.saglik.gov.tr](http://bilgi.saglik.gov.tr)) were included in this retrospective study.

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## TÜRKİYE ATAKSİ REHABİLİTASYONUNDA NEREDEDİR? BİBLİYOMETRİK ANALİZ ÇALIŞMASI

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**Özet:** Bu araştırma ile Web of Science veri tabanına dayalı olarak ataksi rehabilitasyonuna ilişkin yayınların sistematik ve nicel bir değerlendirmesini yapmayı amaçlanmaktadır. Verilerin analizi için VOS viewer paket programı kullanılmıştır. Web of Science veri tabanından 1129 makale indirilmiştir. Veriler, yayınların yılı, yazarı, atıfları, yazar iş birlikleri, anahtar kelimeler gibi değişkenler açısından analiz edilmiştir. Bu inceleme sonucunda ataksi rehabilitasyonuna ilişkin yayınlarla ilgili olarak; en fazla çalışmanın 2019-2021 yılları arasında yayınlandığı, ABD'nin bu konuda ön sıralarda yer aldığı; John Hopkins Üniversitesi'ne bağlı araştırmacıların bu konuda en fazla yayın yaptığı; en fazla yayının Serebellum Dergisi'nde yayınlandığı; konuya en fazla katkı yapan araştırmacının Jose L. Perez Velazquez olduğu; ataksi konusunda en fazla atıf alan yayının ise Iwabuchi K.'nin çalışması olduğu görülmüştür. Türkiye'den Ayvat E. bu alana katkı yapan isimlerin başında gelmektedir. Çalışmamızın, araştırmacılara araştırma eğilimleri ve sınırları, işbirlikçileri hakkında yararlı bilgiler sağlayacağını düşünmekteyiz. Yüksek kaliteli ataksi rehabilitasyon çalışmaları için araştırma desteği ve işbirliği artırılmalıdır.

**Anahtar kelimeler:** Ataksi, Rehabilitasyon, Bibliometrik analiz, Vosviewer

### Where is Türkiye in Ataxia Rehabilitation? Bibliometric Analysis Study

**Abstract:** This research aims to make a systematic and quantitative evaluation of the publications on rehabilitation of ataxia based on the Web of Science database. VOSviewer package program was used for data analysis. 1129 articles were downloaded from the Web of Science database. The data were analyzed in terms of variables such as year of publication, author, citations, author collaborations, keywords. As a result of the study, regarding the publications on ataxia and its rehabilitation; the most studies were published between 2019-2021, the USA was at the forefront in this regard; The researchers affiliated with John Hopkins University have the most publications on this subject; most publications were published in the journal Cerebellum; the researcher who contributed the most to the subject is Jose L. Perez Velazquez; It was seen that the most cited publication on ataxia was the work of Iwabuchi K. Ayvat E. from Türkiye is one of the leading contributors to this field. As a result of the findings, it has been observed that the publications on ataxia and its rehabilitation have increased in recent years. We believe that our study will provide researchers with useful information about research trends and boundaries, collaborators. Research support and collaboration should be increased for high quality ataxia rehabilitation studies.

**Keywords:** Ataxia, Rehabilitation, Bibliometric analysis, Vosviewer

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### 1. Giriş

"Ataksi", kaslarda herhangi bir kuvvet kaybı olmaksızın ekstremitelerde görülen koordinasyon problemi olarak tanımlanır (Fogel ve Perlman, 2006; Trouillas ve ark., 1997). Serebellar ataksili hastalarda, primer olarak koordinasyon ve denge bozukluğu semptomları görülür. Ataksi, periferik sinir sistemindeki anormalliklerden de kaynaklanabilir ve duyu ataksi olarak isimlendirilir (Sghirlanzoni ve ark., 2005). Duyusal ataksinin semptomları arasında, göz kapanmasıyla koordinasyonun kötüleşmesi veya kaybı, pozitif Rhomberg işareti, bozulmuş eklem pozisyon hissi, duyu ataksi uyarana karşı azalmış duyarlılık ve bozulmuş tendon refleksi yer alabilir (Caronni ve ark., 2019; Pandolfo ve Manto, 2013)

Fizyoterapi egzersizlerinin ve uygulamalarının ataksi semptomlarını iyileştirdiğine dair kanıtlar vardır (Salcı ve ark., 2017; Milnes ve ark., 2018). Çeşitli ataksilere sahip 42 hastayı değerlendiren bir çalışmada iki grup oluşturulmuştur. Bir grup diğer gruptan daha önce çalışmaya dâhil edilmiştir. Çalışmaya daha geç alınan grup, ilk gruptan 4 hafta sonra rehabilitasyona başlatılmıştır. Böylece araştırmacı rehabilitasyonun kısa vadeli etkilerini randomizasyon yoluyla değerlendirmiştir. Tedavinin uzun vadeli etkileri gözlemsel çalışma yoluyla elde edilmiştir. Tedaviye erken başlayan gruptaki hastaların ataksi, yürüyüş hızı ve günlük yaşam aktivitelerinde anlamlı iyileşme ve düşmelerde azalma olduğu, ayrıca ataksideki iyileşmenin



12. ve 24. haftalarda devam ettiği gösterilmiştir (Miyai ve ark., 2012). Afferent yolların serebellar dejenerasyonu ile ilişkili ataksili 16 hastanın katıldığı başka bir çalışmada, koordinasyon eğitiminin 4 hafta boyunca ataksik semptomlar üzerindeki etkinliği değerlendirilmiştir. Sonuçlar, motor performans ve ataksik semptomlarda önemli bir azalma olduğunu göstermiştir (Ilg ve ark., 2009). Salcı ve ark.'larının yaptığı çalışmada 42 multipl skleroz hastaları 3 gruba ayrılmıştır. Bir gruba sadece denge egzersizleri verilirken diğer iki gruba denge egzersizlerine ek olarak lomber stabilizasyon ve görev odaklı egzersizler verilmiştir. Lomber stabilizasyon ve görev odaklı egzersiz verilen grubun ataksi oranlama ölçeği, iki dakika yürüyüş testi ve kompozit denge testi, sadece denge egzersizleri verilen gruba göre daha anlamlı iyileşme göstermiştir. (Salcı ve ark., 2017)

Ataksinin egzersizle tedavi maliyetine yönelik herhangi bir maliyet analiz çalışması yapılmamış olsa da egzersizin Ataksi Rehabilitasyonu (AR)'nın olumlu etkilerini gösteren pek çok çalışma vardır (Milne ve ark., 2018; Li ve ark., 2017; Portaro ve ark., 2019; Hartley ve ark., 2019). Günümüzde, rehabilitasyon alanında farklı araştırmalar mevcuttur (Tijsen ve ark., 2019; Sihvonen ve ark., 2017). AR'na verilen önem ile bu alan daha popüler hale gelmiştir. Ancak, AR yönelik araştırmaların mevcut durumu ve eğilim değişimi özetlenmemiş ve analiz edilmemiştir.

Bibliyometri, araştırma konularını, araştırma durumunu ve yayın kalitesini objektif ölçümle analiz etmek için yaygın olarak kullanılan bir yöntemdir. Rehabilitasyon çalışmalarının ilerleyişini görmek açısından bibliyometrik analiz önemlidir. Mesleki Rehabilitasyon, travmatik beyin yaralanması, spinal kord ve hücre tedavisi, depresyon ve ağrı ile ilgili rehabilitasyon alanında yapılmış sınırlı bibliyometrik çalışma vardır (Liu ve ark., 2018; Feng ve ark., 2013; Wang et al., 2020). Akademik dergi atıfları arasındaki ilişkiyi izlemek ve AR araştırmalarının eğilimlerini takip etmek için ülke, dergi, yazarlar, kategori, enstitü, anahtar kelimeler dâhil olmak üzere farklı yönlerden çok sayıda yayını taramak ve sınıflandırmak yararlı olabilir. Bu çalışmada, Web of Science'ın (WoS) yerleşik aracını kullanarak dünya genelinde 1981 ve 2021 yılları arasında AR ile ilgili araştırma eğilimlerini analiz etmek ve yayınların özelliklerini özetlemek için bibliyometrik bir analiz çalışması yapılmıştır.

## 2. Materyal ve Yöntem

Bu çalışmada AR alanındaki tematik değişim, bibliyometrik analiz yöntemiyle incelenmiştir. Pek çok yazılım tarafından desteklenmesi nedeniyle WoS veri tabanı kullanılmıştır. WoS veri tabanından text olarak alınan veriler Excel formatına da dönüştürülmüştür. Bibliyometrik haritalama oluşturmak ve görselleştirmek için VOSviewer version 1.6.11 programı kullanılmıştır. Vosviewer programı, (Rodrigues ve ark., 2014) bir haritanın tüm ayrıntılarının incelenmesini sağlayan, her bir haritanın farklı bir yönünü vurgulayan, farklı şekillerde görüntüleyebilen bir yazılım aracıdır.

### 2.1. Makale Seçimi

WoS'ta makale taraması 23 Şubat 2021 tarihinde yapılmıştır. Çalışmaya WoS'da yer alan ataksi alanında yapılmış SCI-EXPANDED, SSCI, A&HCI, CPCI-S, ESCI endeksleri kapsamındaki rehabilitasyon çalışmaları dâhil edilmiştir. Arama "ataksi" ve "rehabilitasyon" veya "ataksi rehabilitasyonu" anahtar kelimeleri kullanarak yapılmış, herhangi bir zaman kısıtlamasına gidilmemiştir. 1981-2021 zaman aralığında yapılmış çalışmalar baz alınmıştır. Bu veriler, kamuya açık veri tabanlarından indirilmesi ve bunlarla ilgili herhangi bir etik sorun olmaması nedeniyle, etik onay için başvuru yapılmamıştır.

### 2.2. Dâhil Edilme ve Çıkarılma Kriterleri

(1) Ataksi rehabilitasyonu ve fizyoterapi, diğer rehabilitasyon yöntemleri ile ataksinin klinik tedavisine ilişkin 1981-2021 yıllarında yayınlanmış araştırma makaleleri çalışmaya dâhil edilmiştir.

(2) Özgün araştırma, bildiri, notlar, mektuplar, tartışma ve kitap bölümleri çalışmaya dâhil edilmemiştir.

### 2.3. İstatistik Analiz

Alınan makaleler, WoS ve Visualization of Similarities (Vosviewer ) görüntüleyicisi 1.6.11 kullanılarak analiz edildi. Vosviewer, nesnelere arasındaki benzerlikleri görselleştirmek için kullanılan yeni bir yöntemdir (van Eck & Waltman, 2010). WoS veri tabanından dışarı aktarılan veriler, yazarlar tarafından makalelerinde kullanılan anahtar kelimelerin bir arada bulunup bulunmadığını keşfetmek için VOSviewer'a aktarıldı.

WoS'tan, ülkelerin/bölgelerin, kurumların dağılımı ve son kırk yılda en çok atıf alan ilk 20 makalenin dağılımı dâhil olmak üzere AR ile ilgili araştırmaların yayın eğilimleri elde edildi. Ek olarak, VOSviewer yazılımını kullanarak alınan makaleler üzerinde veri madenciliği, haritalama ve kümeleme yapıldı. VOSviewer analizi sonucu farklı renklerde ve şekillerde çıktılar elde edildi. Etiket boyutu ve bir ögenin dairesi, ögenin ağırlığına göre belirlendi. Bir ögenin ağırlığı ne kadar büyükse, ögenin etiketi ve dairesi de o kadar büyüktür.

## 3. Bulgular

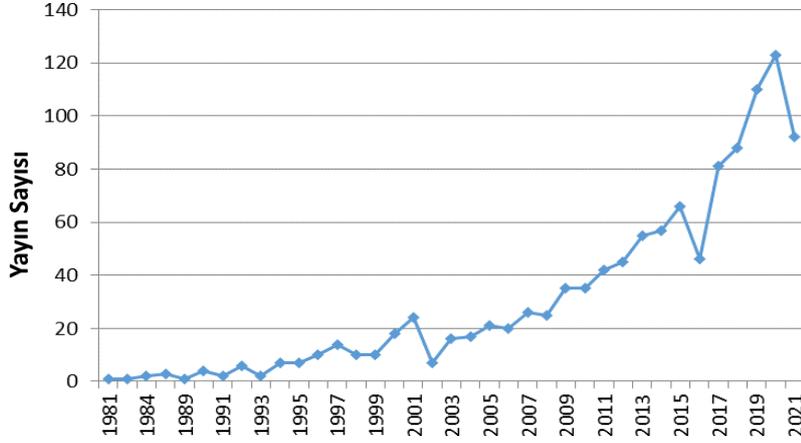
WoS veri tabanında yapılan arama sonuçlarına göre, konu ile ilgili olarak dünyada 1981-2021 yılları arasında toplam 1129 adet yayın yapılmıştır. Bu yayınların yıllara göre dağılımı incelenerek elde edilen veriler aşağıda gösterilmiştir (Şekil 1). 1990'da yapılan bir çalışma ile AR alanında yapılan çalışmalar süreklilik kazanmıştır.1990'dan itibaren çalışma süresi tabakalara ayrılmıştır. Katmanlar, 1981-1990; 1991-2000; 2001-2010; 2011-2021 şeklinde dört katmandan oluşmaktadır. 1981 ve 2021 yılları arasında AR ile ilgili çalışmaların düzenli bir artış gösterdiği ifade edilebilir. Konu ile ilgili en fazla yayın 2009-2021 yılları arasında yapılmıştır. 2020 yılında 123 yayın ile en yüksek yayın sayısına ulaşılmıştır. (Şekil 1).

### 3.1. Ülke Dağılımının Analizi

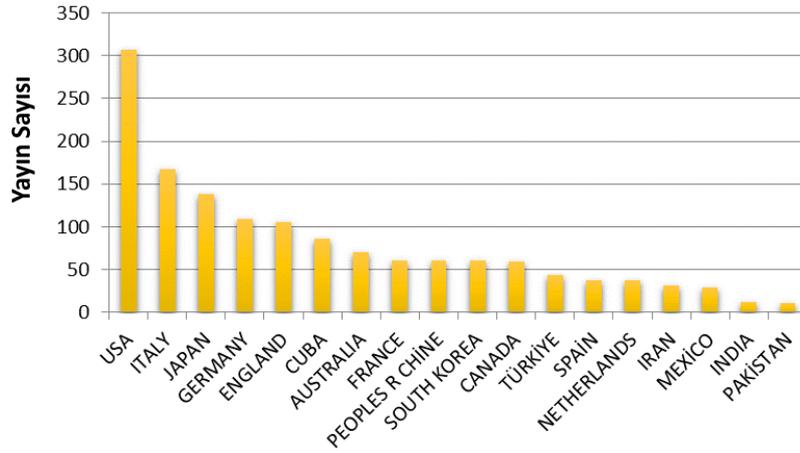
Son kırk yılda toplam otuz yedi ülkede AR ile ilgili makale yayınlanmıştır. Bu konuda çalışma yayınlayan otuz yedi ülkenin makale sayısı Şekil 2'de listelenmiştir. Bu listede

Türkiye’de sınırlarını zorlamaktadır. AR alanındaki çalışmalarda, ülkelerin yayın sayısına bakıldığı zaman Amerika Birleşik Devletleri (ABD) (307, %27.11) en fazla sayıda makale ile ilk sırada yer aldığı, ardından İtalya (167 %14.75) ve Japonya (138, %12.22) sırasıyla konuya katkıda bulunmaktadır (Şekil 2). Türkiye 43 yayın 269 atfı ile 12. sırada yer almaktadır. VOSviewer yazılımını kullanarak, ülkeler arasındaki ortak yazarlık ilişkisinin ağ

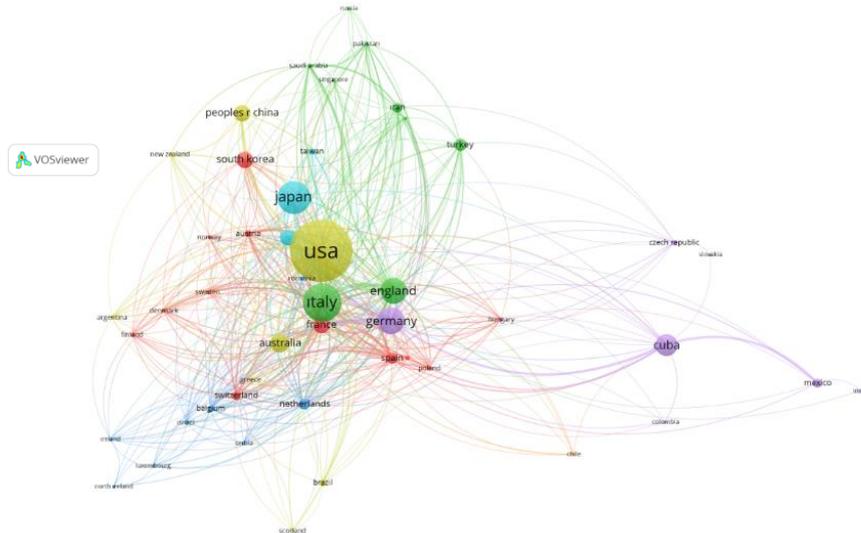
görselleştirmesi analiz edildi. En az 3 atfı almış, 3 makaleye sahip ülkeler dâhil edildi ve 48 ülke eşliği karşıladı. Şekil 3’de görüldüğü üzere, Amerika Birleşik Devletleri, AR ile ilgili araştırmanın merkezindedir. İtalya, Japonya ve Almanya ile yakın koordinasyon içindedir. Bununla birlikte, Türkiye USA, Japonya ve İtalya gibi diğer ülkeler arasında önemli araştırma işbirlikleri de görülmektedir (Şekil 4).



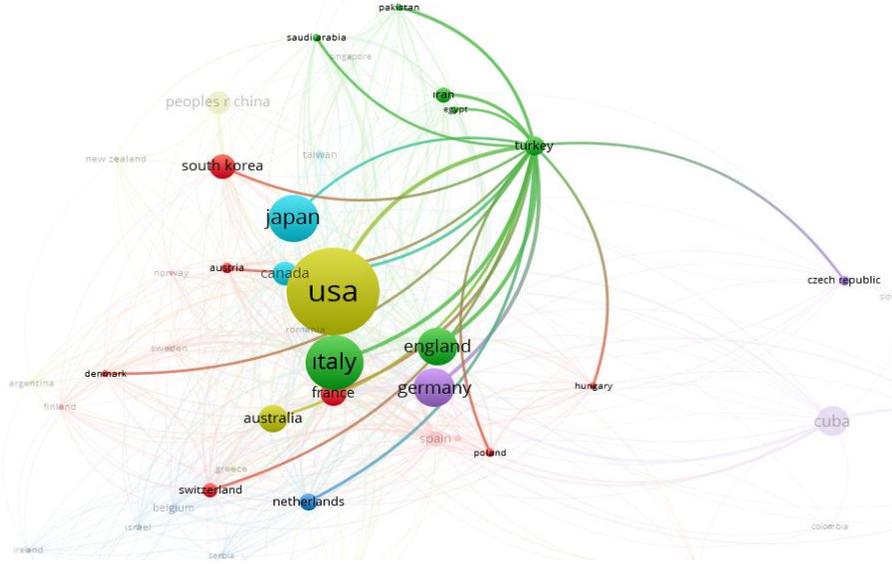
Şekil 1. Yayınların yıllara göre analizi.



Şekil 2. Yayınların ilk on ülkeye göre analizi



Şekil 3. Yayınların ülkelere göre bibliyometrik analizi



Şekil 4. Yayınların Türkiye İçin Bibliyometrik Analizi

## 2.2. Yayınların Kurumlara Göre Analizi

Kurumların dağılımına göre 1981-2021 yılları arasında toplam 308 kurum veya kuruluş makale yayınladı ve AR ile ilgili araştırmaya çoğunlukla ABD'nden kurumlar aktif olarak katıldı. En iyi 10 kurum ve kuruluş Şekil 5'de listelenmiştir. Bunların arasında ABD'den 1 kurum ve Avustralya'dan 3 kurum, Almanya'dan 2, İtalya'dan 2 ve Türkiye'den 1 kurum vardı. Londra Üniversitesi, 51 makale ile en çok katkıda bulunurken, onu Sapienza Üniversitesi (47 makale) ve Genoa Üniversitesi (44 makale) izledi. Alıntılarla ilgili olarak, John Hopkins Üniversitesi 679 alıntı sayısı ile birinci sırada yer almaktadır. Hacettepe Üniversitesi 17 makale ile 34. sırada yer almaktadır. Bu analizde, ülkeler arası çizginin kalınlığı kurum veya kuruluşlar arasında ortak yazarlık işbirliği sıklığını yansıtmaktadır (Şekil 6).

## 2.3. Araştırma Kategorileri ve Makale Türleri

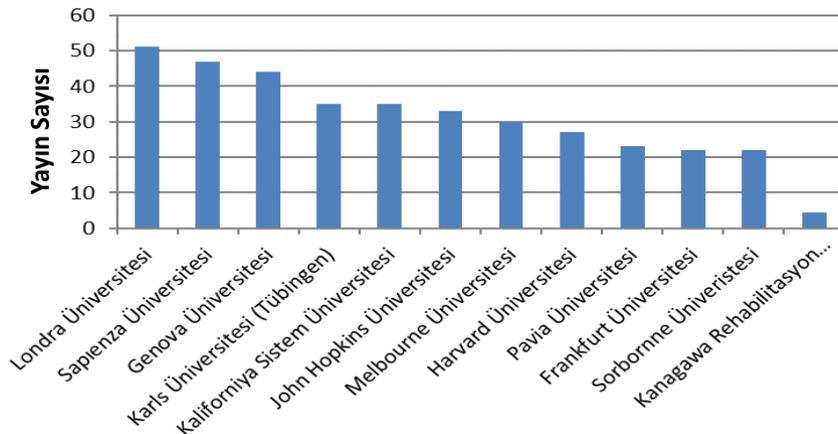
AR makaleleri hakkında klinik nöroloji (407), rehabilitasyon (361), spor bilimi (207) olmak üzere toplam 96 dergi kategorisi var (Şekil 7). Artan sayıda klinik uygulama göz önüne alındığında, Science Citation Index Expanded (SCIE) (998), Emerging Sources Citation Index (114), oluşturmaktadır.

## 2.4. İlk 5 Aktif Yazar ve En Çok Alıntı Yapılan 10 Makale

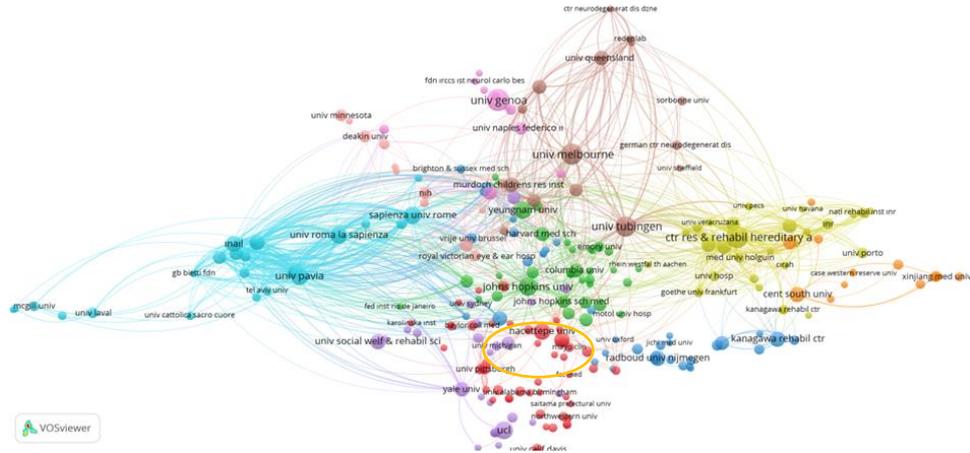
Şekil 8'de görüldüğü gibi AR alanında en aktif yazarları WoS veri tabanından alınarak analizi yapıldı. ABD'den yazar Jose L. Perez Velazquez 58 makale, 658 alıntı ile yazarlar arasında en çok katkıda bulunan kişidir (Velázquez-Pérez ve ark., 2011). Türkiye'den ise Ayvat E., 5 makale 6 atıf, Kılınc M. 6 makale 9 atıf, Armutlu K. 5 makale ve 31 atıf ile bu listeye katkı vermektedir (Şekil 8). Yayınların atıf sayılarına bakıldığı zaman Iwabuchi K. 1214 atıf sayısı ile en fazla yayın atıf-alan yazardır (Velázquez-Pérez ve ark., 2011).

## 2.5. Anahtar Kelime Analizi

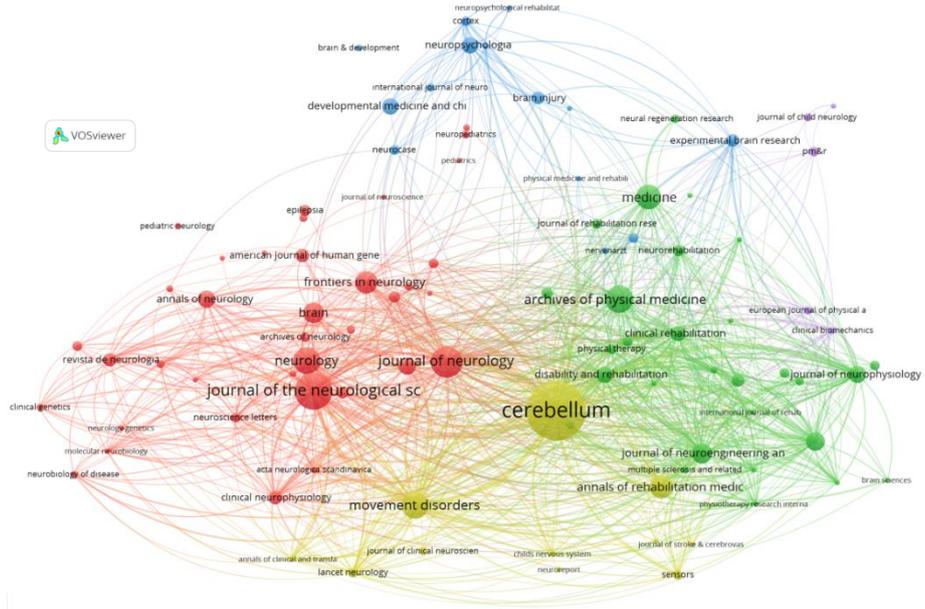
Literatürdeki AR ile ilgili anahtar kelimeler, VOSviewer yazılımı ile analiz edilmiştir. 2669 anahtar kelimenin her biri için, diğer anahtar kelimelerle birlikte oluşma bağlantılarının toplam gücü hesaplandı. Sonuçlar, "ataksi", "rehabilitasyon" ve "serebellum" un en yaygın anahtar kelimeler olduğunu gösterdi. Toplam 247 anahtar kelime, 40 yıllık bir dönemde en çok kullanılan anahtar kelimeler olarak belirlendi. Araştırma anahtar kelimelerinin dinamik değişimini daha iyi anlamak için, her yıl en sık kullanılan kelimelerin evrimi gözlemlendi (Şekil9).



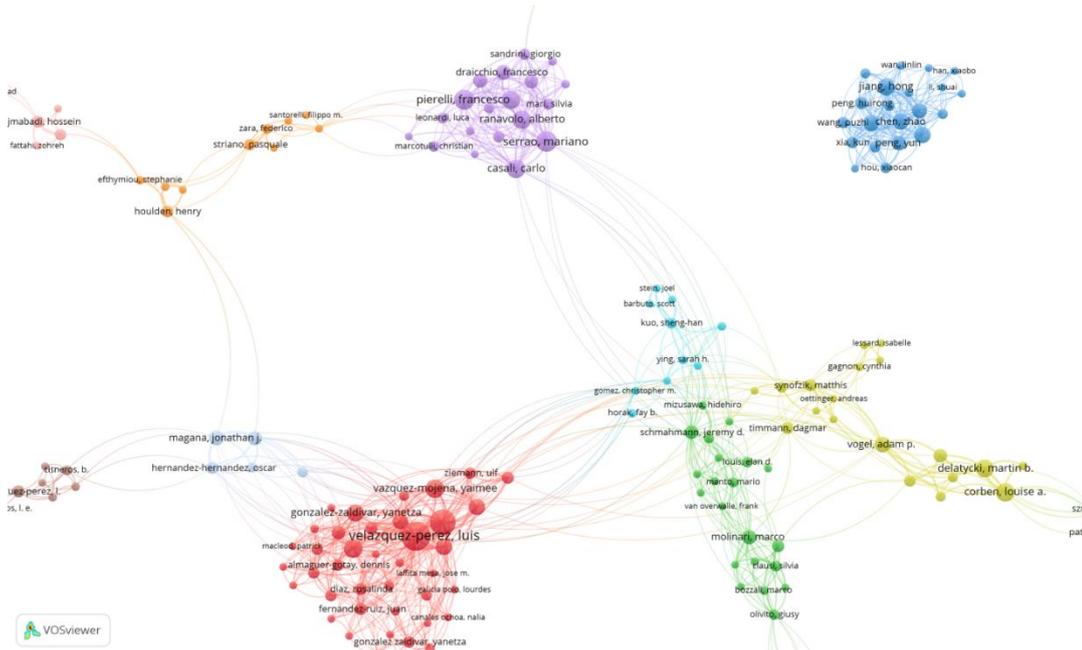
Şekil 5. Yayınların kurumlara göre bibliyometrik ağ analizi



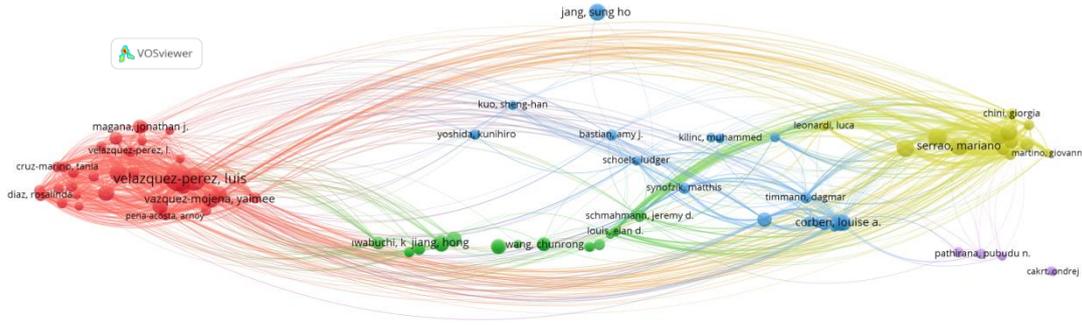
Şekil 6. Yayınların kurumlara göre bibliyometrik ağ analizi



Şekil 7. Yayınların dergilere göre dağılımı.



Şekil 8. Yayınların araştırmacılara göre ağ analizi.



Şekil 9. Yayınların atf sayılarına göre ağ analizi

#### 4. Tartışma

Bu çalışmanın amacı ataksi rehabilitasyonuna ilişkin yayınların sistematik ve nicel bir değerlendirmesini yapmaktır. Tüm araştırmacılar için en büyük endişe, bir araştırma alanının popüler olup olmadığı ve araştırma eğilimlerinin hangi konular üzerinde yoğunlaştığıdır. Bu soruları yanıtlamak için, dünya çapında 1981 ve 2021 yılları arasında AR üzerine bir bibliyometrik analiz gerçekleştirdik. Yapılan analiz sonucunda AR alanında yayın sayısının her geçen yıl arttığı gözlemlenmiştir. Özellikle son 10 yılda (2010-2020) yayın sayısı artmıştır. Buna göre, konuya ilişkin yayınların hazırlanmasında ekip çalışmasına önem verildiği ve finansman desteği sağlandığı; dolayısıyla da AR çalışmalarına literatürde daha fazla rastlandığı ifade edilebilir. Bu çalışma, araştırmacılara AR ile ilgili konularının tercih edilmesinde destekleyici olacağı ve AR'nin uluslararası durumunu yakından takip edebilecek uygun ekip ve araştırma platformları bulma konusunda rehberlik edebilecektir. Yayınlar ülke dağılımı açısından incelendiğinde, hiç şüphesiz ki (ABD), AR ile ilgili en fazla makale sayısı ile birinci sırada yer almaktadır. Her ülkenin yıllık yayınlarının daha ayrıntılı analizi ile Türkiye'nin yayın sayısında önemli bir paya sahip olduğu görülmektedir. Bu durum, AR üzerine yapılan çalışmaların Türk araştırmacıların ilgisini çektiğini ortaya koymaktadır. Analize göre, Türk araştırmacılar arasında Ayvat E., AR alanında altı yayın ile en fazla katkı yapan araştırmacı olarak görülmektedir. Aynı zamanda bu alanda çalışan Karabudak R., Armutlu K., Yıldırım Aksu S., Kılınc M., Aksoy S., Salcı Y., Fil A., Ayvat F. ve diğer yazarlar AR alanının Türkiye'deki gelişimine ciddi katkıda bulunmuşlardır (Armutlu ve ark., 2001; Ayvat ve ark., 2018; Salcı, Fil, Keklice, ve ark., 2017; Ayvat et al., 2022; Ayvat ve ark., 2022; Ayvat ve ark., 2021). Fakat Türk araştırmacıların AR alanında farklı ülkelerdeki yazarlarla işbirliğini içeren bir çalışmaya rastlanmamıştır. Genellikle yapılan çalışmalar Türkiye ile sınırlı kalmıştır. Yurt dışında yapılan çalışmalar incelendiği zaman bu konuda en fazla çalışma yapan Avustralyalı yazarlar Corben La ve Delatycki MB ikilidir (Delatycki & Corben, 2012). Bu iki yazarın birlikte yaptığı "Clinical features of Friedreich ataxia" çalışma yüz otuz beş atıf almıştır (Delatycki & Corben, 2012). Ülkeler veya kuruluşlar arasındaki ortak yazarlık ilişkisinin ağ görselleştirmesinden, ABD enstitülerinin AR'nin merkezinde olduğu ve Japonya,

İtalya ve Almanya enstitüleriyle işbirliği içerisinde olduğu görülmektedir. AR üzerine ortak araştırma yayınlayarak, farklı kuruluşlardan veya ülkelere araştırmacılar, çapraz konular, enstitüler ve çok uluslu bilimsel araştırma işbirliği oluşturulmuştur. John Hopkins, Melbourne ve Hacettepe Üniversitesi arasındaki yakın işbirliği yayın atf sayısı üzerinedir. Dikkati çeken diğer husus ise Hindistan, Pakistan, Ortadoğu ve Afrika gibi ülkelere AR ile ilgili çalışma sayısının bir-iki çalışma ile sınırlı kalmasıdır. WoS'ta listelenen dergilerde yayımlanan makaleler içinde en çok atıf alan yayınlar incelenmiş ve Wrisley'in "Reliability, internal consistency, and validity of data obtained with the functional gait assessment" isimli çalışması iki yüz yetmiş dört atf sayısı almıştır (Wristly ve ark., 2004). Dergi analizinde Klinik Nöroloji dergisi 147 yayın ile ilk sıradadır. Bu yayınların büyük kısmı araştırma makalesi ve sistematik inceleme yazısından oluşmaktadır. Çalışma anahtar kelime açısından incelendiğinde son 5 yılda, "spinoserebellar ataksi", "wallenberg sendromu", "düşme", "nöroplastisite" ve "egzersiz" anahtar kelimeleri gittikçe daha fazla kullanılır hale geldiği görüldü (Delatycki & Corben, 2012; Velázquez-Pérez ve ark., 2011). Bu AR'nin endikasyonlarının genişlediği yönünde bir izlenim vermektedir. Ayrıca, AR konusundaki yayınların anahtar kelimeleri incelendiğinde "rehabilitasyon" ve "ataksi" kelimelerinden sonra en fazla karşılaşılan kelimelerin başında "serebellar ataksi" ve "multiple skleroz" kelimelerinin gelmesinin doğru bir değerlendirme olduğu görülmektedir. Ataksi rehabilitasyonu en fazla multiple skleroz ve spinoserebellar atakside karşımıza çıkmaktadır (Salcı, Fil, Armutlu, et al., 2017; Delatycki & Corben, 2012). Araştırma kategorileri açısından AR, nörobilim, nöroloji, fizyoloji, rehabilitasyon ve mühendislik ile ilgilenen disiplinler arası bir araştırma alanıdır (Shirai ve ark., 2019; Chen ve ark., 2021; Lacorte ve ark., 2021; Schmitz-Hübsch ve ark., 2006; Rodríguez-Díaz ve ark., 2018). Son zamanlarda, ataksi rehabilitasyonunda, ataksin değerlendirilmesi ve tedavisinde yeni değerlendirme ve tedavi metotlarının kullanılması klinisyenler ve hasta açısından avantajlı olacaktır (Chen ve ark., 2021; Lacorte ve ark., 2021; Schmitz-Hübsch et al., 2006; Rodríguez-Díaz ve ark., 2018). AR alanındaki çalışmalarda yayınlanan 1129 çalışma 1981'den 2021'e kadar WoS'ta yalnızca 29017 alıntı sağladı. Bu sayı araştırmacının yayın atf oranı için uygun

olsa da, gelecekte yayınların atıf sayısını artırma ihtiyacı vardır.

AR alanında yapılan bu kapsamlı bibliometrik analiz, bilimsel çıktılarının 1981'den beri artan bir performans sergilediğini gösterdi. Ayrıca Türk araştırmacılarının bu konudaki araştırmalarının giderek arttığı gözlemlendi. Yüksek kaliteli yayınlar olmasına rağmen, yüksek atıf sayılarını ve ortalama atıfları artırmak için bilimsel makalelerin hem niteliğini hem de niceliğini artırmaya ihtiyaç vardır. Bu çalışma aynı zamanda Türk araştırmacıların bilimsel çıktılarını iyileştirmek için araştırma işbirliğini uluslararası olarak genişletmelerini önermektedir.

## Limitasyon

Bu çalışmanın bulguları yalnızca WoS veritabanı ile sınırlıdır. AR alanındaki gelecek araştırmaların, araştırma üretkenliğini tespit için araştırmacılar, diğer veri tabanlarındaki araştırma çıktılarını incelemeye odaklanabilir.

## Katkı Oranı Beyanı

Konsept: FE (%100), Tasarım: FE (%100), Denetim: FE (%50) ve İC (%50), Veri toplama ve/veya işleme: FE (%50) ve İC (%50), Veri analizi ve/veya yorumlama: FE (%50) ve İC (%50), Kaynak taraması: FE (%50) ve İC (%50), Yazma: FE (%100), Eleştirel inceleme: FE (%50) ve İC (%50), Gönderim ve revizyon: FE (%50) ve İC (%50). Tüm yazarlar makalenin son halini incelemiş ve onaylamıştır.

## Çatışma Beyanı

Yazarlar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

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Bu çalışma için veriler Web of Science'dan alındığı için etik kurul izni alınmamıştır.

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## DO HUMOR STYLES OF PATIENTS AFFECT THEIR INTENSIVE CARE EXPERIENCES?

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**Abstract:** The study was conducted in order to examine the correlation between the humor styles of the patients and their intensive care experiences. This study was conducted in descriptive and correlational design. The population of the study consisted of the patients who were treated in the general surgery, neurosurgery, neurology, and organ transplantation intensive care units of a university hospital. Its sample consisted of 204 intensive care patients. The data were collected using the Personal Information Form prepared by the researchers, Humor Styles Questionnaire, and Intensive Care Experience Questionnaire. The descriptive statistics, independent samples t test, One Way ANOVA, post-hoc tests, Correlation analysis and Cronbach's Alpha reliability analysis test were used to assess the data. In the study, it was found that the intensive care patients mostly used the affiliative and aggressive humor style and they had a positive intensive care experience. Additionally, there were a positive significant weak correlation between the affiliative humor and the subscale of "satisfaction with care" of ICEQ and a negative significant weak correlation between the subscales of "frightening experiences" and "recall of experience". As a result of the study, it was observed that the patients using the affiliative humor style had less pessimistic experience, remembered the intensive care experiences less, and were satisfied with the care provided the intensive care unit.

**Keywords:** Humor style, Patient, Intensive care experience

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### 1. Introduction

Humor, which is a basic human need, may be defined as seeing the entertaining part of the events and situations instead of being serious all the time (Yue, 2014; Ford et al., 2014). Humor is an effective method, providing a different point of view in managing the challenging experiences of life and in problem-solving. In other words, humor functions as an instrument that decreases the emotional burden in the situations causing stress or emotional stress (Ashwort, 1999; Öz, 2010).

Humor and laughing has many physiological, social, and psychological benefits. Physiologically the muscle strain reduces during laughing by the contraction and relaxation of the muscles and the circulation accelerates, the heart rate and the blood pressure increases, the respiratory rate and depth increase and the immunoglobulin a level increases and strengthens the immune system and the pain endurance increases (Aydın, 2005). Socially; by acting as a bridge between the individuals, it helps to establish new relations or to make the friendships stronger, contributes to the resolution of the disputes, and provides satisfaction by improving the ingenuity and productivity. Psychologically, it helps to experience positive emotions by reducing stress, tension and their negative effects (Balick and Lee, 2006, Alan and

Tiryaki, 2016). Humor allows reducing the stressful emotions and establishing more intended positive emotions (Yue et al., 2014).

People, by his/her nature, come across many difficulties and obstacles that are required to be overcome. One of the difficulties in this process is the intensive care experience. The intensive care units are the care centers which are used to provide the maximum possible benefit to the individuals, whose lives are under threat, and in which there is a lot of life-saving technological equipment and an interdisciplinary team approach is compulsory. Even though having the patients survive with the intensive care support may be considered as a successful result especially in recent years, these patients are also exposed to negative emotional results during the period they stay in the intensive care unit (Demir et al., 2009).

Factors such as life under threat, unfamiliar environment, and people, limitation of movement, irregular sleeping pattern, being confined to bed, being without the family members and relatives, the feeling of dependency on the equipment or the intensive care unit, and not being informed enough on the disease, treatment and applications cause the psychological symptoms to occur (Kaçmaz, 2002). This intensive care experience affects the individual at various levels. It is known that patients



use various coping methods during this experience. However, in the literature review; no study evaluating the correlation between patients' humor styles and intensive care experiences was found. For this reason, the aim of this study was to examine the correlation between the humor styles of the intensive care patients and their intensive care experiences.

## 2. Material and Methods

The descriptive and correlational study was conducted in the general surgery, neurosurgery, neurology, and organ transplantation intensive care units of a university hospital located in the eastern Türkiye. The population of the study consisted of the adult patients who were followed up in the intensive care and were conscious. The sample of the study consisted of 204 intensive care patients with significance level of 0.05, confidence level of 0.95, and the power to represent the population of 0.95 as a result of the power analysis. The data of the study were collected between 01 March 2017 and 15 April 2017 by using the face-to-face interview technique performed by the researcher on Monday, Wednesday, and Friday every week. The data were collected using the Personal Information Form, Humor Styles Questionnaire, and Intensive Care Experience Questionnaire prepared by the researchers. The data were collected at the hours when the intensive care conditions and the patients were suitable and each interview lasted for 15 minutes.

### 2.1. The Participant Information Form

The Personal Information Form consisted of a total of 10 questions including the socio-demographic data and the intensive care experiences of the patients.

### 2.2. Humor Styles Questionnaire

It was developed by Martin et al., and adapted to Turkish by Yerlikaya (2003). The questionnaire was developed in order to assess the four different dimensions related to the individual differences in the use of humor. There are four subscales in the scale designed to assess the two adaptive (affiliative and self-enhancing) and the two maladaptive (aggressive and self-defeating) uses of humor. The items in the Humor Styles Questionnaire are answered in the range of "1-Strongly disagree and 7-Totally agree". The eleven items in the scale are scored reversely. High score obtained from the subscales indicate the frequency of use of the related humor style. For the subscales, the Cronbach's Alpha coefficients are 0.78 for self-enhancing humor, 0.74 for the affiliative humor, 0.69 for the aggressive humor, and 0.67 for the self-defeating humor (Yerlikaya, 2003). In this study, the Cronbach's Alpha coefficients of the subscales were 0.47 for the self-enhancing humor, 0.67 for the affiliative humor, 0.63 for the aggressive humor, and 0.75 for the self-defeating humor.

### 2.3. The Intensive Care Experience Questionnaire

The questionnaire was developed by Rattray et al. (2004) to assess the experiences of intensive care patients.

Demir et al. (2009) conducted its validity and reliability study and adapted it to the Turkish society. The Cronbach's alpha coefficient of the questionnaire consisting of a total of 19 items was determined as 0.79 (Demir et al., 2009). In this study, the Cronbach alpha coefficient of the questionnaire was found as 0.63. The questionnaire consists of four subscales. The first six items assess the "awareness of surroundings" situation (6-30 points); 7th-10th items assess the "Frightening experiences" (4-20 points); 11th-14th items assess the "Recall of experiences" (4-20 points); and 15th-19th items assess the "satisfaction with care" (5-25 points). While the lowest score to be taken from the scale is 19, the highest score is 95. The situation of the patients who get high scores from the scale is evaluated as the high awareness and more positive experiences (Demir et al., 2009).

### 2.4. Statistical Analysis

Descriptive statistics, independent samples t-test, One Way ANOVA, Kruskal Wallis, Correlation and Cronbach's Alpha reliability analysis were used to assess the data. The results were assessed at the confidence interval of 95% and significance level of  $P < 0.05$ .

## 3. Results

Table 1 shows the socio-demographic characteristics and the intensive care experience of the patients.

In the study, it was determined that the age averages of the patients were  $50.8 \pm 13.7$ , 52.7% were males, 35% were high school graduates, 37.4% were housewives, the income of 57.6% was equal to their expense, 32.5% were followed up in the organ transplantation intensive care, their length of intensive care stay was approximately  $4.97 \pm 6.25$  days, the patients stayed in the intensive care for  $1.54 \pm 1.03$  times on the average, 38.9% felt fear in the intensive care process, and 31% felt bad.

Table 2 shows HSQ and ICEQ mean scores of the patients (Table 2). In the study, it was determined that the HSQ affiliative humor subscale mean score of the patients was  $34.4 \pm 5.8$ , the ICEQ mean score was  $64.2 \pm 7.5$ , and mean score of the subscale "awareness of surroundings" was  $20.7 \pm 3.1$ .

Table 3 shows the comparison of HSQ and ICEQ mean scores according to the socio-demographic characteristics of the patients. In the study, it was observed that the difference between mean scores of the subscales "Awareness of surroundings" and "Recall of experience" was statistically significant ( $P < 0.05$ ).

The difference between the mean scores of affiliative and aggressive humor subscales and the ICEQ, its subscales "Awareness of surroundings", "Recall of experience" and "the satisfaction with care" in terms of their educational level was found as statistically significant ( $P < 0.05$ ). After the Bonferroni correction, it was observed that the difference resulted from the group with the educational status of university graduate and higher.

**Table 1.** The socio-demographic characteristics and the intensive care experience of the patients

The characteristics of the patient	Number (N)	%	X± SD
Age	203		50.8±13.7
Gender			
Female	96	47.3	
Male	107	52.7	
Educational level			
Illiterate	41	20.2	
Primary school	50	24.6	
High school	71	35.0	
University and higher	41	20.2	
Profession			
Civil servant	36	17.7	
Retired	26	12.8	
Employee	42	20.7	
Housewife	76	37.4	
Other	23	11.3	
Income status			
Income is less than expense	42	20.7	
Income is equal to expense	117	57.6	
Income is more than expense	44	21.7	
Intensive care			
Organ transplantation	66	32.5	
General Surgery	42	20.7	
Neurosurgery	57	28.1	
Neurology	38	18.7	
Height of intensive care stay			4.97±6.25
Number of intensive care stays			1.54±1.03
The feelings of the patients during the intensive care			
I am scared	79	38.9	
I felt pain	31	15.3	
I felt bad	63	31	
I did not feel bad	30	14.8	
TOTAL	203	100.0	

**Table 2.** HSQ and ICEQ mean scores of the patients

Scale	N	X ± SD
Humor Styles Questionnaire		
Affiliative Humor	203	34.4±5.8
Self-enhancing Humor	203	30.8±6.6
Aggressive Humor	203	31±6.5
Self-defeating Humor	203	29.9±7.6
The Intensive Care Experience Questionnaire (ICEQ)	203	64.2±7.5
F1 = Awareness of surroundings	203	20.7±3.1
F2 = Frightening experiences	203	14±2.7
F3 = Recall of experience	203	15.9±2.3
F4=Satisfaction with care	203	13.9±2.3

**Table 3.** Comparison of HSQ and ICEQ mean scores according to the socio-demographic characteristics of the patents

The characteristics of the patient	Affiliative Humor X±SD	Self-enhancing Humor X±SD	Aggressive Humor X±SD	Self-defeating Humor X±SD	ICEQ X±SD	F1 X±SD	F2 X±SD	F3 X±SD	F4 X±SD
Gender									
Female	34.6±6.4	30.4±6.8	31.6±6.9	30.7±7.7	64.3±6.1	21.2±2.9	13.7±2.1	15.5±2.02	13.8±2.3
Male	34.3±5.2	31.1±6.3	30.5±6	29.2±7.5	64.8±8.6	20.3±3.3	20.3±3.3	16.2±2.6	14±2.3
Statistical test and significance	t=0.289 P=0.773	t=-0.783 P=0.434	t=1.098 P=0.274	t=0.169 P=1.381	t=-0.466 P=0.642	t=2.007 P=0.046	t=-1.392 P=0.166	t=-2.010 P=0.046	t=-0.540 P=0.590
Educational Level									
Illiterate	33.3±7.9	30±9	28.6±10.8	28.1±9.2	61.4±8	20.1±3.1	13±2.4	15±2.3	13.1±2.4
Primary school	33.1±5.5	31.5±6.1	32.3±4.3	31.7±7.3	65.8±5.6	21.7±2.3	13.8±2	15.9±2.24	14.2±2.21
High school	34.8±4.5	30.7±5.9	30.8±4.1	30.2±6.8	64.7±8.7	19.9±3.7	14.5±3.6	16.3±2.6	13.8±2
University and higher	36.7±5.1	30.7±5.4	32.3±5.9	29.2±7.4	66.1±5.7	21.5±2.5	14.2±1.7	15.9±2.3	14.4±2.6
Statistical test and significance	F=3.548 P=0.015	F=0.361 P=0.781	F=3.164 P=0.026	F=1.787 P=0.151	F=3.638 P=0.014	F=4.694 P=0.003	F=2.598 P=0.053	F=2.935 P=0.035	F=2.662 P=0.049
Income status									
Income is less than expense	31.5±7.4	28.7±8.3	28.9±9.8	27±9	63.2±8.4	20.1±3.2	13.2±2.9	16.1±2.6	13.7±2.4
Income is equal to expense	35.4±5.2	31.6±5.8	31.6±5.5	30.6±7.1	64.5±7.7	20.8±3.2	13.8±2.4	15.8±2.4	14±2.2
Income is more than expense	34.7±4.8	30.4±6.2	31.4±4.2	30.8±7	66±5.7	21.2±2.7	15.1±3	15.9±2	13.7±2.3
Statistical test and significance	F=0.475 P=0.754	F=0.328 P=0.859	F=1.206 P=0.31	F=5.137 P=0.001	F=4.901 P=0.001	F=3.986 P=0.004	F=1.172 P=0.005	F=7.526 P=0.000	F=4.163 P=0.003

In the study, it was observed that the difference between the HSQ self-defeating subscale mean scores of the patients according to the income status was statistically significant ( $P<0.05$ ). As a result of the post-hoc test, it was determined that the difference resulted from the group whose income was higher than expense. Similarly, it was found that the difference between the mean scores of the ICEQ\*, F1\*, F4\*, F2\* and F3\*\* subscales in terms of income status of the patients was statistically significant (\*= $P<0.05$ , \*\*= $P<0.001$ ).

After the Bonferroni correction, it was determined that

the difference was associated with the group whose income was higher than the expense for ICEQ, F1, F2, and F3, the difference was associated with the group whose income was equal to the expense for F4.

Table 4 shows the comparison of the intensive care characteristics of the patients regarding with their HSQ and ICEQ mean scores. In the study, no significant difference was observed between intensive care where the patients were followed and HSQ subscales and the ICEQ mean scores ( $P>0.05$ ).

**Table 4.** The comparison of the intensive care characteristics of the patients with their HSQ and ICEQ mean scores

Intensive care	Affiliative Humor	Self-enhancing Humor	Aggressive Humor	Self-defeating Humor	ICEQ	F1	F2	F3	F4
Organ transplantation	33.9±6.2	29.9±6.5	30.5±7.5	28.1±7.6	63.8±9.7	20.6±3.5	13.6±3	16±2.8	13.6±2.7
General Surgery	34.6±7.6	30±8.1	30.4±6.9	28.5±9.1	66.8±6.1	20.7±2.9	14.9±2.7	16.5±2.2	14.5±1.8
Neurosurgeon	35.3±4.9	31.1±5.7	31.3±5.3	31.4±6.8	64.1±6.2	21±2.9	13.7±2.5	15.4±1.9	13.8±2.4
Neurology	33.8±3.8	31.8±6	32.2±5.7	32.5±6.1	64.3±6	20.6±3.2	14±2.7	15.6±2.2	13.8±1.6
Statistical test and significance	F=0.799 P=0.496	F=0.753 P=0.522	F=0.746 P=0.526	F=4.118 P=0.207	F=1.536 P=0.206	F=0.204 P=0.894	F=2.371 P=0.072	F=1.675 P=0.174	F=1.431 P=0.235
Patient's feelings in intensive care unit									
I am scared	35.1±4.5	30.5±5	31.9±5.4	30.4±7.03	65.4±6.6	21.6±2.5	16.1±2.1	16.1±2.1	13.9±2.4
I felt pain	35.1±4.8	28.1±5.2	30.4±5.6	26.6±5.3	64.6±9.9	19.6±3.7	15.8±2.6	15.8±2.6	13.7±2.5
I felt bad	33.4±7.5	30.8±8.3	29.3±8.6	29±8.8	63.3±8.2	20±3.3	15.7±2.2	15.7±2.2	13.8±2.2
I did not feel bad	34.2±5.5	34.2±6.1	33±3.3	34.1±6.8	64.9±4.5	21.2±3	15.7±2.9	14.1±1.8	14.1±1.8
Statistical test and significance	F=1.117 P=0.343	F=4.682 P=0.003	F=3.119 P=0.027	F=5.513 P=0.001	F=0.958 P=0.414	F=4.779 P=0.003	F=3.254 P=0.023	F=0.312 P=0.817	F=0.15 P=0.929

In the study, no significant difference was determined between the feelings of the patients in the intensive care and affiliative humor subscale mean scores\*; whereas, a significant difference was determined between the feelings of the patients in the intensive care and the other subscale mean scores\*\* (\*= $P>0.05$ , \*\*= $P<0.01$ ). According to the post-hoc test result, it was observed that the difference was associated with the group who did not feel bad among all the groups. No significant difference was found between the feelings of the patients in the intensive care and ICEQ, F3 and F4 mean scores\*; whereas, a significant difference was found between the F1 and F2 mean scores\*\* (\*= $P>0.05$ , \*\*= $P<0.01$ ).

After the Bonferroni correction, it was observed that the difference was associated with the group that stated "I

felt scared in the intensive care process".

Table 5 shows the examination of the correlation between the number of intensive care hospitalization and length of intensive care stay, and the HSQ and ICEQ mean scores. In the study, it was determined that the correlation between the number of intensive care hospitalization and the length of intensive care stay, and the HSQ and ICEQ subscale mean scores was not statistically significant ( $P>0.05$ ).

Table 6 shows the examination of the correlation between the HSQ and ICEQ mean scores of the patients. In the study, a positive significant weak correlation between the Affiliative humor and ICEQ F4 subscale and a negative significant weak correlation between F2\*\* and F3\* subscales were determined (\*= $P>0.05$ , \*\*= $P<0.01$ ).

**Table 5.** The examination of the correlation between the number of intensive care hospitalization and length of intensive care stay of the patients, and HSQ and ICEQ mean scores

	Affiliative Humor	Self-enhancing Humor	Aggressive Humor	Self-defeating Humor	ICEQ	F1	F2	F3	F4
Number of intensive care stay	r=0.037 P=0.603	r=0.103 P=0.142	r=0.016 P=0.825	r=0.109 P=0.12	r=0.017 P=0.814	r=0.12 P=0.862	r=-0.043 P=0.539	r=-0.008 P=0.906	r=0.097 P=0.167
Length of intensive care stay	r=0.048 P=0.496	r=-0.073 P=0.299	r=0.000 P=0.999	r=-0.051 P=0.469	r=0.012 P=0.87	r=0.117 P=0.096	r=-0.026 P=0.714	r=-0.055 P=0.432	r=-0.035 P=0.621

**Table 6.** The examination of the correlation between the HSQ and ICEQ mean scores of the patients

	ICEQ	F1	F2	F3	F4
Affiliative Humor	r = 0.116 P=0.099	r=0.016 P=0.826	r=-0.295 P=0.000	r=-0.152 P=0.030	r=0.16 P=0.022
Self-enhancing Humor	r=0.096 P=0.172	r=0.037 P=0.598	r=0.09 P=0.202	r=0.066 P=0.351	r=0.086 P=0.224
Aggressive Humor	r=0.003 P=0.967	r=0.1 P=0.154	r=-0.058 P=0.409	r=0.018 P=0.794	r=-0.077 P=0.274
Self-defeating Humor	r=-0.004 P=0.953	r=0.079 P=0.26	r=-0.042 P=0.554	r=-0.135 P=0.054	r=0.067 P=0.344

#### 4. Discussion

Humor strengthens the coping skills of the individual by supporting the physical, emotional, social and cognitive development and increases his/her problem solving skills (Hurren, 2006). Previous studies has shown that humor reduces stress (Yalçın and Aştı, 2011; Traş et al., 2011). The intensive care may be an emotionally unsettling environment for the patients and their relatives and it is a process in which the patients and their relatives may also experience psychological problems at different levels (Toraman, 2000). The results of this study conducted to examine the correlation between the humor styles of the patients and their intensive care experiences were discussed with the literature.

In the study, it was determined that the intensive care patients used the affiliative and aggressive humor style more than the other humor styles. As there is no study examining the humor style of the patients in the

literature, it is thought that the humor styles of the patients are related to their personal characteristics. In the study, it was determined that the patients had positive intensive care experience. While it has been reported in the literature that the experiences of the intensive care patients are generally negative, there are studies in parallel with the result of the present study (Hindistan et al., 2009; Özdemir, 2010; Adsay and Dedeli, 2015). The positive experiences in the intensive care are generally related to the positive characteristics of the nursing care and the nurses (Granja et al., 2005).

In the study, no significant difference was found between the humor styles of the women and men ( $p>0.05$ )(Table 3). Also in the study conducted by Otrar and Findıklı with the school managers, similarly, no significant difference was found between the humor styles in terms of the gender (Otrar and Findıklı, 2014). While there was no significant difference between the ICEQ, F2 and F4 subscale mean scores in terms of the genders of the

patients ( $P>0.05$ ), it was observed that the difference between the F1 and F3 subscale mean scores was statistically significant ( $P<0.05$ ) (Table 3). In parallel with this study, in the study by Akdemir (2013) entitled "Determining the intensive care experiences of the patients and the effective factors", no significant difference was found between the ICEQ, F2 and F4 mean scores of the female and male patients. In the study by Adsay and Dedeli (2015), the mean scores of the female patients from the F1 subscale were found to be higher than the mean scores of the male patients. Similarly, in the study by Karadağ (2013), it was determined that the difference between the scores of the patients in the F3 subscale in terms of the gender was statistically significant. The study supports the studies by Adsay and Dedeli (2015), and by Karadağ (2013).

A significant difference was found between the groups in the HSQ affiliative humor and aggressive humor subscales between the groups in terms of the educational status in the study ( $P<0.05$ ); whereas, no significant difference was found in the subscales of self-enhancing humor and self-defeating humor ( $P>0.05$ ) (Table 3). In the study by Akdur and Batıgün (2014), it was stated that the use of affiliative humor by the participants increased as educational level of their mothers increased and the use of aggressive humor increased as their fathers' educational level increased. In Erözkan's (2009) study, it was found that despite being in a different context from the study, the change at the class level did not affect the humor style. The results support Akdur and Batıgün (2014) results in terms of affiliative humor and aggressive humor and support Erözkan's (2009) results in terms of self-enhancing humor and self-defeating humor.

As the educational level increased, the patients were expected to use the coping methods more effectively (Özer et al., 2009). Humor has an important place among these coping methods (Öz, 2010). In the study, a significant difference was found between the groups in all the subscales except for the ICEQ and F2 subscales in terms of educational level ( $P<0.05$ ) (Table 3). Although there are studies stating that educational level affected the intensive care experience supporting the study in the literature, there are also studies stating that the educational level did not affect the intensive care experience (Akdemir, 2013; Tuna et al., 2014; Adsay and Dedeli, 2015).

In the study, any significant difference was not determined ( $P>0.05$ ) between the income status and the scores from the humor styles subscales except for the self-defeating humor style ( $P<0.05$ ). In parallel with the study, also in the Erözkan's (2009) study, no significant difference was found between the groups in terms of the socio-economic levels related to the humor styles. The result of the present study supports the result of Erözkan (2009).

It is known that the patients and their relatives with low income level have difficulties in fulfilling the medical or

personal needs of the intensive care patients. In the study, a significant correlation was determined between the ICEQ and all the subscales in terms of the income status ( $p<0.05$ ). In their study, Yaya and Koyuncu (2006) shared the experiences of the patients, examined the reason for the noncompliance of the patients to the treatment, and determined that "he/she would not pay the hospital charge, her husband/his wife cannot receive his/her salary for three months and he/she wants to leave the hospital for these reasons". In this context, the results of the present study support the literature.

In the study, no significant difference was found between intensive care where the patients were followed and scale mean scores ( $P>0.05$ ). Humor is a mechanism that affects the efficiency directly when it is used in various living spaces (Kuğuoğlu and Demirbağ, 2015). As the intensive care environments are similar to each other in general lines and the humor styles of the patients did not change in such a short time, it was thought that the difference was not significant. In parallel with this study, in the study by Adsay and Dedeli (2015), no significant difference was found between the intensive care where the patients were followed and the intensive care experience. The result of the study supports Adsay and Dedeli (2015).

In the study, it was observed that the patients, who did not feel themselves bad in the intensive care process, used self-enhancing, aggressive, self-defeating humor styles more and the awareness of surroundings and their frightening experiences mean scores of the patients who felt scared in this process were significantly high ( $P<0.05$ ). The fact that humor reduces stress, develops the feeling of confidence and is effective in the conditions like coping with fear are included in the literature (Kuğuoğlu and Demirbağ, 2015). In this context, it can be asserted that the patients who used humor in intensive care process did not feel bad. In the study by Wong and Arthur on the feelings of the intensive care patients, it was found that the patients experienced anxiety and the fear of the unknown (Wong and Arthur, 2000). The patients stated the negative experiences as fear, anxiety, pain or discomfort, sleeplessness, and cognitive disorder and the positive experiences as security, being in a safe environment and the feeling of trust provided by the nurses (Stein and McKinley, 2009). The results of the study are compatible with the literature.

In the study, no significant correlation was determined between the number of intensive care hospitalization and the length of intensive care stay, and the HSQ, ICEQ and its subscales ( $P>0.05$ ) Parallel to the study, it was found in Akdemir's (2013) study that the number of intensive care hospitalization did not affect the intensive care experience. Also in the study by Özdemir (2010) to examine the experiences of the patients in the coronary intensive care, no significant correlation was determined between the length of intensive care stay and the intensive care experience. According to the study by Özdemir (2010) and Maddox et al. (2001) the patients

considered the period they stayed in the intensive care as the recovery process and did not perceive this situation negatively. Also, the most important issue, the patients have focused on, was the physical healing process.

In the study, a negative significant weak correlation was determined between the affiliative humor styles of the patients and the ICEQ frightening experiences\* and recall of experiences\*\* subscales; whereas, a positive significant weak correlation was determined between the humor styles of the patients and the ICEQ satisfaction with care subscale (\*= $P<0.05$ , \*\*= $P<0.01$ ). In the literature, no study was found examining the humor styles of the patients and the intensive care experiences. It was determined that the patients using the affiliative humor had less frightening experiences in the intensive care, remembered their experiences less, and were satisfied with the care in the ICU. In the study by Svebak et al. (2004) to examine the concrete correlation between humor and health, it was found that humor increased the health and symptom perception, the skills to cope with the diseases and the tendency to seek for health care service. Additionally, the individuals using the affiliative humor can improve their relations by using respectful interactions both for themselves and the others. They can make jokes by keeping the self-acceptance feelings and tell something funny about themselves (Martin et al., 2003.) From this point of view, it may be asserted that the patients using the affiliative humor in the intensive care had stronger coping mechanisms, less stress, and more positive experiences.

## 5. Conclusion

As a result of the study, it was found that the intensive care patients mostly used the affiliative and aggressive humor styles and they had a positive intensive care experience. Also, it was observed that the patients using the affiliative humor style experienced less frightening experience, remembered the intensive care experiences less, and were satisfied with the care provided the intensive care unit.

In accordance with these results, it is recommended that especially the nurses evaluate not only what kind of care or treatment the intensive care patients receive but also how this process affects the patients, that the humor style of the patients are determined and the patients are encouraged to use the positive humor styles, that the nurses question their own humor styles and they are informed on the positive humor styles and the effects of these on the recovery process and also that the study is repeated in the larger and different groups.

The nurses evaluate not only what kind of care or treatment the intensive care patients receive but also how this process affects the patients, that the humor style of the patients are determined and the patients are encouraged to use the positive humor styles.

## Limitations

The limitations of the study are that the study was conducted only in one institution and the patients were selected by the improbable random sampling method.

## Author Contributions

Concept: S.Ç.A. (34%), S.S. (33%) and S.T. (33%), Design: S.Ç.A. (34%), S.S. (33%) and S.T. (33%), Supervision: S.Ç.A. (34%), S.S. (33%) and S.T. (33%), Data collection and/or processing: S.Ç.A. (34%), S.S. (33%) and S.T. (33%), Data analysis and/or interpretation: S.Ç.A. (34%), S.S. (33%) and S.T. (33%), Literature search: S.Ç.A. (34%), S.S. (33%) and S.T. (33%), Writing: S.Ç.A. (34%), S.S. (33%) and S.T. (33%), Critical review: S.Ç.A. (34%), S.S. (33%) and S.T. (33%), Submission and revision S.Ç.A. (34%), S.S. (33%) and S.T. (33%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest.

## Ethical Approval/Informed Consent

Research was conducted in line with the Declaration of Helsinki. Before starting the study, written permission was received from the İnönü University Health Sciences Scientific Research and Publication Ethics Committee (Decision No: 2018/5-17) and Head Physician of Turgut Özal Medical Center.

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## THE EFFECT OF ATTITUDE TOWARDS UNCERTAINTY AND PERCEIVED CONTAMINATION COGNITION ON MENTAL STATUS OF NURSES DURING THE COVID-19 PANDEMIC

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**Abstract:** In epidemics, nurses often work on the front line. Therefore, there is a need for studies on the factors affecting the mental states of nurses. This study was conducted to examine the effect of nurses' attitudes towards uncertainty and perceived contamination cognition on mental state during the coronavirus disease pandemic. The study was completed with 328 nurses who filled the data collection forms. Data were tested Mann-Whitney U, Kruskal-Wallis one-way analysis of variance and Spearman correlation tests. In the relational questions were used with simple and multiple linear regression analysis. The average age of the nurses participating in the study was  $31.81 \pm 7.69$ , and 84.1% of them were women. All of the participants worked actively during the coronavirus disease pandemic process and 75.0% of them provided care to patients diagnosed with coronavirus disease. Moreover, 68.6% of the participants defined the coronavirus disease pandemic process as frightening/worrying. It was determined that the nurses had high levels of depression, anxiety and stress. While the average score of intolerance of uncertainty was  $41.83 \pm 8.40$ , their contamination cognition was  $80.34 \pm 1.59$ . A positive relationship was found between intolerance of uncertainty and contamination cognition, depression, anxiety, and stress in nurses. A positive relationship was also determined between contamination cognitions and depression, anxiety, and stress.

**Keywords:** Mental status, Contamination cognition, Uncertainty, Nurse

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### 1. Introduction

Pandemics are a condition that exists at every stage of human history and appears as the latest coronavirus disease (Covid-19). Coronavirus is a disease characterized by fever and respiratory distress (Li et al., 2020a). Due to the rapid spread of these symptoms in other countries and regions of the world, the coronavirus epidemic has been defined as a pandemic (Shigemura et al., 2020).

It has been reported that the mental states of nurses and other health professionals were negatively affected in previous epidemics and the Covid-19 pandemic (Kang et al., 2020; Wu et al., 2009). In other epidemics or pandemics like Covid-19, mental distress such as fear, anxiety, depression, posttraumatic stress disorder has emerged in healthcare professionals for reasons such as being isolated, working in high-risk positions and contacting with infected people (Chong et al., 2004; Maunder et al., 2003; Wu et al., 2009). Besides, it has been reported that intolerance of uncertainty, whose severity and importance increases during epidemic and pandemic periods, is an important determinant of psychological well-being (Satici et al., 2020).

#### 1.1. Intolerance of Uncertainty and Mental State

Certainty and uncertainty are fundamental existential dilemma for human beings. Most people do not want to know about the negativities that will happen to them in their lives. According to (Gigerenzer and Garcia-Retamero, 2017), this is called regret of knowing. Because of human nature, person wants to be sure of the future and guarantee it (Grenier et al., 2005). Moreover, people want to understand existing threats and experience a sense of control. Therefore, uncertainty in the current situation can be accepted as an important risk factor that adversely affects the mental state. It is reported that uncertainties increase during epidemics (Li et al., 2019). Unlike other epidemics, Covid-19 spread rapidly and turned into a pandemic. During this pandemic, nurses working in the front lines faced the uncertainty brought about by the Covid-19 pandemic process, in addition to the difficulties they experienced in the supply of personal protective equipment such as masks, gloves and gowns (Jackson et al., 2020). The behavior of individuals against this uncertain pandemic threat plays an important role in minimizing the rate of spread of the pandemic and possible loss of life.



When individuals perceive a situation that threatens their health or encounter a disease, they are stressed and react to this situation cognitively and emotionally (Çırakoğlu, 2011; Hagger and Orbell, 2003). Cognitive processes are thought to be important in dealing with Covid-19 uncertainty as well as in dealing with stress. When individuals first encounter a threat situation, they first evaluate the extent of the danger and then evaluate what can be done to overcome, prevent or decrease. This process involves a complex assessment of a person's coping options (Li et al., 2020b). As a result of these evaluations, individuals may feel threatening, uncontrollable and stressful, as well as higher levels of psychological symptoms and dysphoric mood (Peacock and Wong, 1990). There are many studies reporting that intolerance of uncertainty that emerged during this period negatively affects the mental state of individuals (Rosser, 2019; Swee et al., 2019; Mertens et al., 2020; Parlapani et al., 2020; Satici et al., 2020). However, the number of studies examining the effect of intolerance of uncertainty, which is an important concept in terms of psychopathology, on the mental states of nurses, who has an important place in the Covid-19 process, is quite limited (Aksoy and Koçak, 2020).

### 1.2. Contamination Cognition and Mental State

Pandemic affects the mental state of individuals as well as their behavior. As a precautionary behavior in possible epidemic or pandemics like Covid-19, people have behaviors such as paying attention to personal hygiene, avoiding contact with others by staying at home, using a face mask when going out, preferring isolated areas (cottage, farm) (Kristiansen et al., 2007). In pandemic situations, individuals' anxiety level and protective behaviors such as excessive hand washing increase. This situation shows that individuals have a fear of contamination during the epidemic or pandemic process (Wheaton et al., 2012). Contamination is one of the most unusual fears in humans. People with an abnormally high fear of contamination may overestimate the likelihood and potential seriousness of this situation (Deacon and Olatunji, 2007). A certain concern about the epidemic can be positive in terms of focus, and motivation of appropriate protective behavior. However, when anxiety becomes excessive, it may impair the functionality of individuals by causing avoidance behaviors (Wheaton et al., 2012).

As a result, the risk of infection to nurses increases due to the fact that Covid-19 is a contagious disease and nurses are at the center of the treatment and care services offered (Huang et al., 2020). This situation affects the threat perceptions of nurses towards their environment and can lead to cognitive and psychological changes. These changes can be reflected in the behaviors of the individual as a result of his/her cognitive evaluations. Nurses may show avoidance behavior in order to remove the perceived threat from their environment and the health behaviors they apply may be out of the ordinary. Particularly, individuals who are afraid of contamination

during the pandemic process can make negative cognitive evaluations. The mental state of individuals who may exhibit different health behaviors due to the threat they perceive may be adversely affected. When the literature was examined, it was observed that the studies evaluating the intolerance of uncertainty and mental state of nurses regarding the Covid-19 pandemic were quite limited (Aksoy and Koçak, 2020; Kang et al., 2020), and there was no study on contamination cognitions. Therefore, the study was conducted to examine the effect of nurses' attitudes towards uncertainty and perceived contamination cognition on mental state during the Covid-19 pandemic, which is a source of uncertainty and a high risk of contamination. Cognitive processes are closely related to mental health and can be changed by training such as psychoeducation and awareness. It is thought that the results of the study will contribute to the literature in the creation of preventive counselling programs that will be offered to nurses who are at the center of health services in this process.

## 2. Materials and Methods

### 2.1. Research Questions

The questions in the research are presented below;

- i. During the Covid-19 pandemic, do intolerance of uncertainty, contamination cognitions and mental status in nurses change according to socio-demographic variables?
- ii. Is there a relationship between intolerance of uncertainty, contamination cognitions and mental state during the Covid-19 pandemic?
- iii. Did the intolerance of uncertainty in the Covid-19 pandemic affect the contamination cognition of nurses?
- iv. Did the intolerance of uncertainty, and contamination cognitions affect the mental states of nurses during the Covid-19 pandemic?

### 2.2. Methods

#### 2.2.1. Study design and sample size

Data were collected between June 2020 and November 2020. The population consisted of 1200 nurses working in a public hospital during the Covid-19 pandemic period. The sample calculation was made with a known population. In the sample calculation, case numbers of the Ministry of Health on June 2020 were based and the sample size was determined as 328 people with 95% reliability. The nurses included in the study were selected by a simple random method. Considering that there might be missing data, it was decided to collect data from 335 nurses. The study was completed with 328 nurses who completed the data collection forms. Nurses over the age of 18, who did not have any mental illness, and who agreed to participate in the study were included in the study.

### **2.2.2. Data collection tools**

The data were collected using "Introductory Information Form", "Intolerance of Uncertainty Scale (IUS-12)", "Depression, Anxiety and Stress Scale (DASS-21)" and "Contamination Cognition Scale". The data were collected online due to the Covid-19 pandemic.

### **2.2.3. Introductory information form**

In this form prepared by the researcher based on the literature (Ekiz et al., 2020), there are a total of 10 questions about the individuals' age, gender, educational status, and professional experience.

### **2.2.4. Short form of intolerance of uncertainty scale (IUS-12)**

The Turkish validity and reliability adaptation of the scale, which was developed by Carleton, Norton, and Asmundson (2007), was made by (Sarıçam et al., 2014). The scale evaluates the tendency to negatively react emotionally, cognitively, and behaviorally to uncertain events and situations (Sarıçam et al., 2014). The Cronbach  $\alpha$  coefficient for the total of the scale was determined as 0.88 (Sarıçam et al., 2014). In our study, this value was determined as 0.86.

### **2.2.5. Depression, anxiety and stress scale (DASS-21)**

Sarıçam (2018) made the psychometric properties of the Turkish version in normal and clinical samples of the scale, which was developed by Lovibond and Lovibond (1995). Test-retest correlation coefficients in the normal sample were  $r = 0.68$  for the depression subscale,  $r = 0.66$  for the anxiety subscale, and  $r = 0.61$  for the stress subscale. When an individual gets a score of 5 points and above from the depression sub-dimension, 4 points or more from anxiety, 8 points or more from stress, it is indicated that he/she has a problem (Sarıçam, 2018). In our study, Cronbach's  $\alpha$  values were determined as 0.89 for anxiety, 0.91 for depression, and 0.80 for stress.

### **2.2.6. Contamination cognition scale (CCS)**

Deacon and Olatunji (2007) developed it to evaluate the perceived threat level regarding the possibility of contamination and the consequences of this possibility. Its Turkish validity and reliability were performed by İnözü and Eremsoy (2013). The Cronbach's  $\alpha$  value of the scale was found to be 0.97 (İnözü and Eremsoy, 2013). In our study, this value was determined as 0.97.

### **2.2.7. Data collection**

Current situation regarding the coronavirus process was not fully clear, so the data forms were sent to the nurses via Google Forms. An "Informed Volunteer Form" was placed in the Google Form and the volunteer approval tab was necessary. A preliminary interview was held with the nurses included in the sample, their phone numbers were taken and a link to the questionnaire was sent.

### **2.3. Statistical Analysis**

The data obtained from the research were evaluated in the SPSS 25 (IBM SPSS Statistics Standard Concurrent User V 25) package software. Number (n), percentage (%), mean and standard deviation (SD) were used as descriptive statistical methods. The Kolmogorov-Smirnov

test and QQ plot were used to evaluate the suitability for normal distribution of the data and it was observed that there was no normal distribution ( $p < 0.05$ ). For this reason, the Mann-Whitney U test was used in the evaluation of double independent groups, and the Kruskal-Wallis one-way analysis of variance was used in the comparison of three or more independent groups. Spearman correlation was used for correlation analysis. Relational questions were tested with simple and multiple linear regression analysis. In all comparisons,  $p < 0.05$  was considered statistically significant.

### **3. Results**

The average age of the nurses participating in the study was  $31.81 \pm 7.69$ , 84.1% were women, 77.1% had a bachelor's degree, 36.9% had been working for 11-15 years, 55.2% were married, 51.5% did have children, and 79% of them had no chronic disease. All of the participants worked actively during the Covid-19 pandemic, around 44.8% of them knew a person who diagnosed with Covid-19, 75.0% gave care to the patient diagnosed with Covid-19, and 90.0% of them reported that their cleaning habits changed during this process. Furthermore, 68.6% of the participants defined the Covid-19 pandemic as frightening/worrying.

Table 1 shows the mean scores obtained by the nurses from the scales according to their sociodemographic characteristics. Accordingly, it is seen that intolerance of uncertainty does not differ according to gender ( $P > 0.05$ ), whereas women's contamination cognition, depression, anxiety and stress mean scores were higher than men ( $P < 0.05$ ). When the scale scores were examined according to marital status, it was determined that the mean scores of anxiety did not differ according to the groups ( $P > 0.05$ ), and the mean scores of the married individuals were higher than the singles in all other scales ( $P < 0.05$ ). Besides, it was observed that having children did not affect anxiety scores similarly ( $P > 0.05$ ), and in all other scales, the mean scores of those who had children were higher than the mean scores of those who did not have children ( $P < 0.05$ ). Moreover, it was found that the average scores in all scales of those with a working period of 11-15 years were higher than individuals with other working periods ( $P < 0.05$ ). It was observed that the contamination cognition, anxiety and stress mean scores of those with chronic diseases were higher than individuals without chronic diseases ( $P < 0.05$ ). Moreover, it was determined that the mean scores of nurses who evaluated the Covid-19 process as frightening/worrying were higher than other groups ( $P < 0.05$ ).

**Table 1.** Score means of IUS-12, DASS-21 and CCS scales according to the descriptive characteristics of the nurses (n = 328)

Variables	IU	CC	D	A	S
Mean ± SD (Median)					
<b>Gender</b>					
Female	42.13±8.23 (43.00)	80.55±10.40 (80.00)	10.32±5.85 (10.00)	8.58±5.54 (8.00)	10.67±5.50 (11.00)
Male	40.25±9.21 (39.50)	70.23±20.04 (70.00)	7.80±5.47 (8.00)	6.46±5.38 (6.00)	8.88±4.73 (9.00)
Statistical analysis	Z*-1.511 P=0.131	Z*-4.772 P<0.001	Z*-2.742 P<0.01	Z*-2.525 P<0.05	Z*-2.117 P<0.05
<b>Marital status</b>					
The married	43.12±8.30 (43.00)	80.70±10.40 (81.00)	10.56±5.99 (10.00)	7.88±5.62 (9.00)	11.13±5.39 (11.00)
Unmarried	40.25±8.28 (40.00)	70.91±10.71 (71.00)	9.13±5.60 (9.00)	7.68±5.47 (6.00)	9.46±5.33 (10.00)
Statistical analysis	Z*-3.089 P<0.01	Z*-4.674 P<0.001	Z*-2.062 P<0.05	Z*-1.786 P=0.074	Z*-2.672 P<0.01
<b>Having a child</b>					
Yes	43.05±8.23 (43.00)	80.71±10.40 (81.00)	10.63±5.92 (10.00)	8.61±5.52 (9.00)	11.10±5.24 (11.00)
No	40.53±8.41 (40.00)	70.96±10.69 (71.00)	9.16±5.70 (9.00)	7.86±5.61 (7.00)	9.62±5.52 (10.00)
Statistical analysis	Z*-2.878 P<0.01	Z*-4.435 P<0.001	Z*-2.169 P<0.05	Z*-1.288 P=0.198	Z*-2.429 P<0.05
<b>Working time</b>					
0-1 year	39.57±8.64 <sup>a</sup> (39.00)	80.05±10.50 <sup>a</sup> (84.00)	8.95±5.61 <sup>ab</sup> (9.00)	7.59±5.59 <sup>ab</sup> (6.00)	9.18±5.60 <sup>a</sup> (9.00)
2-5 years	41.96±7.77 <sup>ab</sup> (42.00)	70.57±20.07 <sup>a</sup> (81.00)	8.17±5.06 <sup>a</sup> (9.00)	6.68±5.09 <sup>a</sup> (6.00)	8.87±4.41 <sup>a</sup> (9.00)
6-10 years	42.30±8.49 <sup>ab</sup> (43.50)	80.65±10.35 <sup>b</sup> (91.00)	10.19±5.90 <sup>ab</sup> (9.50)	8.30±5.65 <sup>ab</sup> (8.00)	11.20±5.40 <sup>ab</sup> (11.50)
11-15 years	43.38±8.13 <sup>b</sup> (43.00)	80.67±10.44 <sup>b</sup> (91.00)	11.14±6.06 <sup>b</sup> (11.00)	9.30±5.52 <sup>b</sup> (11.00)	11.36±5.42 <sup>b</sup> (11.00)
Statistical analysis	KW**11.610 P<0.01	KW**21.363 P<0.001	KW**11.223 P<0.05	KW**9.435 P<0.05	KW**13.331 P<0.01
<b>The situation of chronic diseases</b>					
There is	43.32±8.26 (44.00)	80.91±10.17 (83.50)	10.67±6.64 (12.00)	10.23±6.62 (11.00)	11.59±5.77 (13.00)
None	41.50±8.41 (42.00)	80.22±10.64 (83.00)	9.75±5.67 (9.00)	7.81±5.22 (7.00)	10.12±5.32 (10.00)
Statistical analysis	Z*-1.689 P=0.091	Z*-2.917 P<0.01	Z*-1.138 P=0.255	Z*-2.670 P<0.01	Z*-2.024 P<0.05
<b>Familiarity with COVID-19</b>					
There is	42.40±8.06 (42.00)	80.40±10.48 (84.50)	10.89±5.84 (11.00)	9.08±5.78 (9.00)	11.29±5.53 (11.00)
None	40.09±8.66 (42.00)	80.05±10.68 (83.00)	9.13±5.73 (9.00)	7.57±5.30 (7.00)	9.64±5.23 (9.00)
Statistical analysis	Z*-0.768 P=0.443	Z*-0.254 P=0.799	Z*-2.714 P<0.01	Z*-2.403 P<0.05	Z*-2.718 P<0.01
<b>General thoughts on the COVID-19 process</b>					
A normal process	38.14±5.57 <sup>a</sup> (38.00)	60.60±20.60 <sup>a</sup> (70.50)	7.07±7.24 <sup>a</sup> (4.50)	6.07±5.38 <sup>a</sup> (6.50)	8.00±5.87 <sup>a</sup> (7.50)
An uncertain process	39.21±9.24 <sup>a</sup> (40.00)	80.15±10.65 <sup>ab</sup> (84.50)	8.38±5.46 <sup>a</sup> (9.00)	6.79±5.27 <sup>a</sup> (6.00)	9.19±5.34 <sup>a</sup> (9.00)
A frightening / worrying process	43.10±7.91 <sup>b</sup> (43.00)	80.53±10.41 <sup>b</sup> (85.50)	10.71±5.76 <sup>b</sup> (10.00)	8.96±5.57 <sup>b</sup> (9.00)	11.00±5.33 <sup>b</sup> (11.00)
Statistical analysis	KW**15.991 P<0.001	KW**9.827 P<0.01	KW**13.103 P<0.01	KW**11.646 P<0.01	KW**10.601 P<0.01

\*Mann-Whitney U test, \*\*Kruskal-Wallis test, IU= intolerance of uncertainty, CC= contamination cognitions, D= depression, A= anxiety, S= stress, SD= standard deviation

Correlations between variables are given in Table 2. A positive and significant relationship was found between intolerance of uncertainty and contamination cognitions ( $r=.211, P<0.001$ ), depression ( $r=.402, P<0.001$ ), anxiety ( $r=.369, P<0.001$ ), stress ( $r=.415, P<0.001$ ) and age ( $r=.162, P<0.01$ ) variables. A positive and significant relationship was found between contamination

cognitions and variables of depression ( $r=.161, P<0.01$ ), anxiety ( $r=.169, P<0.01$ ), stress ( $r=.244, P<0.001$ ), and age ( $r=.209, P<0.001$ ). Furthermore, there was a positive and highly significant relationship between depression and anxiety ( $r=.853, P<0.001$ ) and stress ( $r=.880, P<0.001$ ) variables.

**Table 2.** Mean scores (standard deviation (SD) and bivariate correlations among the study variables (n = 328)

Variables	Mean (SD)	1.	2.	3.	4.	5.	6.
1. IU	41.83 (8.40)	1					
2. CC	80.34 (1.59)	.211**	1				
3. D	9.92 (5.86)	.402**	.161*	1			
4. A	8.25 (5.57)	.369**	.169*	.853**	1		
5. S	10.38 (5.42)	.415**	.244**	.880**	.866**	1	
6. Age	31.81 (7.69)	.162*	.209**	.149*	.103	.149*	1

\* $P<0.01$ , \*\* $P<0.001$  (p values according to the Spearman's rho test); IU= intolerance of uncertainty, CC= contamination cognitions, D= depression, A= anxiety, S= stress

The predictive effect of intolerance of uncertainty on contamination cognition in nurses is examined in Table 3. According to Model 1, nurses' intolerance of uncertainty explained their contamination cognition by 4.6%. According to the standardized regression coefficients ( $\beta$ ), the relative effect of intolerance of uncertainty on contamination cognitions was  $\beta=0.214, t=3.953, P=0.001$  (Table 3).

The predictive effect of nurses' intolerance of uncertainty and contamination cognitions on the mental state (depression, anxiety, and stress) is examined in Table 4. Accordingly, it is seen that intolerance of uncertainty and contamination cognitions had a significant effect on the mental state (depression, anxiety, stress). According to

Model 2, intolerance of uncertainty ( $t=7.36, P=0.001$ ) and contamination cognitions ( $t=2.20, P=0.028$ ) had a significant effect on depression. Intolerance of uncertainty and contamination cognitions explained 17.5% of the variance in depression. According to Model 3, intolerance of uncertainty ( $t=6.70, P=0.001$ ) and contamination cognitions ( $t=2.28, P=0.023$ ) had a significant effect on anxiety. Intolerance of uncertainty and contamination cognitions explained 15.5% of the variance in anxiety. In Model 4, it is seen that intolerance of uncertainty ( $t=7.58, P=0.001$ ) and contamination cognitions ( $t=3.69, P=0.001$ ) had a significant effect on stress and 21.1% of the variance in stress was explained by this model.

**Table 3.** Predictive effect of intolerance of uncertainty on contamination cognitions (n=328) §

Variables	B	Std. Error	$\beta$	t	P
Model 1 Contamination Cognitions	R=0.214;	R <sup>2</sup> =0.046;	Adjusted R <sup>2</sup> :0.043;	F <sub>(1,326)</sub> :15.628;	P<0.001
Intolerance of Uncertainty	0.041	0.010	0.214	3.953	0.001*

§Simple linear regression, \* $P<0.01$

**Table 4.** Predictive effect of intolerance of uncertainty and contamination cognitions on mental state (n = 328) §

Variables	B	Std. Error	$\beta$	t	P
Model 2, Depression	R=0.419;	R <sup>2</sup> =0.175;	Adjusted R <sup>2</sup> :0.170;	F <sub>(2,325)</sub> :34.588;	P<0.001
Contamination Cognitions	0.418	0.189	0.114	2.205	0.028*
Intolerance of Uncertainty	0.265	0.036	0.380	7.363	0.001**
Model 3, Anxiety	R=0.393;	R <sup>2</sup> =0.155;	Adjusted R <sup>2</sup> :0.149;	F <sub>(2,325)</sub> :29.722;	P<0.001
Contamination Cognitions	0.417	0.182	0.119	2.286	0.023*
Intolerance of Uncertainty	0.232	0.035	0.350	6.704	0.001**
Model 4, Stress	R=0.460;	R <sup>2</sup> =0.211;	Adjusted R <sup>2</sup> :0.207;	F <sub>(2,325)</sub> :43.574;	P<0.001
Contamination Cognitions	0.634	0.172	0.186	3.695	0.001**
Intolerance of Uncertainty	0.247	0.033	0.382	7.584	0.001**

§Multiple linear regression, \* $P<0.05$ , \*\* $P<0.01$ .

#### 4. Discussion

As in other pandemics in the world, healthcare professionals, especially nurses, are actively involved in the Covid-19 pandemic and their psychological conditions are negatively affected (Kang et al., 2020; Wu et al., 2009). In our study, it is seen that the participants' mean scores for depression, anxiety, and stress were moderate and high. It is very important to reveal the reasons for the psychological status of nurses, who are one of the pioneers of health care services, in such pandemics. In this study, it was first examined whether there was a relationship between the demographic characteristics of the nurses and their scores on the scales. In our study conducted for this purpose, it is seen that there was no significant change in the average of intolerance of uncertainty according to gender ( $P>0.05$ ). This finding is consistent with the data of (Aksoy and Koçak, 2020) study with Turkish nurses and midwives. Furthermore, it was found that the contamination cognition, depression, anxiety and stress mean scores of the women were high ( $P<0.05$ ). In the study conducted by Arpacioğlu et al. (2021), it was found that the mean scores of fear of Covid-19, burnout and depression were high in female health care professionals. Considering the relationship between cognition and emotion, this finding seems to be supported. It has been also reported that the fear of contamination is higher in women (Gilbert, 2019). Besides, it has been stated that intolerance of uncertainty, fear and depressive symptoms associated with Covid-19 are more common in women (Parlapani et al., 2020). This may be due to the fact that the right orbitofrontal cortex and amygdala are more active in women. This activation means that emotional and cognitive processing work largely in parallel (Koch et al., 2007). There are also data that women use more negative coping skills as they get older (Nolen-Hoeksema and Aldao, 2011). In our study, it was observed that all variables were negatively affected by the increase in working time. Moreover, the majority of the participants were women and had six years or more years of working. In addition to being a woman and advancing age, it is thought that negative experiences in a long working life and exhaustion may also have had an effect on this negative situation.

In our study, it is seen that participants who were married and having child had high averages in terms of all variables except anxiety. At the time of the study, due to factors such as the high infectiousness of the Covid-19 virus and the lack of a vaccine, intolerance of uncertainty and negative cognition score averages may have increased. In addition, considering the responsibilities of these participants towards their spouses and children, it can be interpreted as an expected result that their anxiety to infect their close relatives and their mental state were negatively affected. Similar to our study, there are also studies reporting that intolerance of uncertainty and cognition for contamination negatively affect the mental state (Hill and Hamm, 2019; Jalal et al., 2018;

Tanriverdi and Tanriverdi, 2021).

In our study, it was found that the mental states of the nurses, who knew people diagnosed with Covid-19, were negatively affected. Tanriverdi and Tanriverdi (2021), in their study examining the effects of Covid-19 on the mental health of health care professionals, reported that individuals had to cope not only with the threat of the disease, but also with the burden of illness or death of their relatives.

In this study, all of the nurses worked actively in this process and witnessed the negative effects of the Covid-19 virus on individuals. The fact that these negative consequences also happened to relatives/friends or the possibility of them may have negatively affected the mental state of the participants.

Besides, it was observed that the nurses who evaluated the Covid-19 process as frightening/worrying had high mean scores for all scales. This finding partially complies with the findings study of Aksoy and Koçak (2020). This situation can be explained by the argument that cognitive processes cannot be considered separately from emotional processes. It is known that emotion and cognition are not separate systems, and there are rich and dynamic interactions between brain networks in complex cognitive-emotional and behavioral processes (Pessoa, 2008). Therefore, the mental state of the participants who perceived and evaluated the situation negatively may also be negatively affected (Table 1).

For the other questions of our study, a positive significant relationship was found between study variables (Table 2). Moreover, it was observed that intolerance of uncertainty and contamination cognitions negatively affected the mental state (anxiety, depression, stress) both separately and together (Table 3 and Table 4). We believe that these findings should especially be highlighted and will contribute to the literature. It has been reported in previous studies that intolerance of uncertainty increases fear of Covid-19 and negatively affects mental state (anxiety, depression, stress, anxiety, etc.) (Mertens et al., 2020; Rosser, 2019; Swee et al., 2019). During the Covid-19 pandemic, which was great uncertainty, intolerance of uncertainty, which had a psychologically transdiagnostic nature (Rosser, 2019), increased and negatively affected mental health (Swee et al., 2019). Carleton (2016) also reported that intolerance of uncertainty is a transdiagnostic vulnerability factor. Considering the current Covid-19 pandemic, it was observed that the high level of uncertainty increased the fear of coronavirus and negatively affected the contamination cognition. In this context, contamination cognition is thought to be a defense model similar to intolerance of uncertainty.

It is known that the Covid-19 pandemic negatively affected the mental state of healthcare professionals, especially nurses (Kang et al., 2020). We think that our study will make a significant contribution to the literature in terms of revealing the reasons for this negative situation in nurses. Moreover, Covid-19 may

have increased the perception of the danger of individuals due to its high risk of contamination and morbidity and mortality risk (Li et al., 2020a). 68.6% of the participants described the Covid-19 pandemic as frightening/worrying. In addition, the fact that the vast majority (75.0%) of the nurses participating in the study had close contact with patients diagnosed with Covid-19 and had a decisive role in the spread of contamination (Kharma et al., 2015) may have negatively affected the cognition of contamination. Besides, the fact that more than half of the participants were married and had children and increased the sense of responsibility towards their spouses and children might have negatively affected their intolerance of uncertainty and contamination cognition. As a conclusion, this negativity may have increased the anxiety, depression and stress levels of the nurses.

## 5. Conclusion and Implications

It is known that the mental state of all healthcare professionals, especially nurses, was negatively affected in Covid-19-like pandemics. In this process, different consultancy programs for health professionals are also carried out. It is thought that it would be beneficial to add specific topics such as contamination cognition in addition to anxiety, depression and stress coping skills to these programs. Furthermore, it is thought that investigating intolerance of uncertainty and other factors that affect the development of contamination cognition will contribute to the regulation of these cognitive structures. It is remarkable that the mental states of nurses who were married and had children were affected more in our study. Nurses and their families should be encouraged to participate together in the counselling programs that are offered for this purpose.

## Limitations and Strengths of Study

It should be accepted that our study has some limitations. Since this study has a cross-sectional design, the results involve instant assessments. It is thought that a longitudinal research will be a more suitable design for investigating, in terms of the established model, the relationships and causality over time. Also, although our research sample was considered adequate for analyzing the established model, it is assumed that a larger sample will allow us to go beyond our existing analysis level for studying the differences of both dependent and independent variables (e.g. gender and age). The answers given by the participants to the data collection instruments, which were used for the dependent variables in the established model, were considered correct, but the answers given to the study are limited with the scale items. Strengths of the research are sufficient sample size and statistical method used.

## Author Contributions

Concept: M.E. (50%) and N.Ş. (50%), Design: M.E. (50%) and N.Ş. (50%), Supervision: M.E. (50%) and N.Ş. (50%), Data collection and/or processing: Ö.Ö. (100%), Data analysis and/or interpretation: M.E. (50%) and N.Ş. (50%), Literature search: M.E. (34%), Ö.Ö. (33%) and N.Ş. (33%), Writing: M.E. (34%), Ö.Ö. (33%) and N.Ş. (33%), Critical review: M.E. (34%), Ö.Ö. (33%) and N.Ş. (33%), Submission and revision M.E. (34%), Ö.Ö. (33%) and N.Ş. (33%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest. The authors alone are responsible for the content and writing of the article.

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## Ethical Approval/Informed Consent

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## SEZARYEN OPERASYONLARINDA UYGULANAN ANESTEZİ TEKNİĞİNİN DEĞERLENDİRİLMESİ: MESAI İÇİ VE DIŞI SAATLERİN KARŞILAŞTIRILMASI

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**Özet:** Çalışmamızda Ocak 2012 – Aralık 2013 tarihleri arasında Uludağ Üniversitesi Tıp Fakültesi Hastanesi'nde mesai saatleri içinde ve dışında alınan sezaryen olgularında sezaryen endikasyonlarını, uygulanan anestezi tekniğini ve teknik seçimini etkileyen faktörleri belirlemeyi amaçladık. Sezaryen olan 1025 olgunun ve doğan bebeklerinin verileri retrospektif olarak kaydedildi. Mesai içi/dışı saatler tanımlanarak olgular gruplandırıldı. Olguların %51,3'ünün mesai içinde, %48,7'sinin mesai dışında alındığı çalışmamızda genel anestezi %76,4, spinal anestezi %14,4, kombine spinal epidural (KSE) anestezi %6,2, epidural anestezi %3 oranlarında uygulanmıştı. Spinal ve genel anestezi uygulanma oranı mesai içinde ve dışında eşitken, KSE anestezi uygulanma oranının mesai içinde daha fazla olduğu saptandı (P=0,003). Rejyonal anestezi oranları %91,3'ü başarılı %8,7'si başarısızdı. Başarısız rejyonal anestezi oranı her iki grupta da benzerdi. Mesai içi sistolik ve diyastolik arter basınçları (SAB/DAB) daha düşük (P=0,001), gebelik haftası daha yüksekti (P<0,001). Mesai dışında preeklampsi oranı daha yüksek (P<0,001), doğum ağırlığı, Apgar 1. ve 5. dakika skorları daha düşüktü (P<0,001). Mesai içinde eski sezaryen, plasenta anomalileri ve vajinal kaynaklı problemler; mesai dışında akut fetal distres (AFD) gibi endikasyonlar daha fazlaydı (P<0,001, P=0,003, P<0,05, P<0,001). Rejyonal anestezi oranlarımız diğer çalışmalara oranla düşüktür. Hastanelerde gece nöbetlerinde çalışan ekibin deneyimi, cerrahi ekibin rejyonal anesteziye bakış açısı, yeterli malzemenin temin edilebilmesi gibi faktörler rejyonal anestezinin mesai dışı saatlerde uygulanma sıklığını etkilemektedir. Hastanın obstetrisyen ve anesteziist tarafından doğru bilgilendirilmesiyle, rejyonal anestezi hakkındaki ön yargıları giderilip anne ve bebek için en doğru anestezi tekniğine karar verilmelidir.

**Anahtar kelimeler:** Sezaryen, Rejyonal anestezi, Genel anestezi, Apgar skoru

### The Assessment of Anesthesia Techniques Used in Patients Undergoing Cesarean Section: Comparison of Day and Night Shift Periods

**Abstract:** In our study at Uludağ University Medical Faculty Hospital between the periods of 2012 January and 2013 December, we aimed to evaluate cesarean indications, anesthesia techniques used for the cesarean sections and the factors affecting the technical choice during day and night shift periods. Data of 1025 cesarean section patients and neonates were recorded retrospectively. Day and night shifts were determined and patients were divided into two groups accordingly. Fifty-one percent of patients were operated on during day shifts, while 49% of patients were operated on during night shifts. General anesthesia was administered to %76.4, spinal anesthesia was administered to 14.4%, combined spinal epidural (CSE) anesthesia was administered to 6.2% and epidural anesthesia was administered to 3% of the patients. Spinal and general anesthesia were used equally in day and night shifts whereas CSE anesthesia rate was higher during day shifts (P=0.003). In 91.3% of patients who were administered regional anesthesia the procedures were successful, whereas in 8.7%, they were not. Failed regional anesthesia rate was similar in both groups. The systolic and diastolic blood pressures were statistically lower (P=0.001) and gestational age was higher in the day shift group (P<0.001). The preeclampsia rate was higher, the Apgar scores at 1 and 5 minutes and birth weight were significantly lower in the night shift group (P<0.001). A previous cesarean section, placentation abnormalities and vaginal problems as indications for cesarean section were significantly higher in the day shift group (P<0.001, P=0.003, P<0.05). In night shift group acute fetal distress (AFD) rate was significantly higher (P<0.001). Regional anesthesia rates are lower than those of other studies. Factors like professional experience of the night shift personnel, surgical team's perspective on regional anesthesia and obtaining sufficient materials affect the use of regional anesthesia during night shifts. It is appropriate to decide the most suitable anesthesia technique for both the mother and the baby by correctly informing the patient by an obstetrician as well as an anesthetist.

**Keywords:** Cesarean section, Regional anesthesia, General anesthesia, Apgar score

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## 1. Giriş

Sezaryen obstetrik cerrahinin en önemli girişimlerinden biridir. Dünya Sağlık Örgütü tarafından ideal oran %10-15 olarak belirtilmiş olsa da bu oran tüm dünyada giderek artmaktadır (Yeşilçiçek, 2018; Karaca, 2020). Özellikle gelişmiş ve gelişmekte olan ülkelerde sezaryen insidansı artarak tüm doğumların yaklaşık %25'ini oluşturmaktadır. Sezaryen oranlarındaki artışın en sık nedeni fetal distress endikasyonlarının genişlemesi ve mükerrer sezaryenlerdir (Birnbach, 2010). Sezaryen sırasında hem annenin hem de fetusun güvenliği sağlanmalıdır. Seçilen anestezi yönteminin anne ve yenidoğan üzerine direkt etkili olması sebebiyle sezaryen anestezisi özelliğindedir. Bu sebeple sezaryen operasyonlarında anestezi uzmanı için en güvenli ve konforlu, yenidoğanda en az depresyon yapan ve obstetrisyen için optimal çalışma koşullarını sağlayabilen anestezi yöntemini seçmelidir (Frölich, 2015). Sezaryende anestezi tercihi cerrahi girişimin aciliyeti, hasta ve cerrahın seçimi ve anestezi uzmanının becerisine bağlı olarak değişmektedir.

Çalışmamızın amacı, mesai saatleri içinde ve dışında alınan sezaryen olgularında endikasyonları, uygulanan anestezi tekniklerini, teknik seçimini etkileyen faktörleri belirlemektir.

## 2. Materyal ve Yöntem

### 2.1. Çalışma Tasarımı

Çalışma protokolünün Yerel Etik Komite tarafından onaylanmasını takiben 1 Ocak 2012 - 31 Aralık 2013 tarihleri arasında hastanemizde Kadın Hastalıkları ve Doğum Anabilim Dalı'nda sezaryen uygulanan gebeler ve yenidoğanları çalışmaya dahil edildi. Çalışmaya dâhil edilen 1025 gebe ve yenidoğanların medikal verileri hastane bilgi sistemi, doğumhane ve arşiv kayıtları kullanılarak retrospektif olarak incelendi. Mesai saatleri olarak hafta içi 08.00-16.00 arası kabul edildi. Nöbet ekibinin kaldığı hafta içi saat 16.00-08.00 arası, cumartesi ve pazar günleri ile resmi tatiller de mesai dışı olarak kabul edildi.

### 2.2. Veriler

Gebelerin yaşı, gebelik, parite, yaşayan, abortus sayıları, gebelik süresi, sistemik hastalığı ve kullandığı ilaçlar, sezaryen endikasyonu, sezaryen uygulanma zamanı, anestezi tekniği, indüksiyon öncesi SAB (sistolik arteriyel basınç) ve DAB (diyastolik arteriyel basınç) değerleri, vazopressör ihtiyacı olup olmadığı, varsa çoğul gebelikler, bebeklerin 1. ve 5. dakika (dk) Apgar skorları, doğum ağırlığı, sağlık problemleri ve bebeğe yapılan girişimler kaydedildi. Sezaryenlerde tercih edilen anestezi yöntemi genel anestezi (GA) ve rejyonal anestezi (RA) olarak gruplandırıldı. Rejyonal anestezi ise spinal anestezi (SA), epidural anestezi (EA), kombine spinal-epidural anestezi (KSEA) şeklinde kaydedildi. RA yöntemlerinden herhangi birindeki başarısızlık, başarısız RA olarak belirtildi. Doğumhanede ağrısız doğum amacıyla yerleştirilen epidural kateteri olan ve acil sezaryen için

ameliyathaneye alınan ancak GA uygulanan olgular da başarısız RA olarak kabul edildi.

Sezaryen endikasyonları; eski sezaryen, fetal makrozomi, akut fetal distress, ağır preeklampsi, HELLP sendromu, kordon prezentasyonu, intrauterin gelişme geriliği (IUGG), geçirilmiş uterin cerrahi veya uterin rüptür, sefalopelvik uyumsuzluk (CPD), malprezentasyon, plasenta anomalileri, geçirilmiş vajinal kozmetik/rektal düzeltici cerrahi veya vulvar lezyon varlığı maternal kaynaklı gebelik dışı nedenler (psikiyatrik, vajinismus, aort stenozu, vs.) olarak gruplandırıldı. Gebede kardiyak, solunum sistemi, renal, endokrin ve metabolik hastalıklar, nörolojik ve psikiyatrik hastalıklar, koagülasyon bozuklukları, kas-iskelet sistemi hastalıkları gibi patolojiler kayıt altına alındı. Bununla beraber prenatal yandaş hastalıklar olarak gestasyonel diabetes mellitus (GDM), gestasyonel hipertansiyon (GHT), gestasyonel trombositopeni, gestasyonel kolestaz, preeklampsi, eklampsi ve HELLP sendromu olan hastalar belirlendi. Ağır preeklampsi, HELLP sendromu, süperempoze preeklampsi, ablasyo plasenta, kordon prezentasyonu, IUGG, fetal AV blok gibi bebeği strese sokan acil durumlar AFD başlığı altında değerlendirildi. Gebelikte kullanılan ilaçlar kayıt altına alındı.

Çoğul gebelikler de (ikiz/üçüz) çalışmaya dahil edildi ve doğan bebekler ayrı ayrı değerlendirildi. Yenidoğanlar sağlıklı ve sağlık problemi olanlar olarak 2 gruba ayrıldı. İUGG, multipl anomaliler, sendromlar, kardiyak hastalıklar, fetal iskelet displazisi, fetal Arnold Chiari malformasyonu, fetal pelvik ektazi, hidrops fetalis, diyafram hernisi, omfalosel, gastroşizis, duodenal atrezi, intraabdominal kitle, yarı dudak-damak, hidrosefali vb saptanan bebekler sağlık problemleri olanlar grubuna dâhil edildi. Bebekler 1. ve 5. dk Apgar skorlarına göre değerlendirilerek, gerektiğinde kardiyopulmoner resüsitasyon yapılan bebekler kaydedildi.

### 2.3. İstatistik Analiz

Verilerin tanımlayıcı istatistiklerinde ortalama, standart sapma, medyan en düşük, en yüksek, frekans ve oran değerleri kullanılmıştır. Değişkenlerin dağılımı Kolmogorov-Smirnov testi ile ölçüldü. Nicel verilerin analizinde ANOVA (Tukey test), Kruskal-Wallis, Mann-Whitney U test ve Bağımsız örneklem t test kullanıldı. Nitel verilerin analizinde Ki-Kare test, Ki-Kare test koşulları sağlanmadığında Fischer testi kullanıldı (Genç ve Soysal, 2018; Önder, 2018). Anlamlılık düzeyi  $P < 0,05$  olarak belirlendi. Analizlerde SPSS 22.0 programı kullanılmıştır.

## 3. Bulgular

Çalışmada toplam 1025 sezaryen ameliyatı retrospektif olarak incelendi. Çalışma dışı bırakılan olgu olmadı. Olguların demografik verileri ve gebelikle ilgili bilgileri Tablo 1'de verildi. Olguların %7'inde ( $n=74$ ) çoğul gebelik, %28'inde ( $n=287$ ) abortus öyküsü mevcuttu. 643 (%63) olguda parite  $>1$  idi.

**Tablo 1.** Olguların demografik verileri ve gebelikle ilgili bilgileri

	Ort ±SS (min-maks)
Gebe Yaşı (yıl)	30 ±5,4 (17-49)
SAB (mmHg)	137±20 (95-259)
DAB (mmHg)	85±14 (40-165)
Gebelik Süresi (Hafta)	37±4 (17-42)
Gebelik Sayısı (adet)	2,5±1,6 (1-11)
Doğum Sayısı (adet)	1,0±1,1 (0-7)
Abortus sayısı (adet)	0,5±1,0 (0-10)
Yaşayan Çocuk Sayısı (adet)	0,9±0,9 (0-5)

SAB= Sistolik arteriyel basınç, DAB= Diyastolik arteriyel basınç, Ort±SS (min- maks)= ortalama±standart sapma (minumum-maksimum).

Olguların %51,3' ü (n=526) mesai içi, %48,7' si (n=499) mesai dışı saatlerde alındı. En sık uygulanan anestezi yöntemi GA idi (%76,4). SA %14,4, KSEA %6,2, EA %3 oranında uygulandı. RA uygulanan olguların %91,3' ü başarılı %8,7' si başarısız oldu. Başarısız olan olgulara GA uygulandı (Tablo 2). GA ve RA uygulanan olgular arasında yaş farkı bulunmadı (P>0,005).

Mesai içi ve mesai dışı saatlerde sezaryen uygulanan olgular karşılaştırdığı zaman yaş, çoğul gebelik oranı ve abortus oranları açısından fark bulunmadı (P>0,05). Mesai saati içinde sezaryene alınan olguların ise SAB ve

DAB değerleri mesai dışındaki olgulardan anlamlı olarak daha düşüktü (P=0,001, P=0,000). Mesai içinde alınan olgularda gebelik haftası, gebelik sayısı mesai dışı gruptan anlamlı olarak daha yüksekti (P=0,000, P=0,018). Mesai içinde ve dışında eşit sayıda çoğul gebelik alındığı gözlemlendi (n=37, n=37) (Tablo 3). Parite oranı ve yaşayan çocuk oranı mesai içi alınanlarda daha yüksek bulundu. Mesai içinde alınan yaşayan çocuğu olan olgu sayısı 347 (%55,5), mesai dışı alınanlarda ise 278 (%44,5)'di.

**Tablo 2.** Olguların mesai içi / mesai dışı olma, anestezi türü ve RA başarı dağılımı

		n	%
Mesai Saati	Mesai içi	526	%51,3
	Mesai Dışı	499	%48,7
	Spinal	148	%14,4
Anestezi Türü	KSEA	64	%6,2
	Epidural	30	%3,0
	Genel	783	%76,4
RA Başarısı	Başarılı RA	221	%91,3
	Başarısız RA	21	%8,7

KSEA= Kombine Spinal Epidural Anestezi, RA= Regional Anestezi, n (%).

**Tablo 3.** Mesai içi ve mesai dışı saatlerdeki olguların karşılaştırmalı demografik verileri ve gebelikle ilgili bilgileri

	Mesai İçi (Ort ±ss)	Mesai Dışı (Ort ±ss)	P
Gebe Yaşı (yıl)	30,8 ±5,3	30,1±5,5	0,051
SAB (mmHg)	135,1±18,0	139,8±20,9	0,001*
DAB (mmHg)	83,2±13,7	86,7±14,9	0,000**
Gebelik Süresi (hafta)	37,4±3,0	36,1±4,1	0,000**
Gebelik Sayısı (adet)	2,6±1,6	2,4±1,6	0,018*
Doğum Sayısı (adet)	1,05±1,02	0,95±1,12	0,014*
Yaşayan Çocuk Sayısı (adet)	0,93±0,87	0,86±1,02	0,012*
Abortus Sayısı (adet)	0,52±1,11	0,46±0,93	0,555

SAB= Sistolik arteriyel basınç, DAB= Diyastolik arteriyel basınç.

Mesai içinde alınan olguların bağ doku hastalığı oranı mesai dışı gruptan anlamlı olarak daha yüksekti (P<0,05). Mesai dışındaki olgularda ise nörolojik hastalık oranı mesai içi gruptan yüksekti (P<0,05) (Tablo 4). Diğer hastalıklar açısından olgular arasında fark bulunmadı.

Mesai içi ve mesai dışında gestasyonel diyabetes mellitus (GDM), gestasyonel hipertansiyon (GHT), gestasyonel trombotikopeni, gestasyonel kolestaz, eklampsi, HELLP sendromu oranı anlamlı farklılık göstermedi (P>0,05). Mesai dışında preeklampsi oranı mesai içi gruptan anlamlı olarak daha yüksekti (P<0,001).

SA ve GA uygulanan olgularda preoperatif antihipertansif kullanım oranı KSEA uygulananlara göre anlamlı olarak daha yüksek (P<0,05) bulunurken diğer anestezi grupları arasında antihipertansif kullanımı açısından farklılık göstermedi. İnsülin, antikoagülan, kortikosteroid, astım/KOAH ilacı kullanan hastalar uygulanan anestezi türüne göre karşılaştırıldığı zaman olgular arasında anlamlı farklılık görülmedi (P>0,05).

İntraoperatif vazopressör ihtiyacı olan olguların oranı

KSEA, SA ve EA uygulananlarda GA uygulananlara göre daha yüksek bulundu (P<0,05). KSEA uygulananlarda 19 (%29,7), SA uygulananlarda 33 (%22,3), EA uygulananlarda 3 (%10), GA uygulananlarda ise 3 olguda (%0,4) vazopressör ihtiyacı oldu.

Sezaryen endikasyonu olarak eski sezaryen, plasental anomaliler ve vajinal kaynaklı nedenler mesai saatleri içinde alınan olgularda mesai saatleri dışında alınan olgulardan daha yüksek bulundu (P=0,000, P=0,003, P=0,026). Mesai dışında AFD oranı mesai içi gruptan anlamlı olarak daha yüksekti (P<0,001). Mesai içi ve mesai dışında endikasyon olarak fetal makrozomi, uterin nedenler, CPD, malprezentasyon ve maternal kaynaklı nedenler arasında fark bulunmadı (P>0,05) (Şekil 1 ve 2). Fetal makrozomi, uterin nedenler, malprezentasyon, vajinal kaynaklı ve maternal kaynaklı nedenler ile sezaryene alınan olgulara uygulanan anestezi türleri arasında (P>0,05) farklılık saptanmazken diğer endikasyonlarda uygulanan anestezi türü farklılık gösterdi (Tablo 5). Mesai içi rejyonel blokların %92,8'i

başarılı, %7,2'si başarısızken, mesai dışı saatlerde rejyonel blokların %89,4'ünün başarılı, %10,6'sının ise başarısız olduğu görüldü. Mesai içi ve dışında RA başarısı anlamlı farklılık göstermedi ( $P>0,05$ ). SA ve KSEA olgularında başarı oranı EA grubundan anlamlı olarak daha yüksekti ( $P<0,001$ ,  $P<0,001$ ). SA ve KSEA uygulamaları arasında başarı oranı farklılık göstermedi ( $P>0,05$ ).

Mesai içi saatlerde sezaryen uygulanan olguların bebeklerinin 1. dk Apgar skorlarının  $8,1\pm 2,0$  ve mesai içinde ise  $7,2\pm 2,7$  olduğu görüldü ( $P<0,001$ ). 5. dk Apgar skorları ise mesai içinde  $9,2\pm 1,6$  ve mesai dışında ise  $8,7\pm 2,1$ 'di ( $P<0,001$ ). Mesai dışı olgularda yenidoğan doğum ağırlıkları ( $2652\pm 1001$  gr) mesai içinde alınanlardan ( $3023\pm 847$  gr) anlamlı olarak daha düşüktü ( $P<0,001$ ). Mesai içi ve mesai dışı saatlerde sezaryen uygulanan olguların bebek ölüm oranları farklılık göstermedi ( $P>0,05$ ). Mesai saatleri dışında anomalili bebek doğum oranı ( $n= 209$ , %41,9) mesai saatleri içi gruptan ( $n=126$ , %24) daha yüksekti ( $P<0,001$ ). Mesai saatleri dışında kardiyopulmoner resüsitasyon yapılan

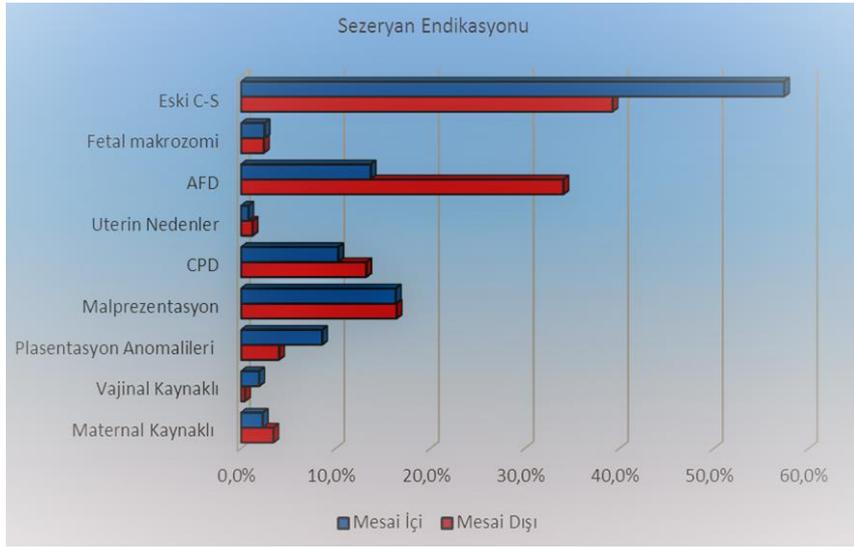
bebek oranı ( $n= 84$ , %16,8) mesai saatleri içinde alınan olgulardan ( $n= 38$ , %7,2) anlamlı olarak daha yüksekti ( $P<0,001$ ).

GA grubunda, 1. dk Apgar, 5. dk Apgar ve doğum ağırlığı değerleri SA, KSEA, EA gruplarından anlamlı olarak daha düşüktü ( $P<0,001$ ). 1. dk Apgar, 5. dk Apgar ve doğum ağırlığı değerleri GA uygulanmayanlar arasında anlamlı farklılık göstermedi ( $P>0,05$ ) (Tablo 6). GA uygulanan olgularda 29 (%4), SA uygulananlarda ise 1 (%1) tane bebek ölümü gözlemlendi, KSEA ve EA uygulananlarda bebek ölümü görülmedi, olgular arasında fark bulunmadı ( $P>0,05$ ). Mesai içi saatlerde alınan olgularda Apgar 1. dk  $8,1\pm 2$ , 5. dk  $9,2\pm 1,6$  görülürken bebek doğum ağırlığı  $3023\pm 847$  gr bulunurken mesai saatleri dışında alınan olgularda Apgar 1. dk  $7,2\pm 2,7$ , 5. dk  $8,7\pm 2,1$  görülürken bebek doğum ağırlığı  $2652\pm 1001$  gr olarak bulundu. Apgar 1 ve 5. dk' lar ve doğum ağırlığı açısından mesai içi ve mesai dışı saatler arasında farklılık saptandı ( $P=0,001$ ). Mesai içinde bebek ölümü %2 ( $n=11$ ) ve mesai dışında %4 ( $n=19$ ) olarak bulundu, aralarında istatistiksel fark saptanmadı ( $P=0,103$ ).

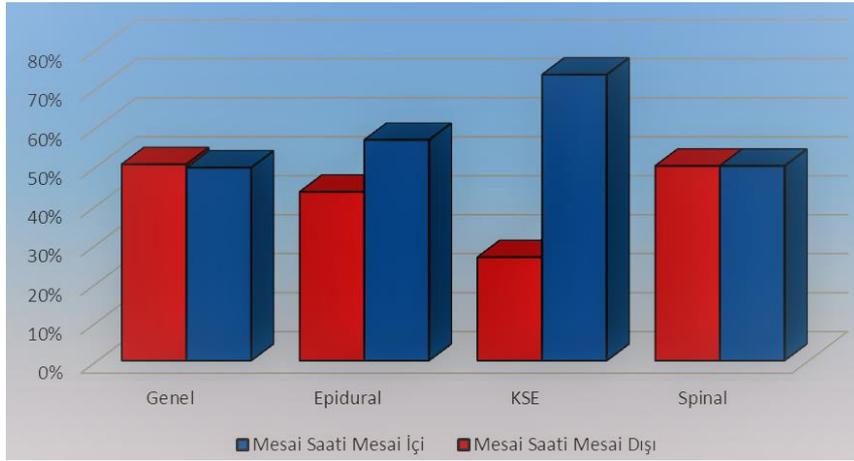
**Tablo 4.** Mesai içi ve mesai dışı saatlerde sezaryen uygulanan olguların yandaş sistemik hastalık dağılımı

	Mesai içi		Mesai dışı		P
	n	%	n	%	
Sistemik H.	224	%42,6	214	%42,9	0,923
Kardiyak ve Hemodinamik H.	58	%11	69	%13,8	0,174
Renal H.	14	%2,7	14	%2,8	0,888
Endokrin ve Metabolik H.	112	%21,3	86	%17,2	0,100
Solunum Sistemi H.	24	%4,6	21	%4,2	0,782
Nörolojik H.	7	%1,3	19	%3,8	0,012*
Psikiyatrik H.	2	%0,4	2	%0,4	0,958
Bağ doku H.	17	%3,2	6	%1,2	0,028*
Kronik Enfeksiyöz H.	15	%2,9	13	%2,6	0,809
Trombofili/Trombotik Bozukluk	11	%2,1	4	%0,8	0,086
Kan H./Koagülasyon Bozukluğu	30	%5,7	29	%5,8	0,941
GIS H.	9	%1,7	7	%1,4	0,691
İskelet Sistemi H.	1	%0,2	3	%0,6	0,291
Perinatal H.	109	%20,7	136	%27,2	0,358
GDM	42	%8,0	25	%5,0	0,054
GHT	4	%0,8	10	%2,0	0,086
Gestasyonel Trombositopeni	6	%1,1	8	%1,6	0,524
Gestasyonel Kolestaz	5	%1,0	4	%0,8	0,798
Preeklampsi	41	%7,8	77	%15,4	0,000**
Eklampsi	6	%1,1	2	%0,4	0,178
HELLP Sendromu	5	%1,0	10	%2,0	0,160

H= hastalık, GIS= Gastrointestinal Sistem, GDM= gestasyonel diyabetes mellitus, GHT= gestasyonel hipertansiyon; \* $P<0,05$ , \*\* $P< 0,001$ .



Şekil 1. Mesai içi ve mesai dışı saatlerdeki olguların sezaryen endikasyonları (%) (C-S= sezaryen, AFD= akut fetal distress, CPD= sefalopelvik uyumsuzluk).



Şekil 2. Mesai saati içinde ve dışında anestezi yöntemlerinin dağılımı (%). KSE= kombine spinal epidural.

Tablo 5. Sezaryen endikasyonlarının uygulanan anestezi türüne göre dağılımı

	SA		KSEA		EA		GA		p
	n	%	n	%	n	%	n	%	
Eski Sezaryen	85	%57,4	37	%57,8	11	%36,7	365	%46,6	0,021*
Fetal Makrozomi	4	%2,7	1	%1,6	3	%10,0	17	%2,2	> 0,05
AFD	17	%11,5	2	%1,6	4	%13,3	219	%28,0	0,000**
Uterin Nedenler	2	%1,4	1	%1,6	0	%0,0	7	%0,9	> 0,05
CPD	14	%9,5	13	%20,3	10	%33,3	83	%10,6	0,000**
Malprezentasyon	30	%20,3	10	%15,6	4	%13,3	124	%15,8	0,566
Plasenta Anomalisi	3	%2,0	1	%1,6	0	%0,0	61	%7,8	0,008*
Vajinal Kaynaklı	1	%0,7	0	%0,0	0	%0,0	11	%1,4	> 0,05
Maternal Kaynaklı	5	%3,4	0	%0,0	0	%0,0	24	%3,1	> 0,05

AFD= akut fetal distress, CPD= sefalopelvik uyumsuzluk,\*= P<0.05,\*\*= P< 0.001, SA= spinal anestezi, KSEA= kombine spino epidural anestezi, EA= epidural anestezi, GA= genel anestezi.

Tablo 6. Yenidoğan Apgar skorları ve doğum ağırlıklarının anestezi şekline göre dağılımı

	SA	KSEA	EA	GA	P
Apgar Skor 1. (dk)	8,5 ± 1,6	9,2 ± 0,8	8,9 ± 1,3	7,3 ± 2,6	0,000*
Apgar Skor 5. (dk)	9,5 ± 1,4	9,8 ± 0,5	9,8 ± 0,5	8,8 ± 2,0	0,000*
Doğum Ağırlığı (gr)	3032 ± 742	3287 ± 496	3519 ± 663	2744 ± 988	0,000*

\*= P< 0.001, SA= spinal anestezi, KSEA= kombine spino epidural anestezi, EA= epidural anestezi, GA= genel anestezi.

#### 4. Tartışma ve Sonuç

Çalışmamızda mesai içi ve mesai dışı saatlerde alınan toplam 1025 olgu incelendi. En sık tercih edilen anestezi yönteminin GA olduğu bunu sırayla SA, KSEA ve EA' nin takip ettiği görüldü. SA, GA, EA uygulanma oranları mesai içinde ve dışında benzer bulunurken KSEA' nin mesai içinde daha yüksek oranda uygulandığı saptandı. RA uygulamalarının büyük kısmının başarılı olduğu görüldü. Başarısız rejyonal anestezi oranının mesai içi ve dışı olgularda benzer bulundu. Mesai saatleri dışındaki olgularda gebelik haftası, 1. ve 5. dk Apgar skoru ile doğum ağırlığının daha düşük olduğu, mesai saatleri içinde elektif olguların; mesai saatleri dışında ise acil olguların daha sık alındığı, mesai saatleri dışında preeklampatik olguların daha fazla olduğu, bununla orantılı SAB ve DAB değerlerinin daha yüksek saptandığı ve bu gebelere GA'nin daha sık uygulandığı saptandı.

1990-2014 yılları arasında yapılan bir çalışmada, tüm dünyada sezaryen oranı %18,6 bulunmuştur (Betran, 2016). T.C Sağlık Bakanlığı verilerine göre Türkiye'de bu oran 2013'de %51,4 ve 2014'de %51, 2015'te %52,42 şeklindedir. Bu oran diğer ülkelerin çok üstündedir. Sezaryen doğumlar ülkemizin batısına doğru artış göstermektedir. Sağlık Bakanlığı'na bağlı hastanelerde bu oran %36 iken, üniversitelerde %63, özel hastanelerde ise %67,9' dur (T.C. Sağlık Bakanlığı Sağlık İstatistikleri Yıllığı, 2016). Sezaryen ile doğum tüm doğumların %25' ine ulaşmıştır. İnfertilite tedavileri sonucu artan çoğul gebelikler ve ileri yaş gebelikleri sayılarındaki artış artan sezaryen oranının en önemli nedenleri arasındadır (Çağlayan, 2011). Sezaryen oranının artması ile birlikte son yıllarda tercih edilen anestezi şekillerinde değişiklikler olmuştur. Diğer cerrahi türlerinden farklı olarak sezaryende anestezi annede gebeliğe bağlı gelişen fizyolojik, anatomik değişiklikleri göz önünde bulundurarak, postoperatif dönemde annenin adaptasyon sürecini etkileyecek faktörleri değerlendirerek, anne için en güvenli ve rahat, yenidoğan için en az depresan ve cerrah için uygun çalışma koşulları sağlayan anestezi yöntemini seçmelidir (Gürsoy, 2014). Amerikan Anestezi Derneği (ASA)'nin Obstetrik Anestezi Rehberinde tanımlandığı üzere sezaryenlerde anestezi tekniğinin seçimi; anestezi, anne ve fetal risk faktörlerine, gebenin isteğine ve anesteziistin tercihine göre yapılmalıdır (Practice Guidelines for Obstetric Anesthesia, 2016).

GA' ye bağlı maternal morbidite ve mortalite riskinin yüksek oluşu ve fetal etkilenme riskindeki artış sebebiyle sezaryenlerde genellikle RA tercih edilmektedir. GA, genel olarak RA'ye engel durumlarda ve fetal durum bozukluğunda zaman faktörü nedeniyle tercih edilirken çoğunlukla acil sezaryenlerde uygulanmaktadır (Töre, 2009; Devroe, 2015). RA maternal ve fetal olarak daha güvenli bir anestezi yöntemi olarak benimsenmiştir (Özkan, 2019; Orhon Ergun, 2020). Lai ve ark. (2014) sezaryen olgularında anestezi tekniğini inceledikleri 25.606 olgulu bir çalışmada RA oranı %95 olarak saptanmıştır. Yılmaz ve ark. (2022) 2017 yılında sezaryen vakalarında RA oranını %76 olarak bulmuşlardır. Kinsella ve ark.

(2008)'nin 5080 olguyu inceledikleri çalışmada %63 SA, %26 EA, %5 KSEA, %5 GA kullanıldığı, Tekin ve ark. (2005) yaptığı çalışmada ise sezaryen olgularının %55,5'ine GA, %44,5'ine RA uygulandığı, RA uygulanan olguların %54,4'ünü SA, %25 EA ve %20'sini KSEA yöntemlerinin oluşturduğu belirtilmiştir. Bizim çalışmamızda ise 1025 olgunun %76,4'üne GA, %14,4'üne SA, %6,2'sine KSEA, %3'üne EA uygulandı. Olguların %51,3'ünün mesai içi, %48,7'sinin ise mesai dışı saatlerde alındığı çalışmamızda RA oranımız %23,6 olarak bulundu. SA ve GA uygulanan olguların %50'si mesai içi saatlerde, %50'si mesai dışı saatlerde alındı. KSEA mesai içi saatlerde %73, mesai dışı saatlerde %27, EA ise mesai içi saatlerde %57, mesai dışı saatlerde %43 oranında uygulandı. SA ve GA mesai içi ve mesai dışı saatlerde eşit oranda uygulanırken, KSEA' nin mesai içi saatlerde daha fazla uygulandığı saptandı. Sezaryenlerde uygulanan anestezi tekniğini klinisyenlerin çalışma saatlerine göre değerlendiren bir çalışma yoktur. Operasyonun aciliyeti, sezaryen endikasyonu, nöbete kalan anestezi ve cerrahi ekibin deneyimi ile gebenin acil şartlarda vereceği karar mesai saatleri dışında anestezi yöntemi tercihini etkileyebilir.

Gülhaş ve ark. (2012)'nin çalışmasındaki olguların SAB ortalaması 115±18 mmHg, DAB ortalaması 83,5±12 mmHg idi. Bizim çalışmamızda ise SAB ortalaması 137±20 mmHg, DAB ortalaması ise 85±14 mmHg olarak saptandı. Mesai dışı saatlerde ve GA uygulanan olgularda SAB ve DAB anlamlı düzeyde yüksek bulundu. Bu farkın mesai dışı saatlerde preeklampsi gibi yandaş hastalığı olan olguların acil statüsünde daha fazla alınmasından kaynaklandığını düşünüldü.

Gebelerde gebelik dönemi hastalıkları ve yandaş sistemik hastalıkların sezaryende anestezi tekniği seçimi üzerine etkisinin değerlendirildiği bir çalışmada olguların %83,4'ünde ek hastalık yokken, hipertansiyon %1,1, kapak hastalığı %1,7, diabetes mellitus %2,3, preeklampsi %8,3, HELLP sendromu %1,1, diğer hastalıklar ise %1,7 olarak bulunmuştur (Gülhaş, 2012). Hastanemiz Güney Marmara Bölgesi' ne hizmet veren üçüncü basamak bir kurum olduğundan planlı sezaryen uygulanacak olgular genellikle ek hastalığı olan, yüksek riskli gebelik takibi yapılan, ASA II-III hasta gruplarından oluşmaktaydı. Bizim çalışmamızda yandaş hastalığı olmayan olgular %67 oranındaydı. En sık görülen patolojilerin endokrin, metabolik, kardiyak hastalıklar ve koagülasyon bozuklukları olduğu çalışmamızda yandaş hastalığı olan gebeler mesai içinde ve mesai dışında eşit oranda alınmıştı. Sadece preeklampi tanısı olan gebelerin mesai dışında daha fazla olduğu ve bu gebelere sıklıkla GA uygulandığı saptandı.

Literatürde sezaryen endikasyonlarından en sık eski sezaryen görülürken bunu ilerlemeyen eylem, AFD, kord prolapsusu, anormal fetal pozisyon, multipl gebelik, gebenin medikal rahatsızlıkları, fetal anomaliler, plasenta yerleşim anormallikleri takip etmektedir. (Gori, 2007; Kinsella, 2008; Karaca, 2020) Bizim çalışmamızda da sezaryen endikasyonları arasında mesai içinde %5,4,

mesai dışında %39,3 oranlarıyla eski sezaryen ilk sırada yer aldı. Sezaryen olgularının mesai içi ve dışı alınması hastanın endikasyonu ile yakından ilişkilidir. Mesai içinde eski sezaryen, plasenta anomalileri ve geçirilmiş vajinal kozmetik/rektal düzeltici cerrahi veya vulvar lezyon varlığı gibi nedenlerle elektif sezaryen yapılan olgular; mesai dışı saatlerde ise AFD gibi acil endikasyonlarla sezaryen yapılan olguların daha sık olduğu görüldü. Acil olguların oranı mesai içinde %13,7 iken mesai dışında %34,1 saptandı. Elektif vakalarda anestezi tekniğinin belirlenmesinde gebenin isteği ön planda tutulsa da acil olgularda fetomaternal iyilik halinin devamı için uygun yöntem klinisyenler tarafından belirlenir. AFD gibi acil endikasyonla alınan olgularda GA kullanımı daha sık görülmektedir. Gebelerin perinatal kaygı düzeyleri, daha önceki anestezi deneyimleri, sosyokültürel ve eğitim düzeyleri, obstetrisyenin anestezi yöntemine bakış açısı anestezi yönteminin belirlenmesinde önemli olan faktörlerdir. Çalışmamızda hem mesai içi hem de mesai dışı saatlerde alınan elektif/acil olgularda en sık kullanılan anestezi yöntemi GA oldu.

Literatürde anestezi tekniği ile neonatal sonuçların değişmediğini gösteren yayınlar (Kavak, 2001; Karaman, 2005) olduğu gibi RA ile daha iyi neonatal sonuçların saptandığı çalışmalar (Gori, 2007; Algert, 2009; Saygı, 2015; Karaca, 2020) da mevcuttur. Apgar skoru subjektif bir değerlendirme olmasına karşın, obstetride yenidoğan iyiliğini belirlemede konvansiyonel ve sık kullanılan bir yöntemdir. Dolayısıyla, elektif sezaryen ile gerçekleşecek doğumlarda anestezi şeklini belirlerken gebenin sistemik sorunları ve isteği dikkate alınıp anne ve yenidoğan açısından avantaj ve dezavantajların göz önünde bulundurulması uygun olacaktır. Şener ve ark. (2003) genel ve epidural anestezinin fetal iyilik hali üzerindeki etkilerini araştırdıkları çalışmalarında, 1. dk Apgar skorunun genel anestezi grubunda daha düşük olduğunu, 5. dk Apgar skorlarının ise her iki grupta benzer olduğunu bulmuşlardır. Algert ve ark. (2009) çalışmasında GA ile spinal/epidural anestezi, neonatal entübasyon ve 5.dk Apgar skorunun 7' nin altında olması sonuçlarına göre karşılaştırılmış ve genel anestezi daha riskli bulunmuştur. Çalışmamızda GA uygulanan olgularda yenidoğanların 1. ve 5. dk Apgar skorları RA uygulanan olgulara göre daha düşük bulundu. RA türleri arasında 1 ve 5. dk Apgar skorları açısından fark yoktu.

GA'ye bağlı maternal mortalite oranlarının yüksekliği, anne ve bebek için rejyonel anestezinin daha güvenilir olması nedeniyle RA sezaryenlerde sıklıkla tercih edilen teknik haline gelmiştir (Özkan, 2019). Çalışmamızda RA oranlarımız literatürdeki benzer çalışmalara oranla daha düşük bulundu. Hastanelerde mesai dışı saatlerde anestezi ve cerrahi ekibin deneyimi, gerekli malzemenin temin edilebilmesi, uygun hasta seçimi, sezaryen işleminin aciliyet derecesi gibi çok çeşitli faktörler RA' nin mesai dışı saatlerde uygulanma sıklığını etkilemektedir. Toplamda RA oranımız düşük olmasına rağmen mesai saatleri içinde ve dışında SA oranı eşittir. Uygulanması kolay ve hızlı olan, sezaryen operasyonu için yeterli ve

etkili anestezi oluşturan bu yöntem nöbet şartlarında acil vakalarda da tercih edildi. Uygulanması tecrübe gerektiren ve zaman alan KSEA ve EA ise mesai saatleri içinde daha fazla oranda kullanıldı. KSEA ve BE konusunda tecrübesi ve klinik pratiği daha fazla olan klinisyenlere mesai saatleri içinde daha kolay ulaşılabilmenin bu durumun sebebi olduğu düşünüldü.

Mesai saatleri içinde ve dışında GA' nin daha çok tercih edildiğini saptadığımız çalışmamızda RA gibi konforlu ve daha az komplikasyonu olan bir tekniğin hastanemizde sezaryenlerde ne kadar az uygulandığını göstererek farkındalık oluşturduğumuzu düşünmekteyiz.

### Katkı Oranı Beyanı

Konsept: Ö.Ö. (%20), A.N.B. (%20), E.E. (%20), Ş.Ş. (%20) ve Ş.G.K. (%20), Tasarım: Ö.Ö. (%20), A.N.B. (%20), E.E. (%20), Ş.Ş. (%20) ve Ş.G.K. (%20), Denetim: Ö.Ö. (%20), A.N.B. (%20), E.E. (%20), Ş.Ş. (%20) ve Ş.G.K. (%20), Veri toplama ve/veya işleme: Ö.Ö. (%20), A.N.B. (%20), E.E. (%20), Ş.Ş. (%20) ve Ş.G.K. (%20), Veri analizi ve/veya yorumlama: Ö.Ö. (%20), A.N.B. (%20), E.E. (%20), Ş.Ş. (%20) ve Ş.G.K. (%20), Kaynak taraması: Ö.Ö. (%20), A.N.B. (%20), E.E. (%20), Ş.Ş. (%20) ve Ş.G.K. (%20), Yazma: Ö.Ö. (%20), A.N.B. (%20), E.E. (%20), Ş.Ş. (%20) ve Ş.G.K. (%20), Eleştirel inceleme: Ö.Ö. (%20), A.N.B. (%20), E.E. (%20), Ş.Ş. (%20) ve Ş.G.K. (%20), Gönderim ve revizyon: Ö.Ö. (%20), A.N.B. (%20), E.E. (%20), Ş.Ş. (%20) ve Ş.G.K. (%20). Tüm yazarlar makalenin son halini incelemiş ve onaylamıştır.

### Çatışma Beyanı

Yazarlar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

### Etik Onay/Hasta Onamı

Çalışma yerel etik kurul (2014-1/27, 2014/01/07) onayı alındıktan sonra Helsinki Bildirgesi ilkelerine uygun olarak yürütülmüştür.

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lack of information about infection prevention and control, and long-term exposure to infected patients are effective (Yen et al., 2015; Atkinson et al., 2020). Therefore, the implementation of infection control guidelines and precautions in healthcare settings during a contagious pandemic is essential to protect the health of healthcare workers and reduce the risk of cross-contamination and infection in the hospital. However, studies of all healthcare professionals' knowledge of infection prevention and control protocols in healthcare settings are limited, and compliance levels are uncertain during the pandemic (McMahon et al., 2016; CDC, 2020; Karadede et al., 2021).

This study, it was aimed to investigate the relationship between the level of compliance of health personnel working in Covid-19 clinics with isolation measures, the level of knowledge about infection prevention and control protocols for Covid-19, and the characteristics of healthcare workers. The results are important to identify strategies and interventions needed to strengthen workplace policies in healthcare settings and to preserve the health system's capacity to combat the pandemic and maintain primary health care.

## 2. Material and Methods

Study; It is a cross-sectional study. The research was carried out by face-to-face interviews with 136 healthcare professionals working in the Covid-19 clinics (service, intensive care, and emergency medicine unit) of Çukurova University Faculty of Medicine Balcalı Hospital and treating patients with Covid-19 and suspected patients between 1 and 30 June 2020. Between the dates of the research, 250 people worked, and the sample consisted of 136 (54.4%) volunteers to participate in the research.

### 2.1. Data Collection

The data were collected using the "Personal Information Form" and the "Scale for Compliance with Isolation Precautions". Participants filled out the form individually. The information of the researchers conducting the research is kept confidential. The time to fill out the forms is approximately 10 minutes. Since the beginning of the pandemic process, all healthcare professionals have been given training on infection prevention and control protocols/isolation measures by the Hospital Infection Committee.

### 2.1.1. Personal information form

The form prepared by the researchers; is a literature-based questionnaire consisting of 13 questions, in which the introductory characteristics of health professionals working in Covid-19 clinics are recorded. (CDC, 2020; Fawaz et al., 2020; T.C. Sağlık Bakanlığı, 2020). In the first part of the questionnaire, which consists of two parts, there are a total of 6 questions, including six questions about personal and professional characteristics (age, gender, education level, occupation, number of patients given daily care, isolation, and education about Covid-19). It consists of 13 questions consisting of seven questions (Covid-19 related transmission routes, possible/definite Covid-19 patient care criteria, patient transfer principles, symptoms, diagnostic tests used, in which situations PPE is used and the order of wearing PPE).

### 2.1.2. The scale of compliance with isolation precautions

It was developed by Ulupınar and Tayran (2011) to determine the compliance of healthcare workers with isolation precautions and the Cronbach alpha reliability coefficient was determined as 0.85. In this study, Cronbach's alpha value was found to be 0.933 for the total scale, 0.948 for "Transmission Route", 0.827 for "Employee and Patient Safety", 0.743 for "Environmental Control", and 0.796 for "Hand Hygiene/Glove Use" in its sub-dimensions (Table 1). The lowest score to be obtained from the 5-point Likert-type scale consisting of eighteen items is 18 and the highest score is 90. Rating; 1 = strongly disagree, 2 = disagree, 3 = no idea, 4 = agree, 5 = strongly agree. Negative statements in the scale are items 18, 22, 24, and 34 and are scored in the opposite direction as 1=5, 2=4, 3=3, 4=2, 5=1 (Tayran ve Ulupınar, 2011).

### 2.2. Statistical Analysis

Statistical analyzes were performed using a package program called SPSS (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used to interpret the findings. Non-parametric methods were used for the measurement values that did not conform to the normal distribution. By non-parametric methods, the "Mann-Whitney U" test (Z-table value) was used to compare the measurement values of two independent groups, and the "Kruskal-Wallis H" test ( $\chi^2$ -table value) method was used to compare the measurement values of three or more independent groups.

**Table1.** Descriptive statistics and reliability of sub-dimensions of the scale of compliance with isolation measures

Subscales (n=136)	Substances	Min-max scores on the scale	Mean scores on the scale $\bar{X} \pm SD$	Min-max scores on the patients	Alfa
Mode of transmission	3, 8, 9, 10, 11	5-25	21.60±4.48	5.0-25.0	0.948
Personnel-patient safety	2, 5, 12, 14, 16, 17	6-30	25.65±5.01	6.0-30.0	0.827
Environment control	1, 13, 15, 18	4-20	16.83±3.42	4.0-20.0	0.743
Hand hygiene-use of gloves	4, 6, 7	3-15	12.09±2.71	4.0-15.0	0.796
Total score	18	18-90	76.16±14.02	22.0-90.0	0.933

X= mean, SD= standard deviation, Min= minimum, Max= maximum.

Don't like leaving unnoticed Bonferroni pairwise comparisons for three or more groups. In examining the differences between the groups; Expressions such as [in groups in 1-2,3s] used in three or more models are valid. [1-2, 3] is that it appears between 1 and 2 and between 1 and 3 from this expression.

### 3. Results

In the study; the mean score of the transmission route subscale of the DSQ was 21.60±4.48; the employee and patient safety subscale were 25.65±5.01; the environmental control subscale is 16.83±3.42 and the hand hygiene/glove use subscale is 12.09±2.71. The total mean score of BSES was 76.16±14.02 (Table 1).

When personal and professional characteristics are examined; the mean age of health professionals is 34.11±7.65 (years), 64.7% of them are women and 39% of them have undergraduate education. Of the health professionals participating in the research, 64.7% were nurses, 47.1% were Covid YB employees, 44.2% cared for 6-15 patients daily, 86% received training on isolation precautions, and 69%, It was determined that 9 found the education sufficient (Table 2).

**Table 2.** Distribution of descriptive characteristics (n=136)

Variable	n	%
Age [ $\bar{X} \pm SS \rightarrow 34,11 \pm 7,65$ (yıl) ]		
<30	45	33.1
30-34	25	18.4
35-39	35	25.7
≥40	31	22.8
Gender		
Female	88	64.7
Male	48	35.3
Job		
Nurse	88	64.7
Doctor	17	12.5
Nurse	16	11.8
Other	15	11.0
Clinic studied		
Urgent	12	8.8
Covid outpatient clinic	18	13.2
Covid service	42	30.9
Covid intensive care	64	47.1
Number of patients given daily care		
≤5	41	30.1
6-15	60	44.2
>15	35	25.7
Getting an Education		
Yes	117	86.0
No	19	14.0
Education qualification		
Yes	95	69.9
No	41	30.1

According to the gender of the participants; When the total and sub-dimension mean scores of PSS are compared, the means of transmission, employee/patient safety, hand hygiene/glove use, and total PSS scores differ significantly (P<0.05). Female participants; route of

transmission, employee/patient safety, hand hygiene/glove use, and total IDS score averages are significantly higher than men.

According to educational status; When the total and sub-dimension mean scores of SSES are compared, the mean scores of employee/patient safety and total SSES differ significantly (P<0.05). When the difference is examined, the average the employee/patient safety and total score of those with a master's degree are significantly higher than those with an associate degree.

According to the training status of infection prevention and control protocols/isolation measures; When the total and sub-dimension mean scores of the BSQ were compared; route of transmission, employee/patient safety, and total HSQ scores differ significantly (P<0.05). The means of transmission, employee/patient safety, and total IAS scores of those who received training on isolation precautions were significantly higher than those who did not receive training (Table 3).

When the answers given to the questions evaluating the level of knowledge about Covid-19 are examined; The ways of transmission of covid-19 among the participants are 70.8%, the criteria to be considered in the care of patients with probable/definite covid-19 diagnosis 71.6%, the principles of patient transport 71.0%, the symptoms of Covid-19 76.7%, the diagnosis of Covid-19 It was determined that 78.3%, 78.8%, the correct response to the use of full WCE, and 84.6% of the order of dressing for WCEs were correct in the tests (Table 4).

There is no statistically significant relationship between the education status of the participants and their knowledge of Covid-19 transmission routes, patient care criteria, patient transport, Covid-19 general symptoms, Covid-19 diagnostic tests, full personal protective equipment, and the order of removing personal protective equipment (P>0.05).

### 4. Discussion

Covid-19 infection is a very contagious disease, and the main transmission is through droplets. In addition, it is transmitted by the droplets dispersed by sick individuals through coughing and sneezing, and by contacting and contacting the mucous membranes of the mouth, nose, or eyes after contact with the hands of other people (TC Sağlık Bakanlığı, 2020). Compliance with infection prevention and control (IPC) protocols/isolation measures are among the important issues to prevent the transmission of Covid-19 infection from patient to patient or patient to healthcare personnel. In this context, increasing the compliance of health professionals with infection prevention and control protocols/isolation measures plays an important role in preventing transmission and maintaining health services without interruption. (CDC, 2019; WHO, 2020; WHO, 2021).

The participants' CIPS total score average was high; transmission route, employee and patient safety, environmental control, and hand hygiene/glove use CIPS sub-dimension mean scores are also high (Table 1).

**Table 3.** Comparison of the mean scores of the scale of compliance with isolation measures according to the variables

CSIM Variable (n=136)	n	Transmission route		Employee/Patient safety		Environmental control		Hand hygiene/gloves		Total- IOUO	
		X ± S.S.	Median [IQR]	X ± S.S.	Median [IQR]	X ± S.S.	Median [IQR]	X ± S.S.	Median [IQR]	X ± S.S.	Median [IQR]
Female	88	21.64±5.22	24.0 [5.0]	25.85±5.77	28.0 [7.0]	16.74±3.90	18.0 [5.0]	12.61±2.67	13.5 [4.0]	76.84±16.21	81.5 [15.0]
Male	48	21.53±2.68	21.0 [4.0]	25.27±3.20	25.0 [5.8]	17.00±2.33	17.0 [4.0]	11.13±2.56	11.0 [4.0]	74.92±8.71	74.5 [11.8]
Statistical analysis*		Z=-2.060		Z=-2.450		Z=-0.722		Z=-3.381		Z=-2.623	
Possibility		P=0.039		P=0.014		P=0.470		P=0.001		P=0.009	
<b>Education Level</b>											
High School (1)	50	20.56±5.29	21.0 [5.0]	24.50±5.82	25.5 [7.0]	16.14±3.98	17.0 [4.3]	11.58±2.93	12.0 [4.3]	72.78±16.14	75.0 [14.5]
Assoc deg (2)	7	20.29±4.99	20.0 [4.0]	24.00±3.21	23.0 [4.0]	15.42±2.94	16.0 [5.0]	12.29±2.06	12.0 [4.0]	72.00±10.88	72.0 [10.0]
Bachelor (3)	53	22.17±4.10	24.0 [5.0]	26.19±4.85	27.0 [5.5]	17.25±3.20	18.0 [4.0]	12.38±2.53	13.0 [4.0]	77.98±13.29	81.0 [15.5]
Master (4)	26	22.77±2.80	24.0 [4.0]	27.19±3.36	29.0 [5.3]	17.69±2.46	18.5 [5.0]	12.42±2.80	13.5 [4.3]	80.08±10.23	83.0 [18.3]
Statistical analysis		χ²=6.637		χ²=8.126		χ²=6.466		χ²=2.516		χ²=7.894	
Possibility		P=0.084		P=0.043		P=0.091		P=0.472		P=0.048	
Difference				[2-4]						[2-4]	
<b>Job</b>											
Nurse	88	21.85±4.87	23.5 [5.0]	25.93±5.43	28.0 [7.0]	16.85±3.64	18.0 [5.0]	12.56±2.54	13.0 [4.0]	77.19±15.12	80.0 [16.0]
Doctor	17	22.18±2.96	22.0 [4.5]	26.06±3.49	26.0 [6.5]	17.35±2.47	17.0 [5.0]	11.65±2.96	11.0 [5.0]	77.24±10.21	78.0 [17.0]
Nurse	16	20.88±2.27	20.0 [1.8]	24.37±3.36	25.0 [4.5]	16.44±2.22	16.0 [3.8]	11.88±2.40	11.0 [2.8]	72.88±7.19	72.5 [10.3]
Secretary	9	21.67±2.55	21.0 [5.0]	26.78±3.19	27.0 [6.5]	18.00±2.18	19.0 [4.0]	10.78±3.15	11.0 [4.5]	77.22±8.64	81.0 [14.5]
Statistical analysis		χ²=6.748		χ²=6.137		χ²=2.920		χ²=7.733		χ²=6.976	
Possibility		P=0.080		P=0.105		P=0.404		P=0.052		P=0.073	
<b>Gettingan Educ</b>											
Yes	117	22.18±3.41	23.0 [5.0]	26.18±4.19	27.0 [7.0]	17.18±2.89	18.0 [5.0]	12.27±2.65	13.0 [4.0]	77.80±11.43	80.0 [17.0]
No	19	18.00±7.75	21.0 [14.0]	22.37±7.88	24.0 [7.0]	14.68±5.31	17.0 [6.0]	11.00±2.92	11.0 [6.0]	66.05±22.53	72.0 [30.0]
Statistical analysis		Z=-2.100		Z=-2.030		Z=-1.794		Z=-1.848		Z=-2.001	
Possibility		P=0.036		P=0.040		P=0.073		P=0.065		P=0.045	

**Table 4.** Distribution of answers to questions about Covid-19

Reply Variable	True		False	
	n	%	n	%
<b>Covid-19 transmission routes</b>				
Droplet (T)	118	86.8	18	13.2
Contact (T)	88	64.7	48	35.3
Breathing (T)	83	61.0	53	39.0
TOTAL	289	70.8	119	29.2
<b>Possible/Definite Covid 19 is one of the patient care criteria?</b>				
Patients should be isolated individually (T)	126	92.6	10	7.4
Patients should not be hospitalized in the same room (F)	111	81.6	25	18.4
If there is a need for a companion, it should be limited to 1 person (T)	97	71.3	39	28.7
Care materials to be used should not be taken out of the room (Stethoscope, thermometer, glucometer....) If they are to be used on another patient, they should be disinfected and used (T)	124	91.2	12	8.8
They should be followed in rooms with absolute negative pressure (F)	39	28.7	97	71.3
For inhaled drugs, a metered dose inhaler should be used instead of a nebulizer (T)	87	64.0	49	36.0
TOTAL	584	71.6	232	28.4
<b>How should the principles of covid 19 patient transport be?</b>				
The patient should not be transported unless necessary (T)	120	88.2	16	11.8
It is sufficient to wear a surgical/medical mask to the patient (T)	98	72.1	38	27.9
Healthcare workers should always use full PPE (F)	124	91.2	12	8.8
Surgical/medical mask is sufficient if there is no aerosol formation (T)	71	52.2	65	47.8
N95 mask, eye/face protection should be used in all cases (F)	70	51.5	66	48.5
TOTAL	483	71.0	197	29.0
<b>Covid-19 general symptoms</b>				
Fire (T)	134	98.5	2	1.5
Shortness of breath (F)	134	95.5	2	1.5
Loss of smell and taste (T)	108	79.4	28	20.6
sore throat (T)	105	77.2	31	22.8
Dry cough (T)	127	93.4	9	6.6
Fatigue (T)	101	74.3	35	25.7
Joint pain (T)	95	69.9	41	30.1
Nasal congestion (T)	97	71.3	39	28.7
watery eyes (F)	88	64.7	48	35.3
headache (T)	83	61.0	53	39.0
Diarrhea (T)	107	78.7	29	21.3
Pneumatic infiltration (T)	73	53.7	63	46.3
TOTAL	1252	76.7	380	23.3
<b>Covid-19 diagnostic tests</b>				
Antibody Ig-G/Ig-M (T)	95	69.9	41	30.1
Antigen Orapharangeal (T)	118	86.8	18	13.2
TOTAL	213	78.3	59	21.7
<b>In what situations should full PPE be used?</b>				
During sampling (T)	119	87.5	17	12.5
During sample transport (F)	61	44.9	75	55.1
In cases where there is a risk of contact with patient printouts (T)	111	81.6	25	18.4
In case of contact with certain/probable Covid 19 patients closer than 1 meter (T)	120	88.2	16	11.8
In aerosol-forming procedures (aspiration, bronchoscopy, intubation.....) (T)	125	91.9	11	8.1
TOTAL	536	78.8	144	21.2
Personal protective equipment wearing order	115	84.6	21	15.4

The literature review has shown that many studies evaluating compliance with infection prevention and control protocols/isolation measures have similarly shown studies in which healthcare professionals have high average scores on the Compliance with Isolation Precautions Scale (Zencir et al., 2013; Erden et al., 2015; Özden and Özveren, 2016; Arlı and Bakan, 2017; Karahan et al., 2019; Şatır et al., 2019; Sarier and Kurşun, 2020; Geçit and Özbayır, 2020). There are limited studies in the literature about the compliance of healthcare workers with isolation during the Covid-19 outbreak. In the study conducted by Lai et al. in China, the compliance behavior of healthcare workers with infection prevention and control protocols with the emergence of the risk of Covid-19 was examined and it was reported that there was a significant increase (in the study of Ashinyo et al. (2021) it was revealed that compliance with infection prevention and control protocols is high among healthcare workers exposed to Covid-19 in treatment centers (Lai et al., 2020)). In the study conducted by Özlü et al. (2021) to determine the compliance of emergency health personnel with isolation measures during the Covid-19 pandemic, it was shown that there was an average level of compliance with isolation measures. Many factors are effective in compliance with infection prevention and control protocols/isolation measures. Clear infection prevention and control protocols guidelines are critical in supporting healthcare compliance with effective communication, support from administrators, training, easy access to PPEs and equipment safety, and infection prevention and control protocols (Geçit and Özbayır, 2020; Ashinyo et al., 2021). Compliance with infection prevention and control protocols plays a critical role in reducing the exposure of healthcare workers to SARS-CoV-2. In contrast, non-compliance with infection prevention and control measures is a major risk factor for Covid-19 infection among healthcare workers (Xiong et al., 2020). WHO, in its guidelines on infection prevention and control protocols, recommends strict adherence to these protocols in the management of Covid-19 patients (WHO, 2021). Healthcare workers; The fact that the vast majority of them received training on infection prevention and control protocols/isolation measures and evaluated the training as sufficient may explain the high compliance with isolation precautions. Moreover; the fact that healthcare workers face the risk of contamination with SARS-CoV-2 can be counted as one of the reasons for high compliance.

It was determined that almost all of the participants received training on isolation precautions, and the majority found this training sufficient (Table 2). In the study of Özlü et al. (2021) most of the participants received training on isolation precautions. In the study conducted by Sarier and Kurşun (2020) to determine the compliance level of nurses working in intensive care units with isolation measures, almost all of the participants received training on isolation measures and

found this training highly sufficient. In addition, the mean scores of the trainees' PPS are significantly higher. It has been reported that healthcare-associated infections can be reduced by approximately 30% with the correct implementation of isolation measures by healthcare professionals (Arlı and Bakan, 2017).

Therefore, continuous and effective training on isolation measures is one of our defense mechanisms in preventing infections. In the study; Periodic training on infection prevention and control protocols/isolation measures, which are considered adequate, will prevent contamination of healthcare workers, while at the same time reducing/preventing cross-contamination.

In the study, all occupational groups have high CIPS score averages, and it is seen that their compliance with the isolation measures applied due to Covid-19 is good. Female participants; route of transmission, employee and patient safety, hand hygiene/glove use, and the total mean scores of IDS is significantly higher than that of men. In general, as the education level increased, the mean scores of PSAs increased, but the mean of employee/patient safety and total PSIS scores of graduate students were significantly higher than those with associate degree degrees. The means of transmission, employee/patient safety, and total IAS scores of those who received training on isolation precautions were significantly higher than those who did not receive training (Table 3).

It is possible to say that individual factors also affect compliance with infection prevention and control protocols. As in the study; in the study of Şatır et al. (2019) the isolation compliance levels of female health workers were found to be higher. Studies in the literature, especially in the sample group of nurses, have shown that the level of compliance with isolation measures is high (Zencir et al., 2013; Erden et al., 2015; Özden and Özveren, 2016; Arlı and Bakan, 2017; Karahan et al., 2019; Sarier and Kurşun, 2020; Karadede et al., 2021). In line with this result, it can be said that women's compliance with isolation measures is better than men's.

It has been determined that the education level of healthcare workers affects their compliance with isolation measures. Although it did not show any significance, as the level of education increased, the level of compliance increased. In the study by Zencir et al. (2013) similar to the study, it was found that those with a master's degree had a higher PPS score. This situation; can be attributed to the higher level of awareness and knowledge of health professionals with higher education.

It was determined that high rates of correct answers were given to the questions evaluating the level of knowledge about Covid-19 disease and its care (Table 4). There are limited studies on the knowledge and attitudes of health professionals about Covid-19. In the studies of Özlü et al. (2021) it has been shown that emergency medical personnel have a high level of knowledge about the Covid-19 pandemic. In a study by Parikh et al. on the knowledge of the public and healthcare professionals

about Covid-19, it was revealed that more than 90% of healthcare professionals know and follow the precautions (Parikh et al., 2020). In the study conducted by Huynh et al., the knowledge and attitudes of healthcare professionals about Covid-19 were investigated and it was determined that 88.4% of the participants had sufficient information (Huynh et al., 2020). In the study conducted by Khasawneh et al. (2020) the knowledge, attitudes, and precautions of medical students about Covid-19 were investigated and it was determined that the participants had the expected level of knowledge and applied appropriate strategies to prevent the spread of the virus. In a study by Hussain et al. (2021) investigating the knowledge, attitudes, and practices of healthcare professionals in a tertiary hospital about Covid-19, it was determined that the participants had sufficient knowledge about the virus and applied accordingly. A study by Aydın and Balci, in which nurses' knowledge of Covid-19 was investigated, showed that participants had extensive knowledge of Covid-19 (Aydın and Balci, 2020).

In Ashinyo et al.'s study, participants' correct use of PPE, especially in aerosol-generating procedures, was quite high following the protocol, similar to the study. Because aerosol-generating procedures are high-risk procedures associated with the risk of SARS-CoV-2 transmission to healthcare workers (Ashinyo et al., 2021). WHO recommends the use of special respirators, gloves, gowns, and eye protection during aerosol-generating procedures (WHO, 2021). According to epidemiological research, SARS-CoV-2 is highly contagious and can spread very quickly in human populations. The main mode of transmission is respiratory droplets and physical contact (Xiong et al., 2020). Proper adherence to the use of PPE is effective in preventing hospital-acquired transmission of SARS-CoV-2 (Verbeek et al., 2020; Zhao et al., 2020).

### 5. Conclusion

As a result; It was determined that almost all of the participants received training on isolation measures and found this training sufficient. All occupational groups have a high mean score of IÖÖÖ, and their compliance with the isolation measures applied due to Covid-19 is at a good level. Moreover; High rates of correct answers were given to the questions in which the level of knowledge about Covid-19 disease and care was evaluated. Infection prevention and control efforts to combat the spread of COVID-19 in hospitals should involve all workers. In this way, it will be possible to reduce healthcare-associated transmission of COVID-19 in healthcare settings. In the study, it is important to create a management plan for the pandemic process to maintain this harmony, even though all healthcare professionals have a high PPS score. During the pandemic period, providing training on infection prevention and control protocols to cover all healthcare personnel regardless of their education level, brochures, plaques,

etc. It is necessary to increase the regular use of stimulating materials such as In addition, it should be ensured that the necessary sensitivity to the PPE needs of healthcare workers is shown and addressed.

While there are studies in the literature on the compliance of physicians and nurses with isolation measures, the number of studies covering all healthcare professionals is insufficient. In this direction, it is recommended to increase scientific studies covering all healthcare professionals.

### Limitations

The study was conducted in a single center and the sample reflects only one region of Türkiye. The results of this study can only be generalized to the study group. Another limitation of the study is the decrease in the sample size because the entire population of the study did not accept to participate in the study. It is recommended to conduct studies with a larger sample.

### Author Contributions

Concept: D.A. (25%), D.G. (15%), E.G. (15%), H.Ş. (15%), R.A. (15%) and S.A. (15%), Design: D.A. (25%), D.G. (15%), E.G. (15%), H.Ş. (15%), R.A. (15%) and S.A. (15%), Supervision: D.A. (25%), D.G. (15%), E.G. (15%), H.Ş. (15%), R.A. (15%) and S.A. (15%), Data collection and/or processing: D.A. (25%), D.G. (15%), E.G. (15%), H.Ş. (15%), R.A. (15%) and S.A. (15%), Data analysis and/or interpretation: D.A. (25%), D.G. (15%), E.G. (15%), H.Ş. (15%), R.A. (15%) and S.A. (15%), Literature search: D.A. (25%), D.G. (15%), E.G. (15%), H.Ş. (15%), R.A. (15%) and S.A. (15%), Writing: D.A. (25%), D.G. (15%), E.G. (15%), H.Ş. (15%), R.A. (15%) and S.A. (15%), Critical review: D.A. (25%), D.G. (15%), E.G. (15%), H.Ş. (15%), R.A. (15%) and S.A. (15%), Submission and revision D.A. (25%), D.G. (15%), E.G. (15%), H.Ş. (15%), R.A. (15%) and S.A. (15%). All authors reviewed and approved final version of the manuscript.

### Conflict of Interest

The authors declared that there is no conflict of interest.

### Ethical Approval/Informed Consent

For study; Taken from Turkish Ministry of Health covid research (2020-05-27T22\_08\_23). More Çukurova University Medical Non-Interventional Clinical Research Ethics Committee Approval (Date: 15.05.2020 Number: 99 Decision No: 33), written consent from Çukurova University Medical Faculty Balcalı Hospital, and written consent was obtained after the informed consent form for the purpose. The study was conducted by the principles of the Declaration of Helsinki.

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## TÜRKİYE'DE AĞRIYA YÖNELİK REİKİ UYGULAMASI İLE İLGİLİ YAPILMIŞ HEMŞİRELİK TEZLERİNİN İNCELENMESİ

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**Özet:** Bu sistematik derleme, Türkiye'de ağrı ile ilgili reiki uygulamalarını içeren lisansüstü hemşirelik tezlerini incelemek amacıyla yapılmıştır. Araştırmaya veri toplamak için öncelikle literatür taranmış, ardından YÖK Ulusal Tez Merkezi Veri Tabanı "ağrı" ve "reiki" anahtar kelimeleri ile taranmıştır. Tarama sonucunda 2000-2022 yılları arasında Sağlık Bilimleri Enstitüsü Hemşirelik Anabilim Dalı'nda konu ile ilgili 8 tez belirlenmiştir. Araştırmada incelenen tezlerin tamamı dahil edilme kriterlerini karşılamıştır. Tüm tezler doktora düzeyinde olup, veriler kontrol ve deney grupları oluşturularak toplanmıştır. Reiki'nin ağrıya etkisini inceleyen ilgili ilk tezin 2012 yılında, huzurevinde yaşayan yaşlıların ağrısına reikin etkisinin incelendiği ikinci çalışma 2013 yılında yayınlandığı, diğer 6 tezin ise son beş yılda yapılmış olduğu tespit edilmiştir. Çalışmalar incelendiğinde; çalışmaların çoğunun (%37,5) postoperatif ağrı üzerinde reikin etkisini değerlendirmek amacıyla yapıldığı ve Türkiye'de reiki ile ilgili araştırmaların çoğunun hemşirelik araştırmalarında olduğu görülmüştür. Çalışmamızda incelenen deneysel araştırma desenli tüm tezlerin (n=8) sonuçları bütüncül olarak değerlendirildiğinde, tezlerin deneysel niteliğinin yüksek düzeyde kanıt sağladığı ve reiki'nin ağrıyı azaltmada etkili bir yöntem olduğu gösterilmiştir.

**Anahtar kelimeler:** Ağrı, Hemşirelik, Reiki

### Investigation of Nursing Thesis Related To Reiki Application on Pain in Türkiye

**Abstract:** This systematic review was made in order to examine postgraduate nursing theses containing pain-related reiki practices in Türkiye. In order to collect data for the research, firstly, the literature was scanned, then the National Thesis Center Database of the Council of Higher Education was scanned with the keywords "pain" and "reiki". At the end of the screening, 8 theses related to the subject were determined in the Department of Nursing of the Institute of Health Sciences between the years 2000-2022. All of the theses examined in the study met the inclusion criteria. All thesis are at the doctorate level and data were collected by forming control and experimental groups. It was determined that the first thesis examining the effect of reiki on pain was published in 2012, the second study examining the effect of reiki on the pain of the elderly living in nursing homes was published in 2013, and the other 6 theses were made in the last five years. When the studies are examined; it was seen that most of the studies (37.5%) were conducted to evaluate the effect of reiki on postoperative pain, and most of the studies on reiki in Türkiye were in nursing studies. When the results of all the theses (n=8) with experimental research design examined in our study were evaluated holistically, it was shown that the experimental quality of the theses provided a high level of evidence and that reiki was an effective method in reducing pain.

**Keywords:** Pain, Nursing, Reiki

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### 1. Giriş

Uluslararası Ağrı Araştırmaları Derneği vücut tarafından birçok organın eşlik ettiği karmaşık ve subjektif bir olay olan ağrıyı "gerçek veya potansiyel doku hasarıyla ilişkili olan ya da olmayan, bireyin geçmiş tecrübeleriyle de ilişkili, hoş olmayan duysal ve algısal deneyim" şeklinde tanımlanmaktadır (IASP, 2021). Fiziksel bir nedene bağlı olarak ortaya çıkan ve bireylerin yaşamında duysal ve sosyal sorunlara neden olabilen ağrı her yaş ve cinsiyette karşılaşılabilen önemli bir durumdur (Özveren ve ark., 2018). Ağrının kontrol edilemediği durumlarda, atelektazi, hipoksemi, hipertansiyon, derin ventrombozu, taşikardi ve oksijen tüketiminde artış, mide ve bağırsak motilitesinde azalma, idrar retansiyonu, hiperglisemi,

enfeksiyona eğilim ve yara iyileşmesinde gecikme gibi komplikasyonlar görülmektedir (O'Donnell, 2018). Hoş olmayan ve bireye rahatsızlık veren ağrının doğru tanılanması ve kontrolünün yeterli düzeyde sağlanması etik bir sorumluluktur.

Yeterli düzeyde kontrolü sağlanmayan ağrı bireyi fiziksel, sosyal ve ruhsal yönden olumsuz etkilemekte ve yaşam kalitesini azaltmaktadır. Bu nedenle bireyin tedavi ve bakımından sorumlu sağlık profesyoneli optimal ağrı kontrolünü sağlayabilmek için ağrı algısını etkileyen faktörleri, ağrının kaynağını ve farklı ağrı türlerini bilmeli ve bireye özgü yaklaşım sergilemelidir (Şenyüz ve Koçaşlı, 2017). Non-farmakolojik yöntemler akut ve kronik ağrı yönetiminde ağrının giderilmesi, hastanın rahatlaması ve



ağrı kontrolünün sağlanmasında önemli bir yere sahiptir. Farmakolojik yöntemlere ek olarak uygulandıklarında analjeziklerin etkinliğini arttırdıkları bilinmekle birlikte, özellikle şiddetli ağrılarda tek başlarına etkin olamayabileceği göz önünde bulundurulmalıdır. Hemşireler holistik hasta bakımı çerçevesinde bireyi tüm yönleriyle ele alarak en uygun non-farmakolojik yöntemi hasta ile birlikte seçmeli ve uygulamalıdır (Karadağ, 2021). Üç bin altı yüz seksen beş (3685) katılımcı üzerinde yapılan 46 çalışmanın sistematik bir incelemesi sonucunda reikinin ağrıyı azalttığı bildirilmiştir (Behzadmehr ve ark., 2020).

Ağrı kontrolünde önemli rolü olan hemşirelerin non-farmakolojik yöntemleri klinik uygulamaya yansıtılabilmeleri için bu konuda bilgi sahibi olmaları gerekmektedir. Bunun için bu konuda yürütülmüş tezlerin analiz edilmesi konunun önemi ve yaygınlığı hakkında bilgi verebilir, yöntemin uygulanabilirliğini, etkisini, incelenen yöntemle ilgili genel durumu ortaya koyabilir. Bu nedenlerle yola çıkılarak, bu çalışma ile ülkemizde hemşirelik alanında yapılmış lisansüstü tezlerde reiki uygulamasının ağrı üzerindeki etkisini belirlemek ve hemşirelik uygulamalarına kaynak sağlamak amaçlanmıştır.

## 2. Materyal ve Yöntem

Bu çalışmada sistematik derleme yöntemi kullanılmıştır. Sistematik derleme, herhangi bir alanda daha önceden yayımlanmış tüm araştırmaların taranıp, dâhil etme ve dışlama kriterleri konarak derlemeye alınacak araştırmaların belirlenmesi ve bu araştırmalarda yer alan bulguların sentez edilmesi esasına dayanan bir araştırma yöntemidir (Akers ve ark., 2009). 2000-2022 yılları arasında hemşirelikte ağrı yönetiminde reiki uygulamasının yapıldığı tezlere ilişkin verilerin toplanması amacıyla öncelikle literatür taraması yapılmış, daha sonra Yükseköğretim Kurulu (YÖK) Ulusal Tez Merkezi Veri Tabanı'na, "ağrı", "reiki" anahtar kelimeleri ile girilerek tarama yapılmıştır. Araştırma için belirlenen anahtar sözcüklerin taranması sonucu 2000-2022 yılları arasında Sağlık Bilimleri Enstitüsü Hemşirelik Ana Bilim Dalında konu ile ilgili yapılmış 8 tez belirlenmiştir. Çalışmaya, incelenen tezlerin araştırmaya dâhil edilme ölçütlerini sağlayan 8 tez alınmıştır. Dâhil edilme ölçütlerinde müdahale, karşılaştırma grupları ve araştırma desenlerinde herhangi bir sınırlama yapılmaksızın, problem ve sonuçları bakımından sistematik derleme konusuna uyan tezler araştırmaya alınmıştır. Çalışmamız sistematik derleme olup, etik kurul raporu bulunmamaktadır. Tezler yüksek lisans ve doktora tezleri olarak ayrıldıktan sonra tarih sıralamasıyla incelenmiş, verilerin analizinde sayısal değerlendirmeler kullanılmıştır.

### 2.1. Dahil Edilme Ölçütleri

Araştırmaya dahil edilme ölçütleri;

- Türkiye Cumhuriyeti YÖK Yayın Dokümantasyon Daire Başkanlığı tarafından 2000-2022 yılları süresince arşivlenen hemşirelik anabilim dallarında

yapılmış olan tezlerin,

- Başlığında ağrı, reiki kelimelerinin yer alması,
- Ağrı yönetiminde kullanılması,
- Lisansüstü tez çalışması olması,
- Hemşirelik ve/veya hemşirelik ana bilim dalları tarafından yapılmış olması ve tezin tam metnine ulaşılabilir olmasıdır.
- Araştırmaya dâhil edilmeme ölçütleri ise;
- Başlığında ağrı, reiki kelimelerinin geçmemesi veya geçmesine rağmen tek başına reiki grubunun olmaması
- Tezlerin farklı bilim dalları tarafından yazılmış olmasıdır.

### 2.2. Araştırmaların Dahil Edilme Süreçleri

Bu sistematik derlemede, 2000-2019 tarihleri arasında ağrı şiddetinin azaltılmasında reikinin etkisinin incelendiği lisansüstü hemşirelik alanında yapılmış tezlerin bulguları yer almaktadır. Çalışmaların özellikleri, çalışmaların girişim yöntemleri, gereç ve yöntemlerde kullanılan sonuç ölçütleri ve sonuçları Tablo 1'de özetlenmiştir.

**Tablo 1.** Araştırma sorusunun oluşturulması ve anahtar kelimelerin belirlenmesi

PICOS	Araştırma terimi
Problem	Ağrı
Müdahale ve karşılaştırmalar	Katılımcıların ağrısı üzerindeki etkisini değerlendirmek için reiki uygulanan veya karşılaştırılan herhangi bir müdahale veya müdahale kombinasyonu
Sonuçlar	Reiki uygulamasının ağrı üzerinde etkisi olduğu ve reikin uygulama şekli/yöntemi dahil herhangi bir sonuç
Çalışma deseni	Ağrı üzerinde reiki uygulamasının etkisine ilişkin 2000-2020 yılları arasında yayımlanmış, lisansüstü, hemşirelik alanında yapılmış, deneysel, randomize kontrollü tezler, ön test-ve son test

## 3. Bulgular

Yapılan inceleme sonucunda, çalışmaya dâhil edilme kriterlerini sağlayan 8 adet tez değerlendirmeye alınmıştır. Tezlerin tamamının doktora düzeyinde yapıldığı görülmüştür. Reikin ağrıya etkisini inceleyen ilgili ilk tezin 2012 yılında yapıldığı, huzurevinde kalan yaşlıların ağrısına reikin etkisinin incelendiği ikinci tez (2013) dışında diğer tezlerin (n=6) son beş yılda yapılmış olduğu tespit edilmiştir (Tablo 2).

Çalışmaların %14,3'ünün (n=1) sezeryan ağrısına, %14,3'ünün (n=1) fibromiyalji ağrısına, %14,3'ünün (n=1) onkoloji hastalarının ağrısının azaltılmasında, %14,3'ünün (n=1) abdominal histerektomi geçiren kadınların ağrısına, %14,3'ünün (n=1) laporoskopik

kolesistektomi geçiren hastaların ağrısına, %14,3'ünün (n=1) dismenore ağrısına, %14,3'ünün (n=1) epizyotomi sonrası perineal ağrıya etkisini değerlendirmek amacıyla yapıldığı görülmüştür (Tablo 3).

Çalışmaların sonuçları incelendiğinde, farklı örneklem büyüklüklerinde ve farklı yaş grubundaki hastalarla yapılan deneysel tezlerin tamamında reikinin ağrı üzerine olumlu etkileri olduğu belirtilmiştir (Tablo 3).

**Tablo 2.** İncelenen tezlerin türlerine göre dağılımı

Tez Türü (Yükseklisans/Doktora)	n	%
Doktora	8	100
Yayınlanma Yılı		
2012	1	12,5
2013	1	12,5
2018	3	37,5
2019	2	25
2021	1	12,5
Araştırma Türü (Deneysel/Yarı Deneysel)		
Deneysel	8	100

**Tablo 3.** Sistematik analize dahil edilen tezler

Tez Türü/Yılı/Yazar	Amaç	Yöntem	Sonuç
Doktora, 2012, Sağkal T.	Sezaryen ameliyatı sonrası uygulanan reiki dokunma terapisi ağrı ve anksiyete üzerine etkisi	RKÇ* Deney=45 Kontrol=45	Sezaryen ameliyatı sonrası uygulanan Reiki dokunma terapisi ağrı, anksiyete ve solunum hızı değerlerini azaltmakta, ihtiyaç duyulan analjezik sayısını azaltmakta ve analjeziğe ihtiyaç duyulan süreyi uzattığı görüldü.
Doktora, 2013, Erdoğan Z.	Huzurevinde kalan yaşlılarda reikinin ağrı, yaşam kalitesi ve depresyon üzerine etkisi	RKÇ* Reiki=30 Yalancı Reiki=30 Kontrol=30	Çalışma reiki alan yaşlı bireylerin ağrı, yaşam kalitesi ve depresyon durumlarının yalancı reiki ve kontrol grubuna göre düzeldiğini göstermiştir.
Doktora, 2018, Çınar, H.G.	Fibromiyalji tanısı ile ağrı polikliniğinde takip edilen hastalarda reiki dokunma terapisinin etkisi	RKÇ* Deney=25 Kontrol=25	Reiki uygulamasının Fibromiyaljili hastalarda ağrıyı azaltmaya, yaşam kalitesini arttırmaya, durumluk ve sürekli kaygı düzeylerini azaltmaya, kan basıncını, nabız ve solunumu düzenlemeye olumlu etkilerinin olabileceği saptandı.
Doktora, 2018, Büyükbayram Z.	Onkoloji hastalarında reiki ve yönlendirilmiş imgelem uygulamasının ağrı ve yorgunluk üzerine etkisi	RKÇ* Reiki=60 Yönlendirilmiş İmgelem=60 Kontrol=60	Onkoloji hastalarına uygulanan reiki ve yönlendirilmiş imgelem uygulamasının ağrı ve yorgunluğu azalttığı bulundu.
Doktora, 2018, Utli H.	Abdominal histerektomi ameliyatı geçiren kadınlarda reiki ve sırt masajının ağrı üzerine etkisi	RKÇ* Reiki=34 Sırt Masajı=34 Kontrol=34	Abdominal histerektomi ameliyatı geçiren kadınlarda reiki uygulaması sonrası ağrı düzeyinin azaldığı saptandı.
Doktora, 2019, Anuş Topdemir E.	Laparoskopik kolesistektomi sonrası akupresür ve reiki uygulamasının hastaların ağrı ve konfor düzeyine etkisi	RKÇ* Reiki: 44 Akupresür: 44 Kontrol grubu: 44	Laparoskopik kolesistektomi sonrası hastalara uygulanan reiki ve akupresürün ağrıyı azaltıp, konforu artırdığı görüldü
Doktora, 2019, Taş F.	Dismenoreli adölesanlarda reiki uygulamasının ağrı, yorgunluk ve yaşam kalitesine etkisi	RKÇ* Reiki=38 Kontrol=37	Reiki uygulamasının dismenoreli adölesanlarda ağrı ve yorgunluğa etkili olduğu ve yaşam kalitesi üzerine etkisinin olmadığı belirlendi.
Doktora, 2021, Aydemir H.	Reiki uygulamasının epizyotomi iyileşmesi ve perineal ağrı üzerine etkisi	RKÇ* Deney=40 Kontrol=46	Vajinal doğum yapmış lohusalara uygulanan Reikinin ödem üzerine etkisinden dolayı epizyotomi iyileşmesine olumlu etkisi olduğu ve perineal ağrıyı azalttığı belirlendi.

\*= randomize kontrollü çalışma.

Tablo 3’de görüldüğü gibi doktora tezi olan ilk çalışma sezeryan ameliyatı geçiren kadınlar (n=90) ile gerçekleştirilmiştir (Sağkal, 2018). Bir diğer doktora tez çalışması Uludağ Üniversitesi Tıp Fakültesi Hastanesi’nin Algoloji ünitesinde fibromiyalji tanısı olan (n=50) hastalarla yürütülmüştür (Gökdere Çınar, 2012). Büyükbayram (2018) tarafından yürütülen doktora tezinin örneklemini 180 onkoloji hastası oluşturmaktadır. Utli (2018) doktora tezinde abdomina lhisterektomi geçiren 102 hasta ile çalışmıştır. Anuş Topdemir’in (2019) tez örneklemini laparoskopik kolesistektomi geçiren 120 hasta oluşturmuştur. Aydemir (2019) ise tezinde 86 lohusa kadınla çalışmasını yapmıştır. Tezlerin çoğunluğu Hemşirelik Ana Bilim Dalı kapsamında (6) yürütülürken sadece 1 tanesi Ebelik Ana Bilim Dalı kapsamında yürütülmüştür. Tezlerin araştırma desenleri değerlendirildiğinde hepsinin (n=7) randomize kontrollü çalışma olduğu saptanmıştır (Tablo 2).

#### 4. Tartışma

Ağrının giderilmesi her birey için temel bir hak olup (Akın, 2020), etkin ağrı yönetimi sağlık bakım ekibinin yasal ve etik sorumluluklarından biridir (Baş ve ark., 2016). Ağrının giderilmesinde kullanılan non-farmakolojik yöntemler tek başlarına veya farmakolojik yöntemlerle birlikte kullanıldığında ağrının azaltılmasında etkili olmaktadır. Farmakolojik olmayan yöntemlerin analjezik kullanım sıklığını azaltmaları, kolay uygulanabilir olmaları, yan etkilerinin az olması ve maliyetlerinin düşük olması gibi birçok avantajı bulunmaktadır (Karadağ, 2021). Bu yöntemlerden biri olan reiki, stresi azaltmak, sağlık ve iyilik halini arttırmak amacıyla evrensel enerjiyi kanalize etme tekniğidir ve bu enerji şifa terapisi olarak sınıflandırılır (Kurebayashi ve ark., 2016; Bondi ve ark., 2021).

Reikin vücutta kan-lenf dolaşımı ve parasempatik sistem aktivitesini artırması, immünoglobulin A seviyesini yükselmesi ve kortizol gibi stres hormonlarının salınmasını azaltarak gevşeme sağlaması bu sonuçları sağlamaktadır (Özcan ve ark., 2017). Araştırma kapsamına alınan tezlerde reikin postoperatif ağrı, dismenore ağrısı, kanser ağrısı, fibromiyalji ağrısı ve normal doğum esnasında uygulanan epizyotomiye bağlı perineal ağrı üzerinde etkili olduğu belirlenmiştir. Bunun yanı sıra ağrı ile ilişkili olarak hastanın anksiyete ve yorgunluk düzeylerini azalttığı, yara iyileşmesi, konfor ve yaşam kalitesi düzeylerini arttırdığı gösterilmiştir.

Cerrahi sonrası erken dönemde ve sonrasında ağrı yönetimi hemşirelerin önemli görevlerinden biridir. Kontrol edilemeyen ağrı, hastanın yatakta hareket etme veya hareketli olma yeteneğini etkileyerek cerrahi sonrası komplikasyonların gelişmesine neden olabilir (Janice ve Kerry, 2018). Çalışmada, tezlerin sezeryana bağlı postoperatif ağrıya (n=1), fibromiyalji ağrısına (n=1), kanser ağrısının azaltılmasında (n=1), abdominal histerektomi sonrası postoperatif ağrıya (n=1), laparoskopik kolesistektomi geçiren hastaların

postoperatif ağrısına (n=1) dismenore ağrısına (n=1) epizyotomi sonrası perineal ağrıya (n=1) etkisini değerlendirmek amacıyla yapıldığı görülmüştür. Çalışmaların büyük kısmı (n=3) reikin postoperatif gelişen akut ağrı üzerindeki etkisini değerlendirmek için yapılmıştır.

Deneysel çalışmalar esas olarak yeni bir ürün elde etmek, hastalıkların nedenini araştırıp tedavisine yönelik ilaç ve diğer uygulamaların etkinliğini ortaya koymak amacıyla yapılmaktadır (Okur, 2016). Bu desenlerden randomizasyonu içeren deneysel metodolojinin kullanılması ise bulguların kanıt düzeyini etkileyecektir (Akın ve Koçoğlu, 2017). Çalışmada, tezlerin araştırma desenine bakıldığında, tamamının deneysel araştırma deseninde yürütüldüğü görülmüştür. Araştırmada tezlerin çoğunun randomize olarak yürütülmesi, reikin etkinliğinin değerlendirilmesinde literatüre kanıt değeri yüksek bilgiler sağlamıştır. İncelenen tezler doğrultusunda reikin ağrı düzeyini azaltma konusunda etkili olduğu görülmüştür.

#### 5. Sonuç

Reikin farklı hasta gruplarında ağrı üzerinde etkili non-farmakolojik yöntem olduğunu araştırmalara dayalı sonuçlar göstermektedir. Reikin en büyük avantajı; kolay uygulanması, herhangi bir yan etki ve maliyetinin olmaması, etkili ve güvenilir bir yöntem olmasıdır. Reiki ağrının giderilmesinde ya da şiddetinin azaltılmasında etkili olması analjezi kullanımını da azaltabileceğinden hem hastanın yaşam konforunu arttırmada hem de tedavi maliyetini azaltmada etkili olabilir. Bu yüzden hastanın ağrısının giderilmesinde önemli rol üstlenen hemşirelerin reiki ve diğer non-farmakolojik yöntemler hakkında bilgi sahibi olmaları ve uygulayıcı olarak bağımsız rollerini gerçekleştirmeleri önemlidir. Son yıllarda hemşirelik araştırmalarda kullanımı artan non-farmakolojik yöntemlerden biri olan reiki uygulamasının ele alındığı tezlerin sayısında artış olmakla birlikte, yeterli düzeyde değildir. Araştırma sonuçları göz önüne alındığında reiki konusunda yapılacak olan akademik çalışmaların sayısının artması ile diğer çalışmalar içinde yol gösterici olacağı düşünülmektedir.

#### Katkı Oranı Beyanı

Tüm işlemler H.Ş. (100%) tarafından yapılmıştır; Konsept, Tasarım, Denetim, Veri toplama ve/veya işleme, Veri analizi ve/veya yorumlama, Kaynak taraması, Yazma, Eleştirel inceleme, Gönderim ve revizyon. Yazar, makalenin son halini incelemiş ve onaylamıştır.

#### Çatışma Beyanı

Yazar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

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Araştırma sistematik değerlendirme tasarımına uygun yürütüldüğü için etik kurul izni alınmamıştır.

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## THE EFFECT OF WORKING IN A HOSPITAL OFFERING PANDEMIC-RELATED SERVICES ON THE PERCEIVED STRESS AND ANXIETY LEVELS OF NURSES DURING COVID-19: A CASE OF TWO HOSPITALS

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**Abstract:** This descriptive and comparative study analyzed the effect of working conditions on the stress and anxiety levels of nurses in hospitals treating patients affected by the coronavirus disease 2019 (COVID-19) pandemic. The study was performed with a total of 304 nurses working in one hospital that provided pandemic-related services and another one that did not. An introductory information form, perceived stress scale (PSS), and Beck anxiety inventory (BAI) were used to collect data online. Before starting the study, ethics committee approval, institutional permission, and informed consent from the nurses included were obtained. The mean BAI scores of the nurses who worked in the hospital not offering pandemic-related services were similar to those of the nurses working in the hospital that did, whereas their mean PSS scores were significantly higher. There was a significant positive correlation between PSS and BAI ( $P < 0.001$ ).

**Keywords:** Anxiety, COVID-19, Nurse, Pandemic, Perceived stress

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### 1. Introduction

All countries of the world have faced the threat of the virus alleged to have appeared in Wuhan, China, in December 2019. The epidemic, which reached a global scale within a short time, was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, on which day the first case was encountered in the Republic of Türkiye (RTMH, 2021; WHO, 2020). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly and affected health, education, and the economy worldwide (Chen et al., 2020; Lu et al., 2020). This pandemic is an important global threat to mental health. Studies have reported that symptoms such as anxiety, depression, post-traumatic stress disorder, psychological distress, and stress are seen during viral respiratory epidemics, which include coronavirus disease

2019 (COVID-19) (Luo et al., 2020; Xiong et al., 2020).

Nurses are one of the occupational groups that are affected both physically and mentally during a pandemic (Chew, 2020). Those who care for infected patients are at risk of various mental health conditions (WHO, 2020; Xiang et al., 2020). A study conducted with 1,146 healthcare workers, including nurses working in Asia-Pacific region countries, found that variation in the prevalence of psychological disorders among healthcare workers was independent of the burden of COVID-19 cases within each country (Chew, 2020). A study conducted in Türkiye reported that the anxiety levels of nurses during the pandemic were higher than those of other healthcare professionals (Hacimusalar et al., 2020). During the pandemic, nurses have performed multiple tasks and functions including health education, screening, infection prevention, and surveillance;



ensuring necessary preparations and precautions in nursing homes and institutions where long-term care is provided; protecting high-risk groups; and providing care to acute and critical COVID-19 patients (Chen et al., 2020). Nursing is a highly stressful profession in general, but the COVID-19 pandemic has brought additional difficulties (Mokhtraï et al., 2020). Many physical and psychosocial considerations, such as the risk of exposure to the virus in the work environment, long and intensive work periods involving protective equipment, and worrying about transmitting the virus to family and others, have accentuated the stress and anxiety levels of nurses (Jiang et al., 2020). Stress can be defined as 'strain, tension and pressure' and used to express the different experiences that make individuals feel discomfort (Kaba, 2019). Anxiety can be defined as a state of fear, worry, distress, or tension of unknown origin that comes from within (Engin, 2014). The literature cites patients' deaths, the disease's unknown aspects, the atmosphere of the working environment, professional commitments, and individual characteristics as sources of distress in nurses caring for COVID-19 patients (Galehdar, 2020). Studies conducted in Türkiye reported that nurses had high levels of stress and occupational burnout syndrome, experienced anxiety and fear during the pandemic, reported increased obsessive behaviors or thoughts, and showed depressive symptoms (Kaçkin et al., 2020; Murat et al., 2020).

Nurses have been playing a key role in combating COVID-19 (Jiang et al., 2020; Kiyat et al., 2020) and have endured a great deal of psychological distress while caring for affected patients (Galehdar 2020; Kaçkin et al., 2020; Murat et al., 2020). Evaluating the effect of working in a hospital providing COVID-19 pandemic-related services on the stress and anxiety levels of nurses will shed light on this issue. In addition, this study will provide evidence-based data for future studies to plan and implement interventions to support the mental health of nurses.

The research sought answers to the following questions: What are the perceived stress and anxiety levels of nurses working in a hospital offering pandemic-related services?

What are the perceived stress and anxiety levels of nurses working in a hospital not offering pandemic-related services?

Does working in a hospital providing pandemic service affect the perceived stress and anxiety levels of nurses?

## 2. Materials and Methods

### 2.1. Research Design

This descriptive and comparative study examined the effect of working in a hospital offering COVID-19 pandemic-related services on the stress and anxiety levels perceived by nurses.

### 2.2. Study Population and Sample

The total study population comprised 1,318 nurses, 240

working at the research and practice hospital of a university in Central Anatolia (non-pandemic hospital) and 1,078 working at a city hospital in Eastern Anatolia (pandemic hospital). The study was conducted between July 1 and October 15, 2020, with the 304 nurses who agreed to participate, and sample selection was not performed. The power of the study was calculated to be 95% in a post-hoc power analysis performed with an alpha = 0.05 confidence interval and a 0.50 effect size using the G-Power 3.1.94 program; the sample size was found to be sufficient.

### 2.3. Data Collection Tools

Research data were collected using the descriptive information form, perceived stress scale (PSS), and Beck anxiety inventory (BAI).

### 2.4. Descriptive Information Form

Descriptive information form was prepared by the researcher by making use of the literature (Chew et al. 2020; Galehdar et al., 2020; Hacimusalar et al., 2020; Liu et al., 2020; Maraqa et al., 2020; Murat et al., 2020; Neupane et al., 2020). This included questions on the socio-demographic characteristics of the nurses such as age, gender, educational status, occupational characteristics (such as the duration of employment, the unit worked in before and during the pandemic, and the duration and method of work), how family life was affected by the pandemic, and their greatest concern regarding the pandemic

### 2.5. Perceived Stress Scale

This was developed by Cohen, Kamarck, and Mermelstein in 1983 to determine the level of stress that threatens human health (Cohen et al., 1983). The Turkish validity and reliability study was conducted by Eskin et al. (2013). The PSS consists of two factors: self-efficacy and stress perception. It is a five-point Likert-type scale with 14 items. Participants rate each item on a type scale ranging from 'never (0)' to 'very often (4)'. Seven items containing positive statements are scored in reverse. PSS scores range from 0 to 56, and the higher the score, the higher the perceived stress level. In study of Eskin et al. (2013) the total Cronbach Alpha value of the scale was 0.84 and it was found to be 0.73 in our study.

### 2.6. Beck Anxiety Inventory

This was developed by Beck et al. (1988) to measure the level of anxiety symptoms experienced by an individual. Ulusoy et al. (1988) conducted the Turkish validity study of the BAI. It is a four-point Likert-type scale and consists of 21 items. The scores that can be obtained from the scale range from 0 to 63, and the higher the score, the higher the anxiety level experienced by the person. According to the scores obtained, the anxiety levels of the participants are classified as minimal (0–7 points), mild (8–15 points), moderate (16–25 points), and severe ( $\geq 26$  points). In Ulusoy et al. (1988) study, the total Cronbach Alpha value of the scale was 0.93 and it was found to be 0.95 in our study.

### 2.7. Data Collection

The data-collection tools for this research were delivered

to the nurses online. Initially, a pilot study was conducted with 10 people to test the comprehensibility of the forms; the nurses who were included in the pilot study were not included in the main sample.

**2.8. Statistical Analysis**

Descriptive statistics of the data were calculated, and the conformity of the variables to a normal distribution was examined by visual methods (histograms and probability plots), skewness, kurtosis values, and the Kolmogorov-Smirnov test. The Chi-square test was used for comparing the categorical variables. The Student's t-test was used to compare two independent groups for variables showing a normal distribution; the Mann-Whitney U test was used to compare variables that did not show a normal distribution. For the correlation

studies, the Pearson correlation test was employed for normally distributed data, and the Spearman correlation test was used for non-normally distributed data. The level of significance was accepted as  $P < 0.05$ .

**3. Results**

The age, number of children, and duration of work of nurses working in the hospital offering pandemic-related services were significantly higher than nurses working in the hospital not providing pandemic-related services. The mean BAI scores of the nurses who worked in the hospital not offering pandemic-related services were similar to those working in the hospital that did, but their mean PSS scores were significantly higher (Table 1).

**Table 1.** Introductory Characteristics of the Nurses

Variables	Non Pandemic Hospital (n:172)		Pandemic Hospital (n:132)		t	P+
	Mean±SD		Mean±SD			
Age	30.4±6.9		35.6±7.7 <sup>a</sup>		-6.161	<0.001
BAI	23.9±14.5		21.7±15.0		1.266	0.207
PSS	31.1±6.5 <sup>a</sup>		29.4±7.1		2.205	0.028
	Median (IR)		Median (IR)		Z	P <sup>++</sup>
Number of children	0 (2)		1.5 (2) <sup>a</sup>		-3.331	0.001
Working time in the profession (year)	7 (10)		12 (12) <sup>a</sup>		-5.532	<0.001
	%	n	%	n	x <sup>2</sup>	P <sup>+++</sup>
Study participants	56.6 <sup>a</sup>	172	43.4	132	5.263	0.022
Female gender	76.7	132	67.4	89	3.268	0.071
Married participants	57.0	98	73.5 <sup>a</sup>	97	12.335	0.002
Spouse also health worker	23.3	40	30.3	40	1.936	0.380

<sup>a</sup> Significantly higher than the other group, + Student t- test, ++ Mann-Whitney U test, +++ Chi-square, n= number of participant, SD= standard deviation, IR= interquartile range, BAI= beck anxiety inventory, PSS= perceived stress scale

More than one-half of the nurses working in the hospital that did not offer pandemic-related services were university graduates; 74.4% had a weekly working time of 40–48 hours before COVID-19; 67.4% had a weekly working time of 40–48 hours during COVID-19; 65.7% worked both day and night shifts before COVID-19; 68.6% worked both day and night shifts during COVID; 41.3% stated that their family was negatively affected ( $P < 0.05$ ); 41.9% were worried about infecting their family or others; and 34.3% had received training to handle COVID-19. Of the nurses working in the hospital offering pandemic-related services, 81.1% had a university degree; 81.8% had a weekly working time of 40–48 hours before COVID-19; 71.8% had a weekly working time of 40–48 hours during COVID-19; 57.6% worked both day and night shifts before COVID-19; 70.5% worked both day and night shifts during COVID-19; 47% stated that their family was negatively affected ( $P < 0.05$ ); and 38.6% were worried about infecting their family or others (Table 2).

There was a statistically significant negative correlation between those with less experience (time working in the

profession) and those with more weekly working hours during COVID-19 ( $P = 0.004$ ) (Table 4).

Based on the analysis shown in Table 4, there was a significant positive correlation between PSS and BAI ( $r = 0.542$ ,  $P < 0.001$ ). There was a significant negative correlation between school of graduation (educational level) and PSS and BAI ( $r = -0.214$ ,  $P < 0.001$  and  $r = -0.182$ ,  $P = 0.001$ , respectively). There was a significant negative correlation between age and PSS ( $r = -0.144$ ,  $P = 0.012$ ). There was a significant positive correlation between weekly working hours before COVID-19 and weekly working hours during COVID-19 ( $r = 0.366$ ,  $P < 0.001$ ).

**Table 2.** Educational information, working conditions and causes of anxiety of nurses in hospitals providing pandemic-related services

	Non Pandemic Hospital (n:172)		Pandemic Hospital (n:132)		x <sup>2</sup>	P+
	n	%	n	%		
Graduated School						
Health vocational high School	30	17.4	3	2.3		
Associate degree	22	12.8	14	10.6	25.984	<0.001
Undergraduate	98	57.0	107	81.1		
Graduate	22	12.8	8	6.1		
Weekly Working Time Before COVID-19						
40-48 hours	128	74.4	108	81.8	6.330	0.042
49-56 hours	28	16.3	9	6.8		
≥57 hours	16	9.3	15	11.4		
Weekly Working Time During COVID-19						
40-48 hours	116	67.4	100	75.8	2.586	0.274
49-56 hours	28	16.3	17	11.4		
≥57 hours	28	16.3	17	12.9		
Before COVID-19 Working Schedule						
Day	45	26.2	51	38.6	6.735	0.034
Night	14	8.1	5	3.8		
Daytime and night	113	65.7	76	57.6		
During COVID-19 Working Schedule						
Day	40	23.3	33	25.0	1.598	0.450
Night	14	8.1	6	4.5		
Daytime and night	118	68.6	93	70.5		
How COVID-19 Affects Family Life						
Unresponsive	23	13.4	27	20.5	8.338	0.040
Fear of contagion	41	23.8	16	12.1		
Anxiety and depression	37	21.5	27	20.5		
Negatively affected	71	41.3	62	47.0		
Concern over COVID-19						
Unresponsive	24	14.0	19	14.4	2.276	0.810
Infecting family and loved ones	72	41.9	51	38.6		
Infecting others	12	7.0	11	8.3		
Infecting your child	16	9.3	14	10.6		
Getting sick	29	16.9	17	12.9		
Fear and depression	19	11.0	20	15.2		

x<sup>2</sup> = Chi-square, n= number of participant

**Table 3.** Comparison of age, BAI and PSS scores by gender

Variables	Women (n:221)	Men (n:83)	t	P+
	Mean±SD	Mean±SD		
Age	33.0±7.9	31.9±7.3	1.065	0.288
BAI	24.9±14.4 <sup>a</sup>	17.7±14.3	3.862	<0.001
PSS	31.3±6.4 <sup>a</sup>	28.1±7.4	3.674	<0.001
	Median (IR)	Median (IR)	Z	P++
Number of children	1 (2)	1 (2)	-3.331	0.965
WT (year)	10 (14)	9 (11)	-5.532	0.118

<sup>a</sup> Significantly higher than the other group, + Student t- test, ++ Mann-Whitney U test, n= number of participant, SD= standard deviation, IR= interquartile range, BAI= beck anxiety inventory, PSS= perceived stress scale, WT= working time in the profession

**Table 4.** Correlation analysis of the relationship between age, BAI, PSS, WT, GS, WWTB and WWTBD COVID-19

	WWTB		WWTB		GS		WT		PSS		BAI	
	r	P	r	P	r	P	r	P	r	P	r	P
Age	-0.198	0.001*	-0.055	0.337	0.278	<0.001*	0.921	<0.001*	-0.144	0.012*	0.024	0.678
BAI	0.022	0.703	0.033	0.568	-0.182	0.001*	0.031	0.586	0.542	<0.001*		
PSS	0.074	0.196	-0.008	0.886	-0.214	<0.001*	-0.088	0.126				
WT	-0.164	0.004*	-0.031	0.585	0.142	0.013*						
GS	-0.091	0.113	0.010	0.861								
WWTB	0.366	<0.001*										

r= correlation coefficient, BAI= beck anxiety inventory, PSS= perceived stress scale, WT= working time in the profession, WWTB= weekly working time before COVID-19, WWTB= weekly working time during COVID-19, GS=graduated school

#### 4. Discussion

The present study examined the effect of working in a hospital offering pandemic-related services on the perceived stress and anxiety levels of nurses. While the anxiety levels were similar, the perceived stress levels were significantly higher in nurses working in the hospital not offering pandemic-related services compared to those working in the hospital that did. The age and professional working time of nurses in the hospital offering pandemic-related services were higher compared to the other group. In addition, the perceived stress level decreased as the age of the nurses increased. This suggests that the experience of the nurses working in the pandemic hospital had a positive effect on stress levels. A previous study conducted in Türkiye reported that nurses who were younger and had less work experience felt less confident about their nursing abilities and had higher levels of stress and occupational burnout (Murat et al., 2020). This suggests that as the age of nurses increases, both their life and work experiences also increase, and they develop new techniques to cope with stress.

A study conducted with healthcare workers in Singapore reported that nonmedical healthcare personnel were at the highest risk for psychological distress during the COVID-19 outbreak (Tan et al., 2020). A study conducted with healthcare workers in China reported that those at the forefront of the fight against pandemics were at greater risk in terms of anxiety, insomnia, and general psychological problems than other healthcare professionals (Que et al., 2020)

In the present study, while the anxiety levels of the nurses working in the hospital not offering pandemic-related services were similar to those working in the hospital offering them, their perceived stress levels were higher. This might be associated with the nurses working in the hospital offering pandemic-related services mentally preparing themselves for the situation, and taking comprehensive infection-control measures. More systematic training of employees working in such hospitals, extensive use of protective equipment and clothing, and taking the approach of treating all patients as if they were COVID-19-positive intensified the measures taken. These measures might have reduced the stress levels of nurses working in the hospital providing

pandemic service. Moreover, in the hospital not offering pandemic-related services, routine health services continued, and there was an increase in patient density as people preferred the non-pandemic hospitals. It can be argued that these healthcare professionals came into contact with a large number of patients with uncertain COVID-19 status, and that this uncertainty might have increased the perceived stress level.

In the present study, a positive and significant relationship was found between the perceived stress level and anxiety scores of nurses working in the hospital offering pandemic-related services. Similarly, Mo et al. (2020) found a positive and significant relationship between the stress and anxiety scores of nurses, which supports our findings. In the present study, the nurses working in the hospital offering pandemic-related services experienced moderate anxiety. In a study conducted in China, the overall prevalence of anxiety among healthcare workers fighting against COVID-19 was 12.5%, with 10.35% of these cases being mild, 1.36% moderate and 0.78% severe (Liu et al., 2020). Neupane et al. (2020) found that 88.4% of nurses had normal anxiety levels, whereas 10.5% reported mild-to-moderate anxiety. Roberts et al. (2020) reported the rate of experiencing moderate-to-severe or severe symptoms of anxiety was approximately 21% (40/191), and that young nurses with less experience had high anxiety levels. In the present study, age did not affect the anxiety level.

In our study, the mean PSS score of the nurses was 29.4 ± 7.1 (PSS min = 0, max = 56), which indicated a moderate level of stress. When the studies related to the subject in the literature are examined, Neupane et al. (2020) and Hendy et al. (2020) reported that more than half of the nurses who participated in the study had moderate stress. Wang et al. (2020) reported that the level of stress among healthcare workers was low, which was related to professional commitment and sacrifice.

The present study determined that the perceived stress level decreased with age. This finding suggests that the increase in work experience with increasing age has a positive effect on the stress levels of nurses. Murat et al. (2020) results support this finding.

In the present study, the stress perceived by female nurses was higher than that of male nurses (Murat et al., 2020). Hacımusalar et al. (2020) found that female

healthcare workers had a higher anxiety level than their male counterparts. Wilson reported that the stress level was higher among female healthcare workers, which is similar to our finding (Wilson et al., 2020).

In the present study, the greatest concerns of the nurses working in the hospital offering pandemic-related services were infecting their family, children, loved ones, and others; and fear of getting sick or experiencing depression. A qualitative study noted that nurses experienced many psychological problems while caring for COVID-19 patients, including fear of death, anxiety related to the nature of the disease, fear of infecting family, and fear of disease transmission (Galehdar et al., 2020). Maraqa et al. (2020) found that 91.6% of healthcare workers mentioned that the risk of transmitting the virus to their family was their greatest stressor. According to Wang et al. (2020), healthcare professionals also cited stressors such as being infected with COVID-19, transmitting the infection to family members, and discomfort caused by protective equipment. Similar to our study, Robert et al. (2020) mentioned stressors such as transmitting the virus to other people, contracting the virus, being exhausted, not working safely, not being able to cope, and not getting enough personal protective equipment.

## 5. Conclusions

The present study found that the perceived stress and anxiety levels of nurses working in a hospital offering pandemic-related services were moderate. As the stress levels perceived by the nurses increased, so did their anxiety levels. While the anxiety levels of nurses who worked in the hospital not offering pandemic-related services were similar to those working in the hospital that did, their perceived stress levels were higher. Anxiety and perceived stress levels were found to be significantly higher in women than in men. The perceived stress level of younger nurses was higher. In line with these results, many other psychological and physiological issues, including the perceived stress and anxiety levels of nurses who play a key role in healthcare should be evaluated. It is recommended that studies involve multidisciplinary teams for the effective management of these problems experienced by the nurses.

## Limitations

This study was conducted during a specific time period during the course of the pandemic, which is continuing to change over time; this might have affected the stress and anxiety levels perceived by the nurses. The two hospitals involved were in different provinces, so the COVID-19 burden might have varied between them, which might also have influenced the findings. Differences in the ages of the nurses and the duration of work between the two hospitals could have affected the results of the study. A final limitation is that the study did not explore the physical symptoms of the nurses.

## Author Contributions

Concept: Z.K. (25%), Y.G. (25%), Y.H. (25%) and T.A.A. (25%), Design: Z.K. (25%), Y.G. (25%), Y.H. (25%) and T.A.A. (25%), Supervision: Z.K. (25%), Y.G. (25%), Y.H. (25%) and T.A.A. (25%), Data collection and/or processing: Z.K. (25%), Y.G. (25%), Y.H. (25%) and T.A.A. (25%), Data analysis and/or interpretation: Y.H. (34%), Z.K. (33%) and Y.G. (33%), Literature search: Z.K. (25%), Y.G. (25%), Y.H. (25%) and T.A.A. (25%), Writing: Z.K. (50%) and A.A. (50%), Critical review: Z.K. (25%), Y.G. (25%), Y.H. (25%) and T.A.A. (25%), Submission and revision Z.K. (25%), Y.G. (25%), Y.H. (25%) and T.A.A. (25%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Authors declare that they have no sponsor in the study design, collection, analysis, interpretation of data, writing of the manuscript, and decision to submit the manuscript for publication.

## Ethical Approval/Informed Consent

Ethical approval (approval no: 2020-06-134) was obtained from the Yozgat Bozok University, Zübeyde Hanım Faculty of Health Sciences ethics committee before starting the study. Institutional permission was obtained from the research and application hospital and the city hospital where the study was conducted. Electronic informed consent was obtained from the nurses included in the study.

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## GLOBAL TRENDS IN TRACHOMA

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**Abstract:** The study's goal is to examine the scientific outputs on Trachoma that have been published globally. A descriptive bibliometric analysis study was carried out. The Web of Science Core Collection was used as a bibliographic database and VOSviewer software version 1.6.18 for Windows was used to create the required network visualization. The search was conducted by using the keywords "trachoma" or "Chlamydia trachomatis" in the title. The most extensive timeframe was used, which included the years 1970 through 2021. Other publication genres such as case reports, editorials, and letters were eliminated from the search since they were not peer-reviewed papers. The overall citation counts of each trachoma-related publication published was the study's primary outcome. The topic of the publications, the publishing journal, and the year published, the language, the place of origin, the names of the first authors, the Hirsch (H) indexes, and the number of citations analyzed were all secondary outcomes. A total of 6556 articles were detected. The number of articles has never dropped under 100 articles per year since 1985. The highest number of articles was published in 2021 (n=233). 6251 (95.348%) of the articles were published in Science Citation Index Expanded (SCI-Expanded) journals. The University of California System was the leading affiliation on trachoma research. The USA (n=2585), England (n=910), and Canada (n=336) were the countries with the higher number of publications. The articles from the USA had the highest H indexes and the articles from England had a higher number of average citations per item. Studies on trachoma are increasing worldwide. The USA and England are the leading countries in scientific production in this regard. The USA and England are the leading countries in scientific production on this topic.

**Keywords:** Bibliometric analysis, Vos viewer, Trachoma, Chlamydia trachomatis

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### 1. Introduction

Trachoma is an infectious eye disease, caused by intracellular bacterium named *Chlamydia trachomatis* bacterium, and it is the most common infectious cause of visual impairment that can be prevented (Resnikoff et al., 2004). It spreads easily through direct human contact, sharing towels and clothing, and flies that come into touch with an infected person's eyes or nose. It can spread in regions where there is a lack of access to clean water and sanitation, affecting the world's most disadvantaged populations (Wright et al., 2007).

According to the Centers for Disease Control and Prevention (CDC), this disease affects about 8 million people worldwide, with 500 million individuals at risk of blindness in 57 endemic countries (Resnikoff et al., 2004). According to the World Health Organization (WHO) data, the most of the trachoma cases are from Africa. Also this disease can be seen in Central and South America, Asia, Australia, and the Middle East both have the disease. As of January 2, 2020, 13 countries had stated that they had met their elimination targets. In 2019, 92 622 persons had advanced trachoma surgically treated, and 95.2 million were treated with antibiotics

(URL 1). Despite these achievements, the disease continues to be a major public health concern, with an estimated yearly productivity loss of US\$ 8 billion owing to blindness and visual impairment (Solomon et al., 2022).

The objective of this research was to identify and analyze the trachoma publications. We evaluate the impact of trachoma literature, as well as the progress made in trachoma diagnosis, prevention, and therapy.

### 2. Materials and Methods

In this study, a descriptive bibliometric and visualizing study was carried out. The Web of Science Core Collection (Clarivate Analytics, Philadelphia, USA) was used as a bibliographic database. The Web of Science Core Collection indexes high-impact, high-quality scientific journals from throughout the world. The search was conducted using the terms "trachoma" or "*Chlamydia trachomatis*" in the title. The most extensive timeframe was used, which included the years 1970 through 2021. Other publication genres such as case reports, editorials, and letters were eliminated from the search since they were not peer-reviewed papers. In June 2022, the search



was done. The overall analysis of trachoma-related articles published was the study's primary outcome.

The topic of the publications, the publishing journal, and the year published, the language, the place of origin, the names of the first authors, the Hirsch (H) indexes, and the number of citations and international collaborations analysis were all secondary outcomes.

**2.1. Statistical Analysis**

Microsoft Excel 2010 was used to convert the data in the tables into absolute numbers (frequency and percentage). No advanced statistical analyses tests were used. VOSviewer software version 1.6.18 for Windows was used to create the required network visualization. VOSviewer is a free computer application that was created for the purpose of creating and viewing bibliometric maps (Ahmad et al., 2021; van Eck et al., 2010).

**3. Results**

A total of 6556 articles were found. In the year 1970, the first articles on trachoma were published. The number of articles never drop under 100 article per year since 1985. The highest number of articles published in 2021 (n=233) (Figure 1). 3,124 (47.651%) of the articles were published as Open Access category. 6251 (95.348%) of them published in Science Citation Index Expanded (SCI-Expanded) journals. 6,217 (94.829%)

of the articles were published in English language.

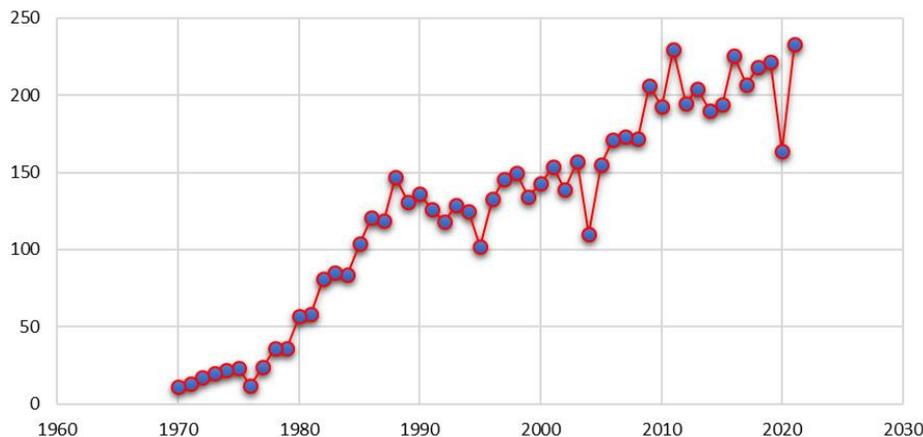
The articles were mostly from Infectious Diseases (n=2071, 31.589%), Microbiology (n=1567, 23.902%) and Immunology (n=1182, 18.029%) research areas (Table 1). The USA (n=2585), England (n=910) and Canada (n=336) were the countries with higher number of publications (Figure 2). The articles were published from 4.406 different affiliations. University of California System was the leading affiliation on trachoma research (Table 2). The main funding sponsor were from the USA and European countries (Table 3). Most of the articles were published in the journal of Sexually Transmitted Diseases (n=348, 5.308%), Infection and Immunity (n=336, 5.125%) and Journal of Clinical Microbiology (n=289, 4.408%) journals (Table 4).

**3.1. Citing Analysis**

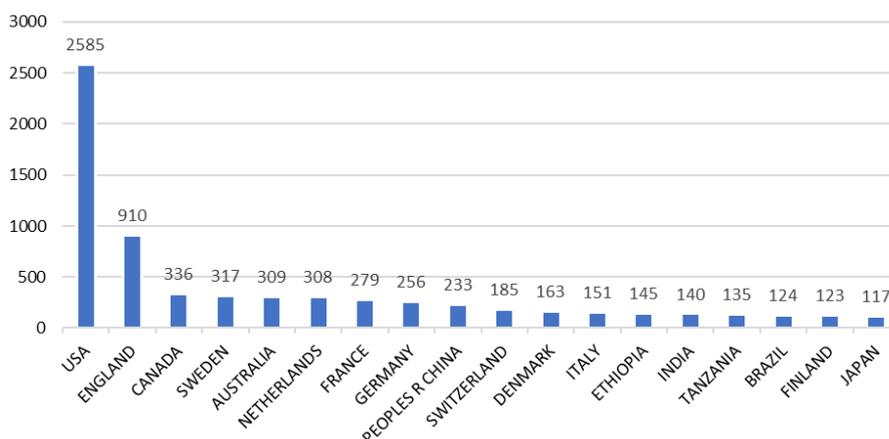
The articles were cited 165865 times (the average was: 25.3 times/ per article) and H index was 138. The number of citations has risen steadily over time (Figure 3). The articles from the USA had highest H indexes and the articles from England had higher number of average citation per item (Table 5).

**3.2. Mapping**

The mostly preferred keywords mapping was given in Figure 4. The map depicts the international collaborative network by using the VOSviewer (Figure 5, Figure 6 and Figure 7).



**Figure 1.** The number of articles published throughout time.



**Figure 2.** The countries with more than 100 articles.

**Table 1.** Research areas\*

Research Areas	n	% of 6.556
Infectious Diseases	2071	31.589
Microbiology	1567	23.902
Immunology	1182	18.029
Obstetrics Gynecology	564	8.603
Public Environmental Occupational Health	558	8.511
General Internal Medicine	473	7.215
Ophthalmology	364	5.552
Biochemistry Molecular Biology	310	4.728
Tropical Medicine	288	4.393
Science Technology Other Topics	247	3.768
Pharmacology Pharmacy	223	3.401
Parasitology	185	2.822
Pathology	184	2.807
Research Experimental Medicine	177	2.700
Reproductive Biology	154	2.349
Pediatrics	128	1.952
Urology Nephrology	117	1.785
Cell Biology	116	1.769
Dermatology	108	1.647
Biotechnology Applied Microbiology	97	1.480
Medical Laboratory Technology	61	0.930
Oncology	56	0.854
Virology	55	0.839
Genetics Heredity	54	0.824
Rheumatology	51	0.778

\*Showing 25 out of 95 entries, 3 record(s) (0.046%) do not contain data in the field being analyzed

**Table 2.** The leading affiliations on trachoma research\*

Affiliations	n	% of 6.556
University of California System	533	8.130
University of London	439	6.696
University of California San Francisco	367	5.598
League of European Research Universities Leru	349	5.323
London School of Hygiene Tropical Medicine	304	4.637
Johns Hopkins University	289	4.408
University of Washington	263	4.012
University of Washington Seattle	262	3.996
National Institutes of Health NIH USA	224	3.417
NIH National Institute of Allergy Infectious Diseases	199	3.035

\*Showing 10 out of 4.406 entries, 71 record(s) (1.083%) do not contain data in the field being analyzed

**Table 3.** The leading funding agencies\*

Funding Agencies	n	% of 6.556
United States Department of Health Human Services	1369	20.882
National Institutes of Health Nih USA	1304	19.890
National Institute of Allergy Infectious Diseases	943	14.384
European Commission	327	4.988
National Eye Institute	198	3.020
Wellcome Trust	170	2.593
UK Research Innovation	140	2.135
Medical Research Council UK	138	2.105
United States Agency For International Development	98	1.495
National Institute of General Medical Sciences	95	1.449

\*Showing 10 out of 1.976 entries, 3.805 record(s) (58.038%) do not contain data in the field being analyzed

**Table 4.** The mostly publishing journals on trachoma\*

Journals	RC	% of 6.556
Sexually Transmitted Diseases	348	5.308
Infection and Immunity	336	5.125
Journal of Clinical Microbiology	289	4.408
Sexually Transmitted Infections	186	2.837
International Journal of STD AIDS	142	2.166
Journal of Infectious Diseases	135	2.059
Plos Neglected Tropical Diseases	126	1.922
Plos One	126	1.922
Ophthalmic Epidemiology	94	1.434
Journal of Bacteriology	89	1.358
Genitourinary Medicine	74	1.129
American Journal of Obstetrics and Gynecology	73	1.113
Antimicrobial Agents and Chemotherapy	62	0.946
BMC Infectious Diseases	62	0.946
British Journal of Ophthalmology	62	0.946
Journal of Medical Microbiology	61	0.930
Journal of Immunology	55	0.839
European Journal of Clinical Microbiology Infectious Diseases	53	0.808
American Journal of Tropical Medicine and Hygiene	52	0.793
Clinical Infectious Diseases	51	0.778
Diagnostic Microbiology and Infectious Disease	50	0.763
Journal of Clinical Pathology	47	0.717
Obstetrics and Gynecology	46	0.702
Fems Microbiology Letters	45	0.686
Molecular Microbiology	44	0.671

\*Showing 25 out of 1.093 entries, RC= record count



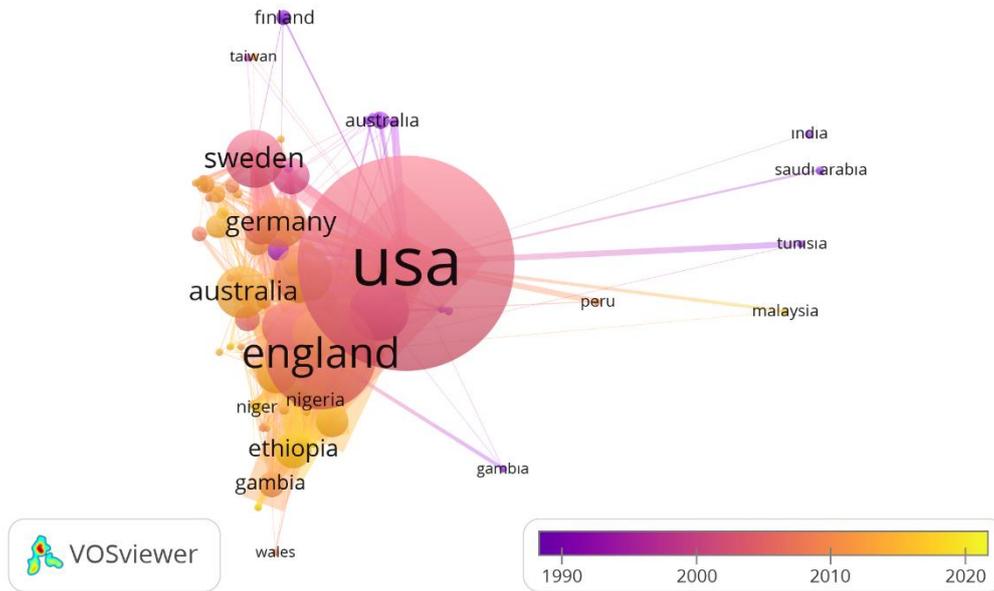


Figure 5. Network visualization map of co-authorship among countries with a minimum of five publications.

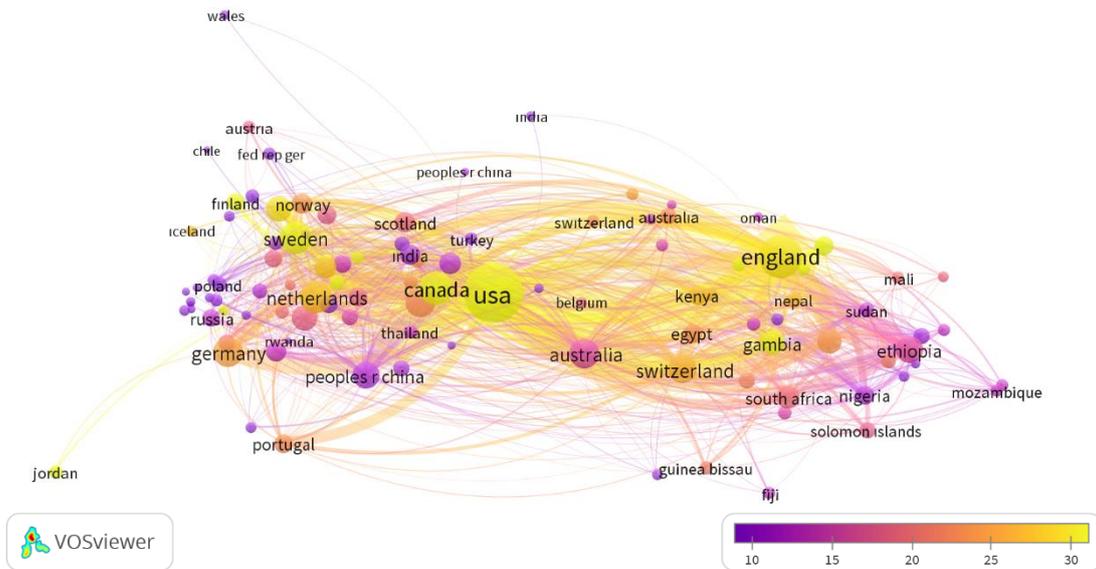


Figure 6. Network visualization map of citation map among countries with a minimum of five publications.

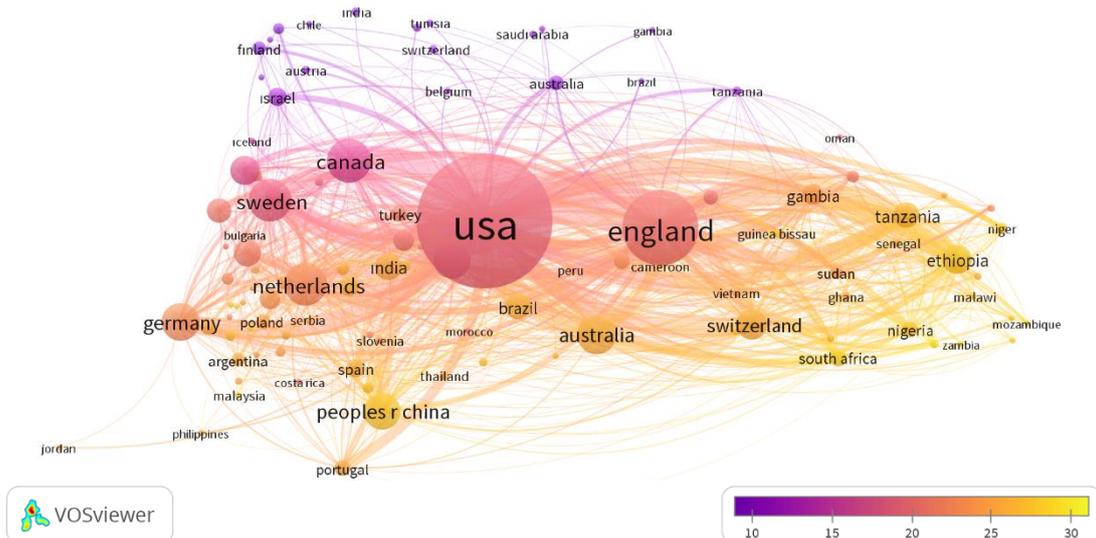


Figure 7. Citation visualization map among affiliations. Line express the cite number.

### 3. Discussion

The most prevalent infectious cause of blindness is trachoma. This infection several times as a child causes severe conjunctivitis, scarring, and possibly blindness inturred eyelashes (trichiasis or entropion) later in life. Trachoma is spread by children with filthy cheeks sharing infectious ocular secretions in resource-poor communities with poor hygiene. The epidemiology and pathophysiology of trachoma have been studied extensively. The SAFE Strategy is being implemented through integrated control programs that include trichiasis surgery, antibiotic mass distribution, facial hygiene promotion, and environmental enhancement. This technique has effectively eradicated trachoma in numerous countries, and global attempts to eradicate blinding trachoma by 2020 are ongoing (Taylor et al., 2014).

Bibliometric studies have become important instruments for assessing scientific activity as they provide a snapshot of the development, amount, and distribution of scientific literature in a certain area. The bibliometric technique entails quantifying broad trends and identifying hidden links or correlations among enormous volumes of data. In recent years, many various bibliometric analysis methods have come to the forefront in the medical literature, and methods like mapping and graphing can help to deepen analytic research. Many methodologies, including as content analysis, comparisons of scientific productivity by years, nations, and citation numbers, can be used to conduct these evaluations. Databases that allow quick and extensive data analysis, such as Pubmed, EBSCO, Scopus, Pro-Quest, and Web of Science, are often used for bibliometric analysis. Additionally, this approach may be used to evaluate other sources such as any database, theses, journals, conferences, and so on (Alkan Çeviker et al., 2021; Dindar Demiray et al., 2021; Durgun et al.2022; Küçük et al.2021; Mızrakçı S, 2022; Nichols et al.2021; Öntürk et al.2021; Özlü A,2022; Özlü, 2021; Şahin S.,2022; Tahmaz et al., 2022; Yıldız E., 2022). We believe that the scientific effectiveness of serious diseases, as well as many other areas in health, should be assessed using this technique, and that a roadmap for future research should be formed. The Wos database was utilized to conduct the research in this study. We did a literature research on trachoma before to doing this study and were unable to find any similar studies. This illness is significant since it is the most prevalent infectious cause of vision loss that can be avoided. This study served as a starting point for developing future policy and research funding to effectively manage trachoma in endemic regions. The trachoma literature has developed dramatically since 1980, with at least 100 new papers being published each year.

As of March 2022, 44 nations, including 26 in the WHO African Region, were recognized to require trachoma interventions (Solomon et al., 2022). The USA has the most studies published, followed by England and Canada.

The current analysis follows the same patterns as many earlier bibliometric studies in many fields, confirming the USA as a global research leader in both quantitative and qualitative terms (Dindar Demiray et al., 2021; Mızrakçı, 2022; Şahin, 2022).

Keywords play an important role to locate any research in showing the required document. In our analysis, the most used keywords were given in Figure 4. Journals are key instruments for disseminating research; hence, the quality and prestige of a journal play a significant role in transferring findings to the target audience (Shah et al., 2021). In our study, most of the articles were published in the journal of Sexually Transmitted Diseases (n=348, 5.308%), Infection and Immunity (n=336, 5.125%) and Journal of Clinical Microbiology (n=289, 4.408%) journals.

Scientometrics may now examine the impact of publications using citation reports, knowledge mapping methodologies, and other quantitative bibliometrics criteria, because to advancements in health informatics (Alshahrani and Owaifeer, 2020). Quantitative data on document types, authors, journals that published the trachoma documents, languages, publication origins, and citation reports were also included in the current bibliometric analysis. Also, we used the VOSviewer for the purpose of creating and viewing bibliometric maps (Figure 4-7). The current analysis was carried out since we believe that a comprehensive review of H-index, number of citations, and citations per article is required, with a special focus on the trachoma literature. The articles from the USA had highest H indexes and the articles from England had higher number of average citation per item.

### 5. Conclusions

On the other hand, one could argue that an increase in the number of publications does not necessarily imply an increase in interest in corneal transplantation, given the number of journals and hence the number of published papers grows year after year. Because the quality of journals, acceptance rates, and acceptance methodology differ from one to the other.

### Limitations

Our research has some limitations. To begin with, it was impossible to read the full texts of all the published articles in order to provide more information. The sorts of parameters that can be analyzed in bibliometric research are also limited by the database programs' options. Other databases, besides Thomson Reuters Web of Science, may be explored in future investigations. The current study only used one database search (WoS), which could affect the number of citations and publication frequency in trachoma. WoS database, on the other hand, is one of the most widely used databases for bibliometric analysis. This limitation must be taken into account while interpreting our data.

## Author Contributions

Concept: M.Y. (50%) and E.K.D.D. (50%), Design: M.Y. (50%) and E.K.D.D. (50%), Supervision: M.Y. (50%) and E.K.D.D. (50%), Data collection and/or processing: M.Y. (50%) and E.K.D.D. (50%), Data analysis and/or interpretation: M.Y. (50%) and E.K.D.D. (50%), Literature search: M.Y. (50%) and E.K.D.D. (50%), Writing: M.Y. (50%) and E.K.D.D. (50%), Critical review: M.Y. (50%) and E.K.D.D. (50%), Submission and revision M.Y. (50%) and E.K.D.D. (50%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest.

## Ethical Approval/Informed Consent

The study complied with the Helsinki Declaration, which was revised in 2013. Ethics committee approval is not required as there is no human or animal research.

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## THE EFFECT OF INDIVIDUAL EXERCISE AND GROUP EXERCISE TRAINING ON PHYSICAL PERFORMANCE IN HEALTHY WOMEN

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**Abstract:** The aim of the study was to compare the effects of individual exercise and group exercise training on the physical performance of healthy women. 26 healthy volunteer women participated in the study. Participants were randomly assigned to two equal groups. Participants completed a general demographic information form and physical performance tests. The Lafayette Manual Muscle Tester was used to evaluate the participants' muscle strength to establish their physical performance. In order to evaluate muscular endurance, the time that participants remained in squat, sit-up and push-up positions was recorded. An agility rating was determined using the Burpee Test, while a flexibility rating was made using the Sit and Reach Test. Exercise training was applied to individuals in both groups as 3 sessions per week for 8 weeks. Wilcoxon Signed Ranks test was used for comparison between groups. Mann Whitney U test was used to determine the difference between the groups before and after treatment. According to the data collected from individuals, in both groups an increase was seen in muscle strength, muscular endurance, agility and flexibility scores ( $p < 0.05$ ). For all parameters, neither group showed superiority ( $p > 0.05$ ). It was concluded that exercise training positively affected physical performance; however, it did not make a difference whether the exercise was done individually or in a group.

**Keywords:** Endurance, Exercise, Flexibility, Muscle strength, Physical performance

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### 1. Introduction

Exercise is included in physical activity. It is a concept that provides protection or improvement in physical fitness parameters such as repetitive, personalised, muscle strength, endurance, flexibility and agility (Ardıç, 2019). Regular exercise benefits body composition and is important in terms of maintaining physical fitness and preventing disorders that may occur later in life, including osteoporosis, balance problems, falls and fractures as a result of balance disorders, diabetes mellitus and cardiovascular disease (Alkadhi, 2018). When one looks at the distribution by gender of these disorders which can be prevented through physical activity, it is seen that they are most common in women (Barker and Eikmeyer, 2020).

Considering the physiological and anatomical structure of women, bone density is 50% less than that of men. Limb length is shorter than men, gynecoid pelvis is present and legs tend to be in a valgus position. Shoulders are narrower and protruding when compared to men, hands and feet are smaller and improvement rates of kyphosis, lordosis and scoliosis are much higher. The strength of joints and ligaments is weaker than men, and bone structure is fragile.

When we consider the low joint strength, less ligament strength and more bone fragility, the risk of injury and

osteoporosis is higher than men.

Muscular strength training, which is among the physical fitness parameters, has a positive effect on the musculoskeletal system and body composition, including bone, joint and tendon structures. It minimises the risk of osteoporosis and fractures, especially in women, by increasing bone density and decreasing fragility (Vanhees et al., 2005; Liberman et al., 2017). Flexibility is crucial to physical fitness as an inflexible individual will struggle during exercise. Aerobic physical activity increases exercise tolerance.

In a study comparing the effects of underwater and aerobic exercise on physical fitness parameters, an increase in physical fitness parameters was found between the groups (Vanhees et al., 2005; Çolak, 2008). In addition, in a study conducted on healthy male individuals doing group exercise training, it was found that male individuals who received group Pilates training experienced a higher increase in flexibility (Akyurt, 2019). There are studies in the literature comparing the effects of individual and group exercise training on some diseases or on healthy individuals (Korkmaz, 2020). However, there is no study comparing the effects of individual and group exercise in evaluating physical performance in healthy females.

Our study aimed to compare the effects of individual



exercise and group exercise training on physical performance in healthy women.

### 2. Materials and Methods

This study was carried out in Hasan Kalyoncu University, Institute of Health Sciences, Department of Physiotherapy and Rehabilitation between 2017 and 2018. The study was initiated with female individuals who read the Volunteers Information and Consent Form and agreed to participate in the study.

13 female individuals for the individual exercise group (age mean,  $33,8 \pm 8,8$ ) and 13 females for the group exercise group (age mean,  $37 \pm 9$ ) participated in the study. Individuals were randomised using the sealed envelope method in which groups A and B were separated. During our 8-week study, no individual was excluded from the study.

The inclusion criteria for the study were presented below;

- No obstacle to exercise
- Without severe cardiovascular and respiratory system distress that would limit exercise capacity
- Not included in any exercise program in the last 6 months
- Cooperative female individuals were included in the study.

The exclusion criteria from the study were presented below;

- Pregnancy status
- Loss of balance due to loss of consciousness or dizziness
- Those who refused to participate in the exercise training were not included in the study (Ağaoğlu, 2015).

After obtaining general demographic information from participants, the physical performances of the individuals were measured. The information recorded for the individuals participating in the study included age, height, weight, body mass index, education level (illiterate, literate, primary school graduate, secondary-high school graduate, university graduate, master's/doctorate degree), profession, diagnosed illnesses and surgical information. Flow diagram of the study are present in Figure 1.

#### 2.1. Exercise Protocol

Participants were given an 8-week programme consisting of a 1-hour exercise programme per day, 3 sets of 10 repetitions, 3 days a week. For their hour-long programme, those taking part in individual exercise did warm-up exercises (brisk walking at a steady pace on a treadmill) for the first 10 minutes, exercises to increase muscle strength and endurance (abdominal strengthening, strengthening of upper and lower extremity muscles with the help of thereband, strengthening of back extensors: each exercise progressively resistant) for the next 40 minutes and cooling exercises (general body stretching) for the last 10

minutes. The individuals doing group exercise also did warm-up exercises (brisk walking at a steady pace on a treadmill) for 10 minutes the next 40 minutes, muscle strength and endurance applications (as progressive resistance exercise, general strengthening exercises for Gross muscle groups, rope skipping, upper and lower extremity strengthening with Bench-press, Leg-press, Butterfly devices, sit-ups abdominal muscle strengthening exercises) and the last 10 minutes cooling exercises (general body stretching) were performed 3 days a week for 8 weeks.

Data were collected from the participants twice using the same questionnaires at 8-week intervals, on the first and last day of exercise. The obtained data were analysed in the SPSS programme.

While evaluating the physical performance of participants, the parameters of muscular strength, muscular endurance, agility and flexibility were used.

The Lafayette Manual Muscle Test device was used to evaluate muscular strength. While the measurements were made, the resistance given by the patient was calculated in Newtons by keeping the device constant. The measurements were evaluated separately for the upper (shoulder flexion, extension, abduction, adduction; elbow flexion; hand dynamometer) and lower (hip flexion, extension, abduction, adduction, knee flexion and extension, foot dorsi and plantar flexion) extremities in the sitting position, and total muscle strength was recorded.

The Push-Up Test, Sit-Up Test and Squat Test were used to evaluate the peripheral muscle endurance of the participants. While applying the tests, it was observed how many seconds the individual maintained the relevant test position.

Agility was evaluated using the Burpee Test, which evaluates how many times a certain movement pattern is made in 2 minutes. However, since the tolerance of the participants was not suitable for evaluating the results within 2 minutes, the number of times that the individual repeated this pattern in 1 minute was recorded.

The Sit and Reach Test was used to test flexibility. This test was carried out using a special tool 30 cm high, 45 cm wide and 100 cm long. The 25 cm inside part of the test vehicle where the feet are placed was taken as the reference point "0". The part towards the individual from the reference point showed negative values and the part towards the opposite side showed positive values.

#### 2.1. Statistical Analysis

SPSS 22.0 (Statistical Package for the Social Sciences) package programme was used for the statistical analysis of the data. In statistical analysis,  $P < 0.05$  was used as a significance value. The number of individuals to participate in the study was determined as 26 individuals, including 13 in each group, by power analysis (G\*Power) using the power of the study as 80% (= 0.20), the confidence interval of 95% and the margin of error  $\alpha = 0.05$ .

Or descriptive analysis, variables determined by

numerical measurement were expressed as arithmetic mean and standard deviation ( $X \pm SD$ ), and frequency values were calculated as percentage (%) for non-numerical data. For analysis, the Wilcoxon Signed Rank test was used for in-group comparison and the Mann-

Whitney U test was used for intergroup comparison. Difference variables were expressed as difference  $\pm$  standard deviation ( $X \pm SD$ ). The p significance value in all statistics was accepted as  $P < 0.05$ .

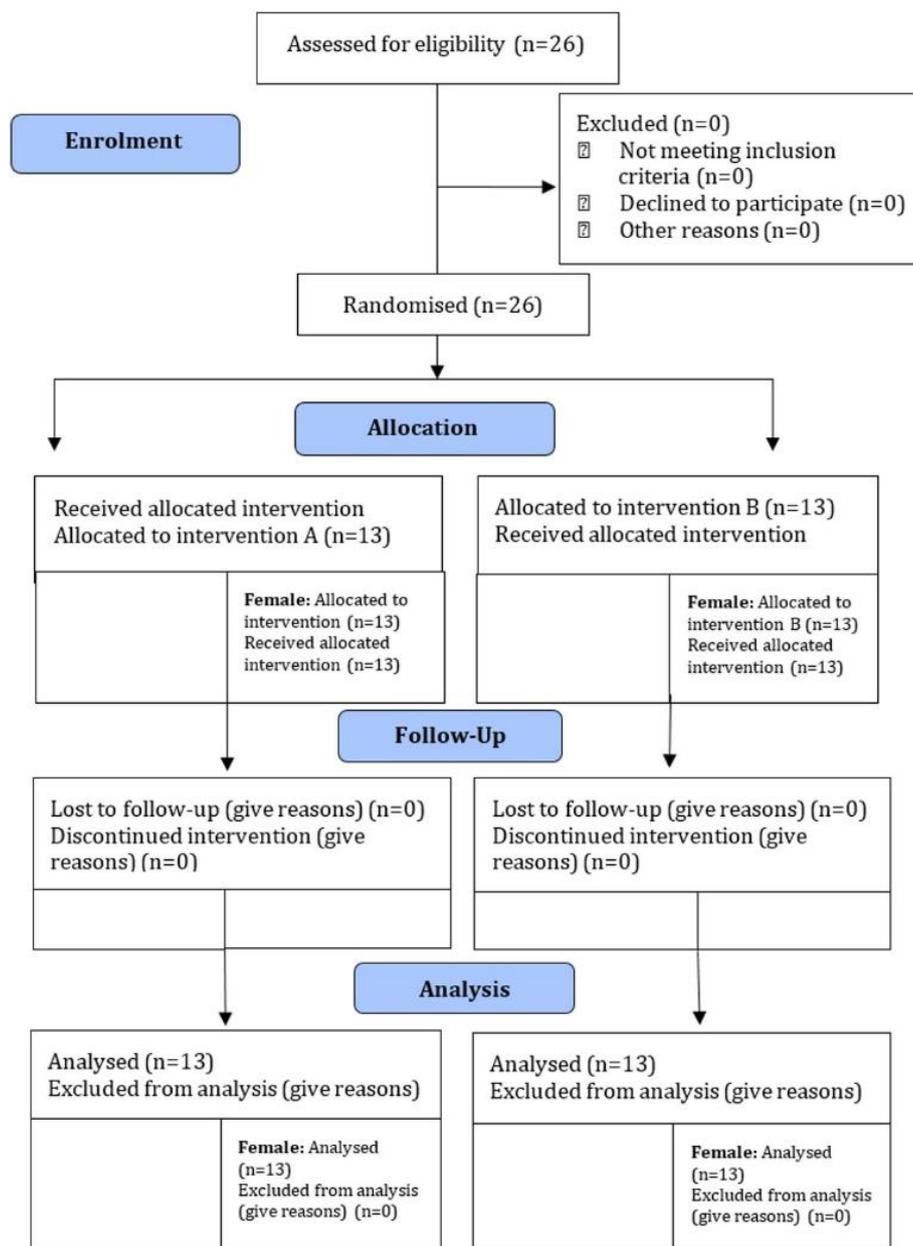


Figure 1. Flow diagram of the study

### 3. Results

In our study, in which we aimed to compare the effects of individual exercise training and group exercise training on physical performance in healthy women, 13 women with an average age of 33.8 years in the individual exercise group and 13 women with an average age of 37 years in the group exercise training group participated. When the physical characteristics (age, height, body weight, body mass index) of the individuals were examined before the training, it was seen that the groups showed a homogeneous distribution ( $P > 0.05$ ) (Table 1).

Muscular strength, muscular endurance, agility and flexibility assessment are among the physical performance evaluation parameters of individuals. The strength measurements of the participants were made separately in the upper and lower extremities using the Lafayette Manual Muscle Test device and total muscle strength was recorded. When the values of individuals participating in the individual and group exercise training before and after the exercise training were compared, an increase was found in the upper and lower extremity muscular strength after the exercise ( $P < 0.05$ ) (Table 2).

**Table 1.** Descriptive data of the individuals

	Individual Exercise Training (n=13)		Group Exercise Training (n=13)		z	P
	X±SD	(Min-Max)	X±SD	(Min-Max)		
Age (years)	33.8 ± 8.8	(23-51)	37 ± 9	(25-53)	-0.745	0.456
Height (cm)	162.7 ± 5.3	(153-173)	163.5 ± 6.6	(158-179)	-0.207	0.836
Weight (kg)	63.3 ± 7.9	(49-73)	62.5 ± 7	(50-72)	-0.564	0.573
BMI (kg/m <sup>2</sup> )	24.1 ± 3.4	(19-28)	23.4 ± 2.9	(20-28)	-0.513	0.608

X= mean, SD= standard deviation, P <0.05, Min= minimum, Max= maximum, BMI= body mass index

**Table 2.** Intra-group comparison of individuals of upper and lower extremity muscle strength total value

	Individual Exercise Training				Group Exercise Training			
	Pre exercise	Post exercise	z	P	Pre exercise	Post exercise	z	P
	X±SD	X±SD			X±SD	X±SD		
ÜEMS-L (N)	214.8±33,3	278±33	-3.180	0.001*	225.2±54.9	270.8±53.5	-2.981	0.003*
UEMS-R (N)	124.1±8.6	278.3±26.2	-2.981	0.003*	123.2±11.7	277.6±47.3	-2.197	0.028*
LEMS-L (N)	173±23.5	226.8±36.4	-2.943	0.003*	178.3±33.7	227.7±48.6	-3.059	0.002*
LEMS-R (N)	174.7±20.7	233.2±33.4	-2.848	0.004*	186.2±40.5	227.5±49.4	-3.059	0.002*

X= mean, SD= standard deviation, UEMS= upper extremity muscle strenght, LEMS= lower extremity muscle strength, N= Newton, L= left, R= right, \*P <0.05

The increase in upper and lower extremity total strength was similar after individual and group exercise training (P >0.05) (Table 3).

The muscular endurance of participants was evaluated before and after exercise with the Push-Up, Sit-Up and Squat Tests. The data of the evaluation are given in Table 4. An increase was observed in the muscular endurance of participants within the same group (P <0.05). When the measurements of muscular endurance of participants in the different groups were compared, the results were similar (P >0.05) (Table 5).

An agility assessment of individuals was made with the Burpee Test, while the Sit and Reach Test was used for flexibility assessment. The data obtained for the evaluations done before and after the exercise are given in Table 6. In comparing the agility and flexibility values of participants of both groups before and after exercise, an increase was observed after exercise (P <0.05). When the agility and flexibility measurements before and after exercise of participants in the different groups were compared, the results were similar (P >0.05) (Table 7).

**Table 5.** Comparison of muscular endurance test pre and post exercise values between groups

	Individual Exercise Training		Group Exercise Training		z	P
	X±SD	X±SD	X±SD	X±SD		
Pre- Post exercise	Push-Up	47.3±17.3	55.3±28.2	-514	.939	
	Sits-Up	30.3±12.2	39.9±19.3	-927	.354	
	Squat	24.4±17.8	18.8±10.3	-360	.719	
	Push-Up	61±21.9	65.2±31.5	-257	.797	
	Sits-Up	44.2±17.5	53.5±24.3	-976	.329	
	Squat	32.5±21.1	29.7±13.2	-.026	.980	

X= mean, SD= standard deviation, P<0.05

**Table 6.** Intra-group comparison of individuals' assessment of agility and flexibility test

	Individual Exercise Training				Group Exercise Training			
	Pre Exercise	Post Exercise	z	p	Pre Exercise	Post Exercise	z	P
	X±SD	X±SD			X±SD	X±SD		
Burpee Agility	7.3±2.5	9.8±2.5	-3.275	0.001*	8.2±3.1	10±2.2	-2.683	0.007
Sit and Reach	-2.9±9.8	0.1±8.7	-3.088	0.002*	-0.8±8.1	2.2±6.6	-2.952	0.003

X= mean, SD= standard deviation, P <0.05

**Table 7.** Comparison of agility and flexibility test pre and post exercise between groups

	Individual Exercise Training	Group Exercise Training	z	P	
	X±SD	X±SD			
Pre - Post exercise	Burpee Agility	7.3±2.5	8.2±3.1	-.857	.392
	Sit and Reach	-2.9±9.8	-0.8±8.1	-.051	.959
	Burpee Agility	9.8±2.5	10±2.2	-.285	.776
	Sit and Reach	0.1±8.7	2.2±6.6	-.180	.857

X= mean, SD= standard deviation, P <0.05

#### 4. Discussion

Our study aimed to compare the effect of individual exercise and group exercise training on physical performance in healthy women. Exercise training increased physical performance parameters such as strength, endurance, flexibility and agility in individual and group exercise training. In our study, which we supported with the literature, exercise training was given 3 days a week, and individuals with active participation were included in an 8-week exercise follow-up. It is possible to have high physical performance and maintain a high quality of life by participating in exercises aimed at increasing muscle strength. Thus, intense physical activity eliminates inactivity and prevents or minimises the formation of chronic diseases such as osteoporosis and cardiovascular diseases caused by inactivity (Haskell et al., 2007).

In our study, the upper and lower extremity total strengths of participants involved in individual exercise and group exercise training were recorded separately. There was an increase in the strength measurements of participants in both groups before and after the training. When the strength increases of the participants in the two groups were compared, their response to exercise was found to be similar. In a pilot study in which Yakut et al., investigated the role of Pilates exercises in patients with knee osteoarthritis, patients divided into two groups (group exercise and home exercise) showed an increase in lower extremity muscle strength after training. This increase also positively affected the Health Assessment Questionnaire scores. Although more positive results were obtained in patients who received group exercise training at the end of the treatment, there was no statistically significant difference between the groups (Yakut et al., 2006). In a study in which Pain et al., investigated the effectiveness of exercise training in terms of pain, spinal mobility, kyphosis and lordosis in patients with osteoporosis, they applied group exercise training to the treatment group and the control group. Other patients in the control group were not included in any exercise programme. While the muscle strength and consequently the spinal mobility of participants who did the 20-week group exercise training programme increased, the values were similar in the control group (Pain, 2010). In this study, which investigated the effectiveness of exercise training, our conclusions are that the exercise content of any exercise programme will increase muscle strength. We are of the opinion that

exercise training with similar working styles and the same intensity will increase muscle strength regardless of the number of people involved. An increase in muscle strength is associated with adaptation, motor skills and neuromuscular activation. Likewise, exercise duration and intensity are important in terms of the occurrence of muscular hypertrophy. With muscle contraction, force is produced only as a result of the increase in the diameter of the fibrils and with neuromuscular activation.

In evaluating the muscular endurance of individuals participating in individual exercise and group exercise training, Push-Up Tests were used for the upper extremities, Squat Tests for the lower extremities and Sit-Up Tests for the trunk muscles. When participants in both groups were evaluated before and after training, it was seen that exercise had a strong effect on muscular endurance. In comparing the two groups, the results were similar. Depending on the increase in the number of adaptive muscle fibres as a result of exercise, the development in strength also positively affected endurance (Katayıfçı et al., 2014). We think that the formation of synergies in the muscles that occur as a response to exercise and the integration of movements into daily life may cause an increase in endurance. There are important parameters that ensure the improvement of performance. One of these is motor development. The most important feature that increases motor development is endurance (Owen et al., 2020). Endurance of lower and upper extremities and trunk muscles were evaluated in an 8-week group exercise training programme in healthy adults. At the end of the training, participants who took part in group exercise observed an improvement in muscular endurance (Balcı et al., 2020). Our study is in line with other studies in the literature.

Physical performance is affected by endurance, balance, flexibility and coordination. Agility is a motor skill and is developed through progressive resistance exercises. An increase in agility depends on factors such as neural adaptation of joint proprioceptors, the Golgi tendon organ and muscle spindle and restructuring of motor programming by neuromuscular conditioning (Castro et al., 2010). Thus, neural adaptation increases with strength, and agility increases as a result of neural adaptation. In a study conducted by Sheppard and Young (2006), it was suggested that the amount of body fat can affect agility. In this context, they found that in two athletes with the same weight, an individual with a lower

fat percentage and higher muscle mass should produce less force per unit muscle mass during acceleration. In our study, we think that the increase in agility in both groups and the similarity between the groups may be related to the decrease in body weight and body mass indexes.

The increase in flexibility in both groups is due to the inclusion of exercise training for muscles that cross double joints in more than one plane (Whitehurst et al., 2005; Weiss et al., 2010). Increased muscle activation increases heart rate and body temperature. The development in neuromuscular excitation that causes an increase in strength, endurance, conduction velocity, enzymatic activations, and so on causes flexibility by reducing tissue viscosity. We think that the fact that only women were included in the study could have led to the improvement in the flexibility parameter in both groups and the similarities between the groups because muscle tendons are weaker in women than in men. Along with the weaker tendons, less muscle tone increases the mobility of the joint. Along with increased mobility, flexibility is more common in women. Considering these features, it has been proven that women are more successful than men when the studies on gymnastics in the literature are examined (Koç and Yüksel, 2015).

Limitation of the study, participants varied in age from 23–53. Although age distributions between the groups give similar results, we believe that if we had narrowed our age range, our results may have varied between groups. It is possible that group exercise training will prove to be more effective, especially in studies conducted on geriatric individuals with various diseases. In this context, we think that if our study is replicated to investigate geriatric individuals, it may yield results that support our hypotheses. If our study had included evaluation parameters for balance and cardiovascular risk factors, this would have increased our knowledge.

## 5. Conclusion

This study shows that exercise training provides a significant increase in muscle strength, endurance, agility and flexibility parameters. The group or individual exercise preference of individuals does not have a negative effect on physical performance. Therefore, individuals should be included in exercise programmes without discrimination depending on their preferences.

## Author Contributions

Concept: T.G. (100%), Design: T.G. (100%), Supervision: T.G. (100%), Data collection and/or processing: T.G. (100%), Data analysis and/or interpretation: Y.Y. (100%), Literature search: T.G. (100%), Writing: T.G. (100%), Critical review: Y.Y. (100%), Submission and revision T.G. (%50) and Y.Y. (50%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

All authors have no conflicts of interest with respect to the data collected and procedures used within this study. Authors declare that they have no sponsor in the study design, collection, analysis, interpretation of data, writing of the manuscript, and decision to submit the manuscript for publication.

## Ethical Approval/Informed Consent

This study obtained the approval of the Hasan Kalyoncu University, Health Sciences Institute, Ethics Committee (Decision no: 2017/08).

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## ANALYSIS OF THE EFFECTIVENESS OF FIRST TRIMESTER NUCAL TRANSLUCENCE, FREE BETA-HUMAN CHORIONIC GONADOTROPIN, AND PREGNANCY-RELATED PLASMA PROTEIN-A IN PREDICTION OF PREGNANCY COMPLICATIONS

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**Abstract:** In this study, we aimed to investigate whether there was an association between fetal nuchal translucency (NT) and the serum markers plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin ( $\beta$ -hCG) measured by the first-trimester screening test, as well as birth weight and hypertension. 454 pregnant women who had undergone the first-trimester screening test for Down syndrome were included in the study. All measurements and values of NT, PAPP-A and  $\beta$ -hCG levels were performed between gestational weeks 11-14. Values of PAPP-A and  $\beta$ -hCG converted to multiples of the corrected median (MoM) were obtained using the PRISCA software package. Regarding the prediction of SGA infants, when the PAPP-A value  $<$  was 0.99MoM as a threshold, and when the free  $\beta$ -hCG value  $<$  was 0.69 MoM, SGA cases could be detected with a sensitivity of 83% and a specificity of 71.9%. Regarding the prediction of hypertension, at a threshold PAPP-A value of  $<$ 0.96 MoM, cases of hypertension could be detected with a sensitivity of 70% and a specificity of 74%. Maternal PAPP-A level in the first trimester was found to correlate with neonatal birth weight ( $\rho$ : 0.56 (95% CI 0.49-0.62),  $P < 0.0001$ ), while  $\beta$ -hCG showed a weak but significant correlation with birth weight ( $\rho$ : 0.137 (95% CI 0.045.) -0.227),  $P: 0.0036$ ). Low PAPP-A levels in the first trimester were an effective predictor of SGA babies and hypertension, while low  $\beta$ -hCG levels were an effective predictor of SGA babies. There is a significant correlation between first trimester PAPP-A and  $\beta$ -hCG levels and birth weight.

**Keywords:** First trimester, NT, PAPP-A,  $\beta$ -hCG, Birth weight, Preeclampsia

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### 1. Introduction

The perinatal mortality rate and the maternal mortality rate are reliable measures of the health status of a society. One of the tests used in prenatal follow-up is the first trimester Down syndrome screening test. Using fetal nuchal translucency (NT) measured at 11-13 6/7 weeks of gestation and levels of free beta-human chorionic gonadotropin (free  $\beta$ HCG) and pregnancy-associated plasma protein-A (PAPP-A) measured in maternal serum, trisomy 21 has been found with 90% accuracy and a false-positive rate of 5% (Kapustin et al., 2022). In the literature, there are associations between low maternal serum-free  $\beta$ HCG and PAPP-A levels in the first trimester and pregnancies with preeclampsia and fetal growth retardation. Increased nuchal thickness is also associated with poor prognosis (Hughes et al., 2019). In this study,

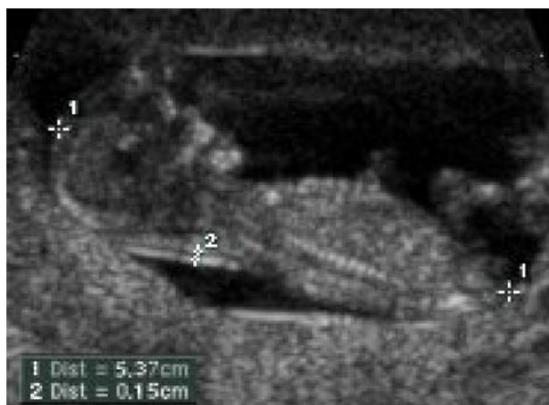
we aimed to identify pregnant women who might develop complications in the early stages by using NT measurement and biochemical markers as part of the first-trimester screening test for Down syndrome (Espid et al., 2021)

### 2. Materials and Methods

This study was designed retrospectively. 618 pregnant women were included in the study who underwent first-trimester screening at the Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, between January 2010 and April 2011. Each patient's 11-14-week screening was performed by a board-certified specialist using a Logic 400 Pro series ultrasound machine (General Electric, USA) via an abdominal transducer. Maternal age was expressed in days, months,



and years. The number of gravidities, parity, abortion, preterm birth, and live infants were questioned and also recorded. Weeks of gestation were calculated separately according to the mother's last menstrual period and the crown-rumb length of the fetus (CRL) (DASCAU et al., 2020). Biometric evaluation of the fetus; was done with CRL measurements (Figure 1).



**Figure 1.** The crown-rumb length of the fetus measurement.

CRL was performed in the neutral position by measuring the distance between the cranial and caudal ends of the fetal body in the sagittal plane. Then, the fetal profile was determined in the neutral position in the sagittal plane. Free  $\beta$ -hCG and PAPP-A were examined with the Immulite 2000 in our lab. Free  $\beta$ -hCG was determined by the chemiluminescence immunoassay method, and for PAPP-A, the enzyme-labelled chemiluminescence immunoassay method was used (Hoseini et al., 2020). PAPP-A and Free- $\beta$ -hCG values measured with the DPC kits are converted to the corrected multiple of median (MoM) values using the PRISCA software package. Preterm births are births that occurred before 37 weeks. Birth before 24 weeks gestation and below was defined

as abortion (Ziolkowska et al., 2019). A systolic blood pressure  $\geq 140$  mmHg and/or a diastolic blood pressure  $\geq 90$  mmHg after 20 weeks' gestation was considered pregnancy-induced hypertension. Babies with birth weights below the 3rd percentile were defined as intrauterine growth retardation (IUGR).

**2.1. Statistical Analysis**

Statistical significance was examined by analyzing the results with the Medcalc program. Linear regression analysis was performed by matching the value CRL with the week of pregnancy. Indicator values and pregnancy outcomes of cases in the groups with complications were compared using Fisher's exact test, chi-square test, and Student t-test. The effectiveness of maternal serum PAPP-A and Free- $\beta$ -hCG levels in predicting pregnancy complications was evaluated by Roc curve analysis. The relationship between marker levels and birth weight was determined by the Spearman correlation coefficient. The P value  $< 0.05$  was considered significant.

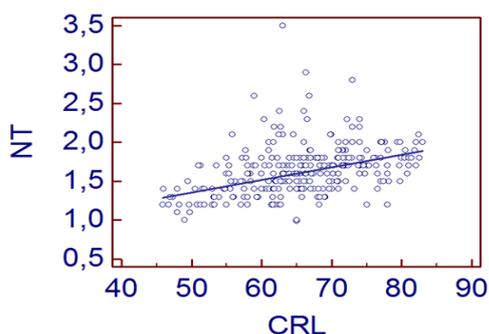
**3. Results**

Our study included 454 mothers who were examined in the perinatology clinic at 11-14 weeks of age and were found to have no major abnormalities. The fetal nuchal translucency (NT) percentiles calculated by weeks of gestation are present Table 1. In 618 cases (73.46%), the mothers called by phone for information. The mean age of the 454 patients was  $27.14 \pm 4.8$  years. The mean number of pregnancies was  $2.33 \pm 1.3$ ; 185 (40%) of the patients were nulliparous. During the study, the mean week of pregnancy was  $12.68 \pm 0.6$ . The mean value of the performed CRL measurements was  $65.7 \pm 8.2$  mm. Regression analysis of the relationship between NT and CRL showed significance, the regression equation NT:  $0.54 + 0.016 \times \text{CRL}$ ,  $r^2 = 0.18$ ,  $P < 0.001$ . This points first-degree correlation between CRL and NT (Figure 2).

**Table 1.** The fetal nuchal translucency (NT) percentiles calculated by weeks of gestation

GW	5. per.	10. per.	25. per.	50. per.	75. per.	90. per.	95. per.
11+6-12+6 (n:175)	1.2	1.2	1.3	1.49	1.6	1.8	2.1
13-13+6 (n:244)	1.2	1.3	1.5	1.67	1.8	2.0	2.13
14-14+1 (n:35)	1.4	1.4	1.62	1.78	2.0	2.0	2.07

GW= gestational weeks



**Figure 2.** The fetal nuchal translucency (NT) values are measured according to CRL data.

In the second trimester, an anomaly was found in three cases. Cardiac anomaly (CRL: 62.5mm, NT:2.4), spina bifida-hydrocephalus (CRL: 60mm, NT:1.6), hydrocephalus (CRL: 55mm, NT:1.2). The patient with cardiac anomaly was included in the high-risk group because the NT value was at the  $> 95$ th percentile. Delivery occurred in these cases. Twenty-eight cases (6.1%) have a NT value of  $\geq 2.1$  (95th percentile) and above. The pregnancy outcomes of these cases were compared with normal NT thickness cases ( $< 95$ th percentile), and there was no significance. (Table 2).

Data from those born small for gestational age were

compared with those born normal or large for gestational age. Mean PAPP-A and  $\beta$ -hCG MoM levels were significantly lower in SGA cases. The rate of hypertensive cases was also significantly higher in this group (Table 3). Hypertensive cases compared to normotensive cases, the

birth week and birth weight were significantly lower in the hypertensive cases. The mean maternal serum PAPP-A MoM level was significantly lower in hypertensive infants (Table 4).

**Table 2.** Comparison of cases with increased nuchal thickness and newborn outcomes of normal ones.

	NT $\geq$ 2.1mm (n:28)	NT<2.1mm (n:426)	P value
Anomaly(n)	1(%3.57)	2(%0.46)	0.44
SGA (n)	3(%10.7)	86(%20.18)	0.32
Hypertensive (n)	9(%32.14)	80(%18.77)	0.13
week of birth (Week $\pm$ SD)	37.6 $\pm$ 3.3	38.3 $\pm$ 2	0.088
Premature Birth (n)	5(%17.8)	45(%10.5)	0.37
Birth weight (Grams $\pm$ SD)	3192 $\pm$ 790	3089 $\pm$ 577	0.37
Birth by cesarean (n)	10(%35.7)	196(%46)	0.38

NT= fetal nuchal translucency, SGA= small for gestational age

**Table 3.** Demographic findings of SGA cases and comparison of first-trimester screening test results and newborn results of AGA-LGA cases.

	SGA (n:89)	AGA- LGA (n:365)	P value
Maternal Age (year $\pm$ SD)	27.5 $\pm$ 4.2	27 $\pm$ 4.94	0.37
Gestational week (week $\pm$ SD)	12.8 $\pm$ 0.67	12.65 $\pm$ 0.58	0.034
Mean NT (mm $\pm$ SD)	1.58 $\pm$ 0.27	1.61 $\pm$ 0.31	0.4
Mean PAPP-A (MoM $\pm$ SD)	0.82 $\pm$ 0.37	1.64 $\pm$ 0.97	<0.0001
Mean $\beta$ -hCG (MoM $\pm$ SD)	0.9 $\pm$ 0.7	1.31 $\pm$ 0.8	<0.0001
Birth week (week $\pm$ SD)	38.14 $\pm$ 1.96	38.35 $\pm$ 2.2	0.4
Birth weight (gram $\pm$ SD)	2422 $\pm$ 356	3263 $\pm$ 515	<0.0001
Hypertensive (n)	35(%39.3)	54(%14.7)	<0.0001

SGA= small for gestational age, AGA= appropriate for gestational age, LGA= large for gestational age, NT= fetal nuchal translucency, PAPP-A= plasma protein-a,  $\beta$ -hCG= free beta-human chorionic gonadotropin, MoM= multiples of the corrected median, SD= standard deviation.

**Table 4.** Comparison of demographic data and newborn outcomes of hypertensive cases with normotensives

	Hypertensive(n:89)	Normotensive(n:365)	P value
Maternal Age (year $\pm$ SD)	27.6 $\pm$ 4.68	27 $\pm$ 4.84	0.29
Gestational week (week $\pm$ SD)	12.96 $\pm$ 0.6	12.6 $\pm$ 0.59	<0.0001
Mean NT (mm $\pm$ Sd)	1.67 $\pm$ 0.32	1.59 $\pm$ 0.3	0.026
Mean PAPP-A (MoM $\pm$ SD)	0.99 $\pm$ 0.65	1.6 $\pm$ 0.96	<0.0001
Mean $\beta$ -hCG (MoM $\pm$ SD)	1.21 $\pm$ 0.92	1.23 $\pm$ 0.76	0.83
Birth week (week $\pm$ SD)	36.5 $\pm$ 3.1	38.7 $\pm$ 1.56	<0.0001
Birth Weight (gram $\pm$ SD)	2498 $\pm$ 635	3244 $\pm$ 477	<0.0001
SGA(n)	35(%39.3)	54(%14.79)	<0.0001

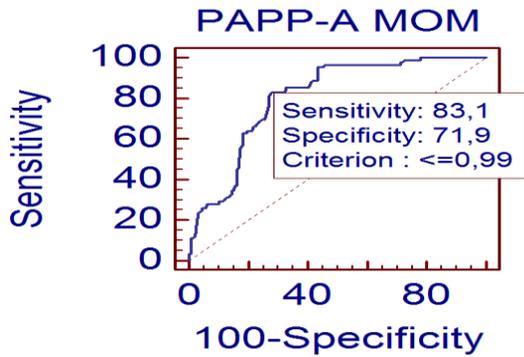
NT= fetal nuchal translucency, PAPP-A= plasma protein-a,  $\beta$ -hCG= free beta-human chorionic gonadotropin, SGA= small for gestational age, MoM= multiples of the corrected median, SD= standard deviation.

The effectiveness of the PAPP-A value in predicting SGA babies was evaluated with the Roc curve. When the cut-off value was < 0.99MoM, SGA cases could be detected with a sensitivity of 83% and a specificity of 71.9% (Figure 3). When the threshold < was 0.69 MoM, SGA cases could be detected with a sensitivity of 57% and a

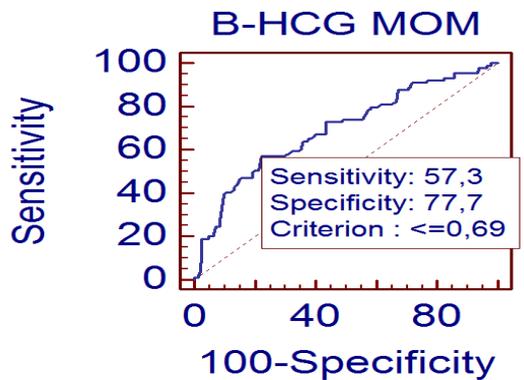
specificity of 77% (Figure 4).

The efficacy of PAPP-A level in predicting hypertension was evaluated by Roc curve. When the threshold < was 0.96 MoM, hypertensive cases could be detected with a sensitivity of 70% and a specificity of 74% (Figure 5). The efficiency of the free beta HCG value in predicting

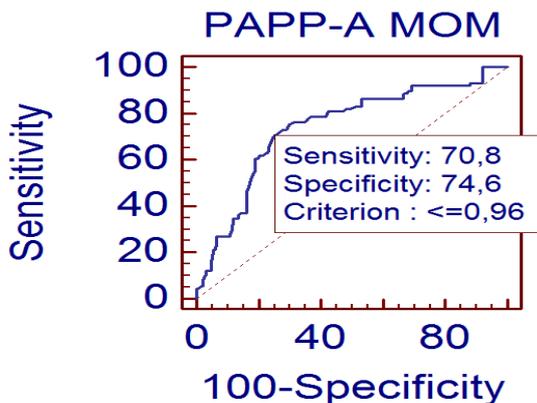
hypertension was evaluated with the Roc curve. When the threshold < was 0.68 MoM, hypertensive cases could be detected with a sensitivity of 42% and a specificity of 76% (Figure 6). Maternal PAPP-A correlates with neonatal birth weight in the first trimester ( $\rho$ : 0.56 (95% CI 0.49-0.62),  $P < 0.0001$ ), whereas free beta HCG showed a weak but significant correlation with birth weight ( $\rho$ : 0.137 (95% CI 0.045.) -0.227),  $P:0.0036$ ) (Figures 7 and 8).



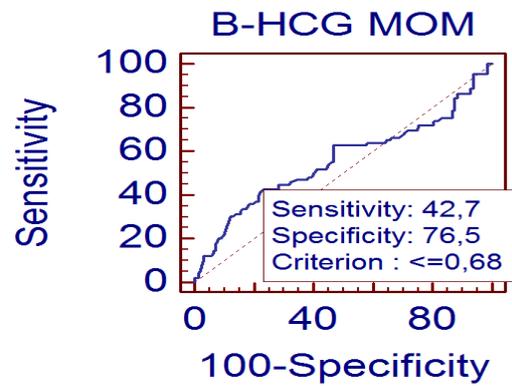
**Figure 3.** Roc curve evaluating the efficiency of maternal PAPP-A level in predicting SGA (AUC: 0.8, standard error: 0.022,  $P < 0.0001$ ). The efficiency of  $\beta$ -hCG value in predicting SGA babies was evaluated by Roc curve.



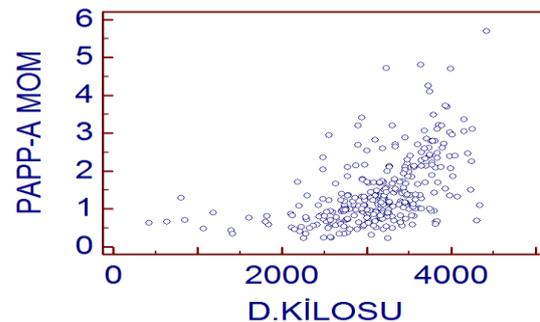
**Figure 4.** Roc curve evaluating the efficacy of maternal  $\beta$ -hCG level in predicting SGA (AUC: 0.69, standard error: 0.032,  $P < 0.0001$ ).



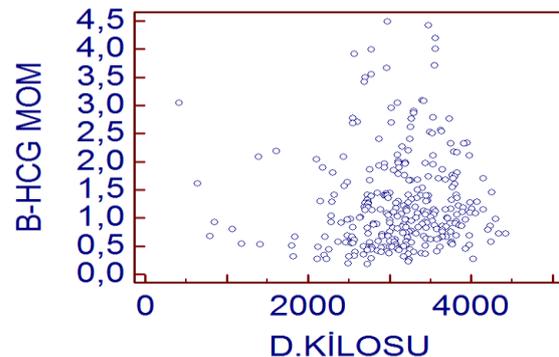
**Figure 5.** Roc curve evaluating the efficacy of maternal PAPP-A level in predicting hypertension (AUC: 0.74, standard error: 0.03,  $P < 0.0001$ ).



**Figure 6.** Roc curve evaluating the effectiveness of maternal  $\beta$ -hCG value in the prediction of hypertension (AUC: 0.55, Standard error: 0.038,  $P: 0.135$ ).



**Figure 7.** Maternal PAPP-A values and distribution of birth weights.



**Figure 8.** Distribution of maternal  $\beta$ -hCG values and birth weights

Roc curve analysis showed that low PAPP-A in the first trimester was a good predictor of SGA babies and hypertension (Boutin et al., 2018). It was found that a low free beta HCG value may be a good predictor of SGA babies. The efficacy of different biochemical marker values in relation to SGA birth weight or prediction of pregnancy-induced hypertension is shown in Tables 5 and 6.

**Table 5.** Efficiency of various values of biochemical markers in Prediction of SGA infants

	Sensitivity (%)	Specificity (%)	+LR	-LR
PAPP-A <0.37 MoM	11.24	99.16	13.45	0.9
<0.58 MoM	28.09	93.87	4.58	0.77
<0.99 MoM	83.15	71.87	2.96	0.23
β-hCG <0.37 MoM	19.1	94.99	3.81	0.85
<0.5 MoM	40.45	89.42	3.82	0.67
<0.69 MoM	57.3	77.72	2.57	0.55

PAPP-A= plasma protein-a, β-hCG= free beta-human chorionic gonadotropin, SGA= small for gestational age, MoM= multiples of the corrected median.

**Table 6.** Efficiency of various values of biochemical markers in the prediction of pregnancy-induced hypertension

	Sensitivity (%)	Specificity (%)	+LR	-LR
PAPP-A <0.37 MoM	5.62	97.77	2.51	0.97
<0.58 MoM	26.97	93.58	4.2	0.78
<0.96 MoM	70.79	74.58	2.78	0.39
β-hCG <0.37 MoM	13.48	93.58	2.1	0.92
<0.5 MoM	30.34	86.87	2.31	0.8
<68 MoM	42.7	76.54	1.82	0.75

PAPP-A= plasma protein-a, β-hCG= free beta-human chorionic gonadotropin, SGA= small for gestational age, MoM= multiples of the corrected median.

**4. Discussion**

Preeclampsia is associated with significant risks for the fetus and the mother. It is among the leading causes of perinatal mortality and morbidity (Livrinova et al., 2019). Recent studies have shown that NT and biochemical markers in the first trimester of Down syndrome

screening test; that it is associated with fetal weight and height at the time of delivery and pregnancy complications such as preterm birth, miscarriage, stillbirth, and pregnancy-related hypertension (Rathakrishnan 2022).

In our study, PAPP-A was found to be significantly lower in the hypertensive group, but there was no significant difference in free β-hCG between the hypertensive and normotensive groups. When 0.96 MOM was taken as the threshold for PAPP-A, the sensitivity was determined to be 70%. PAPP-A could be a parameter to predict the pregnant women who may develop hypertension (Kim et al., 2021).

In the literature, the study by Hendrix et al., compared the biochemical markers of the first-trimester screening test of 222 pregnant women with preeclampsia and 47,770 control cases. Similar to our study, a significantly lower PAPP-A level was found in the patient group, whereas there was no significant difference in free β-hCG between the two groups (Hendrix et al., 2019).

When the threshold for PAPP-A was 0.41 MOM, the detection rate of preeclampsia was 14.6%. In our study, cases born small for their gestational age were compared with those born normal or large. The mean PAPP-A level was significantly lower in SGA cases (Shah et al., 2020). The mean free β-hCG level was also low in this group, but the difference was not significant.

Dieste-Pérez et al. evaluated the relationship between first-trimester maternal serum free β-hCG and PAPP-A levels and pregnancy complications in 5297 pregnant women, 80 of whom were preeclamptic; PAPP-A and free β-hCG were significantly lower in the preeclamptic group than in the control group (Dieste-Pérez et al., 2022).

It was found that 10% of preeclamptic pregnant women had PAPP-A levels below the 5th percentile and 7% of them had free β-hCG levels below the 5th percentile (Hu et al., 2020) Hendrix et al. (2021) studied 8839 pregnant women, of whom 331 were preeclamptic. Similar to our study, the PAPP-A level was significantly lower in the preeclampsia group, whereas free β-hCG did not make a significant difference between the two groups.

The risk of preeclampsia has been found to be increased in pregnant women with a PAPP-A score below the 5th percentile. In a study of 878 pregnant women, it was shown that a PAPP-A value of ≤ 0.5 MoM (10th percentile) predicted 1/3 of women developing SGA (Livrinova et al., 2018). It was also found that the PAPP-A level is not an independent risk factor for preeclampsia. Bouariu et al included 2200 pregnant women in their study. PAPP-A levels were not only determined at standard weeks 10-14 but corrected PAPP-A MoM levels were also calculated (Bouariu et al., 2022)

Patients who developed preeclampsia, severe PIH, spontaneous pregnancy loss, or SGA were included in the case group and compared with the control group. When screening for poor pregnancy outcomes, the sensitivity was 38.7%, the specificity was 81.6%, and the PAPP-A threshold was ≤0.4 MoM.

The risk of fetal loss, preeclampsia, and SGA development was found to be twofold higher in women with low PAPP-A in early pregnancy. In the study involving 4390 pregnant women, it was found that the mean PAPP-A value measured at 11-13+6 weeks of gestation was significantly lower and the mean uterine artery value PI, measured at 22-24 weeks of gestation, was significantly higher in the group with preeclampsia and fetal growth retardation. It was found that there was no significant difference between free  $\beta$ -hCG MoM levels (Noël et al., 2021).

In another study, 289 pregnant women whose PAPP-A was considered low at first-trimester screening ( $< 0.4$  MoM). In these pregnant women, the predictive value of uterine artery Doppler performed at 18 and 22 weeks gestation was compared (Papastefanou et al., 2021). While uterine artery Doppler performed at 18 weeks gestation does not predict low birth weight, preeclampsia, or preterm birth, uterine artery Doppler performed at 22 weeks gestation has been shown to significantly predict it (Chandramohan et al., 2021). In our study, no significant difference was found between the pregnancy outcomes and neonatal findings of the cases with a NT measurement  $\geq 2.1$  (95th percentile) and above with the cases with normal NT thickness ( $< 95$ th percentile).

The first-trimester screening test is now performed in many centers. The use of the same test for preeclampsia screening provides a simple and cost-effective way to identify the population at risk for preeclampsia since the results are available at the end of the first trimester and close monitoring of pregnant women at risk and appropriate treatment will reduce fetomaternal complications. Investigating and explaining the association between pregnancy complications may also elucidate the etiology of some pregnancy complications.

## 5. Conclusion

In our study, it was found that the NT value increased with the week of pregnancy. It was found that the thickness of NT was not a determining factor for the outcome of pregnancy and neonatal findings. As a result of the study, it was found that a low PAPP-A value in the first trimester was effective in predicting SGA babies and hypertension; it was found that a low  $\beta$ -hCG value may be effective in predicting SGA babies. It was found that there was a significant correlation between first trimester PAPP-A and  $\beta$ -hCG levels and birth weight.

## Conflict of interest

The authors declared that there was no potential conflict of interest related to the research, authorship, and/or publication of this article.

## Ethical Approval/Informed Consent

The Clinical Research Ethics Committee of Haseki Research and Teaching Hospital approved this study

(approval number 47 and date 11/10/13), and all patients gave written informed consent to participate in all procedures associated with the study.

## Author Contributions

Concept: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Design: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Supervision: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Data collection and/or processing: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Data analysis and/or interpretation: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Literature search: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Writing: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Critical review: K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%), Submission and revision K.S. (20%), Z.B. (20%), M.B. (20%), M.S. (20%) and B.D. (20%). All authors reviewed and approved final version of the manuscript.

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## THE EFFECT OF DISTANCE EDUCATION ON THE PROFESSIONAL COMPETENCE AND ACADEMIC MOTIVATION OF MIDWIFERY STUDENTS: A QUALITATIVE STUDY

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**Abstract:** With the COVID-19 pandemic, the online teaching model has been used for the first time, and this has led to significant changes in departments such as midwifery, where theory and practice are combined. This study aimed to determine the effect of distance education on the professional competence and academic motivation of midwifery students. This study was carried out at a national university in Kastamonu, Türkiye between March and September 2021. The study adopted a qualitative design, and participants (n = 20) were the third-year midwifery students. Data were collected by conducting in-depth semi-structured face-to-face interviews using a pilot-tested interview guide. The interviews were conducted through webinars and the interviews were recorded. The interviews were held in a relaxed and calm environment where both researchers were present. The interviews were conducted with no more than two students in one day and the interview records were transcribed on the same day. Each interview lasted about 40 minutes. The researchers followed a systematic data analysis procedure which is an appropriate method of analysis when aiming to create knowledge based on experiences and meanings from cross-case analysis. The third-year midwifery students closest to graduating from the Faculty of Health Sciences participated in the study. With the individual and in-depth interviews, the responses of the midwifery students were subsumed under the following six themes: (1) 'a new learning experience, (2) reluctance to learn new information, (3) inadequacy in professional skills, (4) lack of self-confidence, (5) not being able to join a multidisciplinary team, (6) anxiety about future professional life'. It has been determined that distance education in midwifery education in Türkiye has many pleasing and facilitating features as well as obstructive and worrying aspects. In addition, online education negatively affected the psychomotor skill development of students. It is recommended that institutions providing education to midwifery students be aware of the difficulties experienced and follow different methods for psychomotor skills training.

**Keywords:** Online learning, Midwifery, Covid- 19, Motivation, Students

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### 1. Introduction

In December 2019, a novel coronavirus (SARS-CoV-2) emerged, headquartered in Wuhan, China, which led to an epidemic of the acute respiratory syndrome (COVID-19) in humans (Zhou et al., 2020). The virus has spread rapidly to many countries and was declared a pandemic by the World Health Organization (WHO) on March 11th, 2020, as it led to the death of more than 4000 people at the time (Park, 2020). This process has affected individuals and society in many ways (Karataş, 2020). Against the virus that threatens the world, national governments had to take radical measures such as social isolation, quarantine, martial law, and travel restrictions to control the spread of the epidemic (Bourouiba, 2020). The COVID-19 pandemic has affected all aspects of human activities globally, including education, research, sports, entertainment, transportation, worship, social gatherings, economics, and politics (Onyema et al., 2020). In all countries affected by the epidemic, a distance education system was used instead of face-to-face

education to slow down the epidemic with the support of the states (Yamamoto and Altun, 2020). In Türkiye, the Council of Higher Education has made decisions for switching the teaching process to distance education in the spring semester of 2020 to manage this process and the crisis (CHE, 2020). Distance education has also brought some difficulties in universities providing education in the field of health. Midwifery education is a process that integrates theoretical knowledge with training applied in laboratories and clinics. The International Confederation of Midwives (ICM) has developed a minimum educational standard for curricula. It has been emphasized that the midwifery curriculum should include at least 50% practical and 40% theoretical courses (ICM, 2013). During the pandemic, midwifery students have taken a break from clinical training, and clinical training is carried out in the form of simulations, case discussions, and assignments. The clinical setting also allows students to gain professional competence. Midwifery education aims to provide



students with the knowledge, skills, behaviors, and values necessary for professional competence. Students who graduate competently will make a significant contribution to the field of health, such as improving the standards of their profession, ensuring patient safety, and improving the quality of care (Lin et al., 2017). It was stated in the report of the Turkish Medical Association that constantly changing online health education since the beginning of the pandemic will create difficult-to-fill gaps, which will lead to inadequate professional responsibility in the future. In the study, it was observed that most of the students experienced anxiety about their professional experience (Turkish Medical Association, 2020).

Since students who do not have sufficient motivation are not ready to learn, the academic motivation of students is of importance in ensuring professional competence. Academic motivation is an internal process that drives activity aimed at achieving educational success. Studies have reported that motivation to learn is one of the decisive factors in the achievement of learning objectives (Puspitarini and Hanif, 2019), develops a positive attitude towards courses (Akandere et al., 2010), affects their academic achievement, and performance (Khalila, 2015). In addition, online students tend to participate less and have high attrition rates, motivation is a topic that instructional designers should consider when creating online classes (Kyewski and Krämer, 2018). Evaluating the impact of distance education on students' professional competence and academic motivation is important to assess whether midwifery education has achieved its goals and learning outcomes for the students. Also, it is thought that the results obtained from our study will provide guidance for planning and developing midwifery education in unexpected crisis periods. On the other hand, it is thought that it will contribute to revealing the needs for the use of digital tools in education for learning performance and motivation. There is no study on this subject in the literature. Therefore, it is believed that this study will contribute to the literature in this regard. Thus, this study aims to investigate the effect of distance education provided during the COVID-19 on the professional competence and academic motivation of midwifery students.

## 2. Materials and Methods

### 2.1. Research Design

This study was designed as descriptive phenomenological qualitative research. The general purpose of descriptive phenomenological qualitative research is to understand and define a specific topic in-depth based on the experiences of individuals (Creswell and Poth, 2016). The study aims to define, interpret, and understand the effect of distance education given during the COVID-19 pandemic on the professional competence, and academic motivation of midwifery students. The article was written in accordance with the manuscript

checklist (Booth et al., 2014).

### 2.2. Setting

The research was conducted with third grade midwifery students studying at the faculty of health sciences at a state university between March and September 2021. Since the midwifery department of the studied university is a new department, there were no senior students at the time of the research. The closest group of students to take up a position in the profession were third grade midwifery students. In addition, these students were at a disadvantage compared to freshman and sophomore students in terms of improving their clinical field practice skills. Because summer internships, which are effective in improving their knowledge and psychomotor skills, have also been interrupted due to the pandemic and it is difficult to make up for this until they graduate. Therefore, the study was conducted with third grade midwifery students.

### 2.3. Participants

The study was conducted with 20 midwifery students. In this study, maximum diversity sampling which is one of the purposive sampling methods was used. All students who met the inclusion criteria were invited to participate in the study. Those interested in the research were informed about the purpose and methods. The interviews were conducted with the participants who agreed to participate. The researchers have reached all the third-grade midwifery student participants. There was a total of 40 third grade midwifery students. Of the students, 20 refused to participate in the research. The reasons for students' refusal are the lack of time to devote and reluctance to participate. The research inclusion criteria were as follows: being a third-grade student of the midwifery department of the faculty of health sciences, not being a graduate from a health high school, and willing to participate in the research.

### 2.4. Data Collection Tools

#### 2.4.1. Introductory specifications form

Introductory features questionnaire consists of 7 questions to determine age, number of siblings, place of residence, means of accessing the distance education system, place of participation in distance education, and whether it has a room of its own during distance education and difficulty situations of students in the theoretical parts of the courses

#### 2.4.2. Structured open-ended questionnaire

The structured questionnaire was prepared based on the literature (Abbasi et al., 2020; Casafont et al; 2021; Kuliukas et al., 2021). It was consisted of 7 questions, all of which were open-ended, were asked by the researchers to evaluate the experiences of midwifery students in the distance education method during the COVID-19 pandemic process. The form was created to evaluate the effect of distance education process on educational life, the advantages and disadvantages of distance education, the effect of distance education on clinical learning skills and critical thinking skills, and the effect on learning motivation and academic achievement.

## 2.5. Data Collection

Data were collected through a quasi-structured interview guide with a pilot application (Table 1). Since the distance education experience is an individual experience for midwifery students, an in-depth interview method was preferred for collecting separate, multiple, and detailed data. By obtaining permission from the dean's office of the faculty, preliminary information about the research was sent to the students' e-mail addresses taken from the student information system. Those students who volunteered to participate in the study responded positively to the e-mails. After obtaining their consent, a mutually appropriate time and place for meeting with volunteer students were decided. The interviews were conducted through webinars and the interviews were recorded. The interviews were held in a relaxed and calm environment where both researchers were present. The interviews were conducted with no more than two students in one day and the interview records were transcribed on the same day. Each interview lasted about 40 minutes. The interviews were terminated after achieving data saturation, which yields no new data or code (Fusch and Ness, 2015).

**Table 1.** The interview guides

- 
1. Considering your face-to-face education and distance education process, what are the positive and negative sides of distance education?
  2. Do you think that the theoretical education given during distance education increases your professional knowledge?
  3. Do you think that the training provided during distance education improves your profession-specific skills compared to face-to-face education?
    - Ability to independently perform midwifery interventions and practices that will meet the needs of the patient
    - In terms of being able to apply the rationales and principles of medical treatment
    - In terms of coordinating care
    - In terms of multidisciplinary teamwork
  4. Considering your face-to-face education and distance education process, how did this process affect your critical thinking skills and your clinical decision-making ability?
  5. Has distance education changed your motivation for learning?
  6. Did the distance learning of the courses lead to a change in your interest in the courses?
  7. How have the online exams affected your academic success?
- 

## 2.6. Statistical Analysis

Four steps of qualitative systematic text condensation comprise the researchers' method for conducting a systematic examination of the data (Malterud, 2016). First, each recorded interview was transcribed

separately. Then, transcripts were read and studied several times. Then, each researcher independently analyzed each transcript to ensure reliability. The themes that group similar ideas were identified and respective codes were created. These codes were listed and grouped under the themes. In the study, the credibility method was used to ensure internal validity. The criteria of "long-term interaction" and "participant confirmation" were met within the scope of the credibility of the study. In-depth interviews were preferred for long-term interaction, and an average of 40 minutes of interviews was conducted with each participant. Immediately after the data collection, the researcher summarized the data collected to the five participants and asked the participants to express their opinions about their accuracy for participant confirmation, and it was confirmed that data reflect the opinions. To ensure external validity, the purposive sampling method was used in the study. To ensure the consistency of the research, the same interview form and the same webinar program were used during the interviews, and the same researchers participated in each interview.

The data collection tools used in the research, the raw data of the research, the encodings made at the analysis stage, and all other materials are stored for verifiability.

## 3. Results

### 3.1. Introductory Specifications

The average age of the participants was 22.56, the average number of siblings was 1.6, 70% was living in the city center, 80% was attending the courses at home, 85% was attending the courses via a computer, and 60% had their own study room. Most of the students (90%) participating in our study were found to have trouble in the theoretical parts of the courses.

### 3.2. Findings Regarding Student's Distance Education Experiences

Six themes were formed on the student's distance education experiences: (1) 'a new learning experience, (2) reluctance to learn new information, (3) inadequacy in professional skills, (4) lack of self-confidence, (5) not being able to join a multidisciplinary team, (6) anxiety about future professional life'.

Theme 1: A new learning experience

The participants stated that distance education negatively affects their personal lives and their adaptation to new learning methodologies.

*"I'm a visual learner, for example. I cannot learn due to the inappropriate materials used in online education." (P-10).*

*"Although I try to follow the courses on time, I have a hard time following the courses since the website of the distance education center does not refresh automatically and freezes." (P-1).*

*"When all students enter the system at the same time, the system collapses and we cannot log in the system, and then we are trying to connect again. It's not like face-to-face education..." (P-7).*

*"The second major problem was that most of our*

*instructors had no experience teaching online. It was a waste of time every day due to technical problems." (P-5).*

At the socioeconomic level, some students have stated that staying at home and studying at home have various benefits, such as spending more time with their families, saving money spent on transportation, and other expenses they spend.

*"Staying at home has saved me time and energy. I was losing too much time in traffic and on campus. Now I have more time and energy to spend on studying." (P-1).*

*"I was struggling financially when I was at school. Now I'm saving both money and time..." (P-15).*

Some of the participants stated that the opportunity to watch and listen to the lessons again and again with distance education has a positive effect on the learning process.

*"I like this system. I get more information. I have the opportunity to watch the videos again and again." (P-6).*

*"Although this sudden change in the teaching method is unexpected and unusual with all its difficulties, it also has advantages such as listening to the lectures at any time, and being able to repeat it as many times as we want..." (P-12).*

Some participants have noted that sitting in front of the screen for a long time negatively affects their learning process.

*"We look at the screen too much all day. My eyes cannot focus on the presentations. We are getting more tired than face-to-face education." (P-7).*

Some of the participants stated that the distance education system does not allow them to communicate fluently and verbally with teachers and peers.

*"In my opinion, non-verbal communication such as eye contact with the instructor is essential for an effective learning process. I feel its absence a lot in online education." (P-9).*

*"I miss the in-school group discussions. Now, even if the instructor asks a question, we are wasting time when the respondent turns on the microphone and says he/she didn't hear anything..." (P-14).*

Theme 2: Reluctance to learn new information

Some of the participants stated that they were evaluated on assignments and online exams during the COVID-19 pandemic, and during this process, the instructors were not fair, there was no fair assessment, so their interest, and desire to learn reduced.

*"Although I attend my classes on time, I get the same grades as people who have never attended the classes. And then I don't feel like working anymore..." (P-17).*

*"Everyone uploaded identical assignments to the system. There was no fair evaluation system, and I didn't get the grades I deserved." (P-6).*

Some participants stated that their motivation to learn decreased due to the lack of a suitable studying environment in distance learning.

*"Most of the time I couldn't find a suitable place to take my online courses at home and I believe I couldn't learn enough about the course topics since I couldn't follow the*

*lectures regularly." (P-11).*

*"We are four siblings. We all study online. There was a crowd of people at home, I honestly couldn't understand what I was learning." (P-2).*

*"I didn't have a private space at home to attend online classes. Life was going on at home. It was hard for me to concentrate due to all the noise around." (P-20).*

Most of the participants stated that their learning processes were interrupted due to technical reasons and decreased motivations.

*"I live in the district far from the city center, and slow Internet connection was among the frequent technical problems I encountered during the entire period. I had a really hard time following the courses, which depressed me." (P-18).*

*"I was experiencing Internet outages very often during daily online classes; although the problem was not me, it affected my learning." (P-9).*

Theme 3: Feeling inadequate in professional skills

The participants stated that distance education negatively affects the development of their professional skills.

*"Although videos are used for learning technical skills in clinical courses, we cannot master these skills without hands-on training." (P-20).*

*"It is not possible to give birth by imagining. I miss being in the same environment with women, I missed the clinics..." (P-8).*

*"I feel that my professional skills are lost compared to previous years. Honestly, I'm thinking about whether I'll be able to perform blood collection or perform an injection." (P-4).*

*"I'm sure no midwife has given birth by watching videos... We are watching childbirth videos for acquiring professional skills." (P-17).*

Theme 4: Lack of self-confidence

The participants stated that distance education negatively affects their professional self-confidence.

*"The inability to practice what I have learned theoretically at the clinic negatively affects my professional self-confidence." (P-15).*

*"I was practical and had self-confidence when practicing at the clinic. We had too much of a break. I'm feeling a little insecure right now." (P-8).*

Theme 5: Inability to participate in a multidisciplinary team

The participants stated that distance education negatively affects teamwork and the development of a versatile perspective.

*"Practicing with a team was always teaching us how to handle women in all aspects." (P-12).*

*"We were observing very well how care is coordinated, and how a team works in the clinic. Now all this is over with distance learning." (P-11).*

Theme 6: Anxiety about the future professional life

The participants stated that distance education and home quarantine cause concern for their future professional lives.

*"I'm worried that I couldn't learn anything for one year and that I will graduate as a midwife who knows nothing."(P-13).*

*"How long will the process take? It's unknown. Are we going to graduate on time, it's all an unknown?" (P-18).*

*"How are we going to be a midwife in the field when our clinical skills are so low? I'm getting bored the more I think about it." (P-20).*

#### **4. Discussion**

The COVID-19 pandemic has affected all areas of life and caused significant problems in educational life by leading to a rapid transition to the distance education system all over the world and in Türkiye. In this study, it was aimed to investigate the effect of distance education provided during the COVID-19 pandemic on the professional competence and academic motivation of midwifery students. The first theme that arises in the study is the change in the learning process. Students stated that the online system negatively affects their learning processes due to its incompatibility with learning methodologies, problems caused by the online system, inexperience of the instructors with the online system, staying in front of a screen for a long time, and the system's inability to provide an environment to allow them to communicate fluently and verbally with instructors and peers. Like our study, in the studies in the literature, it has been stated that distance education has negatively affected learning of midwifery students and created difficulties during covid-19 (Kuliukas et al., 2021; Topuz et al., 2021; Rasmussen et al., 2022). In our study, despite the negative effects of online education on learning, some of the students also emphasized that distance education has positive aspects. Students have stated the advantageous aspects of saving money and time, spending more time with families, and being able to repeat the information they have learned. In a study conducted with nursing students in the literature, students stated that the distance education provided due to COVID-19 saves time and energy (Suliman et al., 2021). Armstrong-Mensah et al. (2020) in their study with university and graduate students, stated that among the positive aspects of distance education, they do not have to spend money and time to go to campus. Although the studies were conducted with different student groups, similar results were obtained. This situation is important in terms of showing that the sudden and rapid transition to online education, which started with covid 19, leads to similar results for all students.

The second theme that arises in the study is the reluctance to learn. The students stated that they were reluctant to learn due to the lack of a fair assessment system, the lack of a suitable environment for studying, and technical problems hindering the learning processes. It is believed that this is caused by the inability of students to adapt to the sudden change in the education system in Türkiye. Similarly, have stated that it was difficult to get used to the online education they received

during the COVID-19 pandemic, that they were distracted during the lectures, and their motivation decreased (Aguilera-Hermida, 2020; Armstrong-Mensah, 2020; Topuz et al., 2021). In addition, it has been noted that online education negatively affects students' learning due to insufficient online education infrastructure, lack of instructor-student communication and interaction, reduced learning motivation, and lack of an objective assessment (Radu et al., 2020; Armstrong-Mensah et al., 2020). Michel et al. (2021) stated that in the study with nursing students, online learning decreased their knowledge levels, academic averages, student-teacher interaction and increased the homework load. In their study with nursing students, students stated that online learning decreased their knowledge levels, academic averages, student-teacher interaction and increased the homework load. The results of the study showed similar negative results on the learning assessment and interaction of online education.

In the study, the third theme is feeling inadequate in professional skills and the fourth theme is lack of self-confidence. Midwifery education consists of theoretical and practical sections that complement each other. Clinical training allows integrating theoretical knowledge and practice, allowing students to learn by doing and experiencing in a real environment. Together with online education, students have completed their clinical training in the form of case discussion, watching videos, and seminars. This also negatively affected the development of students' psychomotor skills in a clinical setting. In the literature, it was stated that online education is not effective in acquiring clinical and technical skills (Abbasi et al., 2020; Luyben et al., 2020; Kuliukas et al., 2021;), and it was also noted that online education negatively affects students' self-confidence and their preparation for the profession (Choi et al., 2020; Topuz et al., 2021; Kabir et al., 2022). The results of the study showed that, similar to our study, online education is not sufficient to develop clinical skills, professionalism and self-confidence.

One of the main conditions for providing qualified medical care is that team member's work in a team spirit using their communication skills in close cooperation with each other. The fifth theme in the study is the inability to join a multidisciplinary team. The students stated that distance education disrupted teamwork, they miss being a member of a team, and cannot evaluate female patients holistically. With the pandemic, students have been away from clinical learning environments and have been deprived of the opportunity to work with the patient with a holistic approach and other team cooperation. Studies have reported that shortening the duration of clinical practice from previously planned in medical education leads to a gradual decrease in the clinical competence of students and their ability to develop relationships with patients, staff, and clinical staff (Sani et al., 2020; Theoret and Ming, 2020). Although the sample group is different, the results in which team communication and teamwork are negatively

affected are similar in the departments where clinical education is integrated with theoretical education.

The sixth theme that arises in the study is the concern about future professional life. Students, who have experienced unprecedented "home quarantine" experience during the COVID-19 pandemic, have stated that they are worried that they will not be good midwives due to both being away from the clinic and due to the uncertainty of the pandemic. The thought that there is no time to gain professional competence and experience may influence this result in midwifery students, who are the closest group to start a professional life. This is due to the fact that students who are away from clinical learning environments due to the pandemic do not have enough time to develop their clinical skills as their grades increase. In one study, it was found that the pandemic process causes professional anxiety in nursing students (Ramos et al., 2020). In addition, in the previous studies, it was found that professional anxiety also increases as the students' year in school increases (Ceviz et al., 2020; Wang and Zhao, 2020).

### 5. Conclusion

Distance education affect midwifery student's perspective on professional competence and academic motivation. It was stated that most of the students were not satisfied with distance education, they could not practice in clinics, the quality and efficiency of the education decreased, and all of these caused negative feelings about their professional competence and academic motivation. These findings underscore the importance of assessing temporal changes in midwifery education and providing effective programs that enhance their professional competence and academic motivation.

### Author Contributions

Concept: S.S.Ç. (50%) and D.G. (50%), Design: S.S.Ç. (50%) and D.G. (50%), Supervision: S.S.Ç. (50%) and D.G. (50%), Data collection and/or processing: S.S.Ç. (50%) and D.G. (50%), Data analysis and/or interpretation: S.S.Ç. (50%) and D.G. (50%), Literature search: S.S.Ç. (50%) and D.G. (50%), Writing: S.S.Ç. (50%) and D.G. (50%), Critical review: S.S.Ç. (50%) and D.G. (50%), Submission and revision S.S.Ç. (50%) and D.G. (50%). All authors reviewed and approved final version of the manuscript.

### Conflict of Interest

The authors declared that there is no conflict of interest.

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### Ethical Approval/Informed Consent

This study was carried out in accordance with the

principles of the Declaration of Helsinki. The study procedures were approved by the Engineering and Health Sciences Scientific Research and Publication Ethics Committee of Kastamonu University (no: 2020 3/2, Date: 03.10.2021). Prior to inclusion in the study, oral and written informed consent was obtained from each participant and their anonymity was ensured.

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## SCIENTIFIC OUTPUTS OF HYPERTENSIVE RETINOPATHY

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**Abstract:** The goal of this work was to analyze the scientific output in the field of hypertensive retinopathy and its evolution globally and by major countries or regions, with a particular focus on the leading countries and international collaborations. In this bibliometric study, the keywords related to hypertensive retinopathy ("Hypertensive" and "Retinopathy" or "hypertensive retinopathy" or "hypertension" and "eye") were used in a search query in the Web of Science (WOS) search engine. The time span was set from 1970 to 2021. Only research articles were analyzed. Data pertaining to growth of publications, the most active countries and institutions, the most cited journals, and mapping of publications and keywords were analyzed from Web of Science Core Collection. A total of 152 articles included the study. The average number of citations of these articles was 14.69. The H-index of these articles was 22. The majority of the articles were from research areas of Ophthalmology (n=44; 28.94%), Cardiovascular System Cardiology (n=30; 19.73%) and General Internal Medicine (n=21; 13.81%). The leading countries on number of publishing articles was the United States of America (USA) (n=28; 18.42%), Türkiye (n=21; 13.81%) and China (n=20; 13.15%). Akdeniz University, Türkiye (n=5, 3.289%), Capital University of Medicine and China (n=5, 3.289%) were the most productive affiliations on hypertensive retinopathy publications. The number of publications on hypertensive retinopathy have been increasing in the past two decades. The most of the publications from the USA, especially in North America countries. Citation numbers are high but international collaboration needed around the globe this growing and concerning subject.

**Keywords:** Hypertension, Eye, Hypertensive retinopathy, Publications

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### 1. Introduction

Hypertension is a global public health topic that is becoming more prevalent. It is typically defined as persistent blood pressure (BP) of 140/90 mm Hg and, it is one of the leading causes of premature morbidity and mortality in the United States of America (USA) (Elliott, 2007). It is a silent killer that often goes unnoticed (Biswas et al., 2003). Hypertension is anticipated to increase in prevalence by 60% by 2025, affecting 1.56 billion people globally (Kearney et al., 2005). Furthermore, hypertension -related direct and indirect medical expenditures are expected to total \$118 billion in 2015 (Heidenreich et al., 2011).

The hypertensive disease spectrum includes patients with hypertensive emergencies with markedly elevated blood pressure and associated end-organ damage (kidney, heart, eye, blood vessels, etc.) as well as asymptomatic patients with minimally elevated pressures of unknown significance (Axon et al., 2015).

Hypertension is linked to a variety of vision-threatening eye diseases, such as retinal vascular occlusion, retinal macroaneurysm, and non-arteritic anterior ischemic optic neuropathy. Furthermore, hypertension has been

linked to the etiology of age-related macular degeneration and may increase the vision-threatening effects of diabetic retinopathy. Sustained hypertension manifests itself in the eye as hypertensive retinopathy and choroidopathy, indicating a systemic pathology. To ensure that hypertension patients are diagnosed and treated, close collaboration between ophthalmologists and general practitioners/physicians is required. In these patients, prompt management may lessen the risk of vision-threatening and systemic consequences (Fraser-Bell et al., 2017). In well-controlled hypertension, microvascular changes are reversible. Proper hypertension management can slow the progression of diabetic retinopathy and, as a result, visual loss caused by severe retinal diseases such as retinal vascular occlusion (artery and vein), retinal arteriolar emboli, macroaneurysm, ischemic optic neuropathy, and age-related macular degeneration (Resch et al., 2013). But hypertensive retinopathy symptoms are linked to other end-organ damage indications (such as left ventricular hypertrophy and renal impairment) and be a predictor of future clinical events like stroke, congestive heart failure, and cardiovascular mortality (Bhargava et al., 2012).



According to Erden and Bicakci (2012) the severity and duration of hypertension are connected to the increase in the incidence of hypertensive retinopathy. Other factors, in addition to essential and secondary hypertension, have a role in the development of hypertensive retinopathy. Hypertensive retinopathy is more common among Afro-Caribbeans than in Europeans, and it is more common in women than in men. Certain genotypes are linked to an increased incidence of hypertensive retinopathy, therefore genetic factors can play a role (Chatterjee et al., 2002). In Erden and Bicakci (2012) study, 66.3 % of the patients had hypertensive retinopathy. In another study, Kabedi et al. (2014) reported that hypertensive retinopathy affects 83.6 % of all hypertension patients, with chronic renal illness being the most important predictor of severe hypertensive retinopathy.

The goal of this work was to analyze the scientific output in the field of hypertensive retinopathy and its evolution globally and by major countries or regions, with a particular focus on the leading countries and international collaborations, using Web of Science (WOS) database.

## 2. Material and Methods

In this bibliometric study, to identify the most commonly used MeSH terms (keywords), preliminary individual studies were performed on several important hypertensive retinopathy researchers.

The keywords related to hypertensive retinopathy (“Hypertensive” and “Retinopathy” or “hypertensive retinopathy” or “hypertension” and “eye”) were used in a search query in the WOS search engine. The time span was set from 1970 to 2021. Data pertaining to growth of publications, the most active countries and institutions, the most cited journals, and mapping of publications and keywords were analyzed from Web of Science Core Collection [Social Sciences Citation Index (SSCI), Science Citation Index Expanded (SCIE), Emerging Sources Citation Index (ESCI), Arts & Humanities Citation Index (A&HCI or AHCI), Book Citation Index (BCI) and Conference Proceedings Citation Index (CPCI)] were searched in the current study.

Only materials designated as 'journal article' in the Wos database were included in the analysis; reviews, letters, and editorials were excluded. All guidelines were also excluded.

We used the search query and deduced from 277 different type of results to only the journal articles. The VOSviewer software was used to show the maps, which were evaluated to present several bibliometric indications.

As indications of publication impact, the Hirsch (H) index of the publishing journal was utilized.

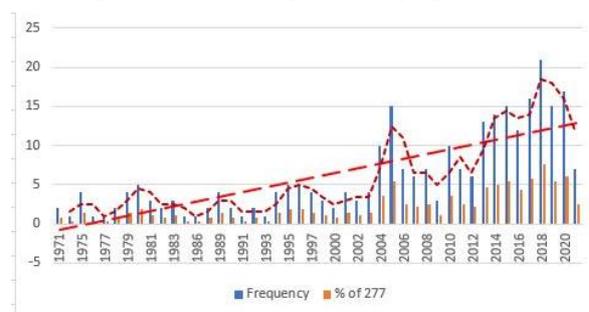
Mapping: To visualize collaborations and keywords, the VOSviewer 1.6.18 for Microsoft Windows systems program was used. From the bibliographic metadata of the articles we collected, we developed co-occurrence networks (e.g., nations, citations and keywords).

## 3. Results

### 3.1. Publications

There were a total of 277 journal articles retrieved, with an average of 10.67 citations per article. The mean H index was of the articles were found to be 25. Even if study search the publications in the period between 1970 and 2021, the first article was published in the year 1973. Distribution of publications according to the years showed in Figure 1.

Annual growth publications showed an increasing pattern during the study period. Retrieved publications were written in 6 different languages, mainly English (n=264; 94.24%) followed by French (n=6; 2.16%), German (n=5; 1.80%). The rest of them were published in Portuguese, Polish and Spanish languages.



**Figure 1.** Graphics of total publication by years between 1987 and 2021 (Dark red dashed line express the moving median, red line express the trend line).

### 3.2. Articles

We found a total of 152 articles after filtering the publications as articles. The average number of citations identified in these 152 articles was 14.69. These articles had an H-index of 22 and were referenced 2233 times in total.

The majority of the articles retrieved were from the fields of Ophthalmology (n=44; 28.94%), Cardiovascular System Cardiology (n=30; 19.73%), General Internal Medicine (n=21; 13.81%), Research Experimental Medicine (n=12; 7.89%), Pharmacology Pharmacy (n=10; 6.57%), and the rest were from other fields.

### 3.3. The Most Active Countries/Nations, Institutions, and Journals

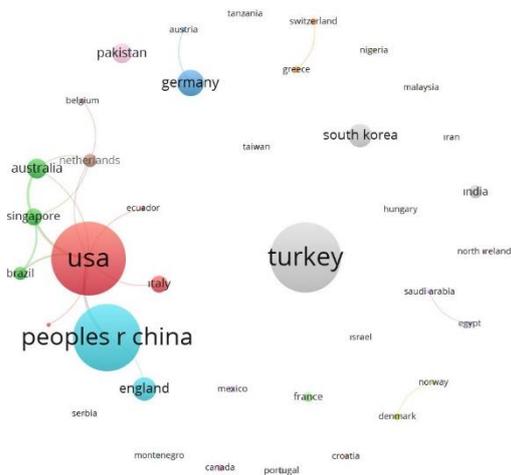
The leading country on number of publishing articles was the USA with (n=28; 18.42%), followed by Türkiye (n=21; 13.81%), China (n=20; 13.15%), Germany (n=10; 6.57%), England (n=9; 5.92%), South Korea (n=7; 4.60%) (Table 1). The active countries/regions represented all of the world regions: mainly Northern and Southern America, Asia and Europe. Other 42 countries which around the globe were (n=42; 35.52%). Akdeniz University, Türkiye (n=5, 3.289%), Capital University of Medicine, China (n=5, 3.289%) and National University of Singapore (n=5, 3.289%), the University of Melbourne, Australia (n=4, 3.289%) and the University of North Carolina (n=4, 3.289%) were the most productive affiliations on hypertensive retinopathy publications.

**Table1.** The list of the top five most active countries/regions in terms of the number of hypertensive retinopathy publications (n=152)

Ranking	Countries/Regions	n	%
1	The USA	28	18.421
2	Türkiye	21	13.816
3	Peoples Republic of China	20	13.158
4	Germany	10	6.579
5	England	9	5.921

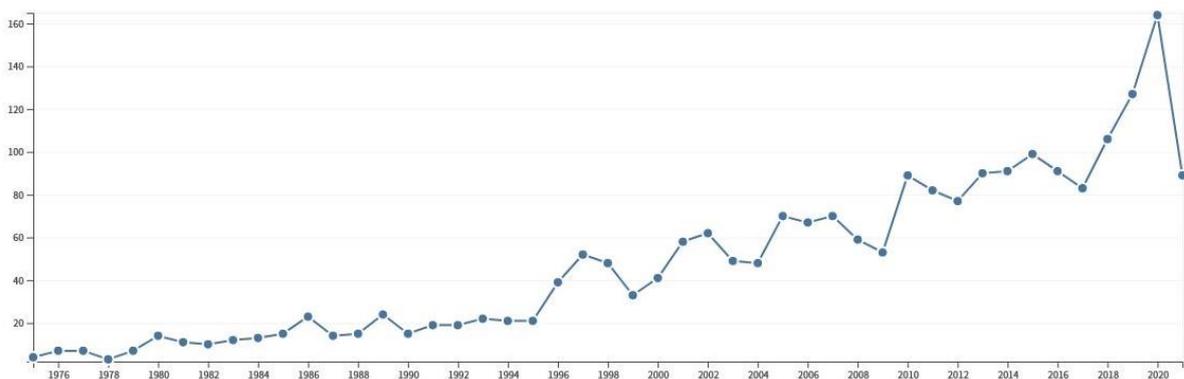
**3.4. International Collaboration Analysis**

Papers co-authored by authors from many countries were designated as "international collaborations." Figure 2 depicts a network map of international collaboration. Using the VOSviewer approach, an examination of international cooperation for active nations with at least one document revealed that there were clusters of international collaboration (Figure 2).



**Figure 2.** Network visualization map of co-authorship among nations with at least one hypertensive retinopathy article. Collaboration was seen with lines linking nations. Stronger cooperation were indicated by thicker lines. Countries with higher circle sizes or font sizes had more articles per capita.

Sum of Times Cited per Year



**Figure 3.** Growth of number of citations over the years (Line express the citing number).

**3.5. Citing Analysis**

The retrieved articles received a total number of citations of 2233, an average of 14.69 citations per article. The mean of H index of the retrieved articles on hypertensive retinopathy was 22. A total of 126 articles (82.89%) were mentioned at least once, while the remaining 26 articles (18.11%) were not cited at all. Annual citation growth on hypertensive retinopathy showed slow growth until 1996s followed by a dramatic increase in last decade. Figure 3 shows the annual growth of the citation on hypertensive retinopathy. The highest number of citations was seen in 2019 (total of 235 citation) (Table 2).

The lines that connect the countries show that they are working together. Stronger cooperation were indicated by thicker lines. Countries with a larger circle or text size had a higher level of international collaboration (Figure 4).

Citation was shown by the lines connecting the authors. Authors with a greater circle size or font size had a higher number of citations (Figure 5).

**3.6. Publishing Journals**

The top three cited articles on hypertensive retinopathy were published in Ophthalmology (245), New England Journal of Medicine (198 citations), British Journal of Ophthalmology (122 citations) journals.

**3.7. Keyword Analysis**

In articles, linked lines indicate occurrence relationships. Keywords denoted by a higher circle size or text size appeared in the articles more frequently (Figure 6) (Table 3).

**4. Discussion**

Uncontrolled hypertension has an impact on multiple systems, including the cardiovascular, renal, cerebrovascular, and retina. Target-organ damage is the term for the harm to these systems (Kabedi et al., 2014). Hypertension causes a cascade of pathophysiological changes that have a major impact on the retinal, choroidal, and optic nerve circulations.



maps after text mining operations. The distribution of publication numbers by authors and the change in publication numbers over time from 1970 to 2021 were also depicted using graphics. At the completion of the data analysis, the top referred articles in this field were displayed in Table 2.

There are many bibliometric analysis studies published in the field of medicine. In some of these studies, Scopus, Pubmed, and WOS datasets were the databases used in these studies. These databases allow bibliometric analysis and mapping or further visualization methods with different programs (Dindar et al., 2021; Köylüoğlu et al., 2021; Malakoutikhah et al., 2021; Özlü, 2022). The following are some of the reasons that WOS was chosen as a search reference: WOS is older than Scopus, which began in 2004, and studies on WOS can be found dating back to the 1970s. Older items can also be accessible, according to several research. The three WOS journal citation indexes, SCI-EXPANDED, SSCI, and Arts and Humanities Citation Index (A&HCI), are well-known and often utilized in research (Akyüz et al., 2022). There are two search methods in this WOS database: a basic search and an advanced search, which allows to craft complex and broad search queries to reach your aim with high validity. This database allows users to search for keywords in titles, abstracts, journal/author names, and affiliations (Web of Science, 2021). In this study, we sought to give a bibliometric overview of literature on hypertensive retinopathy. To accomplish this, we used the well-known WOS database, which has been used in previously published bibliometric studies (Gürler et al., 2021; Şahin et al., 2022).

The collaborations between countries were shown using the VosViewer program developed by the Centre for Science and Technology Studies (bibliometric department of Leiden University, Leiden, Netherlands) (VOSviewer, 2021). Vosviewer identifies each of the clusters in the literature network by selecting sample phrases from the cited literature. By analyzing the citation network and keywords in the time dimension to discover the development, flourishing, and collapse of certain research clusters, we may detect the research hotspots and trends of a given era (Gao et al., 2021).

According to our findings, the difference between co-authorship and citation figures showed that this subject is a global concern and needs to much more international collaboration studies (co-authorship).

Our study showed that publications on hypertensive retinopathy have been increasing and growing rapidly in the past decade. The high H-index number even with low number of publications is a strong indication of the importance of this subject to variety of clinicians and researchers. Top countries were USA and Türkiye. Growing numbers of the study on hypertensive retinopathy in these countries highly eye-catching and needs to be investigating.

## 5. Conclusion

Publications on hypertensive retinopathy have been increasing in the past two decades. The study showed that most of the publications on contributed by USA which has a growing number of publications especially in North America countries. The rest of the world contributed considerable share. This bibliometric analysis showed the growing numbers in the globe. Citation numbers are high but international collaboration needed around the globe this growing and concerning subject.

## Author Contributions

Concept: A.N.K. (50%) and B.A. (50%), Design: A.N.K. (50%) and B.A. (50%), Supervision: B.A. (100%), Data collection and/or processing: A.N.K. (50%) and B.A. (50%), Data analysis and/or interpretation: A.N.K. (50%) and B.A. (50%), Literature search: A.N.K. (50%) and B.A. (50%), Writing: A.N.K. (100%), Critical review: A.N.K. (50%) and B.A. (50%), Submission and revision A.N.K. (50%) and B.A. (50%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest.

## Ethical Approval/Informed Consent

As the study is not an animal or human study, ethical approval was not required.

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## EVALUATION OF COGNITIVE FUNCTIONS IN SCHIZOPHRENIC PATIENTS WITH THE MONTREAL COGNITIVE ASSESSMENT SCALE AND MINI-MENTAL STATE EXAMINATION

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**Abstract:** Schizophrenia is a complex neurodevelopmental disorder. Cognitive deficit is the central feature of the neurodevelopmental disorders. Cognitive impairment is related to social, functional, and clinical symptoms. The aim of this study was to investigate the clinical usability of the Montreal Cognitive Assessment (MoCA) as a screening instrument for cognitive impairment in schizophrenic patients alone, and in correlation with the Mini-Mental State Examination (MMSE). This clinical study included 31 patients diagnosed with schizophrenia. Patients were selected from Psychiatry Clinic. For the assessment of cognitive impairment, we used Montreal Cognitive Assessment Scale (MoCA) and Mini-Mental State Examination (MMSE). Of the total number of patients (n=31), 6/31 (19.4 %) were males and 25/31 (80.6 %) were females; the mean duration of the disorder was 23.5 years (SD=6.69). Seventeen patients (54.8%) of those who were on MMSE scale had a score greater or equal to 24 (normal range) and the MoCA scale had a normal score (>21), while 11 (35.5%) patients reported moderate to severe cognitive impairment. Analysis of the correlation coefficient between the total score of MoCA and the MMSE scale indicates a statistically significant positive correlation with Spearman rho=0.81 and P<0.001. Our findings provide preliminary evidence that the MoCA scale performs well in screening mild and moderate cognitive impairments of schizophrenia patients in outpatient clinics and is more sensitive than MMSE.

**Keywords:** Schizophrenia, Cognitive impairment, MoCA, MMSE

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### 1. Introduction

Schizophrenia is a complex neurodevelopmental disorder and cognitive deficits are considered to be central to the pathophysiology. A growing number of studies show that 75% of schizophrenia patients have a significant cognitive impairment (O'Carroll, 2000; Fisekovic et al., 2012).

Neurodevelopmental model of schizophrenia suggests that cognitive deficits often precede symptoms of psychosis, are stable over time and are only affected by pharmacologic treatment for symptoms (Kurtz MM et al., 2009). Some studies confirmed that cognitive deficits have been shown to correlate with social and functional symptoms (Green et al., 2000; Fisekovic et al., 2012). Cognitive impairment seems to be more related to negative symptoms. For these reasons, cognitive dysfunction is thought to be a primary disorder and also independent of the other psychopathological symptoms (Soygür et al., 2007).

Cognitive functions are affected, particularly executive functions, attention, perceptual/motor processing, vigilance, verbal learning and memory, verbal and spatial working memory and verbal fluency (Fisekovic et al., 2012; Preda et al., 2011). Cognitive dysfunction may

indicate the interplay in the fields including the cortico-cerebellar-thalamic-cortical loops. While memory dysfunctions indicate the loss of temporal-hippocampal functions, executive dysfunctions are associated with the prefrontal cortex in schizophrenia (Soygür et al., 2007). The Prefrontal cortex integrates information directly from the limbic regions, neocortex, brainstem and hypothalamus and indirectly via the thalamus from all regions of the brain. Dysfunctional changes in this part of central nervous system cause disorders of consciousness, planning, concentration, speech, vision, emotion and affect (Lencz et al., 2006).

Schizophrenia is a chronic psychiatric disorder that leads to a high degree of impairment in social, occupational and educational functioning. Over the last two decades, abundant evidence has shown that even first-episode schizophrenia patients -yet not exposed to the effects of antipsychotic drugs- show 1-2 standard deviation impairments on a variety of measures of neurocognitive function including language, attention, episodic and working memory and problem-solving relative to healthy matched controls (Green et al., 2000; Kurtz et al. 2009; Fisekovic et al., 2012;). Reviews suggest that neurocognitive impairments explain 20-60% of the



variance in studies of interpersonal problem-solving abilities, social and occupational functioning and measures of skill acquisition in rehabilitation programs (Fisekovic et al., 2012; Green et al., 2000). Studies suggest that cognitive functioning is the best single predictor of the need for patients to be admitted to the clinic with patients who are examined as well as an emergency case, even better than the diagnosis which is set. Cognitive evaluation facilitates the differential diagnosis and also has significant clinical relevance (Green et al., 2000; Nasreddine et al., 2005; Lencz et al., 2006).

Because the MoCA assesses multiple cognitive domains, it may be a practical cognitive screening tool for psychiatric disorders. In the present study, we compared the Montreal Cognitive Assessment (MoCA), a useful, validated, brief instrument for the detection of mild cognitive impairment (MCI) with the Mini-Mental State Examination (MMSE) as a screening test for cognitive deficits in schizophrenia.

The first aim of the current study was to evaluate and compare the degree of cognitive dysfunction in patients diagnosed with schizophrenia using MoCA and the MMSE alone. The second aim of the study was to compare the psychometric properties and the degree of sensitivity of these two instruments. The third aim of this study was to compare the characteristics of applications that may be appropriate for the clinical utility of these tools.

## 2. Methods

### 2.1. Subjects

A group of thirty-one inpatients meeting DSM-IV (APA, 1994) criteria for Schizophrenia as determined by the Structured Clinical Interview for DSM-IV was recruited for the study at the Psychiatry Clinic. Exclusion criteria for patients included auditory or visual impairment, evidence of mental retardation as indicated by history, presence of history of any neurological disorders, traumatic brain injury with a sustained loss of consciousness and/or criteria met for concurrent substance abuse or dependence. The study was conducted as a descriptive controlled study. All patients were treated with atypical antipsychotics (risperidone, olanzapine, quetiapine and clozapine). All study procedures met with institutional ethical approval. Patients who agreed to take part in the study gave written informed consent. Demographic and clinical characteristics of the sample are presented in Table 1.

### 2.2. Instruments

We used Montreal Cognitive Assessment Test (MoCA) and Mini Mental State Examination (MMSE) for the assessment of cognitive impairments. Neurocognitive testing and scoring were administered by the same member of research team.

The Montreal Cognitive Assessment Test Turkish version (MoCA-TR) as it appears on the official website ([www.mocatest.org](http://www.mocatest.org)) was translated, and it contained certain cultural and linguistic changes from the original

version presented in 2009 by Selekler et al. (2010) and it has been validated in AD in Türkiye. The MoCA is more sensitive to subtle cognitive deficits in patients with Parkinson's disease compared with the conventional MMSE. The MoCA is a 10-min test that briefly evaluates the following seven cognitive domains on one page: visuospatial and executive functions: alternating trail making (1 point), cube copying (1 point), clock drawing (3 points), naming: (lion, rhinoceros, camel) (3 points), attention: forward and backward digit span (2 points), tapping to the letter A (1 point), subtraction from 100 by 7s (1 point); language: sentence repetition (2 points), letter fluency (1 point); abstraction: similarities between train and bicycle, watch and ruler (2 points); memory: 5-min delayed verbal recall of five words (5 points); and orientation to time and place (6 points). As two MoCA tasks (subtracting by 7s and orientation questions) overlapped with identical items on the MMSE, these items were tested only once. To correct for educational effects found in the original study, an additional 1 point was given to subjects with 12 or fewer years of education, following the author's instructions and the procedure adopted in previous studies. The scores on the MoCA-TR ranged from 0 to 30, with higher scores indicating better cognition and scores below 21 indicating cognitive impairment in the Turkish AD population (Selekler et al., 2010, Ozdilek et al., 2013).

**Table 1.** Sociodemographic and clinical characteristics

Variables	Descriptive
	Patients (n=31)
Age (Mean±SD)	41.00±10,57 (Min: 20, Max: 67)
Sex (n, %)	
Male	6 (19,4)
Female	25 (80.6)
Education (year), (Mean±SD)	9.03±3.98
Disease duration (year), (Mean±SD)	9.86±8.22
Age at onset of disease (Mean±SD)	31.09±8.42 (Min: 17, Max: 57)

The Mini Mental State Examination Turkish version (MMSE-TR), which has been validated in the Turkish population, includes items for orientation to time and place (10 points), registration (immediate verbal recall of three words), serial subtraction (from 100 by 7s), memory (delayed verbal recall of three words), naming (pencil, watch), language (repeat a phrase, follow written instruction, follow a 3-step command, write a sentence), and drawing (copy a line drawing of overlapping pentagons). The scores ranged from 0 to 30, with higher scores indicating better cognition, and scores below 24 indicating cognitive impairment (Gungen et al., 2002). The MMSE is the most commonly used screening tool to

detect cognitive dysfunction in patients diagnosed with schizophrenia.

We used Positive and Negative Syndrome Scale (PANSS) for the assessment of positive, and negative symptoms and general psychopathology (Kay et al., 1986). Positive and Negative Syndrome Scale (PANSS), which has been validated in schizophrenia in Türkiye (Kostakoğlu et al., 1999), includes 7 items for positive symptoms, 7 items for negative symptoms and 16 items for the assessment of general psychopathology.

**2.3. Statistical Analyses**

To test the statistical significance of observed differences between groups used a one-way analysis of variance (ANOVA), while testing the interconnection of the observed variables used Spearman’s correlation coefficient, with p value of under 0.05 is considered to be statistically significant.

**3. Results**

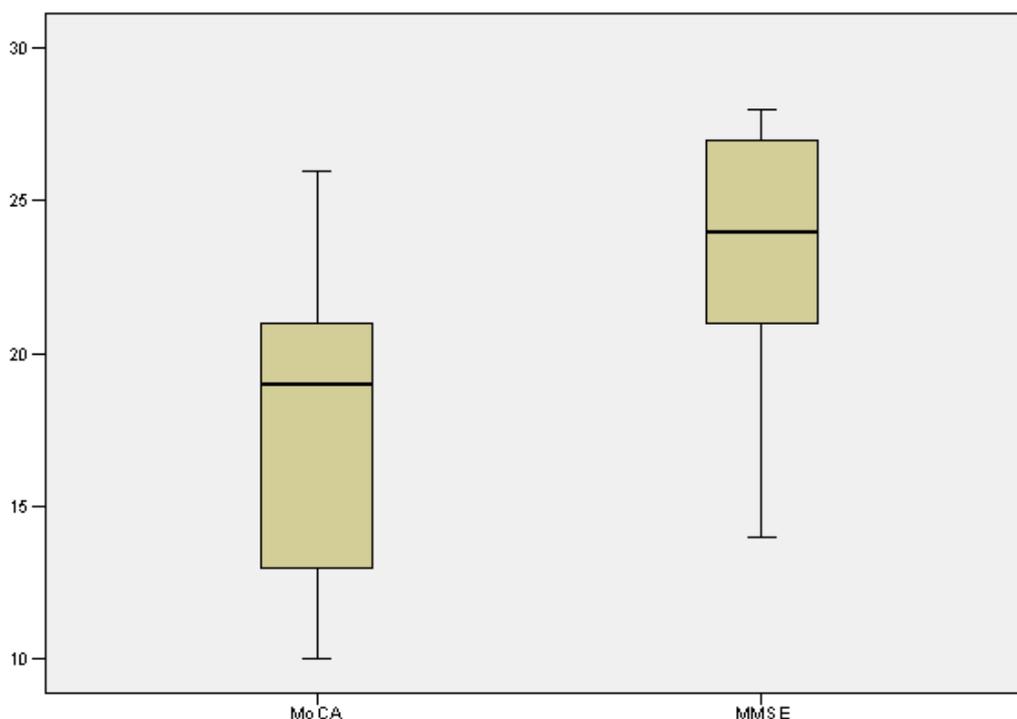
Thirty-one patients diagnosed with schizophrenia were included in this current study. Mean age of disease onset was 31.09±8.42 (Mean±SD) and the age of onset of

disease ranged from 17-57 years. This result may have resulted from the majority of the patients in the sample were women. Demographic data (Table 1) showed that duration of the disorder was 9.86 ± 8.22 (Mean ± SD) in years. As shown in Table 2, mean score on the MoCA scale was 17.54±4.80, corresponding to moderate to severe cognitive impairment, while mean score on the MMSE was 23.48±3.65, corresponding to the result of mild cognitive impairment. Mean duration of test time on MoCA scale was 10.19±3.74 in accordance with general population. Figure 1 shows the MoCA and MMSE scale scores of patients.

17 patients (54.8%) of those who were on MMSE scale had a score greater or equal to 24 (normal range) and the MoCA scale had a normal score (>21), while 11 (35.5%) patients reported moderate to severe cognitive impairment (Table 3). MoCA scores did not significantly correlate with PANSS total or general, positive and negative symptoms subscores. Analysis of the correlation coefficient between the total score of MoCA and MMSE scale indicates a statistically significant positive correlation with Spearman rho=0.81 and P<0.001.

**Table 2.** Clinical scale scores of the patients (n=31)

Variables			
MoCA score (Mean±SD)	MoCA test period (Mean±SD)	MMSE score (Mean±SD)	PANNS score (Mean±SD)
17.54±4.80	10.19±3.74	23.48±3.65	99.20±22.48



**Figure 1.** Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) scores of patients

**Table 3.** Comparison of cognitive impairment according to scales

	Patients (n=31)	Statistics	
		X <sup>2</sup>	P
Cognitive impairment according to the MoCA scale			
< 21	20 (64.5)		
≥ 21	11 (35.5)	8,95	P<0.003*
Cognitive impairment according to the MMSE scale			
< 24	14 (45.2)		
≥ 24	17 (54.8)		

#### 4. Discussion

The clinical value of a screening tool is directly related to either considering cognitive impairment a key aspect of schizophrenic psychopathology and, according to the proposed DSM-V revisions, recommending it as one key dimension to be measured in all patients with a psychotic disorder, or including cognitive deficit as one of the diagnostic criteria for psychoses as suggested by some authors (Lewis, 2004; Keefe et al., 2007; Smith, et al., 2007). The practical utility of the administered tests should not be forgotten when conducting a neuropsychological assessment, and since there is a large number of psychiatric patients (accounting for around 2% of the general population) who require diagnosis, there is a growing need for cost-effective and highly efficient diagnostic tools (Green et al., 2000; Preda et al., 2011; Fisekovic et al., 2012).

In this regard the present study investigates the clinical usability of the Montreal Cognitive Assessment (MoCA) as a screening tool for cognitive impairment in schizophrenic patients alone, and in correlation with the Mini-Mental State Examination (MMSE). Previous studies have shown that the Montreal Cognitive Assessment (MoCA) takes approximately 15 minutes to administer, compared to a mean of around 75 minutes for the administration of a full neuropsychological battery and it has good validity and reliability (Selekler et al., 2010; Ozdilek et al., 2013).

In this study all patients (n=31) were applied MoCA and MMSE scales. The mean MoCA score was consistent with moderate to severe cognitive impairment. Mean score on the MoCA scale was 17.54±4.80 (≥ 21 normal range in Turkish population), corresponding to moderate to severe cognitive impairment, while scores on MMSE scale was 23.48±3.65 (≥ 24 normal range in Turkish population), which is normal to mild cognitive impairment (MCI) cognition score range. These findings are consistent with the results of Preda et al. (2011) for both MoCA and MMSE scales which state the mean MoCA score was 20±4.7 and the mean MMSE score was 27.2±2. According to the research of Preda et al. (2011) 14 patients (77.8%) of those who on the MMSE scale had a score ≥ 26 (normal range) also on MoCA scale had a normal score (> 24), while in 2 or 22.2% of patients was reported moderate to severe cognitive disability. These findings are in contrast with the findings of Preda et al. (2011), where twenty-one patients (84%) of those who

scored ≥ 26 (normal range) on the MMSE had a MoCA score < 26 (MCI range). Twenty-three (85%) of those who scored ≥ 24 on the MMSE (MCI range) had a MoCA score < 24 (moderate to severe cognitive impairment).

MoCA scores did not significantly correlate with any PANSS total or subscores. This result supports the view that cognitive deficits might be an independent schizophrenia symptoms domain.

Analysis of the correlation coefficient between the total score of MoCA and the MMSE scale indicates a statistically significant positive correlation with Pearson Spearman (rho=0.81 and P<0.001) (P<0.05), but this study did not analyze individual subscales as stated in research by Preda et al. (2011) and it is difficult to compare with their findings. The MoCA test validation study has shown the MoCA to be a promising tool for detecting Mild Cognitive Impairment (MCI) compared with the well-known Mini-Mental State Examination (MMSE).

During the past few years, an approach that ensures the construct validity of cognitive assessment of various researchers has suggested a recent exploration of the proposal to apply a generalized deficit in order to determine whether multiple performance deficits in schizophrenia are the result of common underlying processes (Lewis, 2004; Preda et al., 2011; Fisekovic et al., 2012).

#### 5. Conclusion

There is considerable difficulty in comparison of reliably assessment scales. To date, there are no validated brief screening instruments for the diagnosis and assessment of severity of schizophrenia cognitive deficits. The MoCA has higher sensitivity and specificity to detect cognitive impairment than the MMSE. The MoCA is an easy to administer useful screening tool for the assessment of cognitive deficits associated with schizophrenia.

The results of the present study also suggest that the MoCA might be a sensitive test for the assessment of some of the core cognitive deficits in schizophrenia such as speeded attention and executive functioning. Further studies validating MoCA against standard neurocognitive testing batteries are recommended. However, it had been established that the MMSE is not well suited for mild cognitive impairment, which raises the question of whether it is an adequate standard to compare performance with the MoCA.

## Author Contributions

All task made by S.Z. (100%); Concept, Design, Supervision, Data collection and/or processing, Data analysis and/or interpretation, Literature search, Writing, Critical review, Submission and revision. The author reviewed and approved final version of the manuscript.

## Conflict of Interest

The author declared that there is no conflict of interest.

## Ethical Approval/Informed Consent

Our research was carried out in accordance with the Declaration of Helsinki of the World Medical Association. Written consent was obtained from the patients who participated in this study. The dignity of respondent was secured by giving right to reject or discontinue from the research study at any time. The respondent's anonymity was maintained during data collection by giving code number instead of name, and confidentiality of the information was maintained by not disclosing the information to others.

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## CURRENT STATUS OF THALASSEMIA MINOR STUDIES

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**Abstract:** Thalassemia minor carriage is one of the most common causes of anemia in Mediterranean countries. This study aimed to investigate the publications in scientific journals on thalassemia minor, which is an important health problem, especially in Mediterranean countries. The goal of this study was to retrieve data from journals that were indexed in the Web of Science (WoS; Thomson Reuters, New York, NY, USA) database. The WOS Core Collection was used to retrieve comprehensive bibliometric data. Keywords related to "beta-thalassemia carrier," or "beta-thalassemia trait," thalassemia minor" or "heterozygous beta-thalassemia" were used in a search query in the WOS search engine. The time frame was specified since 10 March 2022. The analysis included information on the increase of publications, the most active countries and institutions, the most cited journals, and the mapping of publications and keywords. A total of 8618 publications were retrieved. The first article was published in 1970, and the period between 1970 and 2021 was searched. The maximum number of publications was published in the year 2021. The number of publications had increased since 2009. Most of the publications were articles (61.696 %). The publications were from more than 100 disciplines and most of them were from Hematology (49.176%). The publications were from 274 different countries. Most of the publications were from the USA, Italy, and Greece. The USA is at the top of the list in the number of publications. But with active funding and support from the governments especially the Mediterranean countries, which have a higher prevalence of thalassemia minor, the productivity of scientific research should be increased.

**Keywords:** Thalassemia minor, Publication, Bibliometric analyses

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### 1. Introduction

The term thalassemia comes from the Greek words thalassa (sea) and haima (blood) (Galanello and Origa, 2010). Anemia is a common disease that affects people all over the world. Nutritional anemia is the most common type of anemia in children. However, thalassemia minor carriage is one of the most common causes of anemia in Türkiye and Mediterranean countries (Kabasakal et al., 2018; Arslan Maden et al., 2020). Thalassemia major, thalassemia intermedia, and thalassemia minor are the three main types. Thalassemia minor is also known as "beta-thalassemia carrier," "beta-thalassemia trait," or "heterozygous beta-thalassemia." (Galanello and Origa, 2010).

Beta-thalassemia's are a set of inherited blood illnesses marked by abnormalities in the synthesis of hemoglobin's beta chains, resulting in phenotypes ranging from severe anemia to clinically asymptomatic people. The global yearly incidence of symptomatic persons is estimated to be 1 in 100,000, with 1 in 10,000 people living in the European Union (Galanello and Origa, 2010; Arslan Maden et al., 2020). Thalassemia minor has traditionally been more prevalent in specific parts of the world, such as the Mediterranean, the Middle East, and Southeast Asia (Kattamis et al., 2020).

Because of being a benign hematological disease of the thalassemia trait, diagnosis can be easily missed in hospital admissions of patients who have not been diagnosed yet. Thalassemia trait is a disease which can most often intermingle with iron deficiency. Various formulas have been developed in clinical practice to differentiate or not miss the diagnosis of thalassemia trait (Merdin, 2018).

Testing for Hb electrophoresis immediately in those with high ferritin levels and after iron treatment in those with low levels will enable early detection of thalassemia carriers and make genetic counselling possible (Oğuz et al., 2009). More than 40 mathematical indices have been proposed in the hematological literature to differentiate thalassemia trait from iron deficiency anemia. None of these discriminant indices is 100% sensitive and specific, and also the ordering of discriminant indices is not consistent. In a meta-analysis with the most used discriminant indices, it was found that the M/H (microcytic and hypochromic percent) ratio outperformed all other discriminant indices in distinguishing between iron deficiency anemia and thalassemia trait. While the sensitivity and specificity of the M/H ratio are not high enough to make a definitive diagnosis, it is certainly valuable for identifying patients with microcytic RBC for whom diagnostic testing is



indicated to confirm thalassemia (Hoffmann et al., 2015). However, discriminant indices that are superior in one study may perform worse in another study.

Additional serum iron, total iron binding capacity and ferritin levels should be checked in patients who are thought to be thalassemia trait with Mentzer Index values calculated from the MCV/RBC ratio. In addition to all these basic blood samples, laboratory tests such as hemoglobin analysis (HbA 2 and abnormal Hb) and DNA analysis are key parameters for differentiating thalassemia and iron deficiency anemia (Hoffmann et al., 2015). Newborn and prenatal screening, prenatal diagnosis and counselling are keys to early detection and prevention of thalassemia (Farzana et al., 2015).

This study aimed to investigate, identify, and characterize the publications in scientific journals on thalassemia minor, which is an important health problem, especially in Mediterranean countries.

## 2. Material and Methods

The goal of this study was to retrieve data from journals that were indexed in the Web of Science (WoS; Thomson Reuters, New York, NY, USA) database. The WOS Core Collection was used to retrieve comprehensive bibliometric data and the SCI-EXPANDED, SSCI, A & HCl, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI indexes database, which has previously been regarded the optimal database for bibliometrics (Alkan et al., 2021; Alkan-Çeviker et al., 2021a; Öntürk et al., 2021; Özlü, 2022).

Keywords related to "beta-thalassemia carrier," or "beta-thalassemia trait," thalassemia minor" or "heterozygous beta-thalassemia" were used in a search query in the WOS search engine.

"United Kingdom English and United States English

words utilized" for more accurate results. The time frame was specified since 10 March 2022. The analysis included information on the increase of publications, the most active countries and institutions, the most cited journals, and the mapping of publications and keywords.

As indices of the influence of publications, the Hirsch (h) index of the publishing journal was utilized.

## 3. Results

In this study, a total of 8618 publications were retrieved. The first article was published in 1970, and the period between 1970 and 2021 was searched. The maximum number of publications was published in the year 2021. The number of publications had increased since 2009 (Figure 1).

Most of the publications were articles (61.696%) (Table 1). The publications were from more than 100 disciplines and most of them were from Hematology (49.176%) (Table 2). The publications were published 23.606 by different authors. Suthat Fucharoen from Mahidol University, Thailand was the most productive author on thalassemia minor study with 200 publications.

The publications were from 274 different countries. Most of the publications were from the USA, Italy and Greece. Türkiye ranked 7th (Table 3).

Most of the publications were from the National and Kapodistrian University of Athens, Greece (3.655%) (Table 4).

The United States Department of Health Human Services funded most of the studies (Table 5).

### 2.1. Citing Analyses

8618 publications were cited 112633 times and H index was 116. The number of citations were increased by the years (Figure 2).

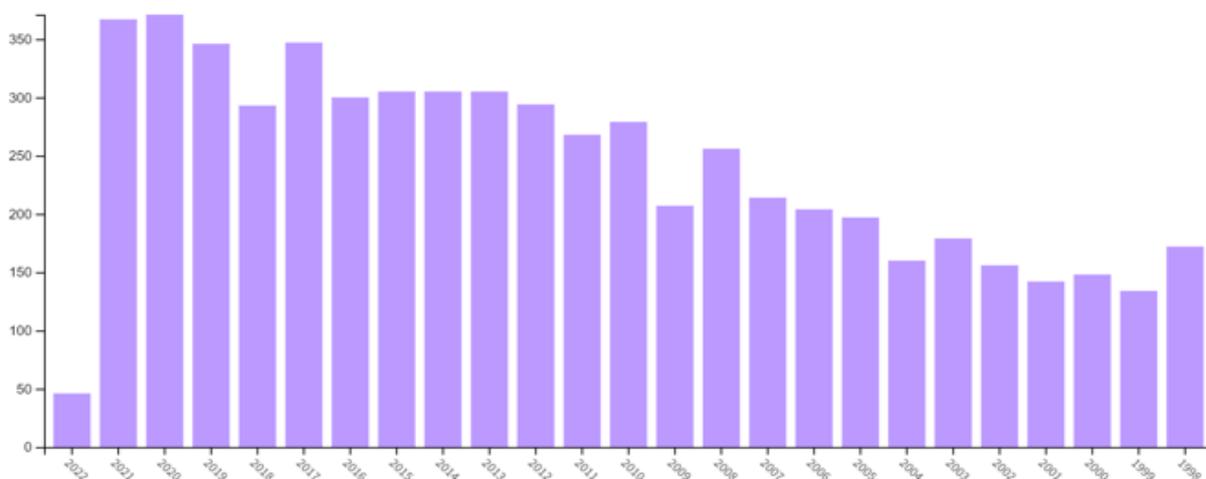
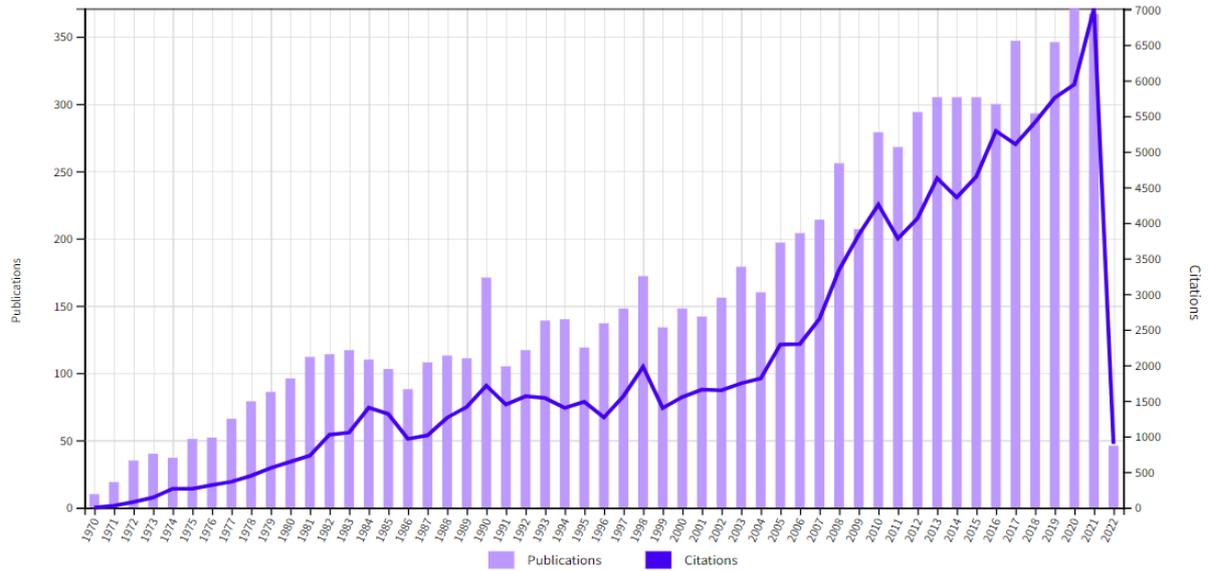


Figure 1. Number of the publications by the years (2022 did not completed yet).



**Figure 2.** Number of publications and citations by the years.

**Table 1.** Types of the documents (n=8787)

Document Types	n	%
Articles	5317	61.696
Meeting Abstracts	1964	22.790
Letters	610	7.078
Review Articles	248	2.878
Notes	211	2.448
Proceedings Papers	171	1.984
Editorial Materials	137	1.590
Corrections	50	0.580
Early Access	41	0.476
Book Chapters	18	0.209
News Items	13	0.151
Corrections, Additions	4	0.046
Discussions	2	0.023
Data Papers	1	0.012

**Table 2.** Study disciplines (n=8618)

Web of Science Categories	n	%
Hematology	4238	49.176
Biochemistry Molecular Biology	994	11.534
Medicine General Internal	787	9.132
Pediatrics	766	8.888
Genetics Heredity	648	7.519
Medicine Research Experimental	516	5.987
Oncology	411	4.769
Immunology	240	2.785
Multidisciplinary Sciences	223	2.588
Obstetrics Gynecology	208	2.414

Showing 10 out of 128 entries, 7 record(s) (0.081%) do not contain data in the field being analyzed.

**Table 3.** Number of publications according to countries (n=8618)

Countries/Regions	n	%
USA	1734	20.121
Italy	1330	15.433
Greece	700	8.123
England	639	7.415
Iran	611	7.090
India	556	6.452
Türkiye	477	5.535
Thailand	471	5.465
Peoples Republic of China	452	5.245
France	396	4.595
Egypt	300	3.481
Israel	272	3.156
Canada	225	2.611
Pakistan	186	2.158
Australia	166	1.926
Germany	159	1.845
Lebanon	153	1.775
Switzerland	132	1.532
Saudi Arabia	122	1.416
Netherlands	118	1.369
Brazil	117	1.358
Japan	117	1.358
Spain	114	1.323

274 record(s) (3.179%) do not contain data in the field being analyzed.

**Table 4.** Number of publications according to affiliations (n=8618)

Affiliations	n	%
National Kapodistrian University of Athens	315	3.655
Mahidol University	304	3.528
University of London	261	3.029
Egyptian Knowledge Bank	260	3.017
Assistance Publique Hopitaux Paris	225	2.611
University of Cagliari	225	2.611
University of California System	209	2.425
University of Milan	207	2.402
University College London	197	2.286
Institute National De La Sante Et De La Recherche Medicale Inserm	192	2.228
University of Oxford	189	2.193
Augusta University	187	2.170
University System of Georgia	187	2.170
Hebrew University of Jerusalem	173	2.007
Universite de Paris	168	1.949
University of California San Francisco	168	1.949
Harvard University	165	1.915
Cornell University	152	1.764
American University of Beirut	149	1.729
Shiraz University of Medical Science	148	1.717
Consiglio Nazionale Delle Ricerche	146	1.694
University of Ferrara	144	1.671
University of Pennsylvania	136	1.578
Laiko General Hospital	135	1.566
Irccs Ca Granda Ospedale Maggiore Policlinico	131	1.520

Showing 25 out of 4904 entries, 277 record(s) (3.214%) do not contain data in the field being analyzed.

**Table 5.** Summary of the funding agencies (n=8618)

Funding Agencies	n	%
United States Department of Health Human Services	451	5.233
National Institutes of Health Nih USA	446	5.175
Nih National Heart Lung Blood Institute Nhlbi	303	3.516
Nih National Institute of Diabetes Digestive Kidney Diseases Niddk	156	1.810
National Natural Science Foundation of China	98	1.137
European Commission	83	0.963
Thailand Research Fund	63	0.731
Fondazione Telethon	45	0.522
Novartis	39	0.453
Shiraz University of Medical Sciences	35	0.406

Showing 10 out of 1518 entries; 6928 record(s) (80.390%) do not contain data in the field being analyzed.

#### 4. Discussion

Bibliometric analysis is a way of quantifying scientific publications to estimate a researcher's, journals, countries, etc. research productivity. Gaps in study areas

can be found and even comparisons of prior studies on a topic (Alkan Çeviker et al., 2021b; Durgun, 2021; Dindar Demiray et al., 2021a; Dindar Demiray et al., 2021b; Gürler et al., 2021; Köylüoğlu et al., 2021; Küçük et al., 2021; Özlü, 2021a; Özlü, 2021b; Mızrakçı, 2022; Akyüz et al., 2022). In bibliometric analysis, Internet databases are commonly used. While this method was widely utilized in earlier years in social field studies, it has successfully been applied in medicine, which is our field. Visualization approaches can be used to examine and map various databases. Several descriptive statistics can be used in the bibliometric analysis, including citation data, network analysis based on citations that cover journals, authors, nations, keywords, academic and research institutions, and frequency analysis. It can also provide information on research clusters, present interests, and emerging topic trends. (Durgun, 2021; Gürler et al., 2021; Köylüoğlu et al., 2021; Küçük et al., 2021; Özlü, 2021a; Akyüz et al., 2022; Mızrakçı, 2022). Similar studies were also conducted in the field of hematology (Okoroiwu et al., 2020; Seo et al., 2020; Chen et al., 2021). There were even bibliometric analyzes on anemia (Awe et al., 2021; Frater, 2021). However, in the accessible literature, there was no similar study published on thalassemia minor. We sought to provide a bibliometric summary of the literature on thalassemia minor from 1970 to 2021 in this study. This work especially will shed light on showing researchers, the most active institutes, citations, countries, and beneficiaries.

A total of 9031 articles on thalassemia minor were published in 10 different fields in the Web of Science research field. The distribution of the top 10 research areas in thalassemia research is listed in Table 2. "Hematology" was undoubtedly the dominant research area with 4238 articles and followed by "biochemistry, molecular biology", "Internal General Medicine", "Pediatrics", "Genetic Heredity" and "Medicine Research Experimental" in Table 2. "Hematology", which made up 49.176% of the total publications, was at the top of the list. This analysis shows that research points come to the fore in basic sciences such as molecular biology, genetics, experimental medicine and clinical sciences such as hematology and pediatrics, which is related to the prevention, diagnosis and treatment of thalassemia.

It was found that the publications were from 274 different countries. Most of the publications were from the USA, as in previous bibliometric analysis on different topics (Durgun, 2021; Gürler et al., 2021; Köylüoğlu et al., 2021; Küçük et al., 2021; Akyüz et al., 2022; Mızrakçı, 2022). Also, Italy and Greece were in the top 3 countries on thalassemia minor research. Among the first 23 countries that published article rates (Table 3), the USA has the biggest share with 20.121 %. Italy follows it with 15.433% and Greece with 8.123% respectively. Türkiye ranked 7th. Most of the publications were from the National and Kapodistrian University of Athens, Greece. The fact that countries excluding the USA are at the top can be attributed to the high prevalence of this disease in

these countries. Almost all of the regions in the top 20 are countries with good economic income. Therefore, it has been suggested that they contribute more easily to valuable scientific and academic publications. It is thought that easy and better access of the patients to health centers for screening and diagnosis and the different effects of environmental genetic factors in Western countries may contribute to this situation.

Scientific efficiency is associated with research and development expenditures (Nag et al., 2013; Acosta et al., 2014, Ebadi and Schiffauerova, 2016). Table 5 lists the 10 most important institutions in this field. United States Department of Health Human Services topped the list with 451 funded articles. In the second place is the National Institutes of Health (NIH) in the USA with 446 articles. In the third and fourth places are NIH National Heart Lung Blood Institute (NHLBI) and NIH National Institute of Diabetes Digestive Kidney Diseases NIDDK, affiliated with NIH. The NIH stands out as one of the world's largest biomedical research funders and the largest funder overall. In addition to these, Novartis pharmaceutical company was included in the top 10 as one of the financing institutions, which the only for-profit pharmaceutical company. The true prevalence of thalassemia in the United States is unknown; however, it is noteworthy that with the increasing Asian immigration in America (Hoppe, 2009), more information is sought on the effect and course of hereditary disorders on diseases. Most of the funding affiliations were from the USA, and this situation may lead to the number of publications from the USA being higher than in other countries. But this topic seems to be important in Mediterranean countries, especially in Greece and Italy.

The 25 most productive institutes between 1970 and 2021 are listed in Table 4. Seven different institutions from the USA, 4 from Italy, 2 from Greece and 2 from the UK are leading the list. This distribution reiterated the numerical superiority of the United States in the field of research on thalassemia minor. The fact that institutions with high publication numbers are predominantly from the USA, Italy, Greece, and the UK indicates that these countries have outstanding academic institutions, talents and research culture in the field of thalassemia minor. One of the world's most historic, largest and oldest university centers, the National Kapodistrian University of Athens has contributed 315 more publications, than any other institution, accounting for 3.655% of the world's publications in this field. Mahidol University in Thailand was the second in efficiency with 304 publications and 3,528% of the total publications. The University of London from the UK and Egyptian Knowledge Bank ranked third and fourth, respectively.

There are certain limitations of this bibliometric analysis. First, we have only used a single medical database-WOS, for our analysis. We chose the WOS database because it offers both basic and advanced search possibilities. It is worth noting that the WOS does not index all journals. Other electronic databases, such as PubMed, Embase,

SCOPUS, Google Scholar, and the Cochrane Library, are not searched or examined. Although different databases return vastly different results (Falagas et al., 2008; Kulkarni et al., 2009) it is acceptable to use a single medical database to identify top-cited medical research articles—many published bibliometric analyses have used the SCIE database for this purpose (Oh and Galis, 2014; Azer and Azer, 2016; Zhang et al., 2016). To find all material on the issue, we searched all publications, including books, journal articles, letters, and clinical trials. We assigned articles to the country of the first author where they had writers from two or more member countries.

Non-English papers were also excluded. Most of the studies in this study are written in English; nonetheless, this limitation may result in a publishing bias. The final constraint is that influential publications were not referred to frequently enough because some potentially influential papers were released recently and could not be cited frequently. Another restriction is that the data for 2022 is incomplete due to the lack of information. And the collaboration and detailed citation analyses did not do, as it needs other programs.

It has been determined that the publication of articles published over the years is generally in an increasing trend, with a few exceptions. The reductions in the number of exceptions decreased from 1998 to 1999, from 2003 to 2004, from 2008 to 2009, and from 2017 to 2018. No significant data and events related to the causes of these decreases were found. While new developments in the treatment of thalassemia, the discovery of targeted therapy molecules, and specialized treatments such as bone marrow transplantation remain current, they may have contributed positively to the emergence of publications in this field as an author comment. However, in general, a net positive and significant relationship was not found with the increase in publications. Overall, the thalassemia minor has attracted increasing attention and has become one of the hottest research areas in hematological research.

A similar upward trend is observed in citations to publications. Specifically, the sharp upward trend in 1990 and 1998 entered a downward trend in consecutive years, 1991 and 1999. The number of citations is also increasing, except for the isolated periods, which have a ripple effect in this generally increasing trend.

The number of publications and citations has increased over the years. This could be due to an increase in global publications on all topics. And also, Patients' access to diagnostic solutions may be easier, health care services may be increased, and genetic screenings and family screenings may be more frequent. For this reason, it became easier to carry out the study by reaching more patient numbers.

### 5. Conclusion

The USA is at the top of the list in the number of publications. But with active funding and support from

the governments especially the Mediterranean countries, which have a higher prevalence of thalassemia minor, the productivity of scientific research should be increased.

## Author Contributions

Concept: G.C. (50%) and C.Ö. (50%), Design: G.C. (50%) and C.Ö. (50%), Supervision: G.C. (100%), Data collection and/or processing: G.C. (50%) and C.Ö. (50%), Data analysis and/or interpretation: G.C. (50%) and C.Ö. (50%), Literature search: G.C. (50%) and C.Ö. (50%), Writing: G.C. (50%) and C.Ö. (50%), Critical review: G.C. (50%) and C.Ö. (50%), Submission and revision G.C. (50%) and C.Ö. (50%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declared that there is no conflict of interest.

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## Ethical Approval/Informed Consent

The study complied with the Helsinki Declaration, which was revised in 2013. Ethics committee approval is not required as there is no human or animal research.

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## SPLenic INFARCTION FOLLOWING THYROIDECTOMY: AN UNUSUAL CASE IN THE EMERGENCY DEPARTMENT

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**Abstract:** Splenic infarction is a rare diagnosis in the emergency department and can easily mimic other causes of acute abdomen. Cardioembolic and hematological disorders, inflammatory (eg pancreatitis) and infectious (eg sepsis) conditions, postoperative conditions, malignant neoplasms and atherosclerosis are some of the risk factors. Papillary thyroid carcinoma is the most common histologic type of differentiated thyroid malignancy and is known as the least aggressive thyroid carcinoma. A 46-year-old male patient was admitted to the emergency department with the complaint of abdominal pain for five day. When the patient's anamnesis was deepened, it was learned that the patient had been operated on 5 days before the papillary thyroid cancer, the abdominal pain started the day after the surgery, and the pain showed an increasing and decreasing course. Contrast-enhanced abdominal CT performed on the patient revealed perfusion defects in the posterior and lateral parts of the spleen. The diagnosis of splenic infarction should also be kept in mind in patients presenting to the emergency department with left upper quadrant pain, especially in patients who have recently undergone a surgical operation, have a previous history of thrombotic and vascular disease, and have any malignancy.

**Keywords:** Splenic infarction, Thyroidectomy, Emergency department

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### 1. Introduction

Splenic infarction occurs when blood flow to the spleen is reduced or completely interrupted for various reasons (Yılmaz, 2019). Splenic infarction is a rare diagnosis in the emergency department and can easily mimic other causes of acute abdomen. The most common symptom in patients is left upper abdominal pain, and other symptoms are nausea, vomiting, constipation and fever (Antopolsky et al., 2009). Cardioembolic and hematological disorders, inflammatory (eg pancreatitis) and infectious (eg sepsis) conditions, postoperative conditions, malignant neoplasms and atherosclerosis are some of the risk factors (Brett et al., 2020).

Papillary thyroid carcinoma is the most common histologic type of differentiated thyroid malignancy and is known as the least aggressive thyroid carcinoma. Total thyroidectomy or isthmusectomy is performed in the treatment of papillary thyroid carcinoma (Vasileiadis et al., 2018).

There are cases of splenic infarction seen following some abdominal and thoracic surgical procedures in the literature (Soriano-Giménez et al., 2017; Oyama et al., 2021). Here, we present a patient who was surprisingly diagnosed with splenic infarction in a patient who had recently undergone thyroidectomy and presented to the emergency department with the complaint of abdominal pain. No case of splenic infarction seen after thyroidectomy was found in the literature.

### 2. Case Report

A 46-year-old male patient was admitted to the emergency department with the complaint of abdominal pain for five day. He had a history of hypertension, type 2 diabetes, peripheral vascular disease (in both lower extremities), thyroidectomy. When the patient's anamnesis was deepened, it was learned that the patient had been operated on 5 days before the papillary thyroid cancer, the abdominal pain started the day after the surgery, and the pain showed an increasing and decreasing course. Pain was localized in the left upper quadrant and did not radiate from any other location. In addition, the patient had loss of appetite. The patient did not complain of constipation, diarrhea and fever. The medications that the patient used regularly were levothyroxine sodium (100 mcg), acetylsalicylic acid (100 mg), clopidogrel (75 mg) and perindopril arginine (5 mg).

At the initial evaluation, blood pressure was 114/65 mm Hg, heart rate was 108 beats per minute, temperature was 36.3°C, respiratory rate was 18 breaths per minute, and oxygen saturation was 97%. There was pain in the left upper quadrant of the abdomen without defense and rebound tenderness, horizontal surgical scar in the anterior cervical region, and the rest of the physical examination was unremarkable. His blood tests were notable for white cell count of  $15.8 \times 10^3/\text{mm}^3$ , elevated lactate dehydrogenase (433 U/L, normal range 70-248



U/L) and high levels for C-reactive protein (104.3 mg/L, normal range less than 5 mg/L). Abdominal ultrasonography was performed first, but no significant finding was detected. Then the patient underwent contrast-enhanced abdominal CT. Perfusion defects appeared in the posterior and lateral part of the spleen, which was reported as infarction by the radiologist

(Figure 1). The patient was transferred to the upper center because our hospital is a secondary level hospital. The patient's antiplatelet medication was discontinued and low molecular weight heparin (LMWH) therapy was started. The patient was hospitalized for 2 days here. The patient, whose complaints regressed and laboratory values were normalized, was discharged.



**Figure 1.** Contrast enhanced-CT scan on admission to the emergency department: Yellow arrow indicates splenic infarct in our patient.

### 3. Discussion

Infarction of the spleen is a rare condition that causes abdominal pain. Splenic infarction occurs with parenchymal necrosis due to complete or partial occlusion of the splenic artery or vein (Ozakin et al., 2015). The occlusion is usually caused by soft or septic embolism as well as venous blockage of abnormal cells (Chapman et al., 2017). This condition is usually caused by underlying diseases. There could be several reasons for this in our case. Venous and arterial thromboembolism are common complications of cancer (Pfrepper, 2020). There is a close relationship between the paraneoplastic syndromes seen in some cancer types and thrombotic processes (Saraiva et al., 2020). One study found that patients with cancer had an overall four to six-fold increased risk of thrombosis compared to patients without cancer (Heit et al., 2000). We know that our patient had recently been operated on for papillary thyroid cancer, which is a risk factor for splenic infarction.

Solid malignancies and surgery are common risk factors for splenic vein thrombosis (Pfrepper, 2020). Postoperative immobilization of our patient may have

caused thrombosis leading to splenic infarction. Thrombosis risk in patients undergoing non-orthopedic surgery is determined by methods such as the extent of the surgical procedure, the assessment of major bleeding risk, and the Caprini risk score (Pai and Douketis, 2019). Our patient also has preexisting peripheral vascular disease. In our opinion, the cause of this vascular disease is the paraneoplastic syndrome that developed due to the patient's solid cancer. In a retrospective analysis of patients with splenic infarction, more than half of the patients had more than 12000 white blood cells (WBC) and increased lactate dehydrogenase (LDH) levels; most of the patients were over 40 years old. (Chapman et al., 2021). In this context, our case is compatible with the literature.

Contrast-enhanced CT scan is the best method for diagnosing splenic infarction. It also enables the detection of other acute abdominal pathologies. Abdominal ultrasonography (USG) has low specificity and high false-negativity for splenic infarction (Caremani et al., 2013). In our patient, splenic infarction was missed by USG, but it was later detected in contrast-enhanced CT.

There is a case of splenic infarction with thyroid papillary cancer previously reported in the literature (Saraiva et al., 2020). However, unlike this case, our patient comes to the emergency department in the postoperative period and receives a very rare diagnosis in the emergency department. In this respect, our case makes a contribution to the literature.

## 4. Conclusion

The diagnosis of splenic infarction should also be kept in mind in patients presenting to the emergency department with left upper quadrant pain, especially in patients who have recently undergone a surgical operation, have a previous history of thrombotic and vascular disease, and have any malignancy. Contrast-enhanced abdominal CT should be preferred among the diagnostic imaging tools of these patients.

## Author Contributions

All task made by N.V. (100%); Concept, Design, Supervision, Data collection and/or processing, Data analysis and/or interpretation, Literature search, Writing, Critical review, Submission and revision. The author reviewed and approved final version of the manuscript.

## Conflict of Interest

The author declared that there is no conflict of interest.

## Ethical Approval/Informed Consent

Written an informed consent form was obtained from the patients for the case presentation and necessary information was given to the family.

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## ANOSMİ VE DÖKÜNTÜ İLE BAŞVURAN COVID-19 VAKASI

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**Özet:** Koronavirüs 2019 hastalığı (COVID-19) hakkında her geçen gün bilgi birikimimiz artmaktadır. COVID-19 özellikle solunum sisteminde etkileri (öksürük, nefes darlığı) olduğu tahmin edilen bir virüsken, artan olgu sayıları ile COVID-19'un karşımıza çok farklı klinik tutulumlarla (örneğin; gastrointestinal, deri tutulumu, merkezi sinir sistemi, kardiyovasküler tutulumlar, göz tutulumu, gibi) gelebileceğini göstermiştir. Hastalığa ait bu farklı sunumlar hekimlerin tanısal anlamda zorlanmasına sebep olabilir. Tanıda gecikme toplumda kişilerin enfeksiyonu yaymasına neden olabilir. Bu yazıda anosmi ve döküntü ile başvuran ancak herhangi bir pulmoner patolojisi veya ateş yüksekliği olmayan COVID-19 vakasını literatüre kazandırılması amaçlandı. Olgu favipiravir ile tedavi edilmiş ve sonrasında şikayetleri tamamen gerilemiştir.

**Anahtar kelimeler:** COVID 19, SARS COV 2, Döküntü, Anosmi

### COVID-19 Case Presenting with Anosmia and Rash

**Abstract:** Our knowledge of the coronavirus disease 2019 (COVID-19) is increasing day by day. While COVID-19 is a virus that is predicted to have effects especially on the respiratory system (cough, shortness of breath), with the increasing number of cases, we encounter COVID-19 with very different clinical involvements (for example, gastrointestinal, skin involvement, central nervous system, cardiovascular involvement, eye involvement, etc.). Has shown that it can come these different presentations of the disease may cause diagnostic difficulties for physicians. A delay in diagnosis may cause people to spread the infection in the community. In this article, it was aimed to bring to the literature a case of COVID-19 who presented with anosmia and rash but did not have any pulmonary pathology or fever. The patient was treated with favipiravir and her complaints completely regressed afterwards.

**Keywords:** COVID 19, SARS COV 2, Rash, Anosmia

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### 1. Giriş

Bilindiği üzere COVID-19 pandemisi yaklaşık iki yıldır tüm dünyayı etkisi altına almıştır (Alkan Çeviker ve Dindar Demiray, 2020). Hastalığa ait ilk bildirilen vakalar SARS COV2 virüsünün sebep olduğu pnömni tablosunda iken, özellikle son dönemlerde deri bulguları/ ishal gibi de çok farklı tutulumlarla karşımıza çıkmaktadır (Dindar Demiray ve ark., 2021; Duygu ve ark., 2021; Joob ve Wiwanitkit, 2021; Özlü ve ark., 2021; Cancan Gürsul ve ark., 2022) ve biz klinisyenleri nerdeyse her hastada COVID-19 varlığı arama durumunda bırakmaktadır. COVID-19'da son dönemlerde deri bulguları ile başvuran hastalar da olduğu bildirilmiştir. Hatta yapılan otopsielerde bile deride histopatolojik bulgular gösterilmiştir. COVID-19'da deri tutulumunun mekanizması tam olarak bilinmemekle beraber, iyatrojenik şekilde ortaya çıktığı düşünülmektedir (Sevimli Dikicier ve Yıldız, 2020).

### 2. Olgu Sunumu

Elli beş yaşında, öncesinde bilinen alerjik rinit ve kronik sinüzit tanıları olan erkek hasta beş gündür olan burun tıkanıklığı ve iki gündür yeni gelişen sırt ve karın cildinde basmakla solmayan, eritematöz makülopapüler kaşıntılı

döküntüler (ekzantem) ile başvurdu. Hasta kulak burun boğaz ve dermatoloji bölümlerine başvurmuştu ve iki gündür adını bilmediği topikal ve oral antihistaminik tedaviler verilmişti. Şikayetleri geçmeyen hasta tarafımıza yönlendirilmişti. Fizik muayenesinde anormal bulguya rastlanmadı. Vital bulguları stabildi. Döküntüleri sırt ve karın bölgesinde lokalize idi. El ve ayak tabanında döküntü yoktu. Aile ve sosyal öykülerinde özellik yoktu. Biyokimyasal ve hematolojik parametreleri normaldi. Eozinofil ve total IgE değerleri normal sınırlarda idi. Hastadan ayırıcı tanı için hepatit markerları (Hepatit B, Hepatit C), Anti HIV, brusella tüp aglütinasyon, anti Toxo IgM, EBV, CMV, rubella, kızamık, varisella serolojileri ve sifiliz ayırıcı tanısı açısından VDRL tetkikleri istendi. Patoloji saptanmadı. COVID-19 enfeksiyonu olduğundan şüphelenilen hastadan nazofaringeal sürüntü örneği alındı. Nazofarenks örneğinin incelenmesinde gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) pozitif tespit edildi. Hastanın öksürük balgam gibi solunum semptomları yoktu. Hastaya başvurduğu dönemdeki Türkiye Cumhuriyeti Sağlık Bakanlığı COVID-19 Tedavi Rehberi önerileri doğrultusunda beş gün süre ile favipiravir 200 mg (2x1600 mg yükleme, 2x600 mg



idame) tedavisi başlandı ve 14 gün ev izolasyonu önerildi (URL 1). 14 gün sonra kontrole gelen hastanın anosmi ve deri döküntüsü şikayetleri tamamen gerilemişti.

### 3. Tartışma ve Sonuç

COVID-19 olgularında döküntüye gerek hastalığın seyrinde gerekse de kullanılan ilaçlara bağlı rastlandığı ülkemizden sunulan raporlarda bildirilmiştir (Öner ve Akdeniz, 2020; Alkan Çeviker ve ark., 2021; Cancan Gürsul ve ark., 2022; Öztürk Deniz ve ark., 2022).

COVID-19 hastalarının kutanöz belirtileri giderek daha fazla rapor edilmekte, ancak potansiyel mekanizmalar araştırılmayı beklemektedir. Yapılan bir metaanaliz çalışmasında deri bulguları olan toplam 507 COVID-19 hastası değerlendirilmiştir ve hastaların %96,25'sinin Avrupa'dan olduğu tespit edilmiştir. Hastaların yaş ortalaması 49.03 (dağılım: 5-91), kadın oranı ise %60,44 idi. Deri lezyonları polimorfik olup, eritematoz ve ürtikeriyal lezyonlar en yaygın lezyonlar olarak bildirilmiştir. SARS-CoV-2 reseptörü ACE-2'nin ciltte, özellikle keratinositlerde eksprese edildiği bulunmuştur (Zhao ve ark., 2020). Bu yazıda sunulan olgu ise öncesinde herhangi bir ilaç kullanmayan, anosmi ve deri döküntüsü olan 55 yaşında bir COVID-19 enfekte hastadır. Hastaya cilt biyopsisi hasta kabul etmediğinden yapılamamıştır. Histopatolojik kanıt olmamasına rağmen favipiravir tedavisi altında lezyonlar tamamen gerilemiştir.

Bu yazı ile sonuç olarak, anosmi/deri bulguları gibi atipik tutulumlarda da SARS COV-2 enfeksiyonunun sunum şekillerinden olabilir. Bu hastada olduğu gibi izolasyon önlemlerinin alınmasının gecikmesinin engellenmesi için hastalığın erken tanınması elzemdir. Kaldı ki bu durum gerek sağlık çalışanlarının sağlığı gerekse de toplumda enfeksiyon kontrolünde önemlidir. Klinisyenler COVID-19'un atipik tutulumları açısından dikkatli davranmalıdır.

### Katkı Oranı Beyanı

Tüm işlemler S.O.M. (100%) tarafından yapılmıştır; Konsept, Tasarım, Denetim, Veri toplama ve/veya işleme, Veri analizi ve/veya yorumlama, Kaynak taraması, Yazma, Eleştirel inceleme, Gönderim ve revizyon. Yazar, makalenin son halini incelemiş ve onaylamıştır.

### Çatışma Beyanı

Yazar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

### Etik Onay/Hasta Onamı

Olgu sunumu için hasta/lardan yazılı aydınlatılmış onam formu alındı ve aileye gerekli bilgiler verildi.

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## METHANOL INTOXICATION WITHOUT OPTIC ATROPHY AND CENTRAL DAMAGE

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**Abstract:** We aimed to present our case of total blindness without intracerebral lesions and optic atrophy after methanol intoxication during the first 3 months. A 28-year-old male patient was consulted to the emergency department with complaints of a sudden decrease in vision, nausea, and dizziness was evaluated in terms of ocular findings. It was learned that he had taken 400-500 ml of alcohol made at home, about 16 hours ago, the evening before his story. In the ophthalmological examination of the patient, the pupils were bilaterally fixed and dilated. Bilateral visual acuity was found to be light perception. There was no pathological feature in anterior segment examination. Intraocular pressure was 15 mmHg in the right eye and 16 mmHg in the left eye by Goldmann's applanation tonometry. The optic disc and macula were observed normally in the examination after dilatation. At the 3rd-month follow-up examination, his visual acuity was at the level of light perception. The patient stated that he had difficulty seeing in daylight due to photophobia and that he could see more easily in the evenings and dim light. Acute alcohol poisoning has high morbidity and mortality and should be taken seriously and managed promptly. Delay of treatment can cause complications, permanent damage or death. However, it can leave permanent damage despite early and full intervention. It may take time for these permanent damage to become visible anatomically.

**Keywords:** Methanol intoxication, Optic atrophy, Central damage

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### 1. Introduction

Methanol poisoning is an emergency cause that can cause severe illness and death. Although methanol itself is not very toxic, its metabolites, which are metabolized to formaldehyde and subsequently to formic acid by the alcohol-dehydrogenase enzyme, are very toxic. In our country, poisoning due to methyl alcohol is mostly caused by the use of methyl alcohol instead of inert alcohol for cheap liquor production (Baydin et al., 2010). Poisoning due to methanol, even in small quantities, can be very dangerous. It can cause severe visual impairment (including irreversible bilateral blindness), metabolic disorders, permanent neurological dysfunctions, and even death (Moschos et al., 2013).

We aimed to present our case of total blindness without intracerebral lesions and optic atrophy in the first 3 months.

### 2. Case Report

A 28-year-old male patient was consulted to the emergency department with complaints of a sudden decrease in vision, nausea, and dizziness was evaluated in terms of ocular findings. It was learned that he had taken 400-500 ml of alcohol made at home, about 16 hours ago, the evening before his story. The respiratory rate was 28 per minute, pulse rate of 88 per minute,

blood pressure of 135/85 mm Hg, and axillary temperature of 36.7 °C and laboratory tests as presented in Table 1.

Ethanol gavage, sodium bicarbonate infusion, and folic acid, pantoprazole intravenous fluids were administered to the patient in the emergency room, and we were consulted after the intervention.

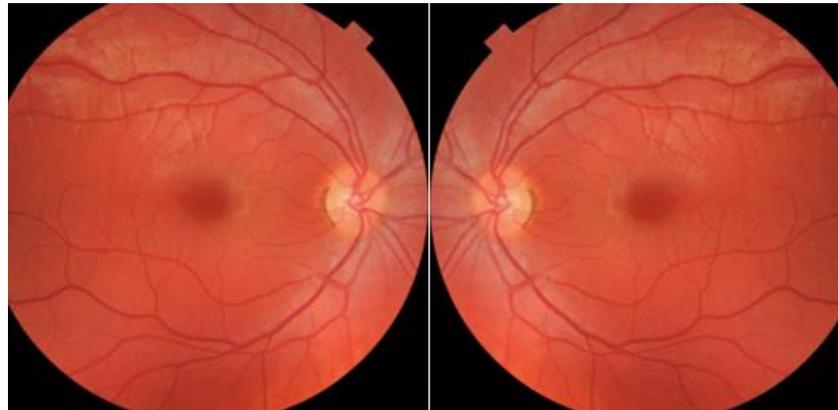
In the ophthalmological examination of the patient, the pupils were bilaterally fixed and dilated. In the ophthalmological examination of the patient, bilateral visual acuity was found to be light perception. The anterior segment was evaluated as normal. Intraocular pressure was 15 mmHg in the right eye and 16 mmHg in the left eye by Goldmann's applanation tonometry. The optic disc and macula were observed normally in the examination after dilatation. Color fundus photos, optic disc tomography (OCT), and retinal nerve fiber thickness (RNFL) were evaluated. (Figure 1, 2, 3) No pathology was detected. Neuropathology was not found in the Computerized Brain Tomography, Diffusion MR and MR cranial angiography of the patient taken in the emergency room.

The patient was evaluated as methanol poisoning since the sudden vision loss, history of drinking, and pH and bicarbonate values were compatible with the metabolic acidosis clinic (ph: 7.14, HCO<sub>3</sub>: 9.6 mmol/L).

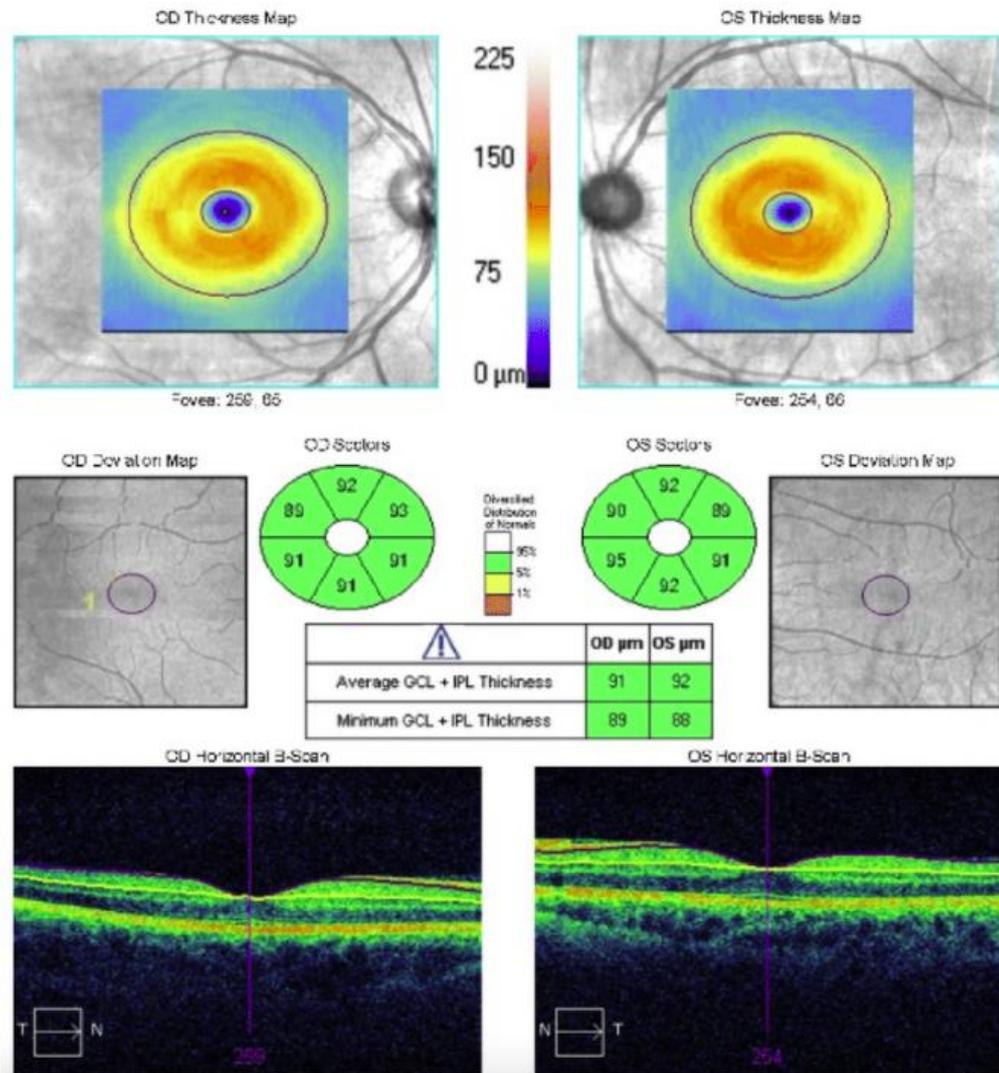


**Table 1.** The results of the laboratory tests

BUN	18	Na	135	WBC	13750	PCO2	39.3
Cr	1.5	K	5.5	RBC	5270	PO2	64
UREA	53	Cl	99	HCT	50.5	HCO3	9.6
ALT	16	Ca	10.3	MCV	86.7	O2 SAT	86.7
AST	23	AG	27.2	PLT	243000	BE	-22.4



**Figure 1.** Fundus Photographs.



**Figure 2.** Optical Coherence Tomography (OCT) images.

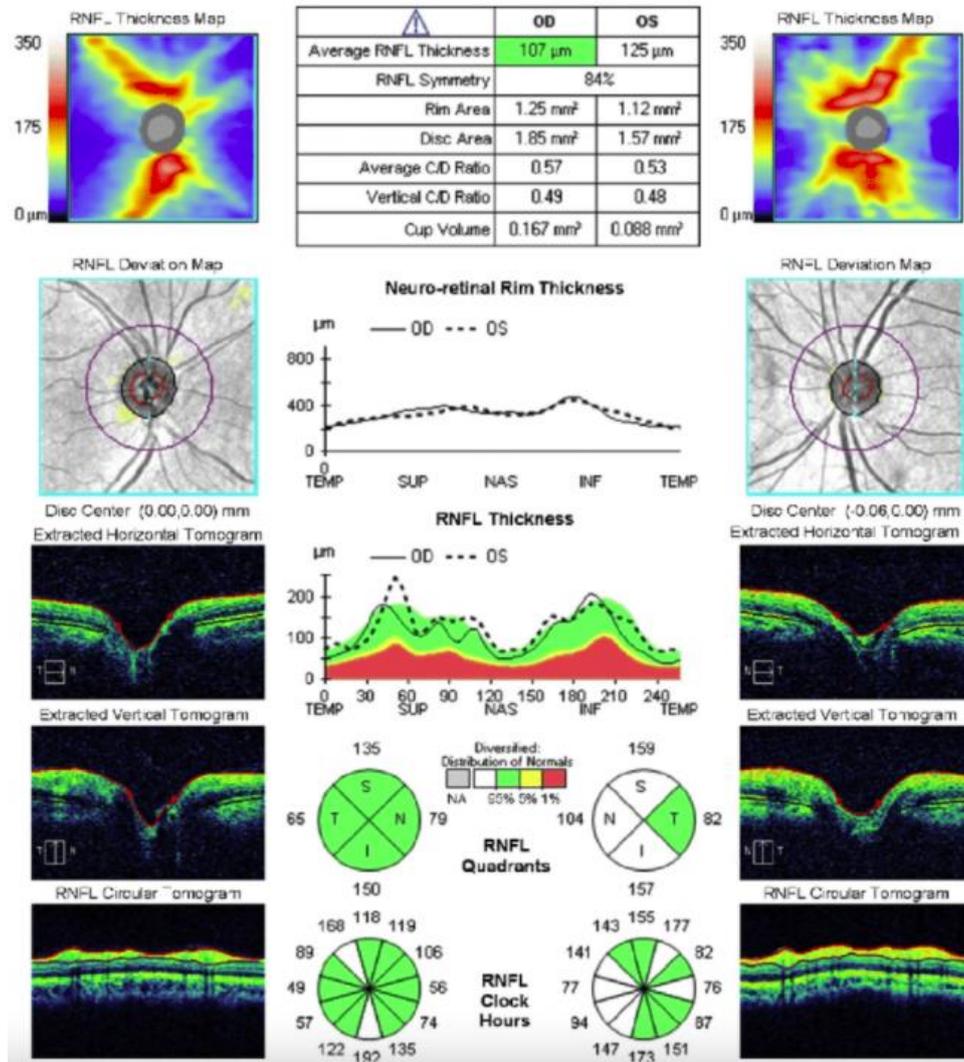


Figure 3. Retinal Nerve Fiber Layer (RNFL) images.

However, the blood methanol level of the patient could not be measured. Bicarbonate supplementation, hemodialysis, and antidote therapy (4 ampoules of fomepizole) were administered to the patient as medical treatment. B vitamin supplementation was given to support the treatment. When the metabolic acidosis picture of the patient improved, discharge was planned. The patient was planned to be seen monthly in the 1<sup>st</sup> week after discharge. No ophthalmological changes were detected until the 3<sup>rd</sup>-month control. At the 3<sup>rd</sup>-month follow-up examination, his visual acuity was at the level of seeing light. The patient stated that he had difficulty seeing in daylight due to photophobia and that she could see more easily in the evenings and dim light. The Ishihara test was used for color vision examination; however, the patient could not distinguish colors. Optic disc pallor (progression to optic atrophy) is seen in the color fundus photographs of the patient at the 3<sup>rd</sup> month. (Figure 4). In the control neurological examination of the patient, no pathology was detected in the EEG and EMG and Cranial MRI findings.



Figure 4. Bilateral Optic Atrophy appearance of fundoscopic evaluation.

### 3. Discussion

Formic acids, which are responsible for the emergence of toxic effects in methanol poisoning, are formed when methanol is metabolized to formaldehyde by alcohol dehydrogenase and then to formic acid by the aldehyde dehydrogenase enzyme. A latent period is required for this transformation. This period is between 12 and 72 hours. The signs and symptoms that occur at the end of this period may vary depending on the intake route of

methanol. There is a wide range of symptoms, from mild symptoms such as vomiting and abdominal pain to coma and respiratory failure, which can be fatal (Koehrer et al., 2011).

It is thought that formic acid is responsible for the damage in the optic nerve, and it does this by causing histological hypoxia, causing both axonal cell death and loss of myelin in the retrobulbar area (Isçan et al., 2013). The level of visual impact can vary from small scotomas to complete loss of vision. Motility of the pupil is impaired due to damage to the photosensitive retinal ganglion cells (Sharma et al., 1999). In the early stages of poisoning, the retinal veins may be dilated with edematous and hyperemic appearance of the optic disc on fundus examination (Önder et al., 1998). While this situation regresses completely and ends with full recovery in the acute period, in most cases it ends with optic atrophy (Önder et al., 1995). In the light of current knowledge, it is blamed that optic atrophy due to methanol poisoning occurs 2 months after the event, and cell loss secondary to acute demyelination is the mechanism (Sharma et al., 1999). Benton and Calhoun described the ocular findings in 320 methanol poisoning cases they examined. They argued that optic atrophy occurs at the end of 2 months and that central involvement is accompanied in the acute phase (Phonka, 2016). On the other hand, in our case, there was vision loss for more than 3 months, although neither central nor optic nerve involvement could be proven. It should also be kept in mind that this development of atrophy does not always accompany vision loss, and the existence of cases where vision is absent despite the optic nerve's natural appearance. In our case, however, we were able to visualize optic atrophy at the end of the 3<sup>rd</sup> month.

#### 4. Conclusion

Acute alcohol poisoning has high morbidity and mortality and should be taken seriously and managed promptly. Delay in treatment it can cause complications, permanent damage or death. However, it can leave permanent damage despite early and full intervention. It may take time for these permanent damage to become visible anatomically.

#### Author Contributions

All task made by F.S. (100%); Concept, Design, Supervision, Data collection and/or processing, Data analysis and/or interpretation, Literature search, Writing, Critical review, Submission and revision. The author reviewed and approved final version of the manuscript.

#### Conflict of Interest

The author declared that there is no conflict of interest.

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Written an informed consent form was obtained from the patient/s for the case presentation, and necessary information was given to the family.

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## A RARE CASE OF SCALP MASS: CLEAR CELL HIDRADENOCARCINOMA

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**Abstract:** Clear cell hidradenocarcinoma is a very rare sweat gland tumor. It has an aggressive course and has a high recurrence rate. Wide excision is the first option in the treatment of this tumor with a high rate of metastasis. Subsequent radiotherapy and chemotherapy are still controversial. In this case, we presented a patient who was operated on and presented with a lipoma-like appearance on the scalp. The pathology result of the patient was Clear cell hidradenocarcinoma. We emphasized that in operations performed with the preliminary diagnosis of lipoma on the scalp, this diagnosis should be included among the preliminary diagnoses and resection should be performed as widely as possible.

**Keywords:** Hidradenocarcinoma, Sweat gland, Scalp

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### 1. Introduction

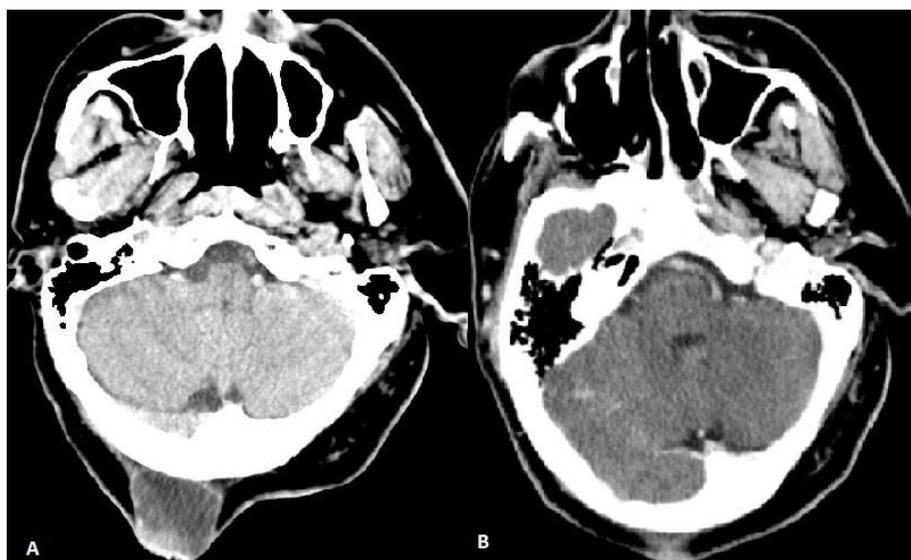
Clear cell hidradenocarcinoma is a rare sweat gland tumor seen in a very limited number in the literature. In the literature, there are names such as clear cell eccrine carcinoma, malignant clear cell acrospiroma, malignant nodular hidradenoma (Balaban et al., 2017). Although there is no typical localization, it is seen in the literature that it is described on the lip, neck, back, chest wall, breast, vulva, and scalp. It is known to be more common in the age range of 50-60 years (de Lima et al., 2021; Elbenaye et al., 2017). These tumors have a high recurrence rate of 50-75%. It has been reported that it metastasizes and its mortality is high. Its 5-year surveillance is around 30% (Elbenaye et al., 2017). Wide local excision is recommended for treatment. Although adjuvant radiotherapy is recommended afterward, it is controversial. Systemic chemotherapy is recommended in metastatic disease (Miller et al., 2015).

### 2. Case Report

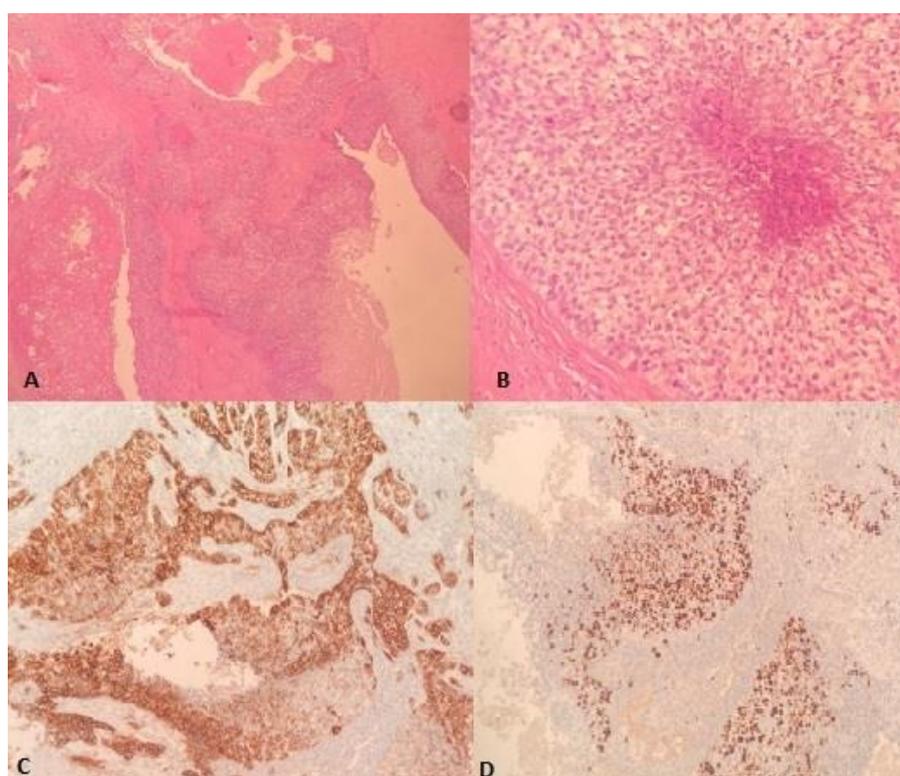
In the physical examination of a 57-year-old male patient who applied with the complaint of swelling on the back of his head, a soft-consistent subcutaneous mass tissue was found in the right occipital region. A 4×3 cm mass without bone invasion was seen in the computed tomography (Figure 1a). Lipoma was considered in the foreground. The patient has no comorbid disease other than diabetes mellitus. The patient was operated and the mass tissue was excised. Histological examination revealed multinodular, solid-cystic, and poorly

differentiated carcinoma located in the dermis. The stroma was fibrotic and partially hyalinized. On closer examination, a tumoral lesion consisting of atypical cell groups-lobules with prominent nucleoli, large, pleomorphic, partially hyperchromatic nuclei, eosinophilic and clear vacuolized cytoplasm in many parts was observed. Cystic degeneration was observed in a large area. In some areas, there were large areas of necrosis, some of which had the appearance of comedo necrosis. Ductal differentiation and keratinization, suggestive of squamous cell differentiation, were remarkable. Up to 10 mitoses were observed in 10 high-magnification fields, and the presence of atypical mitosis was also observed. In immunohistochemical analysis, tumor cells stained strongly for EMA, Cytokeratin AE1/AE3, Vimentin, P63, P53, and insufficient focal staining for S100. Ductal structures were stained positively with CEA. GCDFP-15 and Melan A were negative. The Ki-67 proliferation index was found to be approximately 60% (Figure 2). According to the histopathological findings and immunohistochemical examination results, the patient was diagnosed with a skin malignant adnexal tumor and hidradenocarcinoma. Thereupon, a systemic scan was performed by the oncology department. No metastases were found. No recurrence was detected in the 6-month follow-up of the patient. Contrast-enhanced brain tomography revealed a non-contrast-enhancing appearance compatible with postoperative changes (Figure 1b).





**Figure 1.** Pre-operative computer tomography image (A), Post-operative computer tomography image (B).



**Figure 2.** Tumor cells arranged in nodules with comedonecrosis (H&E,  $\times 40$ ) (A), Atypical cell groups with prominent nucleoli, eosinophilic, and mostly clear vacuolized cytoplasm (H&E,  $\times 200$ ) (B), EMA positivity in neoplastic cells (EMA,  $\times 100$ ) (C), Ki67 staining in %60 of neoplastic cells (Ki67,  $\times 100$ ) (D)

### 3. Discussion

Hidradenocarcinoma is a rare, aggressive, metastatic tumor of eccrine sweat glands. It constitutes less than 0.01% of all skin cancers and is mostly seen between the ages of 50-60, as in our case.(Elbenaye et al., 2017; Soni et al., 2015) In the literature, recurrence rates and metastasis rates have been reported as over 50%, and in our 6-month follow-up, no significant findings and radiological images were found in terms of metastasis and recurrence.(de Lima et al., 2021) In empirical

treatment, wide resection is considered first.(Elbenaye et al., 2017; Soni et al., 2015) However, in our case, we performed total resection because we did not consider a malignant skin appendage tumor in the preliminary diagnosis. After learning the pathology result, we decided not to consider a surgical intervention again and to follow up closely. Although adjuvant radiotherapy after surgery is recommended in some sources, there is no definite consensus on it.(Soni et al., 2015) We did not consider radiotherapy because of the good clinical

condition of our patient and the absence of recurrence and metastasis in the early and 6-month follow-ups. It is stated in the literature that systemic chemotherapy can be given to metastatic hidradenoma. Since no metastasis was detected in our case, systemic chemotherapy was not considered.

### Author Contributions

Concept: G.K. (25%), S.T. (25%), S.D. (25%) and A.K. (25%), Design: G.K. (25%), S.T. (25%), S.D. (25%) and A.K. (25%), Supervision: G.K. (25%), S.T. (25%), S.D. (25%) and A.K. (25%), Data collection and/or processing: G.K. (25%), S.T. (25%), S.D. (25%) and A.K. (25%), Data analysis and/or interpretation: G.K. (25%), S.T. (25%), S.D. (25%) and A.K. (25%), Literature search: G.K. (25%), S.T. (25%), S.D. (25%) and A.K. (25%), Writing: G.K. (25%), S.T. (25%), S.D. (25%) and A.K. (25%), Critical review: G.K. (25%), S.T. (25%), S.D. (25%) and A.K. (25%), Submission and revision G.K. (25%), S.T. (25%), S.D. (25%) and A.K. (25%). All authors reviewed and approved final version of the manuscript.

### Conflict of Interest

The authors declared that there is no conflict of interest.

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Written an informed consent form was obtained from the patient/s for the case presentation, and necessary information was given to the family.

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## ÜRİNER İNKONTİNANS TEDAVİSİNDE POSTERİOR TİBİAL SİNİR STİMÜLASYONUN ETKİNLİĞİ

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**Özet:** Üriner inkontinans (Üİ) istemli olarak idrar tutamama ya da istemsiz idrar kaçırma olarak bilinir. Üİ üretral yoluyla veya ektoptik üretra nedeniyle olabilir. Konservatif tedavi, üriner inkontinans hastalarının birçoğunda minimum yan etki ve semptomları kötüleştirmemesi nedeniyle birinci basamak tedavi yöntemi olarak kabul edilir. Fizyoterapi yaklaşımında mesane eğitimi, pelvik taban kaslarının eğitimi, biofeedback, elektrik stimülasyonu yer alır. Elektrik stimülasyonu, fizyoterapi klinik uygulamada Üİ tedavisi için kullanılabilir yöntemler arasındadır. Transkutanöz tibial sinir stimülasyonu (TTNS), tibial sinir yolundaki elektrostimülasyon yoluyla detrusor kasının inhibisyonunu kolaylaştırmayı amaçlar. TTNS, hastalar için konservatif ve etkili tedavi olarak kabul edilen basit, non-invaziv, iyi tolere edilebilen bir tekniktir. Ayrıca bu tedavi yönteminin kolay uygulanabilir olması, cihazın kolay taşınabilir olması ve hastalarda ağrıya neden olmaması gibi avantajları mevcuttur. Posterior tibial sinir medial malleolusun üstüne boyunca uzanan bölgede, yüksek yanıt ve geleneksel olarak çeşitli üriner şikayetlerin giderilmesini amaçlayan akupunktur noktasına (spleen-6) karşılık gelen bir alan belirlenmiştir. Trankutanöz Posterior Tibial Sinir Stimülasyonu (TPTSS) non-invaziv bir girişimdir ve sistemik bir yan etki bulunmamaktadır. Tarama başlangıç tarihi 2012 yılından itibaren (son on yıl) belirlenen veri tabanlarında Şubat 2022 tarihine kadar yer alan konuyla ilgili tüm araştırmalar incelenmiştir. Tibial sinir ve üriner inkontinans "tibial nerve and urinary incontinence" anahtar kelimeleri yazılarak arama yapıldığında, Pubmed, Science Direct ve Google Scholar' da gelişmiş aramalarda sadece başlıklar seçilerek yapılan taramada 29 çalışmaya rastlanmıştır. Yapılan tarama sonucunda ilgili makaleler detaylı olarak incelenmiş ve yedi makalenin dahil edilme kriterlerine uygun olduğu belirlenmiştir. İncelenen çalışmalarda TPTSS tedavi yönteminin daha çok kullanıldığı, bu yöntemin plasebo gruplarıyla veya farklı bölgelere uygulanarak kıyaslandığı belirlenmiştir. Genel olarak TPTSS tedavi yönteminin uygulandığı grubun sonuçlarının, diğer karşılaştırılan gruplara göre daha anlamlı olduğu saptanmıştır (P<0.05). TPTSS, tam olarak standardize edilmemiş bir tedavi tekniğidir. Bu bağlamda elektrik stimülasyonun optimal parametrelerini, en etkili tedavi protokollerini, tedavi yönteminin uzun vadeli etkinliğini ve hastalara uygulanabilirliğini belirlemek amacıyla yeni çalışmalara ihtiyaç vardır.

**Anahtar kelimeler:** Posterior, Transkutanöz, Tibial sinir stimülasyonu, Üriner inkontinans

### Efficacy of Posterior Tibial Nerve Stimulation in the Treatment of Urinary Incontinence

**Abstract:** Urinary Incontinence (UI) is known as voluntary urinary incontinence or involuntary urinary incontinence. UI may be via the urethra or due to the ectopic urethra. Conservative treatment is considered first-line therapy for most urinary incontinence patients, as it has minimal side effects and does not worsen the patient's symptoms. The physiotherapy approach includes bladder training, pelvic floor muscle training, biofeedback, and electrical stimulation. Electrical stimulation physiotherapy is one of the methods that can be used for the treatment of UI in clinical practice. Transcutaneous tibial nerve stimulation (TTNS) aims to facilitate the inhibition of the detrusor muscle through electrostimulation in the tibial nerve pathway. TTNS is a simple, non-invasive, well-tolerated technique that is considered a conservative and effective treatment for patients. In addition, it has advantages such as being easy to apply, being easily portable and not causing pain in patients. In the region extending along the posterior tibial nerve above the medial malleolus, an area corresponding to the acupuncture point (spleen-6), aimed at the high response and the traditional relief of various urinary complaints, has been identified. TPTSS is a non-invasive procedure and has no systemic side effects. All researches related to the subject in 2012 (last ten years) and until February 2022 in the determined databases were examined. When searching by typing "tibial nerve and urinary incontinence", 29 studies were found by selecting only titles in advanced searches in PubMed, Science Direct, and Google Scholar. These results have been studied in detail. At the end of the review, seven articles were found to be suitable. TPTSS was used more in studies and compared with placebo or application to another site. In general, the results of the TPTSS group were more significant than the other groups (p<0.05). TPTSS is not a fully standardized technique. In this context, new studies are needed to determine the optimal parameters of electrical stimulation, the most effective treatment protocols and long-term efficacy and applicability to patients.

**Keywords:** Posterior, Transcutaneous, Tibial nerve stimulation, Urinary incontinence

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## 1. Giriş

Üriner İnkontinans (Üİ) istemli olarak idrar tutamama ya da istemsiz idrar kaçırma olarak bilinir. Üİ, üretral yoluyla veya ektopik üretra nedeniyle olabilir. Uluslararası Kontinans Derneği'ne (UKD) göre Üİ; istemsiz idrar kaçırmanın objektif olarak gösterilebilen, sosyal ya da hijyenik sorunlara yol açan durum olarak tanımlanır (Abrams ve ark., 2003). Dünya' da ve Türkiye' de yaygın olması bu sorunun önemini göstermektedir (Kaşıkçı ve ark., 2015).

Üİ, yaşlılar ve kadınları daha çok etkileyen önemli halk sağlığı sorunudur. Üİ, yaşam kalitesini, önemli derecede azaltmaktadır. Üİ Avrupa popülasyonunda %1.8-30.5, Amerika Birleşik Devletleri' nde %1,7-36.4 ve Asya popülasyonlarında %1.5-15.2' dir (Padilha ve ark., 2020). Irwin ve ark. (2010) yaptığı çalışmaya göre Dünya' da 20 yaşından büyüklerin %8,7' si (>423 milyon), kadınların %12,4'ü (303 milyon), erkeklerin ise %5' i (121 milyon) üriner inkontinans hastasıdır (Irwin ve ark., 2011). Ülkemizde yapılan bir araştırmada, <65 yaş 543 kadının % 43,6' sında Üİ tespit edilmiştir (Bilgili ve ark., 2008). Yapılan başka bir çalışmada, ortalama yaşı 72 olan erkek hasta grubunda Üİ prevalansının %21,5 olduğu saptanmıştır (Ateşkan ve ark., 2000).

UKD' nin sınıflandırmasına göre, üriner inkontinansın en sık görülen tipleri; Stres Üİ, Urge Üİ ve miks Üİ' dir. Stres inkontinans; efor, hapsirme, gülme veya öksürük esnasında, urge inkontinans; sıkışma esnasında ya da hemen sonrasında oluşan inkontinanstır. Miks tip inkontinans ise urge ve stres inkontinansın birlikte görüldüğü inkontinans tipidir (Abrams et al. 2003). Literatürde, stres inkontinans oranının %10-39, urge inkontinans oranının %1-7, miks inkontinans oranının %7-15 arasında olduğu belirtilmiştir (Irwin ve ark., 2011). Üİ sadece alt üriner sistem enfeksiyonlarına ve perinal döküntülere yol açan ciddi bir tıbbi sorun olarak değil, aynı zamanda utanma duygusu ve olumsuz benlik algısı yaratan psikososyal sorun olarak da sınıflandırılmalıdır. Bu durum kişilerin yaşam kalitesini, sosyal ilişkilerini, psikososyal sağlık durumunu, mesleki yaşantısını ve seksüel hayatını önemli ölçüde etkiler. Üİ sorununun sosyal etkileşimde ve fiziksel aktivitelerde azalmaya neden olduğu, psikososyal sağlık durumunu olumsuz etkilediği, yaşam kalitesini azalttığı ve depresif semptomlarla ilişkili olduğu belirtilmiştir. Utanma duygusu ve sosyal ilişkilerde dışlanmaya neden olan bu sorun kişilerin eğitim süreçlerini, mesleki hayatlarını ve sosyal aktivitelerinin kısıtlanmasına neden olmaktadır (Özdemir ve Surmeli, 2017).

Üİ yaşla artan bir sorun olmakla birlikte, genç yaşta da görülmektedir. Kadınlarda daha sık görüldüğü belirtilmiştir (Altınboğa ve ark., 2012). Alta yatan nedenler arasında: fiziksel aktivitenin azlığı, gebelik, östrojen eksikliği, obezite, kabızlık, pelvik organ prolapsusları, anatomik anomaliler, diyabetes mellitus, depresyon ve histerektomi yer almaktadır (Onur ve Bayrak, 2015). Genç erkeklerde daha nadir görülmekle birlikte, yaşla beraber oranın arttığı ve prostatektomi gibi

cerrahi girişimlerden sonra daha sık görüldüğü saptanmıştır. Ayrıca ileri yaş, demans, kognitif problemler ve santral sinir sistemi lezyonlarının her iki cinsiyeti de eşit oranda etkilediği belirtilmiştir (Khandelwal ve Kistler, 2013).

### 1.2. Konservatif Tedavi

Üİ tedavisi için çeşitli tedavi seçenekleri mevcut olmakla birlikte başlangıçta cerrahi olmayan yöntemler tercih edilmektedir. Konservatif tedavi, birçok Üİ hastasında yan etkinin minimum olması ve hastanın semptomlarını kötüleştirmemesi nedeniyle birinci basamak tedavi olarak kabul edilmektedir (Schreiner ve ark., 2010).

Üİ tedavisinde, yaşam tarzı değişiklikleri, ilaç tedavisi veya cerrahi müdahale yöntemleri uygulanmaktadır. Tedavi önerileri Üİ tipine göre değişmektedir, ancak tüm tiplerin tedavisi, hastalığa yönelik sonuçlardan ziyade, öncelikle hastanın yaşam kalitesinin iyileştirilmesine odaklanmaktadır. Bu nedenle hastanın tercihinine göre tedavi yöntemi uygulanmalıdır. Üİ olan tüm hastaların baş etme becerilerini geliştirmek ve genel yaşam kalitesini iyileştirmek amacıyla psikolojik destek alması sağlanmalıdır (Irwin ve ark., 2019). Yaşam tarzı değişikliği (diyet uygulanması, kafeinsiz içecekler tüketilmesi, sıvı alımının azaltılması, fiziksel aktivitenin artırılması, sigara kullanımının azaltılması veya bırakılması) semptomları azaltmaktadır. Üİ' de konservatif tedavinin amacı semptomları azaltmak ve günlük yaşam aktivitelerine katılımı arttırmaktır. Üİ tedavisinde, mevcut rehberler, konservatif tedavinin uygulanmasını önermektedir (Schreiner ve ark., 2013). Üİ' de birinci basamak tedavi olarak inkontinans tipine yönelik ilaç tedavisi veya cerrahi olmayan yöntemlerin kullanılması önerilmektedir. Özellikle doğurganlık sürecini tamamlamamış ve hafif semptomları olan kadınlar için konservatif tedavi ve fizyoterapi seçeneği önemli bir tedavi yöntemidir. Fizik tedavi yöntemleri, Üİ ve diğer alt üriner sistem semptomlarını tedavi etmek için yaklaşık 20-30 yıldır kullanılmaktadır. Çeşitli disiplinler tarafından benimsenmiş olan bu yöntemler birçok farklı şekilde uygulanmaktadır (Özdemir ve Surmeli, 2017).

#### 1.2.1. İlaç tedavisi

Urge inkontinanstaki antikolinergik tedavi ve trisiklik antidepressanlar farmakoterapinin ana unsurudur. Detrusor kasının istemsiz kontraksiyonları azaltmaya yardımcı olmaktadır. Stres inkontinanstaki ilaç tedavisinin sınırlı etkisinin olduğunu belirten çalışmalar olmasına rağmen serotonin, noradrenalin re-uptake inhibitorlerinin etkinliğini destekleyen çalışmalar mevcuttur (Hashim ve Abrams, 2006). Tedavide kullanılan ilaçların yan etkileri ya da tedavi sürecindeki bazı eksiklikler nedeniyle çeşitli alternatif tedavi yöntemleri oluşturulmaya çalışılmaktadır

### 1.2. İnkontinans Tedavisinde Fizyoterapi

Üİ tedavisinde fizyoterapinin amacı; zayıf olan pelvik taban kas kuvvetini artırmak, üriner semptomları azaltmak, hastalığın sosyal ve emosyonel sağlık üzerine olan olumsuz etkilerini en aza indirmek (Güler ve Yağcı, 2006). Fizyoterapi yaklaşımında mesane eğitimi, pelvik

taban kaslarının eğitimi, biofeedback, elektrik stimülasyonu yer almaktadır (Ladi-Seyedian, Sharifi-Rad, and Kajbafzadeh 2019; Gaspard ve ark., 2014).

### 1.2.1. Mesane eğitimi

Hastaya idrar günlüğü doldurularak gün içinde tuvalete çıkma sıklığı belirlenir. İlk hafta idrar sıklığı 30-60 dk. olarak tanımlanır ve hastada bu idrar sıklığı olmasa bile belirlenen zaman aralığına göre tuvalete gitmesi istenir. Hastaya süre gelmeden önce idrar hissi olsa bile tuvalete çıkmaması gerektiği, zaman aralığı dolduğunda ise idrar hissi olmasa da idrar yapmaya çalışması gerektiği ifade edilir. İdrar sıklığı hastanın programa olan uyumu ve başarısına göre her hafta 15-30 dk. arasında düzenli olarak artırılır. Böylece mesane kapasitesi ve kompliansı artarak idrar yapma aralığı 3-4 saate kadar çıkarılmaya çalışılır (Güler ve Yağcı, 2006).

### 1.2.2. Pelvik taban egzersizleri

İlk kez 1948' de Arnold Kegel tarafından tanımlanmıştır. Pelvik Taban Egzersizleri (PTE)'nde hedef; pelvik taban kaslarını kuvvetlendirme, üretral sfinkter fonksiyonunu daha iyi hale getirmektir. PTE ile daha yüksek kortikal kontrol ve kas kuvvetinde artış sağlanması hedeflenir (Imamura ve ark., 2013). Bertotto ve ark. (2017), post-menopozal inkontinansı olan 49 kadın ile yaptıkları çalışmada, pelvik taban egzersizleri ve pelvik taban egzersizleri+biyofeedback gruplarında maksimum istemli kontraksiyonda, kontraksiyonun kasılma süresinde ve öksürme sırasındaki kontraksiyonda anlamlı derece artış olduğunu saptamıştır.

### 1.2.3. Biofeedback

Pelvik taban kaslarının kontraksiyonu ve gevşemesi görüntü ve ses aracılığı ile hasta tarafından anlaşılır hale getirilir. Böylece hastanın pelvik taban kas fonksiyonlarını istemli düzenlemesi sağlanır. Bu yöntemle hasta pelvik taban kaslarının kasılmasını belirleyebilir ve abdominal kaslarda kontraksiyon olmaksızın pelvik taban kasları seçici olarak kullanabilmeyi öğrenir (Güler ve Yağcı, 2006).

### 1.2.4. Elektriksel stimülasyon

İlk kez 1963' te Calwell tarafından uygulanmıştır (Özcan ve Ötünçtemur, 2021). Üriner inkontinansın elektriksel stimülasyon (ES) ile tedavisinde faradik akım veya enterferansiyel akım ya da yüksek frekanslı akım olan transkutaneal elektrik stimülasyonu kullanılır. Fakat faradik akım ağrıya neden olması ve toleransının zor olması ve hastada yanık olma olasılığı nedeniyle günümüzde tercih edilmemektedir (Gümüşsoy ve Kavlak, 2016). ES' de temel yöntem, pudental sinirin iyi bir şekilde uyarılmasıdır. Pudental sinir afferentlerin elektriksel uyarılması polisınaptik refleks cevaba yol açar. Pudental sinirin uyarılması ile hipogastrik ve pelvik sinirin refleks stimülasyonu ile detrüsor inhibisyonu sağlanır (Akman ve Soyuer, 2017). Bu etkiyi oluşturmak için frekansı daha küçük olan 5-10 Hz arasında değişen enterferansiyel akım kullanılır (Güler ve Yağcı, 2006; Gümüşsoy ve Kavlak, 2016).

### 1.3. Tibial Sinirin Stimülasyonu

Tibial sinirin stimülasyonu, miksiyon reflekslerinin periferik halkaların uyarımı ile nöral cevabın oluşması amaçlanır. İlk uygulaması 1966'da McPherson tarafından yapılmıştır. McPherson kediler üzerinde yaptığı deneysel çalışmada periferik stimülasyon yaparak tibial siniri de stimüle etmiş ve bu stimülasyon detrüsor kasının inhibisyonuyla sonuçlanmıştır (McPherson 1966).

Nervus İschadicus, L4 - S2 vertebral aralığındaki köklerden çıkan, vücutta bulunan en uzun sinirdir. Peroneal ve posterior tibial olmak üzere iki dala ayrılır. Tibial sinir L5, S1-S2 radikallerden lifler alır. Bacağın arkasından, orta hattan en distale gelir. Ayak tabanı, topuk, parmakların duyusunu sağlar ve ayağın plantar fleksiyonunu yapan kasları innerve eder. Bacakta derin ve yüzeysel kaslar arasında a. tibialis posterior ile birlikte iç malleolun arkasına kadar uzanır (Aydos, Nas ve Önen, 2020).

Elektrik stimülasyonu fizyoterapi klinik uygulamada Üİ tedavisi için kullanılacak yöntemler arasında yer almaktadır. Transkutanöz tibial sinir stimülasyonu (TTNS), tibial sinir yolundaki elektrostimülasyon yoluyla detrüsor kasının inhibisyonunu kolaylaştırmayı amaçlar. Tibial sinir, mesanenin parasempatik yolunu (S2-S4) innerve eden köklerle aynı kök olan L5-S3 sinir köklerinden köken alan mikst bir sinirdir. Tibial sinirin doğrudan uyarılmasının S2-S3 afferentlerini inhibe edebileceği ve böylece detrüsor hiperaktivitesini azaltabileceği görülmüştür. Bu mekanizma ile TTNS, hastalar için konservatif ve etkili tedavi olarak kabul edilen basit, non-invaziv, iyi tolere edilebilen bir tekniktir (Padilha ve ark., 2020). Ayrıca bu tedavi yönteminin kolay uygulanabilir olması, cihazın kolay taşınabilir olması ve hastalarda ağrıya neden olmaması gibi avantajları mevcuttur (Agost-González ve ark., 2021).

#### 1.3.1. Posterior tibial sinir stimülasyonu

PTSS 1970-1980'lerde sakral nöromodülasyonda, McGuire 1983'te tibial sinir stimülasyonunu ilk kez kullanmıştır. Nörolojik bir detrüsor aşırı aktivitesi olan 15 hastada transkutanöz posterior tibial sinir stimülasyonunu uygulamıştır (McGuire ve ark., 1983). McGuire'in çalışmasından ilham alan Marshall Stoller, alt üriner sistem disfonksiyonunda tedavi olarak perkütan tibial sinir stimülasyonu (PTNS) üzerine araştırmalara başlamıştır. Maymunlarda yapılan ilk testlerden sonra, PTSS umut verici sonuçlar ortaya çıkmıştır. Bu yeni girişim, PTNS'nin dünya çapında geliştirilmesinin başlangıcıdır (Stoller ve ark., 1987). 1999'da PTSS klinikte ilk kez kullanılmaya başlamış olup, ilk yayın van der Pal tarafından 2006'da, ilk randomize kontrollü çalışma Peter tarafından 2009'da yapılmıştır (Wolff ve Krlin, 2018). PTSS üriner inkontinans, kronik pelvik ağrı ve cinsel işlev bozukluğunun tedavisinde kullanılmaya başlanmıştır (Findlay ve Maxwell-Armstrong, 2011).

Posterior tibial sinir, L4-S3 tarafından uyarılan, pelvik tabanın otonomik, somatik sinirlerini ve sakral sinir dallarından oluşur. Direkt mesane ve üriner sfinkter tarafından innerve olan karışık etkili bir motor duyu

siniridir. Medial malleolun üstüne posterior tibial sinir boyunca uzanan bölgede, yüksek yanıt ve geleneksel olarak çeşitli üriner semptomların giderilmesini amaçlayan akupunktur noktasına karşılık gelen bir alan belirlenmiştir. Posterior Tibial Sinir Stimülasyonu (PTSS) non-invaziv bir uygulamadır ve sistemik bir yan etkisi bulunmamaktadır. Nadiren mide ağrısı yan etkisi olabilmektedir (Bertotto ve ark., 2017; Sucar-Romero ve ark., 2014). PTSS ucuz, (ilk olarak üriner inkontinanslı hastaları tedavi etmek için kullanılır) güvenli ve etkinliği çok sayıda yayında belirlenmiştir (Grepe ve ark., 2009). Tibialis sinirin stimülasyonu implante elektrotlarla, minimal invaziv ve non-invaziv perkutanöz elektrotlarla yapılabilir. Literatürde, transkutanöz tibial sinir stimülasyonunun alt üriner sistem semptomları için etkili, iyi tolere edilen ve güvenli minimal invaziv bir tedavi olduğunu gösteren çalışmalar bildirilmiştir. TTSS bir avantajı, hastaların hastaneye gitmeye gerek kalmadan da evde kendilerini tedavi edebilmeleridir (Zecca ve ark., 2016).

### 1.3.2. Cerrahi Tedavi

Konvansiyonel tedaviye yanıt vermeyen inatçı vakalarda, cerrahi seçenekleri arasında minimal invaziv (botulinum enjeksiyonu, sakral veya tibial nöromodulasyon) veya detrüsor myomektomi gibi daha radikal yöntemler uygulanabilir (White ve Iglesia, 2016).

Günümüzde cerrahi yöntemlerin maliyetinin yüksek olması, iş gücü kaybına neden olması ve cerrahi sonrasında komplikasyon riski barındırması nedeniyle konservatif yöntemlere olan ilgiyi arttırmaktadır. Konservatif tedavi yönteminin temelini pelvik taban egzersizleri oluşturmaktadır. Fakat bireylerin egzersizleri öğrenmesi ve etkili şekilde egzersizi uygulaması zor olabilmektedir (Şahin ve ark., 2021). PTSS tedavi yönteminin kolay uygulanabilir olması, düşük maliyetli olması ve komplikasyon oluşma riskinin çok düşük olması nedeniyle yeni bir tedavi seçeneği olabileceği düşünülmektedir. Bu derleme; Üİ tedavisinde PTSS etkinliğini araştırmak amacıyla planlanmıştır.

## 2. Yöntem

İnkontinans tedavisinde tibialis sinir uyarımının da kullanımı ile ilgili tibial sinir ve inkotinans anahtar kelimeleri yazılarak (tibial nerve and incotinenca) PubMed, Science Direct ve Google Scholar' da tarama yapılmıştır.

Dahil edilme kriterleri;

- 2012-2022 yılları arasında randomize kontrollü çalışmalar, prospektif kohort çalışmaları ve araştırma protokolleri,
- Çalışmanın en az bir kolunda elektrik stimülasyonu kullanılması ve kullanılan tekniğin metodolojide açıkça belirtilmiş olması,

Dışlanma kriterleri;

- Yayın dili İngilizce ve Türkçe dışında olan araştırmalar,

- Üriner inkontinans ile ilgili sonucu olmayan hastalarla yapılan araştırmalar,
- Spesifik olarak elektriksel stimülasyon tedavisi uygulanmamış olan araştırmalar,

Belirlenen veri tabanlarında (Pubmed, Science direct, Google Scholar) Şubat 2012 yılı ile Şubat 2022 tarihleri arasında ki son on yılda konu ile ilgili yapılan araştırmalar incelenmiştir.

Tibial sinir ve üriner inkotinans "tibial nerve and urinary incotinenca" anahtar kelimeleri yazılarak tarama yapıldığında, Pubmed veri tabanında 94, Science direct veri tabanında 396, Google Scholar veri tabanında gelişmiş aramalarda sadece başlıklar seçilerek yapılan taramada 29 çalışmaya rastlanmıştır. Tarama sonuçları detaylı olarak incelenmiş ve dahil edilme kriterlerini sağlayan yedi araştırma değerlendirmeye alınmıştır. Bu derlemenin amacı non-invaziv elektrik stimülasyonun inkotinansa etkilerini araştırmaktır.

İncelenen araştırmalarda tibialis sinir uyarımının inkontinans tedavisinde kullanımı üzerine odaklanılmıştır. Konuyla ilgili araştırma sonuçları Tablo 1' de yer almaktadır. Bu tedavi yaklaşımlarının karşılaştırmalı sonuçları incelenmiştir. Bu derlemede, üriner inkontinans tedavisinde kullanılan elektrik stimülasyonu üzerine yayınlanmış randomize kontrollü çalışmalar, prospektif kohort çalışmaları ve araştırma protokolleri değerlendirilmiştir. Tabloda yer alan çalışma sonuçlarının literatüre önemli katkı sağlayacağı ve yapılması planlanan araştırmalara yol göstereceği düşünülmektedir.

## 3.Sonuç

Çalışmalarda King sağlık anketi, 24-saatlik idrar miktarı, uluslararası inkontinans konsültasyon sorgulama anketi-kısa form, uluslararası inkontinans konsültasyonu aşırı aktif mesane, demans yaşam kalitesi, rezidüel idrar hacmi, idrar günlüğü, gündüz idrar kaçırma sıklığı, vizüel analog skala gibi ölçekler ve değerlendirmeler kullanılmıştır.

Tedavi süreleri incelendiğinde, tedavi süresinin 4-12 hafta arasında değiştiği, haftada bir veya iki seans şeklinde ortalama 30 dk civarında uygulandığı, kullanılan akım parametrelerinin 20Hz, 200µs şeklinde olduğu belirlenmiştir (Booth ve ark., 2021; Valles-Antuña ve ark., 2017; Garcia ve Pereira, 2018).

Elektrotların uygulanma şekilleri aşağıda ki görselde yer almaktadır (Şekil 1). Elektrotlar, ayak bileğinin medial malleolunun hemen arkasına ve bunun yaklaşık 10 cm yukarısına bantla sabitlenecek şekilde yerleştirilmiştir (Padilha ve ark., 2020).

Çalışmalarda TPTSS yönteminin daha çok kullanıldığı, bu yöntemin plasebo gruplarıyla veya farklı bölgelere uygulanarak kıyaslandığı belirlenmiştir. Genel olarak TPTSS tedavi yönteminin uygulandığı grubun sonuçlarının, diğer karşılaştırılan gruplara göre daha anlamlı olduğu saptanmıştır (p<0.05). (Schreiner ve ark., 2013). TPTSS, tam olarak standardize edilmemiş bir tedavi tekniğidir. Bu bağlamda elektrik stimülasyonun

optimal parametrelerini, en etkili tedavi protokollerini, tedavi yönteminin uzun vadeli etkinliğini ve hastalara uygulanabilirliğini belirlemek amacıyla yeni çalışmalara ihtiyaç vardır (Valles-Antuña ve ark., 2017).

#### 4. Tartışma

Kanada Üroloji Derneği Kılavuzu (2017), Yetişkinlerde Üriner İnkontinans için Avrupa Üroloji Birliği Kılavuzu (2018) ve Amerikan Üroloji Derneği, Kadın Pelvik Tıp ve

Ürogenital Rekonstrüksiyon Kılavuzu, Üİ hastalarda TTSS tedavi yönteminin kanıt düzeyini B ve C olarak bildirmişti (Corcos ve ark., 2017; Nambiar ve ark., 2018). Bu tedavi yöntemi de basit, non-invaziv ve yan etkisi olmayan bir yöntemdir. Bu nedenle hastaların terapiyi kabul etmesini kolaylaştıran bir tekniktir. TTNS ile ilgili yapılan çalışmalara plasebo gruplarının da eklenmesi elektrik stimülasyonunun gerçek etkinliğinin değerlendirilmesi açısından önemlidir (Padilha ve ark., 2020).

**Tablo 1.** Tibial Sinir Stimülasyon Uygulamasının İnkontinans Üzerinde ki etkileri

Yazarlar	Çalışma tipi	Örneklem grubu	Örneklem büyüklüğü	Tedavi Grubu	Veri Toplama Aracı	Tedavi Süresi	Sonuç
Padilha ve ark., 2020	RCT	DG 1, 2 KG 1	99	TTSS, PTES	OAB-V8, ICIQ-OAB, KSA, 24-SİM	6hf,12s (10 Hz, 200 µs, 20dk) 4hf,12s	Araştırma protokolü
Schreiner ve ark., 2020	RCT	DG, KG	106	TTNS	UİKSA-KF, KSA,	(10 Hz, 200 µs, 30dk)	TTNS grubunun, yaşam kalitesi kontrol grubuna kıyasla anlamlı derecede arttığı saptanmıştır.
Oliveira ve ark., 2021	RCT	DG 1; DG 2;	32	PTKE, TTNS+ PTKE	PTM, UİKSA-KF, UİKA-AAM,	8hf,16s (20 Hz, 200 µs, 30 dk)	TTNS+PTKE grubunda, PTKE grubuna göre memnuniyet düzeylerinin daha yüksek olduğu belirlenmiştir.
Booth ve ark., 2021	RCT	DG 1; DG 2;	408	TPTSS, SG	DYK	6hf,12s (30 dk)	TPTSS ve SG grupları arasında anlamlı fark gözlenmediği saptanmıştır.
Ibrahim Seada ve ark., 2017	RCT	DG 1; DG 2;	30	MEFP+ SG, MEFP+ PPTNS,	EMG, SÖ, RİH	12hf,36s (40 dk)	MEFP+PPTNS grubunda, sham grubuna göre anlamlı derecede gelişme gözlemlendiği saptanmıştır.
Valles-Antuna ve ark., 2017	PKÇ	TÖ, TS	65	TPTSS	İG, GİKS, GİH,	10hf,10s (20 Hz, 200 µs, 30 dk)	Belirtilen değişkenlerin tüm semptom skorlarında (İG, GİKS, GİH) istatistiksel olarak anlamlı iyileşmeler olduğu saptanmıştır.
Şahin ve ark., 2021		TÖ, TS	13	EES	VAS, EP, 24-SPT)	8hf, 24 s (30dk)	Tedavi sonrasında, üriner inkontinansın yaşam kalitesi üzerine algılanan etkisinde olumlu ve anlamlı yönde gelişme gözlemlendiği saptanmıştır.

RCT= randomize kontrollü, PKÇ= prospektive kohort çalışması, DG= deney grubu, KG= Kontrol Grubu, TTSS= Transkutanöz tibial sinir stimülasyonu, PTES= Parasakral Transkutanöz Elektrik Stimülasyonu, PTKE= Pelvik Taban Kas eğitimi, TPTSS= Transkutanöz Posterior Tibial Sinir Stimülasyonu, SG= Sahte (sham) grup, OAB-V8= Incontinence Overactive Bladder-Validated 8-Question Awareness Tool, ICIQ-OAB= Incontinence Questionnaire Overactive Bladder, KSA= King Sağlık Anketi, 24-SİM= 24-Saatlik İdrar Miktarı, UİKSA-KF= Uluslararası İnkontinans Konsültasyon Sorgulama Anketi-Kısa Form, PTM= Pelvik Taban Monometresi, UİKA-AAM= Uluslararası İnkontinans Konsültasyonu Aşırı Aktif Mesane, DYK= Demans Yaşam Kalitesi, MEFP= Mesane Eğitimi Fizyoterapi Programı, PPTNS= Perkütan Posterior Tibial Sinir Stimülasyonunun, EMG Elektromiyografi, SÖ= Sistometre Ölçümü, RİH= Rezidüel İdrar Hacmi, İG= İdrar Günlüğü, GİKS= Gündüz İdrar Kaçırma Sıklığı, GİHv Gece İdrar Hacmi, EES= Eksternal Elektrik Stimülasyonu, VAS= Vizüel Analog Skala, EP= Endurans Perinometre, 24-SPT= 24 Saatlik Ped Testi, hf= Hafta, sv Seans, HZ= Hertz.



**Şekil 1.** Transkutanöz tibial sinir stimülasyonu (Padilha ve ark., 2020).

Son yıllarda yapılan bir sistematik derleme çalışmasında, TTSS elektroterapi uygulaması için parametreler, seans sayısı ve tedavi süresi gibi protokol standardizasyonunun eksikliğine dikkat çekmiştir. Belirli hasta alt gruplarının etkinliğinin yanı sıra ideal stimülasyon programı ve tedavi süresi ile ilişkili etki boyutlarının büyüklüğünü doğrulamak için daha fazla araştırmaya ihtiyaç olduğu belirtilmiştir. Yapılan prospektif bir kohort çalışmasında, Üİ' li gönüllülerde TTNS ile tedaviden sonra tüm klinik parametrelerde, tedavi sırasında hiçbir yan etki olmaksızın, anlamlı semptomatik iyileşme olduğu saptanmıştır. Literatürde bu tedavi yöntemi ile ilgili hala boşluklar olduğu, bu nedenle TTNS kullanılarak çalışma protokolünün geliştirilmesini güçlendiren daha tutarlı yöntemler ile yapılan çalışmalara ihtiyaç olduğu belirtilmiştir (Padilha ve ark., 2020). Schreiner ve ark. (2010) yaptıkları çalışmada, TTNS' nin (10 Hz/200 ms) 12 hafta boyunca yapılan Kegel egzersizlerine kıyasla urge inkontinans tedavisinde daha etkili olduğunu belirtmiştir (Schreiner ve ark., 2010). Şahin ve ark. (2021) yaptıkları çalışmada, üriner inkontinansı olan hastalara uygulama eksternal elektrik stimülasyonunun algılanan yaşam kalitesini iyileştirdiği ve farkın istatistiksel olarak anlamlı olduğunu belirtmiştir (Şahin ve ark., 2021).

Üİ tedavisinde elektrik stimülasyon tedavi yönteminin kullanılmasının, maliyet etkinliği ile ilgili yeterince çalışma mevcut değildir. Elektrik stimülasyonu inkontinans tedavisinde hastalarda uygulanma kolaylığı nedeniyle en düşük maliyetli tedavi olabilir. Ayrıca yapılan araştırmalarda elektrik stimülasyon yönteminin uygulanması ile ilgili herhangi bir komplikasyon bildirilmemiştir. Bu tedavi yönteminin etkinliğini belirlemek amacıyla daha fazla araştırma yapılması gerekmektedir. Ayrıca sonuçların zaman içinde devam edip etmediğini belirlemek amacıyla uzun süreli takip ve değerlendirmeler yapılması önerilmektedir (Schreiner ve ark., 2013).

Literatürde yapılan çalışmalarda non-invaziv tedavi yöntemlerinden biri olan Tibial sinir stimülasyon yönteminin yaşam kalitesini arttırdığı ve ürodinamik bulgulara daha iyi sonuçlarla karşılaştığı belirtilmiştir

(Seth ve ark., 2018). Üİ' yi tedavi etmek için kullanılan birçok yöntem, başlangıçta iyi sonuçlar oluşturmalarına rağmen zamanla başarısız olmaktadır. Bu nedenle Üİ tedavisinde tedavinin devamlılığı, yeniden tedavi gerektirmemesi, semptomların kalıcı olarak azalması veya tamamen geçmesi temel kriterdir (Van Balken ve ark., 2001; Skeil ve Thorpe 2001).

Stewart ve ark. (2016) yaptığı sistematik derleme çalışmasında elektrik stimülasyon tedavisinin, plasebo tedavisi ve ilaç tedavisine kıyasla daha olumlu sonuçlar verdiğini gösterilmiştir. Yapılan birkaç çalışmada, Üİ tedavisinde üriner atakların en az %50 oranında azalması halinde yapılan uygulamanın etkili olduğu belirtilmektedir (Stewart ve ark., 2016). Schreiner ve ark. (2021) yaptıkları çalışmada, hastaların %82,4 oranında üriner atakların azaldığını ve elektrik stimülasyonun etkili bir tedavi yöntemi olduğunu belirtmiştir. Tekrarlayan semptomları olan hastalarda gerilemenin asıl nedeni hala bilinmemektedir, fakat bu çalışmada elektrik stimülasyonunun faydalı bir tedavi yöntemi olacağı bildirilmiştir (Schreiner ve ark., 2021). Ayrıca PTTS çalışmalarda, hastaların elektriksel stimülasyonun içsel farkındalığına bağlı olarak plasebo etkisini kontrol eden çalışmaların eksikliğidir (Findlay ve Maxwell-Armstrong, 2011).

TPTNS' nin kadınlarda ve nörojenik mesane disfonksiyonu olan erişkinlerde urge veya mix Üİ semptomlarını azaltmada etkili olabileceğine dair çalışmalar mevcuttur. Üİ tedavisinde TPTNS' nin etkisini değerlendirmek amacıyla 10 randomize kontrollü araştırmanın incelendiği sistematik bir derleme çalışmasında, mesane semptomları ve Üİ ile ilişkili yaşam kalitesi açısından iyileşmeler saptandığı bildirilmiştir. İncelenen çalışmalar küçük örneklem gruplarından oluşmasına ve metodolojik zayıflıklar içermesine rağmen TPTNS' nin güvenli, etkin maliyetli ve umut verici bir tedavi yöntemi olduğu belirtilmiştir (Booth ve ark., 2013). Bakım evlerinde yapılan küçük ölçekli bir fizibilite çalışmasında, TPTNS' nin bu popülasyon grubunda Üİ için güvenli, kabul edilebilir ve etkili bir tedavi yöntemi olabileceği belirtilmiştir. Bakım evlerinde rutin uygulama olarak kullanılması önerilmeden önce TPTNS' nin etkinliğine dair daha kesin kanıtlara ihtiyaç olduğu belirtilmiştir (Booth ve ark., 2021).

TPTNS, Üİ olan bireylerde semptomları tedavi etmek için kullanılan ağrısız, güvenilir ve etkili bir konservatif tedavi yöntemidir. Ayrıca istemli kas kontraksiyonu yapamayan hastalar için de iyi bir tedavi seçeneği olabileceği belirtilmektedir. Konu ile ilgili yapılması planlanan çalışmalarda bu uygulamanın inkontinans semptomları üzerindeki uzun dönem sonuçlarının araştırılması önerilebilir. Ayrıca konu ile ilgili yapılan çalışmalarda mevcut sonuçları desteklemek için daha geniş örneklem sayısına sahip gruplarla çalışılması önerilebilir.

#### **Katkı Oranı Beyanı**

Konsept: M.Ç. (%50) ve M.C. (%50), Tasarım: M.Ç. (%50) ve M.C. (%50), Denetim: M.Ç. (%50) ve M.C. (%50), Veri

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## İN VİTRO, İN VİVO VE KLİNİK ÇALIŞMALARLA KANSER TEDAVİSİNDE KALSİYUM ELEKTROPORASYONUN DEĞERLENDİRİLMESİ

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**Özet:** Tıp ve biyoteknolojide birçok uygulamaya sahip olan elektroporasyon (EP), hücre membranını harici, kısa ve yüksek voltajlı elektrik pulsuları ile geçirgen hale getirmek için kullanılan bir yöntemdir. EP sonrasında hücre membranı boyunca artan molekül akışı gözlenir. Elektrokemoterapi (EKT), kemoterapi ile EP tekniğini birleştirerek tümörlerin palyatif tedavisi için kullanılmaktadır. Birçok anti-kanser uygulaması, kalsiyum (Ca<sup>2+</sup>) sinyallerini etkileyerek kanser tedavisinde hedef olarak Ca<sup>2+</sup> yollarını desteklemektedir. EKT uygulamasının yanı sıra Ca<sup>2+</sup> elektroporasyonun (CaEP) kullanılması ATP miktarının azalmasına bağlı olarak tümör hücrelerinin ölümüne neden olur. Bu derlemede, CaEP'nin mevcut in vitro, in vivo ve klinik çalışmaların deney sonuçlarının gözden geçirilmesi ve yeni bir anti-kanser tedavi yöntemi olarak değerlendirilmesi amaçlanmıştır.

**Anahtar kelimeler:** Elektroporasyon, Kalsiyum elektroporasyon (CaEP), Kanser

### Evaluation of Calcium Electroporation in Cancer Treatment with In Vitro, In Vitro and Clinical Studies

**Abstract:** Electroporation (EP), which has many applications in medicine and biotechnology, is a method used to make the cell membrane permeable with external, short and high voltage electrical pulses. After EP, an increased flow of molecules across the cell membrane is observed. Electrochemotherapy (ECT) is used for palliative treatment of tumors by combining chemotherapy and EP technique. Many anti-cancer applications support Ca<sup>2+</sup> pathways as a target in cancer treatment by affecting calcium (Ca<sup>2+</sup>) signals. The use of Ca<sup>2+</sup> electroporation (CaEP) instead of ECT application causes the death of tumor cells due to the decrease in the amount of ATP. In this review, it is aimed to review the experimental results of existing in vitro, in vivo and clinical studies of CaEP and to evaluate it as a new anti-cancer treatment method.

**Keywords:** Electroporation, Calcium electroporation (CaEP), Cancer

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### 1. Giriş

EP, hücreye yüksek yoğunluklu, pulslu elektrik alan (EA) uygulandığı ve membran potansiyelinin kritik bir değeri aştığı durumda hücre membranında geçici olarak nanometre (nm) boyutunda porların oluştuğu biyofiziksel bir olaydır (Dev ve ark., 2000; Miklavcic ve Kotnik, 2004). EP, genellikle hücre zarını geçemeyen hidrofilik moleküllerin ve iyonların hücrelere girmesine olanak sağlar (Ramos ve ark., 2004). Standart bir EP uygulamasında, yoğun EA pulsuları, uygun elektrotlar tarafından hücrelere iletilir ve plazma membranının iletkenliğinde ve geçirgenliğinde hızlı bir artışa neden olur. Elektro-permeabilizasyon bir eşik olgusudur ve puls parametrelerinin özelliklerine bağlı olarak geri dönüşümlü veya geri dönüşümsüz por oluşumuna neden olur (Golberg ve ark., 2010). Porlar, mikrosaniye (µs) içinde oluşur ve uygulanan EA pulsularının büyüklüğüne ve

süresine bağlı olarak saniye (s) veya dakika (dk)'lar süresinde yeniden kapanmaya başlar (Pavlin ve ark., 2005). EP yöntemi, klinik olarak Avrupa'da 140'tan fazla merkezde anti-kanser tedavisi için kemoterapötik ilaçlarla kombine halinde kullanılmaktadır (Belehradek ve ark., 1993; Heller ve ark., 1998; Curatolo ve ark., 2012; Matthiessen ve ark., 2012; Mozzillo ve ark., 2015). EKT, kemoterapötik ilacın hücre içine alınımı ve dolayısıyla sitotoksitesini önemli ölçüde artırır (Gehl ve ark., 1998). Çoğu anti-kanser uygulaması, Ca<sup>2+</sup> sinyallerini etkileyerek kanser tedavisinde hedef olarak Ca<sup>2+</sup> yollarını desteklemektedir (Bergner ve Huber, 2008). Ca<sup>2+</sup> birçok fizyolojik olayda görev alan ikincil habercidir ve zamana, yere, genliğe, frekansa ve süreye bağlı olarak hücre ölümü de dahil olmak üzere çeşitli hücresel süreçlerde rol oynar (Florea ve Busselberg, 2009). Dolayısıyla bu derlemede, kemoterapötik ajanların yanı



sıra  $Ca^{+2}$  ile kombinasyon halinde EP (CaEP) uygulamasıyla in vitro, in vivo ve klinik çalışmaların deney sonuçlarının gözden geçirilmesi ve yeni bir anti-kanser tedavi yöntemi olarak değerlendirilmesi amaçlanmıştır.

### 2. Kalsiyum Homeostaz: Sağlıklı ve Kanser Hücrelerinde

$Ca^{+2}$  plazma membranı boyunca 10-20.000 kat konsantrasyon gradyanına sahiptir. Bu nedenle hücre, kalsiyumu farklı proteinlere bağlanarak şelatlamak, endoplazmik retikulum (ER) ve mitokondri gibi organellere bölmek veya iyon homeostazını sürdürmek için farklı pompalar (ATPazlar) ve değiştiriciler kullanarak kalsiyumu hücre dışına çıkarmak zorundadır (Berridge ve ark., 2000; Brini ve Carafoli, 2000; Berridge ve ark., 2003).  $Ca^{+2}$  esas olarak endoplazmik retikulum (ER), sarkoplazmik retikulum (SR, kas hücrelerinde) ve mitokondride depolanır. Sarko-endoplazmik retikulum kalsiyum ATPaz (SERCA), kalsiyumu ER ve SR'ye pompalar (Lytton ve ark., 1992; Brini ve Carafoli, 2000). Mitokondri içindeki  $Ca^{+2}$ , organelin işlevini, hareketini ve canlılığını düzenleyebilir. Artmış mitokondriyal  $Ca^{+2}$  konsantrasyonu, ATP üretimini artırarak mitokondriyal metabolizmayı modüle edebilir. Ancak mitokondriyal membran geçirgenliği hücre ölümünü, apoptozu veya nekrozu da tetikleyebilir.  $Ca^{+2}$ , ATP'ye bağımlı plazma zarı  $Ca^{+2}$ ATPaz (PMCA) ve ATP'den bağımsız  $Na^{+}/Ca^{+2}$ -değiştirici (NCX) ve  $Na^{+}/Ca^{+2}/K^{+}$ -değiştirici (NCKX) tarafından hücre içinden uzaklaştırılır (Armstrong, 2006; Clapham, 2007; Decuypere ve ark., 2011). Kanser hücrelerinde  $Ca^{+2}$  sinyallerini düzenlemede yer alan proteinler, çoğalmayı sürdürmek ve hücre ölümünü önlemek için normal hücrelere kıyasla sıklıkla düzenlenirler (Roderick ve Cook, 2008).  $Ca^{+2}$  kanalları, pompalar ve  $Ca^{+2}$  değiştiricilerin tümü, normal hücrelerde olduğu gibi kanser hücrelerinde de bulunur fakat bunların lokalizasyonu ve etkinliği farklı olabilir. SERCA2 ve SERCA3 ekspresyonunda bir azalma birkaç farklı kanser hücre hattında ve tümör numunesinde gözlenmiştir. Kanser hücrelerinde, SERCA2 ve SERCA3'ü kodlayan genlerdeki değişiklikler, kalsiyumun sitozolden ER'ye taşınmasını azaltılabileceğini gösterir (Gelebart ve ark., 2002; Endo ve ark., 2004; Bergner ve ark., 2009). Hücrelerin artan farklılaşmasıyla birlikte, normal hücreler ve dokulara kıyasla kanser hücrelerinde ve tümör dokularında PMCA4 ekspresyonunun arttığı ve en düşük PMCA4 ekspresyonunun gözlemlendiği PMCA değişiklikleri de gösterilmiştir (Aung ve ark., 2007; Ribiczey ve ark., 2007; Aung ve ark., 2009; Ruscho ve ark., 2012).

### 3. Elektroporasyon

Hücre membranının lipit çift tabakası içine kararlı bir şekilde gömülü bir dizi farklı protein yapı vardır. Bu yapılar, kanallar ve pompalar olarak işlev görür ve zar boyunca belirli molekülleri taşımada önemli bir rol oynar. Bu proteinler olmasaydı, membran büyük ölçüde aşılmaz

bir bariyer olurdu. Elektriksel olarak hücre membranı, her iki tarafı sulu elektrolit çözeltileriyle çevrelenmiş ince bir yalıtım tabakası olarak görülebilir. Hücre membranı yeterince güçlü bir EA maruz kaldığında elektriksel bozulmaya uğrar ve membranı geçemeyen moleküller için geçirgen hale gelir (Coster ve Simmermann, 1975; Chang ve ark., 1992; Chen ve ark., 2006).

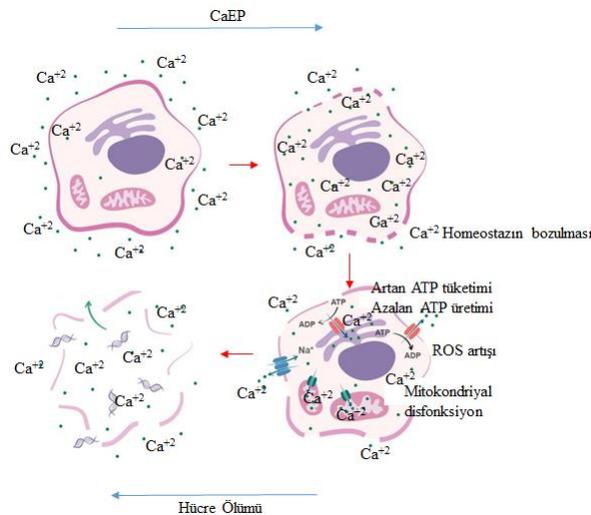
EP, hücre membranında nm boyutunda geçici porlar oluşturmak üzere hücre ve dokulara kısa zamanlı ve çok kuvvetli elektrik pulsları uygulanması işlemidir. EP'nin etkinliği, uygulanan elektrik pulsu parametrelerine (Pulsun şekli, sayısı, süresi ve şiddeti) bağlıdır. Membran elektroporasyonunu sağlayan uygulamalar oldukça kısa süreli (mikrosaniye ( $\mu s$ ), milisaniye (ms)) ve E alan şiddeti ise kV/cm'ler düzeyindedir. Membran boyunca uygulanan EA, hücre membranının lipit moleküllerinde kimyasal değişiklik meydana getirilmeden, pozitif ve negatif yüklerin membran boyunca birikmesine ve konumlarını değiştirmelerine sebep olur. Membran yapısındaki bu değişim hareketine "*flip-flop hareketi*" denir ve böylece EP, büyük moleküllerin hücre içine girişine olanak sağlar. EP yöntemi, kemoterapötik ilaçlar, genler veya kalsiyum gibi farklı iyonları veya molekülleri hücrelere sokmak için in vitro, in vivo ve klinikte kullanılır (Tsong, 1991; Jaroszeski ve ark., 2000; Frandsen ve ark., 2012; Falk ve ark., 2018). EP, puls parametrelerinin özelliklerine bağlı olarak *geri dönüşümlü* veya *geri dönüşümsüz* por oluşumuna neden olur. Hücre membranında geçici sulu gözeneklerin oluşumunu tetiklemek için, uygulanan E alan 200 mV-1V aralığında kritik bir değere ulaşmalıdır. EA şiddeti eşik değerinin altında tutulursa, hücre membranı orijinal durumunu geri kazanabilir ve böylece geri dönüşümlü EP'den bahsedilebilir. Eğer EA eşik değeri aşarsa, hücre membranı hasar görür ve hücre canlılığı tehlikeye girer bu durum ise geri dönüşümsüz EP'dir (Jaroszeski ve ark., 2000; Puc ve ark., 2003; Rebersek ve Miklavcic, 2014). Geri dönüşümlü EP'de, hücre membranında artan geçirgenlik EA'nın kesilmesiyle birlikte belirli bir sürede azalır ve membran onarılır. Hücre homeostazı yeniden kurulur. Por'un kapanması, sıcaklığa, geçirgenlik derecesine, hücre iskeletinin bütünlüğüne ve hücre tipine bağlı olarak değişebilmektedir, sağlıklı hücreler in vitro kanser hücrelerinden daha hızlı onarım sağlar ve por kapanmasını etkiler (Orlowski ve Mir, 1993; Gehl, 2003; McNeil ve Steinhardt, 2003; Frandsen ve ark., 2016). Geri dönüşümlü EP, biyoteknolojide, tıpta, EKT ve gen elektrotransferinde (GET) kemoterapötikler ve nükleik asitler gibi membranı geçemeyen moleküllerin hücre membranından geçişine olanak sağlar (Lambricht ve ark., 2016; Campana ve ark., 2019).

EKT ile ilgili ilk klinik çalışma 1990-1991'de yapıldı (Belehradek ve ark., 1993). O tarihten itibaren EKT, kutanöz ve subkutan metastazlar gibi küçük tümörlerin tedavisinde, göğüs duvarı meme kanseri nüksleri gibi daha büyük tümörlerde ve iç organlardaki derin yerleşimli tümörlerin tedavisi için klinik çalışmalarda kullanıldı (Heller ve ark., 1998; Marty ve ark., 2006; Edhemovic ve ark., 2011, Matthiessen ve ark., 2012; Sersa ve ark., 2012;

Curatolo ve ark., 2012; Bianchi ve ark., 2016; Bimonte ve ark., 2016; Plaschke ve ark., 2017; Egeland ve ark., 2018; Gehl ve ark., 2018). Geri dönüşümsüz EP, özellikle spesifik anatomik konumları nedeniyle cerrahi veya termal ablasyon için uygun olmayan tümörleri tedavi etmek için fokal ablatif bir teknik olarak halihazırda kullanılmaktadır (Geboers ve ark., 2020). Bu nedenle EP, yeni veya mevcut ilaçlarla kombinasyon halinde in vitro, in vivo, pre-klinik ve klinik test edilebilir bir yöntemdir.

#### 4. Kalsiyum Elektroporasyon (CaEP)

Hücre membranı boyunca kalsiyum için konsantrasyon gradyanı, hücrel homeostazi korumak için sıkı bir şekilde düzenlenir. Normal hücrelerde, iyonize kalsiyumun hücre dışı konsantrasyonu yaklaşık 1 mM, hücre içi konsantrasyonu ise yaklaşık 100 nM civarında olacak şekilde tutulur (Brini ve Carafoli, 2000). Tümörigenez,  $Ca^{+2}$  pompaları ve kanallarının regülasyonu, hücre iskeleti ve membran onarımındaki değişiklikler yoluyla hücre kalsiyum homeostazını değiştirir. Bu durumda, aşırı  $Ca^{+2}$  yüklenmesi sonucu kanser hücrelerinde hücre ölümünün indüklenmesi gözlemlenebilir (Aung ve ark., 2007; Papp ve ark., 2012). Anti-kanser tedavisi olarak CaEP hakkındaki ilk bilimsel çalışmada ve sonraki yayınlarla da desteklenen bir etki mekanizması önerilmiştir (Şekil 1.). CaEP,  $Ca^{+2}$ -ATPaz ile diğer ATPazların artan aktivitesi ve ATP üretiminin azalması sonucu ATP tükenmesine bağlı olarak, hücre içi  $Ca^{+2}$  iyonlarının artışı sonucu mitokondri membranında porların oluşması ile meydana gelen elektrokimyasal gradyan kaybıyla ve reaktif oksijen türlerinin üretimi de dahil olmak üzere diğer hücrel etkiler ile apoptoz veya nekroz yoluyla hücre ölümüne yol açar (Cerella ve ark., 2008; Hojman ve ark., 2008; Frandsen ve ark., 2012; Frandsen ve ark., 2017).



Şekil 1. Kanser hücrelerinde CaEP'nin etki mekanizması.

#### 5. İn Vitro, İn Vivo ve Klinik CaEP

CaEP'nin in vivo ve in vitro kanser hücrelerinin ölümünü indüklemekteki etkinliğini gösteren ilk klinik öncesi çalışma 2012'de yayınlandı. Yapılan çalışmada

araştırmacılar, CaEP'nin, ATP'nin artan hücrel kullanımının, mitokondri üzerindeki etkileri nedeniyle ATP üretiminin azalmasının ve ayrıca geçirgenleştirilmiş hücre mebranı yoluyla ATP kaybının bir kombinasyonu nedeniyle akut ATP tükenmesine neden olduğunu göstermişlerdir (Frandsen ve ark., 2012).

Yapılan in vitro bir çalışmada, Çin hamsteri akciğeri fibroblast hücre hattı (DC-3F), murin akciğer karsinom hücre hattı (Lewis Lung Carcinoma) ve insan lösemi hücre hattı (K-562) artan kalsiyum konsantrasyonu (0-5 mM) varlığında 1 Hz tekrarlamalı frekansında 99  $\mu$ s 'lik 8 kare puls parametrelerinde 1,2 kV/cm ve 1,4 kV/cm elektrik alan şiddetinde elektropore edildi. Uygulama sonrası 1 ve 2 günlük inkübasyon sonrasında hücre canlılığında doza bağlı bir azalma ölçülmüştür. Çalışmada, CaEP ve bleomisin kemoterapötik ilacı ile EKT uygulamasının hücre canlılıkları üzerinde benzer etkiler gözlenmiştir. Kalsiyum ve bleomisin'in olası bir katkı etkisi de araştırılmış olup sinerjik bir etki gözlenmemiştir. Çalışmada ayrıca, hücrelerin tek başına kalsiyum ile tedavisinin tek başına bleomisin ile karşılaştırıldığında hücre ölümünü indüklediğini, hücre canlılığında bir azalma sağladığını ancak bleomisin EP ile tedavi edilen hücreler kadar dramatik olmadığı bildirilmiştir (Frandsen ve ark., 2014).

H69 (EGFP ile transfekte edilmiş insan küçük hücreli akciğer kanseri hücre hattı) tümörleri nakledilen bir fare modelinde yapılan çalışmada, tümör çapı ortalama 6,2 mm olan fareler izotonik kalsiyum klorür çözeltisi (168 mmol/L  $CaCl_2$ ) enjeksiyonu ve 1,0 kV/cm'de 100 ms'lik 8 darbe kare puls EP parametrelerinde 6 mm plaka elektrot kullanılarak tedavi edildi. Çalışmada, klinik kullanım için onaylanmış kalsiyum klorür (168 mmol/L) enjeksiyonu ile tedavi edilen tümörlerin %89'unun nekroz ile elimine edilmesiyle önemli bir antitümör tepkisi indüklediği belirlenmiştir (Frandsen ve ark., 2012).

H69 (küçük hücreli akciğer kanseri), SW780 (mesane kanseri) ve U937 (lösemi) hücre hatları 1, 3 ve 5 mM kalsiyum konsantrasyonu ve 1Hz tekrarlamalı frekansında 8 kare puls ve 99  $\mu$ s süresince 0,8, 1,0, 1,2, 1,4 veya 1,6 kV/cm elektrik alan şiddeti ile tedaviden sonra hücre canlılıkları ve hücre içi ATP düzeylerini belirlemek için yapılan çalışmada, hem H69 hem de SW780 hücreleri, hücre içi ATP'de doza bağlı (kalsiyum konsantrasyonu ve elektrik alan) azalma ve düşük canlılık gösterdiği bulunmuştur (Hansen ve ark., 2015).

NMRI- *Foxn1*<sup>nu</sup> farelerinde metformin ile CaEP'nin tümör boyutu, hayatta kalma ve hücre içi ATP üzerindeki etkisini belirlemek için, in vivo yapılan bir diğer çalışmada, CaEP'nin tedavi edilen mesane kanseri tümörlerinin boyutunu ve ATP seviyesini önemli ölçüde azalttığı ancak CaEP ile birlikte metforminin, ne tümör boyutu ne de hayatta kalma ve ATP seviyesi üzerinde artan bir etkisi olmadığı belirlenmiştir (Frandsen ve ark., 2017).

Normal sıçan iskelet kası hücreleri (L6) ve kanser kas hücreleri (Wehi-164-Fibrosarkom) kullanılarak CaEP'nin etkinliği ve güvenliğini belirlemek için iki  $CaCl_2$  (0,5 mM ve 5 mM) konsantrasyonu ve EP (1000 V/cm, 1200 V/cm

ve 1500 V/cm) parametreleriyle birlikte yapılan çalışmada, Ca<sup>2+</sup> ile desteklenen EP'nin Wehi-164 hücreleri için sitotoksik olduğunu ve aynı zamanda normal kas hücreleri için güvenli olduğunu ve 0,5 mM Ca<sup>2+</sup> içeren EP, proliferasyonu artırmak için normal kas hücreleri L6'yı hafifçe uyardığı belirlenmiştir (Zielichowska ve ark., 2016).

3D sferoid hücre kültürü modeli ile kolorektal adenokarsinom (HT29), mesane geçiş hücreli karsinomu (SW780), meme adenokarsinomu (MDA- MB231) ve ayrıca birincil normal insan dermal fibroblastlarında (HDF-n) EKT ve CaEP'nin etkinliğini belirlemek için yapılan çalışmada, CaEP ve EKT'nin tedaviden üç gün sonra üç kanser hücresi sferoidinin hepsinde sferoid boyutunda net bir azalma meydana getirdiği, çarpıcı bir şekilde normal fibroblast sferoidlerinin boyutunun ne CaEP ne de EKT'den etkilenmediği belirlendi. Bu durum tümörlerin EKT gibi CaEP ile tedavi edildiğinde tümörü çevreleyen normal doku üzerinde sınırlı ölçüde olumsuz etkilere sahip olacağını ifade edilmiştir (Frandsen ve ark., 2015). C57BL/6JOLAHSd farelerinde yapılan in vivo çalışmada, 1300 V/cm, 100 µs, 1 Hz, 8 puls EP parametrelerinde ve 50-250 mM kalsiyum konsantrasyonunda CaEP'nin tümör damar sistemi üzerinde EKT'ye benzer şekilde hem normal hem de tümör kan damarlarının yapısında bozulma meydana getirdiği ve tedavi edilen alandaki daha küçük damarlar tahrip olurken, daha büyük damarlar hasar görmüş ancak işlevselliği koruduğu belirlenmiştir (Staresinic ve ark., 2018).

CaEP'nin tümör yanıtını ve EKT ile karşılaştırmak için yapılan randomize çift kör faz II çalışması yakın zamanda tamamlanan ilk klinik deneydir. Çalışmaya meme kanseri ve malign melanomlu 47 kutanöz metastazı olan yedi hasta dahil edilmiş olup, yanıt için toplam 37 metastaz değerlendirilmiştir. Tüm metastazlar, tümör içine 220 mmol/L kalsiyum klorür veya 1000 IU/ml bleomisin enjeksiyonu ile 5 kHz frekansta 8 darbe 100 µs, 400V EP parametreleri kullanılarak tedavi edildi. Tedaviden 7 gün sonra alınan biyopsiler, CaEP ve EKT ile tedavi edilen metastazlarda daha az sayıda kanser hücresi gösterdiği belirlenmiştir. 6 aylık bir takipten sonra, CaEP ve EKT ile tedavi edilen metastazların sırasıyla %66'sında (12/18) ve %68'inde (13/19) tam yanıt olarak bulunmuştur. Çalışmada, ilginç bir şekilde, EKT sonrası ortaya çıkan estetik olmayan hiperpigmentasyonun kalsiyum ile tedavi edilen metastazlarda görülmediği belirlenmiştir (Falk ve ark., 2018).

Yakın tarihte yapılan faz I klinik çalışmasında, CaEP'nin baş ve boyun bölgesindeki mukozal tümörler üzerindeki etkisi araştırılmıştır. Tekrarlayan baş ve boyun kanseri olan altı hasta, intratümöral kalsiyum enjeksiyonları (225 mmol/L) ve ardından 1000 V/cm, 1 Hz'de 100 µs'lik 8 darbe EP parametreleri ile genel anestezi altında tedavi edilerek tümör yanıtı PET/MRG taramaları üzerinde değerlendirilmiştir. Tedavinin güvenliği doğrulanarak ve herhangi bir yan etki, hiperkalsemi belirtisi veya kardiyak aritmi gözlenmediği bildirilmiştir. Klinik yanıtlar

tedaviden iki ay sonra gözlemlenmiş olup, MRG incelemesinde üç kısmi yanıt, bir stabil hastalık ve iki progresyon elde edilirken, PET incelemesinden bir kısmi metabolik hastalık, dördü stabil metabolik hastalıklı ve bir tanesi değerlendirilemez olarak belirlenmiştir. Çalışmada, 12 aylık gözlemden sonra bir hastada klinik hastalık kanıtı bulunamadığı bildirilmiştir (Plaschke ve ark., 2019).

Vissing ve arkadaşları yayınladıkları protokolle, çok merkezli ve randomize olmayan faz II çalışması ile kutanöz veya subkutan malignitesi olan 30 hastanın CaEP tedavisi ile ortaya çıkan birincil yanıtların tedaviden 2 ay sonra, ikincil yanıtların ise MRG ile tedavi yanıtı, anketler ve nitel görüşmeler ile değerlendirilip araştıracaklarını ve bilimsel yayın olarak sunulacağını bildirmişlerdir (Vissing ve ark., 2021).

### 6. Sonuç

Sonuç olarak, kemoterapötik ajanların yanı sıra son yıllarda yapılan çalışmalarda CaEP'nin hücrelere suprafizyolojik dozlarda kalsiyum verilmesi şiddetli ATP azalmasına bağlı olarak tümör hücrelerinin ölümüne neden olabilmektedir. CaEP uygulamasının EKT'ye benzer şekilde hızla kanser hücrelerini öldürdüğü ve sağlıklı hücrelerin etkilenmediği bir tedavi yöntemi olarak görülmektedir. Bu durum yan etkileri fazla ve pahalı olan kemoterapötik ilaçlar yerine kalsiyumun düşük sitotoksitesi, kolay hazırlama, taşıma, saklama prosedürlerine sahip olması, ucuz ve ulaşılabilir olması ile birlikte; günümüzde klinik uygulamalarda kullanılan elektroprotonerler sayesinde CaEP, kemoterapötik ilaçlar olmadan uygulanabilen etkili, yenilikçi bir kanser tedavi tekniğini temsil etmektedir.

### Katkı Oranı Beyanı

Konsept: G.G. (34%), M.A.E. (%33) ve Z.Ç. (%33), Tasarım: G.G. (34%), M.A.E. (%33) ve Z.Ç. (%33), Denetim: G.G. (34%), M.A.E. (%33) ve Z.Ç. (%33), Veri toplama ve/veya işleme: G.G. (34%), M.A.E. (%33) ve Z.Ç. (%33), Veri analizi ve/veya yorumlama: G.G. (34%), M.A.E. (%33) ve Z.Ç. (%33), Kaynak taraması: G.G. (34%), M.A.E. (%33) ve Z.Ç. (%33), Yazma: G.G. (34%), M.A.E. (%33) ve Z.Ç. (%33), Eleştirel inceleme: G.G. (34%), M.A.E. (%33) ve Z.Ç. (%33), Gönderim ve revizyon: G.G. (34%), M.A.E. (%33) ve Z.Ç. (%33). Tüm yazarlar makalenin son halini incelemiş ve onaylamıştır.

### Çatışma Beyanı

Yazarlar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

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## A HOLISTIC APPROACH TO THE EFFECTS OF INTRAUTERINE ANTIMICROBIAL THERAPY ON PREGNANCY RATE AFTER ARTIFICIAL INSEMINATION IN DAIRY COWS

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**Abstract:** Post-partum (pp) infertility following the artificial insemination (AI) can be a very common (around 50%) phenomenon in high-yielding dairy cows kept under poor management and feeding practices in particular. Even in clinically healthy females, intrauterine antimicrobial therapy (Lugol, Gentamicin, Rifaximin, etc.) may increase the fertility rate especially in those cows with latent (sub-clinical) intrauterine infection. Undoubtedly, modern animal husbandry requires to reduce possible calving losses with microbial origin that can prevent conception to occur and/or even terminate the ongoing pregnancy. In livestock farming/breeding, numerous obstacles (related to either the animal, humans or else) would prevent to achieve ultimate goals (regular reproductive cycle, insemination, pregnancy, calving, milking and dry period) that allow acceptable or minimum level of income (profit). For a sustainable herd health in profitable sectoral activity, individual females have to be in good health that would be achieved by strict rules to provide optimum animal productivity at animal welfare level. In this sense, a heavy physiological load of candidate mothers and their sustainable reproduction and milking requires at first good management and feeding practices. Beyond that, regarding the routine health services including treatment of dairy cows as appropriate, a 'holistic approach' is needed for an efficient therapy and speedy pp recovery of milking females. Otherwise, during the critical period, non-pregnant cows in open period may not conceive or peculiar delays in conception may become inevitable. Undoubtedly, in modern practice, holistic approach in farming/breeding animals requires effective management and feeding along with provision of appropriate health services towards meeting animal welfare level (sustainable high milk yield and regular calving annually). These ultimate aims would be easily facilitated by optimum management and good quality feeding, choosing the right individuals (age and breed) and working with dedicated care-takers and experienced Veterinarians. For the latter, provision of health services should incorporate comprehensive factors covering reproductive hormones, major vitamins-minerals and efficient antimicrobials (systemic and/or local) as needed. Finally, numerous profit-limiting factors (climate changes, heat-stress, water and food scarcity, market prices and residual problems) should also be dealt with a great care. Otherwise, undesirable outcomes (ovarian, uterine and mammary disorders) in dairy farming would be inevitable as commonly seen worldwide.

**Keywords:** Breeding, Cattle, Fertility, Infection, Treatment, Uterus

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### 1. Introduction

Reproductive problems (Arthur et al., 1993; Ptaszynska, 2001; Sönmez, 2012; Tohumcu, 2015) are common especially in cross-bred (Brown Swiss and Simmental) cows (Figures 1a and 1b) rather than low-yielding local (indigenous) breeds (Figure 1c) in the Eastern/South-Eastern Anatolia regions (Uçar, 2006; Uçar et al., 2020). Most metabolic disorders (Aktaş et al., 2011; Uçar et al., 2011; Ömür et al., 2016) coincide with indoor shelters during winter (Uçar, 2006; Uçar et al., 2009) that lead the population to unfavourable conditions (warm, crowded or dark environment) along with inadequate management and feeding (Uçar et al., 2004, Uçar, 2006; Çolak and Uçar, 2007; Uçar et al., 2011; Uçar et al., 2020). In Western Anatolia, where industry-dominated dairy

breeds (mainly Holstein) are preferred, such problems are frequently encountered in high-yielding dairy cows (Uçar et al., 2020) under inadequate hygiene and/or welfare problems (Dwyer, 2020). Non-pregnant dairy cows cost a loss of approximately 7 US dollars/day per milking animal. In these peculiar infertility cases (Daşkın, 2005b; Gökçen, 2008), considering the length of days spent in a dairy herd, the amount of milk loss per day, the higher number of non-pregnant animals, and the excessive costs of management-feeding, health and labour as well as the unaffordable rate of economic loss will be even much higher (Daşkın, 2005a, b; Öztürkler and Uçar, 2006; Uçar et al., 2011).

In this challenging period, in terms of metabolic health and reproductive efficiency, appropriate reproductive herd management (Daşkın, 2005b) starting before



calving and ideal care-feeding (Uçar et al., 2004, Uçar et al., 2011; Uçar et al., 2020) contribute to obtaining appropriate body condition score (BCS) at intermediate level (around 3.00 unit, 1-5 scale) (Daşkın, 2005b; Çolak and Uçar, 2007; Uçar et al., 2011). Likewise, sufficient energy (barley/maize, concentrated feed, silage, quality grass/clover) (Uçar et al., 2004; Uçar et al., 2011) and regular vitamin-mineral supplements (such as vitamins of A-D-E, and minerals/elements of calcium, phosphorus, sodium, potassium, chloride, iron, copper, zinc, selenium, etc.) in normally fed pregnant females positively affect metabolic and reproductive parameters (Kaçar et al., 2008; Uçar et al., 2011; Ömür et al., 2016) (Figures 2a, 2b). On the other hand, in the case of insufficient management-feeding (Polat et al., 2009; Uçar et al., 2011) in enterprises where traditional animal husbandry (Uçar, 2006; Tohumcu, 2015) instead of modern animal husbandry (Uçar et al., 2020) is applied, the reproduction processes may be disrupted (Uçar et al., 2011) or completely stopped (Uçar et al., 2004) (Figure 2c). Obviously, holistic (conditional, hormonal and antimicrobial) approaches are critically important for the solution of reproductive problems (Öztürkler and Uçar, 2003, 2006; Uçar, 2006; Gökçen, 2008; Dwyer, 2020; Uçar et al., 2020; Uçar, 2021).

## 2. Metabolic Changes during Peri-Parturient Period in Dairy Cows

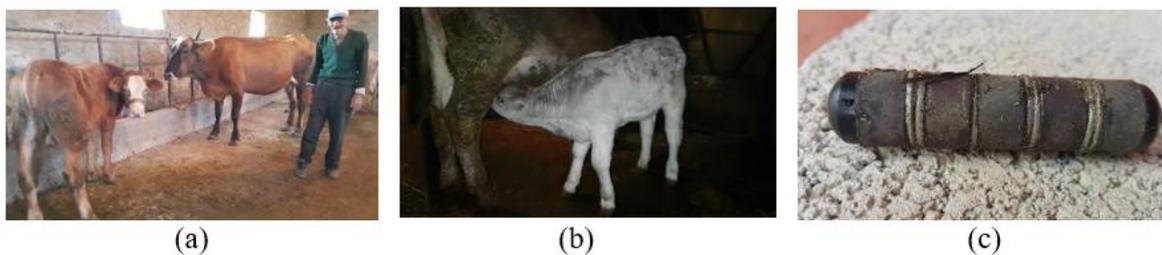
By the end of advanced pregnancy (Arthur et al., 1993; Sönmez, 2012), cows enter the transition period (especially between pre-/post-partum 21 days) (Ömür et al., 2016), as partially overlapping with the dry period (involving 45-75-day pre-partum) (Arthur et al., 1993; Ptaszynska, 2001; Weber et al., 2021). The periodic time flow during these critical processes are roughly as follows; a) colostrum release at calving (Figure 3) and the onset of early lactation period (up to 55<sup>th</sup> day pp) (Aktaş et al., 2011) (Figures 1c, 2b), b) the immediate shedding of foetal membranes (Figure 1a) in the uterus followed

by prolonged involution (up to day 42 pp) (Arthur et al., 1993), c) gradual intrauterine bacterial elimination (up to day 53 pp) (Daşkın, 2005b), d) as coinciding with the end of early lactation period (Aktaş et al., 2011), e) the progesterone hormone returns to normal cycle levels (if there is no new pregnancy until the days 56-63<sup>rd</sup>) (Daşkın, 2005b), f) settling the ovarian luteal/follicular cycle and uterine glands returning to their normal (excretory) function (if there is no infection) (Arthur et al., 1993; Gökçen, 2008; Sönmez, 2012), g) removal of ketone bodies from the blood (Uçar et al., 2004; Aktaş et al., 2011; Ömür et al., 2016) and finally h) occurrence of new pregnancy following oestrus (and artificial insemination) (Sönmez, 2012) only after the first oestrus cycle of 13-26 days long, as the earliest time (Ptaszynska, 2001; Daşkın, 2005b; Gökçen, 2008).

However, the early lactation period (Aktaş et al., 2011) overlaps with the involution and bacterial elimination of the uterus (Daşkın, 2005b) and mobilisation of fat depots of the body due to NEB (negative energy balance) (Uçar et al., 2004; Gökçen, 2008; Aktaş et al., 2011) mainly because of the heavy physiological load of ongoing lactation (Aktaş et al., 2011). Collectively, these extremely critical physiological events would presumably worsen the reproductive health at any time (Uçar et al., 2004; Gökçen, 2008; Uçar et al., 2011). In this period, intrauterine bacterial elimination (from 100% at calving to 10% until day 53<sup>rd</sup> pp) occurs normally during the uterine involution as coinciding with the continuous improvement in BCS, *i.e.* body fat deposits (mainly located at subcutaneous region) (Uçar et al., 2004; Daşkın, 2005b; Çolak and Uçar, 2007; Gökçen, 2008). Due to high lactation and malnutrition (Uçar et al., 2004), progesterone deficiency (Daşkın, 2005a, b) may occur as a result of *lipolysis*, then ketone bodies are removed from the systemic blood as a result of ketosis (*gluconeogenesis*), which can last up to the 83<sup>rd</sup> day (Uçar et al., 2004; Daşkın, 2005b; Aktaş et al., 2011).



**Figure 1.** a) Retentio secundinarum, b) calving by Caesarean operation in a heifer, and c) suckling (bad-tempered) cow with normal calving.



**Figure 2.** a) Artificial insemination-bearing bull-calf (8 months-old), b) 10 days-old artificial insemination calf suckling, and c) orally inserted magnet firmly attached with an old sharp metal piece (permanently perforating the reticular wall leading to chronic severe pericarditis) as resulted in sudden death of cow (with 4.5-months pregnancy) under treatment.



**Figure 3.** Colostrum feeding of Simmental artificial insemination calf born after dystocia.

Under the normal conditions, cows should become pregnant again by day 85 pp (Uçar et al., 2011). Otherwise, candidate mothers that cannot conceive following the artificial insemination due to various reproductive problems may become "*infertile*" after 90 days (Öztürkler and Uçar, 2006; Gökçen, 2008) and especially after 120 days, they are called as "*repeat breeder*" (İleri et al., 2002) (Figures 4a, 4b, 4c).

### 3. Clinical Approaches for Treatment of Genital Disorders in Post-Partum Dairy Cows

Major reproductive hormonal (Öztürkler et al., 2001a; Uçar et al., 2009; Polat et al., 2009) and inflammatory disorders (Öztürkler et al., 2001a, Öztürkler et al., 2001b; Öztürkler and Uçar, 2006; Weber et al., 2021) are frequently observed in high-yielding (Daşkın 2005b; Gökçen, 2008; Uçar et al., 2020), poorly managed-fed pp cows (Uçar et al., 2004; Uçar, 2006; Uçar et al., 2011; Uçar et al., 2020).

When the applications that increase the success of artificial insemination in animals receiving medical (Veterinary) services over the years are evaluated

(Öztürkler and Uçar, 2003; Uçar, 2006, 2021), it is seen that cows frequently encounter clinical findings (anoestrus, *retentio secundinarum*) (Figure 1a) or latent reproductive problems (*suboestrus*, *subclinical endometritis*) originating from both the ovary (mainly hormonal) (Öztürkler et al., 2001a; Polat et al., 2009) and the uterus (inflammatory and/or hormonal origin) (Öztürkler et al., 2001a; Öztürkler and Uçar, 2003, 2006). In this context, in one hand, relevant hormones (mainly PGF<sub>2</sub>α, GnRH, hCG, progesterone) are used alone (Polat et al., 2009) or together as a combined protocol (Daşkın 2005b; Uçar, 2006; Uçar et al., 2009; Uçar et al., 2011) for either synchronisation and/or therapeutic (anoestrus, delayed puberty) purposes (Arthur et al., 1993; Ptaszynska, 2001; İleri et al., 2002). On the other hand, antimicrobial approaches are also important in sub-clinical or clinical cases of inflammatory origin (Öztürkler and Uçar, 2003; Uçar, 2021). Both systemic (injectable penicillin, cephalosporin, etc.) (Ptaszynska, 2001; İleri et al., 2002) and intrauterine antimicrobial (local) treatment solutions (Öztürkler et al., 2001a; Öztürkler et al., 2001b) can be used against possible (*subclinical endometritis*) (Öztürkler et al., 2001b) or clinical uterine disorders (*endometritis*) leading to infertility/repeat breeding (Ptaszynska, 2001; İleri et al., 2002; Daşkın, 2005b; Gökçen, 2008). Undoubtedly, local treatment approaches (Öztürkler et al., 2001b; Uçar, 2021) for combatting/eliminating the source of actual microbial problem (Daşkın, 2005a, b; Gökçen, 2008) are critical in the field (Öztürkler and Uçar, 2003, 2006; Uçar 2006). In this context, different antimicrobial agents, such as simple Lugol solution (2% iodine) (İleri et al., 2002) as an antiseptic or Rifaximin spray, Oxytetracycline, Gentamicin sulphate (300-400 mg) (Öztürkler et al., 2001a; Öztürkler et al., 2001b; Öztürkler and Uçar, 2003, 2006) or Cephalosporin (Ptaszynska, 2001) as antibiotics are frequently used in the field.



(a)



(b)



(c)

**Figure 4.** a, b) Simmental artificial insemination calves of a repeat breeder Simmental mothers treated, and c) Cross-bred (Simmental x Holstein) artificial insemination calf of a repeat breeder Holstein mother treated.

However, in our world under the threat of global warming and climate change (Gardner, 2015), issues such as green energy, ecological agriculture, organic livestock breeding and animal welfare (Dwyer, 2020) are gaining more priority in the modern world (Gökçen, 2008; Uçar et al., 2020; Uçar, 2021). In modern animal breeding culture (Uçar et al., 2020) therefore, residual concerns (for milk and meat) (BAYNOVA Catalogue 2021) encountered when using preventive/therapeutic agents/drugs and organic livestock farming (Gardner, 2015) has become more popular especially in "Disease Free" (especially for Brucellosis and Tuberculosis) dairy cattle farms (İleri et al., 2002; Daşkın, 2005b; Gökçen, 2008, Sönmez, 2012).

In western parts of our country (especially Marmara, Aegean and Mediterranean regions), reproductive disorders are very common especially in high-yielding

dairy farms of certain (large) sizes (Daşkın, 2005b; Gökçen, 2008; Uçar et al., 2020, Uçar, 2021). Of course, the expected infertility (mainly subclinical endometritis) cases, as commonly seen in the field (Gökçen, 2008; Sönmez, 2012), can be prevented by intrauterine treatment (Öztürkler and Uçar, 2006) and thus the economic (milk/meat) losses of the enterprises (Daşkın, 2005b) and the risk of residues (BAYNOVA Catalogue, 2021) are reduced in high-yielding dairy cows. Intensive breeding culture may bring high heat stress, high contamination (respiratory, digestive, feet, udder, uterus) problems (BAYNOVA Catalogue, 2021) in crowded herd especially kept in semi-closed areas (Uçar, 2006; Gökçen, 2008; Gardner, 2015; Weber et al., 2021). Indeed, about half of the oestrus signs observed in cows go unnoticed in dairy farms (İleri et al., 2002; Gökçen, 2008). Moreover, in the field, a worldwide average of 50% conception is observed in the first artificial insemination of cows (Arthur et al., 1993; Öztürkler and Uçar, 2003; Gökçen, 2008; Uçar, 2021). In this case, the loss/missed chance of conception can reach up to 75% following the insemination under poor farming/breeding practices in particular (Gökçen, 2008; Kaçar et al., 2008; Uçar et al., 2011). In addition to the classical intrauterine treatment (by using Gentamycin, Cephalosporin, Rifaximin) commonly used in the field (Ptaszynska, 2001; Öztürkler et al., 2001a; Öztürkler et al., 2001b; Öztürkler and Uçar, 2006), new potential disinfectant/antioxidant as effective agents in respiratory (Bursalı et al., 2021) and digestive systems (Apaydın Yıldırım, 2021) such as Active Anionic Oxygen (AAO) (BAYNOVA Catalogue, 2021) have recently been postulated to contribute positively to fertility in dairy cows (as also proven by our preliminary results, unpublished data). Undoubtedly, the strategic importance of national production of such "organic" solutions in addition to commercial non-organic products (such as Gentamycin, Cephalosporin, etc.) effectively used in health problems (foot, udder, uterus, lung and digestive system) encountered in dairy enterprises (Daşkın, 2005b; Gökçen, 2008) would be of great importance (Uçar, 2006; Apaydın Yıldırım, 2021; Uçar, 2021). This situation may be extremely important both for the legislators of the breeding sector (fulfilling the expectations of the European Union from our country as EU candidate) (Daşkın, 2005b, Gökçen, 2008; Uçar, 2021) and for the consumers (BAYNOVA Catalogue, 2021).

#### 4. Discussion

Considering the farmers/breeders, veterinarians and other sector stakeholders experiencing economic difficulties, the need for healthier and highly productive animals is obvious (Uçar, 2021). Surely, achieving high individual productivity (milk, meat and calves) in dairy herds is possible only with the sustainable health for animal welfare as part of effective herd management (Daşkın, 2005b; Gökçen, 2008). Strategic approaches for one world and one health towards ecological farming/breeding are essential in modern animal

husbandry (Uçar et al., 2020; Dwyer, 2020). By doing so, clean (green) products provide environmental awareness that would help meeting sectoral higher standards in food chain (BAYNOVA Catalogue, 2021).

Therefore, it is vitally important both to spread the awareness culture in breeding animals and to increase the sectoral solidarity among stakeholders in terms of ideal solution to the genital problems encountered in dairy farms (Daşkın, 2005b; Gökçen, 2008; Uçar, 2021). Of course, genitally healthy cows conceive faster, give healthy calves more often and have higher milk yield. These healthy animals (presumably free from uterine infections) can also remain healthy and productive longer on the farm. The ultimate goal for a given herd should therefore be preventing common infertility cases with microbial origin (İleri et al., 2002; Daşkın, 2005b; Gökçen, 2008) through locally effective (Öztürkler and Uçar, 2003; Uçar, 2006) and/or preferably organic treatment (BAYNOVA Catalogue, 2021) in high-yielding dairy cows. Thereby, reducing economic losses (Daşkın, 2005a, b; Gökçen, 2008) and minimising possible residual risk (in milk/meat) (BAYNOVA Catalogue, 2021) in dairy farm would be possible to reach a modern livestock breeding standards (Uçar et al., 2020; Dwyer, 2020; Uçar, 2021).

At last, regarding profitable livestock farming and breeding (Daşkın, 2005b), other critical factors such as recent climate changes, excessive heat-stress during indoor sheltering, environmental water and food scarcity (Uçar, 2006; Uçar et al., 2011; Gardner, 2015), and high market prices should also be dealt with an utmost care. Moreover, subclinical metabolic disorders (Uçar et al., 2004; Aktaş et al., 2011) lowering calf (Gökçen, 2008) and milk yields (Weber et al., 2021) have to be monitored carefully. By doing so, high standards of management and feeding (Uçar et al., 2020) and animal welfare levels (Dwyer, 2020) would be more achievable as part of modern practices in livestock farming/breeding (Daşkın 2005a, b; Gökçen, 2008; Uçar, 2021).

## 5. Conclusion

Collectively, ideal and profitable herd management in dairy farms should incorporate efficient reproductive management of females (and breeding males), candidate/pregnant mothers and milking cows. For these aims, comprehensive factors covering; i) regulatory hormones (GnRH, Progesterone, hCG, PMSG, PGF<sub>2</sub>α) (Öztürkler et al., 2001a; Öztürkler and Uçar, 2006; Polat et al., 2009; Uçar et al., 2009), ii) major vitamins (A, D, E) (Kaçar et al., 2008; Uçar et al., 2011; Ömür et al., 2016) and iii) minerals (calcium, phosphor, sodium, selenium, potassium, chloride, zinc, copper, manganese, etc.) (Uçar et al., 2011; Ömür et al., 2016) should be provided appropriately (Figure 5a). Also, systemic (Penicillin; Penicillin plus Clavulonic acid, Cephalosporin, Oxytetracycline, etc.) and/or intrauterine antimicrobials (Lugol, Gentamicin, Rifaximin, Cephalosporin, etc.) can be used as needed for reproductive inflammations

effectively (Ptaszynska, 2001; Öztürkler et al., 2001b; İleri et al., 2002; Öztürkler and Uçar, 2006; Uçar, 2006) (Figure 5b). Also, a recent disinfectant/antioxidant product (AAO) (BAYNOVA Catalogue, 2021) have also been proposed for residue-free and immediate therapy for numerous inflammations including pulmonary, mammary and possibly uterine disorders. For the latter (AAO) treatment, these recent findings should be confirmed widely in livestock breeding and farming.



(a)



(b)

**Figure 5.** a) Simmental artificial insemination calf born from an infertile mother treated with hormones and vitamins, and b) cross-bred artificial insemination calves born mostly from infertile mothers treated with hormones and vitamins as needed.

## Author Contributions

Concept: Ö.U. (50%) and D.A. (50%), Design: Ö.U. (50%) and D.A. (50%), Supervision: Ö.U. (50%) and D.A. (50%), Literature search: Ö.U. (50%) and D.A. (50%), Writing: Ö.U. (50%) and D.A. (50%), Critical review: Ö.U. (50%) and D.A. (50%), Submission and revision Ö.U. (50%) and D.A. (50%). All authors reviewed and approved final version of the manuscript.

## Conflict of Interest

The authors declare that there is no conflict of interest.

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## UZAY ORTAMINDA ÖĞRENME VE BELLEĞE ETKİ EDEBİLECEK BAZI FAKTÖRLERİN İRDELENMESİ

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**Özet:** İnsanoğlu, antik çağlardan günümüze kadar uzayı daima merak etmiş ve gözlemiştir. Nihayet bu gözlemler, 1900'lü yılların başından itibaren uzaya gitmeye evrilmiştir. Soğuk savaş yıllarında, Amerikalıların ve Rusların karşılıklı hamleleriyle başta yörüngeye, uydu, hayvan, insan gönderilmiş ve en nihayetinde aya insan gönderilerek bu yarış çok büyük bir ivme kazanmıştır. Uzay, yeryüzünde yaşayan (tüm evrimsel süreçlerini dünyada gerçekleştiren) insan için ekstrem bir ortamdır ve uzaya giden insanları (astronot ve kozmonotlar) fizyolojik ve psikolojik olarak etkilemektedir. Bu derlemede; öğrenme ve bellek süreçlerine mikrogravitenin (buna bağlı olarak ortaya çıkan ağırlıksızlık), radyasyonun (kozmetik radyasyon, güneş patlamaları, vs) izolasyonun ve bazı diğer faktörlerin (cinsiyet, kültür ve dil gibi) etkileri irdelenmeye çalışılmıştır.

**Anahtar kelimeler:** Uzay, Mikrogravite, Radyasyon, İzolasyon, Öğrenme, Bellek

### Examination of Some Factors That May Affect Learning and Memory in the Space Environment

**Abstract:** Mankind has always wondered and observed space from ancient times to the present. Finally, these observations have evolved to go into space since the early 1900s. During the Cold War years, with the mutual moves of the Americans and the Russians, satellites, animals, and humans were sent to orbit, and finally, humans were sent to the moon and this race gained a great momentum. Space is an extreme environment for human beings living on earth (who performs all their evolutionary processes on earth) and it affects people who go to space (astronauts and cosmonauts) physiologically and psychologically. In this review; the effects of microgravity (the resulting weightlessness), radiation (cosmic radiation, solar flares, etc.) isolation and some other factors (such as gender, culture, and language) on learning and memory processes have been tried to be examined.

**Keywords:** Space, Microgravity, Radiation, Isolation, Learning, Memory

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### 1. Giriş

Uzay uçuşları ister kısa ister uzun görevleri kapsasın, astronotları hem fizyolojik hem de psikolojik olarak etkilemektedir. Bu etkilerin temel nedenleri, mikrogravite (buna bağlı olarak ortaya çıkan ağırlıksızlık), radyasyon (kozmetik radyasyon, güneş patlamaları, vs) ve izolasyondur. Bu temel nedenlerin dışında, uçuş personellerinin kişisel özellikleri, uçuş aracının fiziksel kapasitesi, aileden uzak kalma gibi başka birçok neden de uzay uçuşlarında uçuş ekibini etkilemektedir. Bu etkilerden dolayı, uzay hareket hastalığı, okülo-vestübüler rahatsızlıklar, intrakraniyal basınç artışı, kas-kemik kaybı gibi birçok sorun ortaya çıkmaktadır. Yapılan bazı çalışmalar bu ekstrem koşulların öğrenme becerisine ve belleğe de etki edebileceğine dair ip uçları vermiştir.

### 2. Uzay Uçuşunda Öğrenme ve Belleğe Etki Edebilecek Faktörler

İnsanoğlu antik çağlardan itibaren, başını gökyüzüne

çevirmiş ve dünyanın dışını daima merak etmiştir. Göksel olayları, önce astroloji daha sonra astronomi ile anlamaya çalışmıştır. Nihayet 20.yy. ortalarında bu arayış önce uzaya uydu göndermek, ardından liaka'nın geriye dönüş olmaksızın yolculuğu (SSCB'nin uzaya gönderdiği köpek) ve Yuri Gagarin ile (Yörüngeye ilk giden kozmonot) hız kazanmıştır. Bugün ise hedeflenen dünya dışında bir gezegene (Mars'a) gitmek olmuştur (Kanas ve Manzey, 2008). Marsa gitme çalışmaları daha çok şeyi düşünmeyi ve tasarlamayı gerektirmiştir. İnsanın uzaydaki bu uzun yolculuğunun (Marsa yolculuğunun) psikolojik ve fizyolojik etkileri de tartışılmaya başlanmıştır. Bu derleme çalışmasında uzayda insanın öğrenme becerisine ve belleğine etki eden mikrogravite, radyasyon, izolasyon ve diğer nedenler irdelenecektir.

#### 2.1. Mikrogravitenin (Ağırlıksızlığın) Etkileri

Diğer tüm canlılar gibi insanlarda yeryüzündeki yer çekimine uygun olarak evrim süreci geçirmiş ve organizmaları buna adapte olmuştur. Hatta tüm fizyolojik süreçler de bu çekimin etkisine göre biçimlenmiştir.



Uzayda, dünyadakine benzer bir durum olmayıp, mikrogravite durum söz konusudur. Mikrogravite (ağırlıksızlık) en genel hali ile düşük yer çekimi olarak ifade edilebilir. Dünyada  $9,807 \text{ m/s}^2$  olarak ölçülen bu çekim, ay yüzeyinde  $1,622 \text{ m/s}^2$ , Mars'ta ise  $3,711 \text{ m/s}^2$  olarak kabul edilmektedir. Görüldüğü gibi bu çekim ay'da dünyanın %16'sı kadar, Mars'ta ise %38 kadarına karşılık gelmektedir (Kanas ve Manzey, 2008, Clement ve Reschke 2008). Bugüne kadar yapılan çalışmalarda mikrogravite ve yüksek bilişsel işlevler arasındaki etkiyi gösteren (olumsuz yönde) çalışmalara rastlanmadığı gibi kafa karışıklığı yaratan sonuçlarda bulunmuştur (Lipnicki ve Gunga, 2009, Clément, 2007, Mammarella, 2020). Yeryüzünde yapılan mikrogravite simülasyon çalışmalarının bir kısmında, genel yaratıcı düşünme sorunları ve matematiksel işlemleri kapsayan hafıza görevlerinde sorunlar ortaya çıktığı bildirilmiştir (Connors ve ark., 1986, Seaton ve ark., 2007). Ancak yeryüzünde yapılan başka çalışmalarda ise katılımcılarda yaratıcı düşünme, bilişsel testler kullanılarak problem çözme, iki ve üç boyutlu işlemleri yürütme becerilerinde azalma olmadığı görülmüştür (Zubek ve MacNeill, 1966, Storm ve Giannetta, 1974, Shehab ve ark., 1998, Koppelmans ve ark., 2015). Hatta yeryüzünde yapılan birkaç araştırmada (uzay simülasyonu çalışmalarında) mekanizması tam olarak açıklanamamakla beraber bazı bilişsel işlemlerin daha iyi olduğu gösterilmiştir (Marishchuk ve ark., 1970, DeRoshia ve Greenleaf, 1993, Pavy Le-Traon ve ark., 1994, Wollseiffen ve ark., 2016). NASA'nın en son yaptığı meşhur ikiz kardeşler çalışması mikrogravitenin yüksek bilişsel işlevler üzerine etkisini anlamak açısından oldukça yararlı olmuştur. Görevden dönen kardeşin (dönüşten 6 ay geçmesine karşın) bazı bilişsel görevlerde, uzaya gitmeyen kardeşe göre daha yetersiz olduğu görülmüştür (Garrett-Bakelman ve ark., 2019). Tüm bu bilgiler ışığında mikrogravite'nin işler belleğe (working memory) ve hafızaya etkilerinin olabileceği ancak görev süresi (uzun veya kısa) ve diğer faktörlerin (sosyal izolasyon, hapsedilme duygusu ve radyasyon gibi) etkilerini daha iyi ortaya koyabilmek için ileri çalışmalara ihtiyaç duyulduğu söylenebilir.

### 2.2. Uzay Radyasyonunun Etkileri

Uzay yolculuğu sırasında, astronotlar 3 kaynaktan gelen radyasyona maruz kalırlar. Bunlar, güneşten gelen parçacıklar halindeki enerji (solar particle events, SPE), galaktik kozmik radyasyon (GCR) ve dünyanın manyetosferinden gelen radyasyondur (Kanas ve Manzey, 2008, Clement ve Reschke, 2008). Alçak dünya yörüngesinde astronotlar, Van Allen kuşağına hapsedilmiş yüklü parçacıklardan büyük ölçüde korunurlar (Kiffer ve ark., 2019). Dünyanın manyetik alanı dışındaki en zararlı radyasyon bileşeni yüksek enerji çekirdeği ve galaktik kozmik radyasyondur. Uzaydaki bu yoğun radyasyon, görevleri sırasında astronotları davranışsal ve bilişsel olarak olumsuz yönde etkileyebilmektedir (Kanas ve Manzey, 2008, Clement ve Reschke 2008). Radyasyon aslında oldukça geniş bir kavram olup, uzaydaki radyasyona kaynak olabilecek onlarca büyük veya küçük

parçacık vardır. İnsanlar üzerindeki zararlı etkilerinden dolayı, bu konudaki çalışmalar rodentler (fare, sıçan) üzerinde yapılmıştır. Rodent çalışmaların da birçok farklı radyoaktif madde kullanıldığı da görülmüştür. Bu çalışmaların çoğunda başta  $^{56}\text{Fe}$  olmak üzere,  $^1\text{H}$ ,  $^{16}\text{O}$ ,  $^{28}\text{Si}$ ,  $^4\text{He}$ ,  $^{48}\text{Ti}$ ,  $^{20}\text{Ne}$  gibi yüklü parçacıklar kullanılmıştır (Kiffer ve ark., 2019). Birçok çalışmanın incelendiği bir derlemede, radyasyonun türüne ve dozuna bağlı olarak rodentlerde öğrenme, bellek, korku, anksiyete ve sosyal davranışların bozulduğu bildirilmiştir (Cekanaviciute ve ark., 2018). Krukowski ve arkadaşlarının yaptığı bir çalışmaya göre erkek farelerin tanıma (recognition memory) hafızaları ve sosyal davranışları bozulurken, dişi farelerde bu yönde bir değişim olmadığı bildirilmiştir. Yine aynı çalışmaya göre erkek farelerin hipokampuslarında mikrogial aktivasyon ve sinaptik kayıp bildirilmiş ve AMPA ekspresye eden sinaptik terminallerde azalma olduğu ifade edilmiştir. Enteresan bir biçimde bu durum dişi farelerde gözlenmemiştir (Krukowski ve ark., 2018) Bu durum cinsiyet farklılığının getirebileceği avantajlara yönelik daha fazla çalışma yapılması gerektiğini düşündürmektedir. İnsanlığın büyük hedeflerinden biri olan Mars'a seyahat, uzun bir yolculuk olacaktır. Bu uzun yolculukta derin uzaydaki radyasyonun etkilerine dair rodent çalışmalarının yanı sıra hücre kültürü çalışmalarına da yer verilmesi yararlı olabilir.

### 2.3. İzolasyonun Etkileri

Kısıtlı bir alanda yaşama (hapsedilme) ve izolasyonun güçlü psikolojik stresörler olduğu bilinmektedir (Schneider ve ark., 2010). Uzay görevlerinde kullanılan araçlar (roket, uzay mekiği, ISS... gibi) çoğunlukla kısıtlı alanlara sahiptir. Bu da astronotların hapsedilmişlik duygusu ve izolasyon duygusu yaşamasına neden olmaktadır (Kanas ve Manzey, 2008). Bu bağlamda, yapılmış en önemli çalışmalardan biri MARS500 projesi olmuştur. Bu proje, Biyo-Tıbbi Sorunlar Enstitüsü (IBMP) ve Avrupa Birliği tarafından (Avrupa Uzay ajansı ESA) ortaklaşa geniş uluslararası katılım bir simülasyon çalışması olmuştur (Brem ve ark., 2020). Bu çalışmada, tıbbi ve biyolojik testleri (fiziksel uygunluk, duygusal sağlamlık gibi) içeren modifiye edilmiş astronot seçim kriterlerine uygun olarak katılımcılar seçilmiştir. Bu çalışmaya göre (DTI data'ya dayalı olarak) uzun süreli kapalı kalma, beyin ak maddesinde mikro yapısal değişikliklere neden olmuştur. Bu deneyin sonunda sağ temporo-parietal kavşakta fraksiyonel anizotropide azalma bildirilmiştir. Bu çalışma ilk kez Difüzyon Tensör Görüntüleme kullanımı ile in-vivo olarak gerçekleştirilmesi bakımında oldukça önemlidir (Brem ve ark., 2020). Yeryüzünde ve sadece izole edilmiş bir alanda yapılmış simülasyon çalışmaları bazı önemli bilgiler sağlasa da, derin uzayda yapılacak ve diğer stres unsurlarının da dahil olduğu (kabinde bulunanların cinsiyetleri, kültürel özellikleri vb. gibi) gerçek bir Mars yolculuğu için bu bilgilerin sınırlı kaldığı ifade edilebilir.

### 2.4. Diğer Faktörlerin Etkileri

Bu derleme çalışmasında, okuyuculara fikir vermesi

açısından, ilgili literatür bilgisi ışığında uzayda insan fizyolojisini, psikolojisini ve doğal olarak öğrenme ve belleği etkileyen mikrogravite, radyasyon ve izolasyon kavramlarından kısaca söz edilmiştir. Ancak, bu faktörlerin dışında, astronotların cinsiyetleri, kültürleri (özellikle Amerikalı ve Ruslar) ve konuştukları dillere (farklı dillerde konuşan astronotların iletişim problemleri ve yanlış anlamalar yaşamasına) bağlı olarak önemli sorunlar yaşadığı bildirilmiştir. Hatta aynı dili konuşanlar arasındaki bile diyalektik farklılıklardan kaynaklanan iletişim sorunları yaşandığı ifade edilmiştir (Kanas ve Manzey, 2008), ayrıca kişilik özelliklerinin de (özellikle liderlik çatışmaları açısından) kimi zaman astronotlar arasında sorun yarattığı ifade edilmiştir.

### 3. Sonuç

Uzun zamandır, dünya atmosferinin dışına gitmek hayal olmaktan çıkmış ve birçok kez başarılıdır. Uzay çalışmaları artık Amerikan ve Rus çekişmesinin etkisinden önemli ölçüde uzaklaşmış, hatta ticarileşmiştir (Örneğin SpaceX). Bugün öncü Amerikan (NASA) ve Rus (Roskosmos) ekollerinin dışında Avrupalı (ESA), Kanadalı (CSA), Çinli (CNSA), Hintli (ISRO), Japon (JAXA) ve birçok diğer uzay ajansı da bu yarışa dahil olmuştur. Günümüzde artık hedeflenenler, uzay turizmini başlatmak, uzayda daha uzun süre kalabilmek, farklı gezegenlere gitmek ve hatta uzay madenciliği yapmaktır. Bu hedeflere ulaşmak için insanların yetenekleri daima önemli bir faktördür. Bu yeteneklerin kazanılması ve geliştirilmesi, insanın öğrenebilme becerisine ve onun hafızası bağlı olduğu söylenebilir. Mars seyahati gibi uzun bir yolculukta öğrenme becerisinin ve belleğin ne ölçüde etkileyeceğini tahmin etmek biraz güç olmakla birlikte, yapılan kimi çalışmalar bazı ipuçları sağlamaktadır.

Yapılan çalışmalara göre Mars seyahatinin yaklaşık 560 ila 1100 günlük süreyi kapsayacağı tahmin edilmektedir. Gelecekte bu seyahatin gerçekleşmesinden sonra, uzun uzay yolculuğunun öğrenme becerisine ve belleğe olan olası etkileri çok daha detaylı bir biçimde anlaşılacaktır.

### Katkı Oranı Beyanı

Konsept: S.S. (50%) ve P.Ö. (%50), Tasarım: S.S. (50%) ve P.Ö. (%50), Denetim: S.S. (50%) ve P.Ö. (%50), Kaynak taraması: S.S. (50%) ve P.Ö. (%50), Yazma: S.S. (50%) ve P.Ö. (%50), Eleştirel inceleme: S.S. (50%) ve P.Ö. (%50), Gönderim ve revizyon: S.S. (50%) ve P.Ö. (%50). Tüm yazarlar makalenin son halini incelemiş ve onaylamıştır.

### Çatışma Beyanı

Yazarlar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

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## GEÇMİŞTEN GELECEĞE ANATOMİ EĞİTİMİ

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**Özet:** Tıp ve sağlık uygulamalarının gelecekte, yeni nesil sağlık profesyonellerini eğitime, yetiştirme ve değerlendirme şeklimize farklı bir yaklaşım gerektirecek temel değişikliklere uğraması muhtemeldir. Doktorlar için insan vücudu günlük olarak araştırma ve müdahalenin odak noktasıdır; bu nedenle anatomi çalışması bir şekilde güvenli tıbbi uygulama için gerekli olmaya devam edecektir. Güvenli bir şekilde pratik yapmak ve iletişim kurmak için çekirdek anatomi bilgisinin tüm doktorlar tarafından özümsemesi gerekmektedir. Anatomi uzmanları, anatominin geçmişine ve bugününe bakarak, mesleğin nerede olduğuna ve 21. yüzyıl tıp eğitiminin ihtiyaçlarını karşılamak için şimdi nereye gitmesi gerektiğine dair vizyoner bir bakışa sahip olmalıdırlar. Anatomi, lisansüstü uzmanlık ve cerrahi eğitimde umut verici bir geleceğe sahiptir. Ayrıntılı bilgi klinik olarak ilgili olduğu, geleceğin uzmanlarının güvenli ve doğru bir şekilde uygulama yapmasına ve ayrıca gelecekteki klinik gelişmeler için güçlü bir temel sağlamasına olanak tanıdığı durumlarda uzmanlık eğitimine entegre edilmelidir.

**Anahtar kelimeler:** Anatomi eğitimi, Aktif öğrenme, Tıp eğitimi

### Anatomy Education from The Past to The Future

**Abstract:** Medical and healthcare practice is likely to see fundamental changes in the future that will require a different approach to the way in which we educate, train, and assess the next generation of healthcare professionals. For doctors, the human body is the focus of investigation and intervention on a Daily basis; for this reason, the study of anatomy in some form will continue to be essential to safe medical practice. Anatomy professionals, by looking at anatomy's past and present, must have a visionary view of where the profession has been and where it needs to go to meet the needs of 21st century medical education. Anatomy has a promising future in postgraduate specialist and surgical training. Detailed knowledge should be integrated into specialist training when it is clinically relevant allowing specialists of the future to practice safely and accurately and also to provide a strong base for future clinical developments.

**Keywords:** Anatomy education, Active learning, Medical education

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### 1. Giriş

Anatomi yüzyıllardır tıbbın köşe taşı olmuş bir disiplindir. Fakat son yıllarda insan anatomisi tıp müfredatlarından ayrıştırmaya başlanmıştır. Anatomi bilgisi hastanın muayenesinde, doğru teşhisin oluşturulmasında, bulguların hastaya ve diğer hekimlere aktarılmasında destekleyici rol oynar. Temel bilimlerin bir doktorun profesyonel hayatı boyunca değişeceği tartışılrsa da insan anatomisinin devamlılığı kesindir ve tüm tıbbi alanlara uygun bilgi platformu da sağlamaktadır. Anatomi bir cerrah için kesin olarak vazgeçilmezdir fakat aynı zamanda invaziv işlem gerçekleştiren, acil süreçleri yöneten, radyolojik görüntüleri inceleyen, hastaların fizik muayenesini yapan, hastaları bir başka hekime yönlendiren hatta hastalarına yapılacak işlemi anlatan kişiler için de büyük öneme sahiptir. Tüm bu görevler temel anatomi bilgisi olmadan, protokol ve yönergeleri takip ederek ve örüntü tanıma kullanarak da gerçekleştirilebilir. Bu yaklaşım daha az maliyetli olabilir ve sağlık kuruluşlarının daha hızlı sağlık hizmeti sunmalarını da sağlayabilir. Ancak anlamadan öğrenmek

gelecek için temel oluşturamaz ve derin öğrenme yaklaşımı olarak kabul edilemez ve geleceğin hekimlerini yetiştirmek için de yeterli kabul edilmemelidir.

Anatomi Gerçekten Düşüşte mi?

Son yıllarda tıp eğitiminde pedagojik düşüncedeki temel değişimler, sağlık bilimlerindeki diğer disiplinler gibi anatomiye de etkilemiş, öğrenme ve öğretme pratiğine yönelik yeni ve uyarlanmış yaklaşımların ortaya çıkmasıyla birlikte önemli bir müfredat değişikliği geçirmesine neden olmuştur (Sugand ve ark., 2010; Estai ve ark., 2016; McBride ve ark., 2018). Birçok programda, anatomi öğretimindeki değişiklikler, anatomi çalışmalarına ayrılan zamanın azalması ve konu sınırlarının kaldırıldığı entegre müfredatların getirilmesi gibi diğer faktörlerden fazlaca etkilenmiştir (Heylings, 2002; Evans ve ark., 2005; Drake ve ark., 2009; Gregory ve ark., 2009; Craig ve ark., 2010; Rizzolo ve ark., 2010; Irby ve ark., 2010; Estai ve ark., 2016; Guimarães ve ark., 2017; Rockarts ve ark., 2020). Yaklaşık 30-40 yıldır cerrah topluluklarının lisans anatomi bilgilerinin yetersizliği hakkında tartışmalar süre gelmektedir. Bu çalışmaların



çoğu anatomi eğitimine ayrılan sürede, öğretim üyesi sayısında ve yapılan diseksiyonlarda düşüş olduğunu bildirmektedir. Anatomi eğitimindeki bu azalmanın şiddetini objektif olarak değerlendirmek oldukça zordur. Ancak yapılan az sayıda çalışmada kalifiye doktorların bilgi seviyesinin kabul edilebilir seviyenin altında olduğu öne sürülmektedir (McKeown ve ark., 2003; Waterston ve ark., 2005; Prince ve ark., 2005). Anatominin tıp eğitiminde yerleşik bir değere sahip olduğu öğrenciler, klinisyenler, anatomistler ve genel kamuoyu tarafından desteklenmektedir. Belki de asıl tartışılması gereken konu anatomideki bu düşüşün, anatomi eğitimine ayrılan zaman ve kaynakların azalmış olması mı, yoksa öğretme metodolojisindeki değişikliklerin bir sonucu mu olduğudur.

### 2. Anatomi Öğretmek ve Öğrenmek

Anatominin nasıl öğretileceği konusu çok fazla tartışılmış ve tartışılmaya devam eden bir konudur. Diseksiyondan yana olanlar ve daha yeni eğitim yöntemlerini tercih edenler olarak iki kutup bulunmaktadır. Bu bakış açıları sırasıyla, gelenekçiler (ağırlıklı olarak cerrahlar ve anatomistler) veya modernistler (ağırlıklı olarak eğitimciler) tarafından desteklenmektedir. Ancak bunlar anatominin düşüşündeki temel sebeplere genellikle değinmemektedirler. Anatomi, gelişmedeki ve hızlı adaptasyondaki başarısızlığı sebebiyle zarar gören bir alandır. Eski tarz tıp eğitimi adı altında, öğrencilerden aradaki ilişkiyi çok az anlayarak detay öğrenmeleri beklenmekteydi. Anatomi öğrenmek açıkça gerekli bir reform ve eğitimsel olarak geçerli bir süreçten ziyade bir geçiş süreci haline gelmiştir. Anatomi aynı zamanda birçok dış baskıya da tabi tutulan bir alandır. Ulusal kurallara ve Avrupa kurallarına uygun bir diseksiyon odası sağlamak oldukça maliyetlidir ve anatomi departmanındaki ve cerrahi eğitimdeki değişimler tıbbi olarak kalifiye anatomi eğitimcilerinin sayısını azaltmıştır (Turney ve ark., 2001). Bu durum, sisteme daha fazla baskı uygulayan tıp öğrencilerinin artışıyla da ilişkilidir.

Sağlık Bakanlığı Ulusal Çekirdek Eğitim Programı (UÇEP) aracılığıyla, tıp fakültesi mezunlarından beklentisinin neler olduğunu bildirmektedir. Ancak kendi müfredatlarını ve değerlendirme yöntemlerini belirleme konusu tıp fakültelerine bırakılmıştır. Gelenekçiler anatomi eğitiminde sebebini modern öğrenme ve öğretme yöntemlerine atfettikleri bir düşüş algılamaktadırlar. Anatominin ne zaman, ne kadar ve nasıl öğretileceği asıl çözümlenmesi gereken konular gibi görünmektedirler.

Tarihsel olarak anatomi lisans eğitiminin ilk yılında veya ilk 2 yılında öğretilmektedir. Geleneksel olarak anatomi eğitimi diseksiyon temellidir. Diseksiyon geleneksel eğitimle eş anlamlı hale gelmiştir ve probleme dayalı öğrenmeye (PDÖ) karşı bir anti tez olarak değerlendirilmektedir. Ancak öğrencilerin pratik ve kendi ilgi alanlarına uygun olarak yeni bir konuyu kendi hızlarıyla keşfetmesi bakımından diseksiyonun, kendi kendine öğrenmeye ideal bir şekilde uygun olduğu görülmektedir. Özel olarak tıp ve anatomi öğrenme

bağlamında PDÖ hakkında birçok şey yazılmıştır (Schmidt ve ark., 1987; Albanese ve ark., 1993; Vernon ve ark., 1993; Verhoeven ve ark., 1998; Turney ve ark., 2001). Genel olarak temel tıp öğretme bağlamında, probleme dayalı olmayan öğrenmenin kısmen daha çok tercih edildiği ancak probleme dayalı öğrenme ile kendine güvenen ve pratik zekalı doktorlar yetiştirildiği düşünülmektedir. PDÖ taraftarları, eğer diğer alanlarda en küçük bir bilimsel bilgi veya gelişim farkı varsa bu durumun metodolojiyi doğruladığını iddia etmektedirler. Bununla birlikte bu çalışmaların çoğu PDÖ'nün artık iyi yapılandırılmış, PDÖ temelli derslere hevesli savunucularla yürütüldüğü merkezlerde yapılmıştır. Diseksiyonu anatomi derslerine dahil etmek için gerekçe oluşturmak zordur ve kesin bir kanıt bulmak pek olası değildir. Gelecekteki çalışmaların bir öğretme metodunun diğerine olan üstünlüğünü kesin olarak kanıtlaması pek olası görünmemektedir. PDÖ kullanışlı ve yapıcı bir yol olarak sunulabilir veya düşük seviyeli ve düzensiz eğitim için bahane de olabilir. Benzer şekilde diseksiyonlar kendi kendine öğrenme ve anatominin üç boyutlu farkındalığı için bir fırsat olabileceği gibi pahalı ve yönlendirilmemiş bir eğitim aracı gibi de algılanabilir.

Anatomi bilgisi her ne kadar birçok mesleki uzmanlık sınavlarında tekrar değerlendiriliyor olsa da eğitimin ileriki aşamalarında anatomi eğitimine çok az maruz kalınmaktadır. Müfredatın, görünürde aşırı derecede alakasız materyallerden oluşması eğitimsel olarak yanlıştır ve öğrenmenin yüzeysel kalmasına neden olmaktadır. Anatomiyi öğretmek için tek bir fırsat verildiğinde miktar olarak ne kadar anatomik detayın dahil edileceğini hesaplamak zordur. Bir ders geleceğin pratisyen ve uzmanlarını mı hazırlamalıdır? Anatomiyi tıp eğitimine dikey olarak entegre ederek öğrencilerin tüm lisans eğitimi boyunca (klinik öncesi ve klinik), mezuniyet sonrası ve ileriki profesyonel eğitimlerinde anatomiye maruz kalması bir çözüm olabilir. Bu durum, eğitimin veya kariyer gelişiminin aşamalarında gereken uygun anatomi detay seviyesini sunabilir. Teorik eğitimi belirli bir uzmanlığa uyarlamak gereksiz teori yükünü azaltabilir. Sonuç olarak bu uzmanlık bilgi düzeyi ancak anatominin tıp eğitimine dikey olarak entegre edilmesi ile sağlanabilir. Anatomi eğitiminin, pedagojik yaklaşımlar değiştikçe ve değişim için yeni itici güçler ortaya çıktıkça sürekli olarak gelişmesi gerekir. Örneğin 2020'deki Covid-19 pandemisi, uzaktan eğitime acilen geçebiliyor olma ihtiyacını ve anatomide birçok öğrenme ve öğretme yaklaşımının çevrimiçi bir bağlam için yeniden düşünülmesini ve uyarlanması gerektiğini göstermiştir (Evans ve ark., 2020; Longhurst ve ark., 2020; Pather ve ark., 2020; Smith ve ark., 2021). Durum ne olursa olsun, anatomi eğitiminin, öğrencilerin sağlık kariyerlerinin ve ilgili işgücü hedeflerinin gelecekteki yönüne hazırlanmalarını sağlamak için uyum sağlaması gerekmektedir. Bu durum muhtemelen sağlık ve ilgili uygulamalarda köklü değişikliklere yol açan yapay zekâ, makine öğrenimi, otomasyon ve robotiğin yükselişinin getirdiği zorluklara verilen yanıtları içerecektir (PwC, 2017).

Sürekli bir müfredat dönüşüm döngüsünün parçası olarak öğrenciye, düzenleyici makamlara ve diğer paydaşlara (hastalar dahil olmak üzere) etkin bir şekilde uygulama hazırlığını ve yetkinliğin güvenini sağlamak için öğrenci bilgi, beceri ve yeterliliklerinin değerlendirilmesini sağlamak esastır. Tıp eğitimi, aktif ve gerçek görevleri vurgulayan çok yönlü bir değerlendirme yaklaşımı geliştirmiştir ve son yıllarda öğrenmenin diyalog, gösteri ve gözlem yoluyla geliştirildiği bir "öğrenme için değerlendirme" paradigmasını benimsemeye ve öğretenlere ve öğrencilere öğrenimlerinin neresinde oldukları, nereye gitmeleri gerektiği ve oraya en iyi nasıl ulaşabilecekleri hakkında bilgi sağlamaya odaklanmaya başlamıştır (Klenowski, 2009; Dannefer, 2013). Değerlendirme uygulamaları, yetkinlik bazlı değerlendirme, portföy bazlı değerlendirme ve artık birçok tıp ve ilgili sağlık eğitimi programında görülen programlı değerlendirme gibi stratejilere göre uyarlanmıştır (Tracy ve ark., 2000; Holmboe ve ark., 2010; Schuwirth ve ark., 2011). Buna rağmen, daha geleneksel özetleyici değerlendirmenin baskınlığı hala yaygındır (Harrison ve ark., 2017; Bird ve ark., 2019). Anatomide uygulamalı ve biçimlendirici değerlendirme yöntemleri uygulanmaktadır ancak sistematik olarak kullanılmamaktadır ve gerçeklere dayalı görevlere ve tıp ve sağlık eğitiminin diğer alanları gibi, özetleyici değerlendirmeye vurgu yapılmasına yönelik algılanan bir eğilim vardır (Heylings, 2002; Evans ve ark., 2014; Brenner ve ark., 2015; Choudhury ve ark., 2017; Samarasekera ve ark., 2020). Bu nedenle müfredatın verilmesinde olduğu gibi, anatomistlerin değerlendirme yaklaşımlarını sorgulamaları ve yansıtmaları ayrıca entegre bilgi, beceri ve tutumların uygulanmasına öncelik veren bütünsel, aktif ve daha özgün yaklaşımları içeren uygun bir dengeyi sağlamaları gerekmektedir. Görünüşte ilgisiz duran bir alanda öğrenme ve değerlendirmeyi gözden geçirmek, farklı bir bakış açısı getirmek ve anatomide kullanılan mevcut yaklaşımlara meydan okumak için bir fırsat sağlamaktadır.

Seçtikleri alanda çalışmaya hazırlanan öğrencilerin öğrenmelerini değerlendirmek için uygun değerlendirme stratejilerini düşünürken mezun olduklarında ve o alana girdiklerinde ne yapacaklarını dikkate almak oldukça önemli görünmektedir. Bunu yaparken, öğrencilerin çalışacakları bağlamları, bu bağlamda başarılı olmak için ihtiyaç duydukları becerileri, bilgileri ve tutumları ve onları hazırlamak için gereken müfredat, öğrenme yöntemleri ve değerlendirmeleri tasarlayanın, ancak bunları yaparken de öğrencilerin öğrenme yaklaşımlarına, tercihlerine ve bağlamlarına uygunluğunun gözetilmesi gerekliliği aşikardır. Müfredat, pedagoji ve değerlendirme literatüründe bu, otantik öğrenme (Herrington ve ark., 2014; Pawlina ve ark., 2016), otantik değerlendirme (Wiggins, 1990; Gulikers ve ark., 2004), eğitici değerlendirme (Herrington ve ark., 2014; Pawlina ve ark., 2016), Wiggins, 1998), eğitici müfredat (Davis ve ark., 2014), akademik değerler (Boud, 1990), üretken öğrenme (Carvalho ve ark., 2014), üretken pedagoji (Gore ve ark.,

2004) veya üretken öğretim (Stiggins, 2007; Dichtelmiller, 2011) şeklinde çeşitli şekillerde tanımlanmaktadır. Bu kolektif özgün müfredat yaklaşımları, öğrenci merkezli, aktif öğrenmeyi teşvik edici ve biçimlendirici değerlendirmeyi kapsamlı olarak kullanacak şekildedir ve "öğrencilerin gerçek dünya pratiğine aktaracakları sağlam bilgiyi geliştirmelerini sağlama amacıyla" tasarlandıkları için geleceğe odaklı olarak kabul edilmektedirler (Herrington ve ark., 2014). Mezunlar, dördüncü sanayi devrimi teknolojilerinin (yapay zekâ, otomasyon, makine öğrenimi, robotik gibi) fiziksel, dijital ve biyolojik alanlara kaynaşması sebebiyle sürekli ve hızla gelişen iş ortamına girerken, geleceğe odaklılık daha önemli hale gelecektir (Schwab, 2016). Bu durum, birçok rolde temel değişikliklere ve sağlık hizmetleri de dahil olmak üzere diğerlerinin kaldırılmasına yol açacaktır.

Samarasekera ve ark. (2020) lisans tıp müfredatındaki geleneksel temel bilim derslerinin ağırlıklı olarak içerik temelli olduğunu ve öğrencilerin bu dersleri dinlerken bilgiden zengin içeriğin "pasif dinleyicileri ve acıları" olma eğilimi gösterdiklerini savunmuştur. Bu durum, gelişmiş kavramsal anlayışa sahip bir derin öğrenme yaklaşımından ziyade yüzeysel veya ezberci bir öğrenme yaklaşımını teşvik etmektedir (Entwistle ve ark., 2001). Bunun çıkarımı, öğrencilerin "bilgi açısından zengin, ancak uygulama açısından fakir" olmaları ve öğrencilerin gireceği birçok meslek için temel olan problem çözme ve eleştirel akıl yürütmeye potansiyel olarak daha az etkili olmalarıdır. Yüzeysel öğrenme yaklaşımını benimseyen öğrencilerin bilgilerini pratiğe dökme konusunda zorluklar yaşadığı gösterilmiştir (Smith ve ark., 2007). Yüzeysel öğrenme çıktıları üzerinde devam eden bu vurgular bazı durumlarda, temel çoktan seçmeli, genişletilmiş eşleştirme, kısa cevaplı sınavlar ve testler ve daha az ölçüde, vaka temelli yaklaşımları gibi, temel bilimler için hala tipik olan değerlendirme rejimlerine atfedilebilir (Heylings, 2002; Rockarts ve ark., 2020; Samarasekera ve ark., 2020). Bununla ilişkili olarak anatomi haksız bir şekilde tamamen bilgi biriktiren bir ders olarak etiketlenebilir ve bilgi birikimi aslen kritik olmasına rağmen anatomi eğitiminin faydaları, klinik akıl yürütme ve teşhis yeteneği geliştirmek için diğer klinik bilimlerle birlikte görselleştirici dil kullanma ve yapı taşlarını güçlendirme gibi mevcut kavramsal öğrenme özelliklerine dayandırılabilir (Miller ve ark., 2002; de Bruin ve ark., 2005; Woods, 2007; Vorstenbosch ve ark., 2016). Aslında birçok program, anatomi eğitimine öncelikle aktif yaklaşımlarla öğretilecek klinik akıl yürütme ve uygulama sağlayan bileşik yaklaşımlara sahiptir (Evans ve ark., 2005; Lachman ve ark., 2006; Rizzolo ve ark., 2010; Elizondo-Omaña ve ark., 2010; Johnson ve ark., 2012). Gelişmekte olan bu özellik ve yaklaşımlar, tasarım eğitimiyle güçlü paralelliklere sahiptir. Daha aktif ve bütüncül bir öğrenme ortamına geçişe rağmen, anatomideki geleneksel değerlendirme rejimlerinin, mevcut tıp ve sağlık eğitimi bağlamı ve tıp ve sağlık uygulamalarının gelecekteki yönü ile bağdaşmıyor olduğuna dair inanın devam ettiği görülmektedir. Bu

durum değerlendirmelerin geçersiz veya güvenilir olmadığı anlamına gelmemektedir; ancak bir değerlendirme aracı olarak kullanılacaklarsa, özgünlük sağlamak ve yeterli biliş düzeylerini değerlendirmek için uygun şekilde tasarlanıp dahil edilmeleri anlamına gelmektedir (Palmer ve ark., 2007; Schuwirth ve ark., 2011; Hift, 2014; Thompson ve ark., 2015).

### 3. Gelecekte Anatomi

Anatomi, doktor yetiştirme ve modern tıp pratiğini destekleme sürecinde hala büyük rol oynamaktadır. Eski ve yeni olmak üzere bütün tıp fakülteleri halen daha anatomi müfredatlarının çekirdeği olarak tutmaktadırlar. Son 20-30 yılda, tüm anatomi müfredatı öğrenciler üzerindeki fiili yükü azaltmak ve diğer öğretim yeteneklerini kazandıracak zamanı yaratmak için indirgenmektedir. Bu indirgenmenin geleceğin cerrahları ve diğer uzmanları üzerinde etkisi mevcuttur ancak belki de anatomistler ve diğer uzmanlar, daha sonraları ve daha uygun bir zamanda gerekli eğitimi sağlamakla yükümlü olan kişilerdir.

Anatomi geleneksel olarak klinik eğitimin ve pratiğin temellerini oluşturmak amacıyla tıp eğitiminin başlarında verilmektedir. Gelenekçilerin, anatomi derslerinin detaylandırılmasına ilişkin dogmatik dayanakları anatominin bir ders olarak gelişmesinde zararlı olabilir. Yenilikçiler bu eğitim yöntemlerinin, büyük ihtimalle getireceği yararları hiç takdir etmeyerek, “demode” ve modern öğrenme pratikleriyle bağdaşmaz olduğunu düşünmekte ısrar edebilirler. Eğer eski stil anatomi eğitimi öldüyse, “anatominin kendisini bir ders olarak tekrar icat etmesi gerekmektedir”. 21. yüzyılda tıp müfredatındaki herhangi bir konunun gereksinimlerini karşılayacak şekilde gelişmelidir. Pasif, didaktif ve fazla detaylandırılmış derslerden, öğretim yöntemlerini gözetmeksizin fonksiyonel ve klinikle ilişkili derslere yönelim konusunda bazı gelişmeler yaşanmıştır. Daha fazla gelişmenin kaydedilebilmesi için gelenekçiler şunu kabul etmelidirler ki fazla miktarda detaylandırılmış anatomi, tıbbi kariyerin büyük çoğunluğunda gereksizdir ve çekirdek bilgi korunacak şekilde bütün öğrencilere uygun olarak özümsemelidir. Bu çekirdek bilginin tanımlanması konusunda da ilerleme kaydedilmiştir. Eğer çekirdek bilginin ne olduğu konusunda hem fikir olunmuşsa özümsemesi yalnızca tıp eğitiminin ilk yılları için değil, hali hazırda devam eden klinik eğitimin ve devamının değerlendirilmesi sürecinde de titizlikle sağlanmalıdır. Çekirdek bilgi konseptinin kabulü aynı zamanda bunun uzmanlık eğitimi için yetersiz olduğunu tanımayı da gerektirir. Daha ayrıntılı anatomi bilgisi gerektiren tıp kariyerlerine giren öğrencilerin, kariyerlerinin sonraki aşamalarında özel anatomi eğitimine erişmeleri gerekecektir. Anatomi bölümlerinin hastane bölümleriyle eğitimsel ve finansal bağlantılar kurması sürdürülebilir bir çözümdür ve bazı tıp fakülteleri bu seçeneği araştırmaktadır. Bu durum, tıp fakültesinin ilk yılından klinik ve uzmanlık eğitimine kadar anatominin tıp fakültesi müfredatına dikey

entegrasyonuna izin verecek ve klinik uygunluğunun takdir edilmesiyle çekirdek anatomiyi güçlendirecektir. Klinik uzmanların katılımı onlara anatomi ders programını iyi klinik uygulamalara ve gelişen tekniklere göre şekillendirme, kendi bilgilerini geliştirme ve anatomi öğretiminde personel eksikliklerini gidermeye yardımcı olma fırsatı verecektir. Uzmanların, anatomik bilgi eksikliği konusundaki eleştirileri doğrudan ele alınacak ve bu durum daha güvenli, daha yetkin hekimler üreterek gelecekte hata yapma ve dava açılma olasılığını daha düşük tutacaktır.

#### Sonuç

Tıp ve sağlık bakımı uygulamaları gelişmeye devam etmektedir ve gelecekte, yeni nesil sağlık profesyonellerini eğitime, yetiştirme ve değerlendirme yöntemimize farklı bir yaklaşım gerektirecek temel değişiklikleri görmemiz muhtemeldir. Bilgili öğrencileri hazırlamakta ve gelecekte etkili bir şekilde uygulama yapma kapasitelerinin temellerine katkıda bulunacak beceri ve yetkinlikleri giderek daha fazla teşvik etmekte tam bir rol oynamaya devam edebilmesi için anatomi biliminin bu zorluklara dahil edilmesi gerekmektedir. Görünüşte ilgisiz bir alanda öğrenme ve değerlendirmeyi gözden geçirmek, farklı bir bakış açısı getirmek ve anatomideki mevcut yaklaşımların uygun şekilde sorgulanmasını sağlamak için bir fırsat sağlamaktadır.

“Anatomi bilgisinden yoksun doktorlar köstebeğe benzerler. Belirsizlik içinde, karanlıkta çalışan elleri ile birçok mezarlar yaratırlar” (Tiedemann: Heidelberg, 1781-1861).

#### Katkı Oranı Beyanı

Konsept: E.Ç. (%34), Z.A. (%33) ve Ez.Ç. (%33), Tasarım: E.Ç. (%34), Z.A. (%33) ve Ez.Ç. (%33), Denetim: E.Ç. (%34), Z.A. (%33) ve Ez.Ç. (%33), Kaynak taraması: E.Ç. (%34), Z.A. (%33) ve Ez.Ç. (%33), Yazma: E.Ç. (%34), Z.A. (%33) ve Ez.Ç. (%33), Eleştirel inceleme: E.Ç. (%34), Z.A. (%33) ve Ez.Ç. (%33), Gönderim ve revizyon: E.Ç. (%34), Z.A. (%33) ve Ez.Ç. (%33). Tüm yazarlar makalenin son halini incelemiş ve onaylamıştır.

#### Çatışma Beyanı

Yazarlar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

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