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EDITORIAL

Our dear readers,

We are happy to publish the second issue of our journal in 2022. We have entered a period that is calm in terms of the COVID-19 pandemic, but intensified in terms of scientific studies and clinical practise. Thus we higly determined to booster our scientific quality. We have started to be indexed in the TUBITAK ULAKBİM index since June. This development made us very happy and encouraged us to make new breakthroughs. Our goal is to increase our scientific quality by being accepted into many new directories in the near future. In this context, our work continues rapidly. We hope this issue will be useful to our readers.

Kind regards,

Assoc. Prof. Alpaslan TANOĞLU, MD
Editor-in-Chief

EDİTÖRDEN

Çok değerli okuyucularımız,

2022 yılında dergimizin ikinci sayısını çıkarmanın mutluluğunu yaşıyoruz. COVID-19 pandemisi açısından sakin ancak bilimsel çalışmalar ve klinik uygulamalar açısından yoğun bir döneme girmiş bulunuyoruz. Böylece bilimsel kalitemizi artırmaya kararlıyız. Haziran ayından itibaren TÜBİTAK ULAKBİM indeksinde indekslenmeye başladık. Bu gelişme bizi çok mutlu etti ve yeni atılımlar yapmamız için bizi cesaretlendirdi. Hedefimiz, yakın gelecekte birçok yeni dizine kabul edilerek bilimsel kalitemizi artırmaktır. Bu kapsamda çalışmalarımız hızla devam etmektedir. Bu sayının okuyucularımız için faydalı olacağını umuyoruz.

Saygılarımla,

Doç. Dr. Alpaslan TANOĞLU
Baş Editör

Original Article / Özgün Makale

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Tip 2 diyabet hastalarında dolaşımdaki B-tipi natriüretik peptidin osteoporoz ile ilişkisi

Association of circulating B-type natriuretic peptide with osteoporosis in patients with type 2 diabetes

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ÖZ

Amaç: Bu çalışmanın amacı tip 2 diabetes mellitus (T2DM) hastalarında dolaşımdaki B-tipi natriüretik peptid (BNP)'in osteoporoz ile ilişkisini değerlendirmektir.

Gereç ve Yöntem: T2DM'li 95 hasta çalışmaya dahil edildi. Hasta dosya sistemlerinde dolaşımdaki BNP seviyeleri olan ve 15 gün içerisinde kemik mineral yoğunluğu (KMY) bakılmış hastalar çalışmaya dahil edildi. Hastalar KMY skorlarına göre normal, osteopeni ve osteoporoz olarak üç gruba ayrıldı. Dolaşımdaki BNP ile diyabetik osteoporoz ve diğer parametreler arasındaki ilişki incelendi.

Bulgular: Çalışmamıza 75'i kadın, 20'si erkek olmak üzere toplam 95 hasta dahil edildi. Hastaların yaş ortalaması 66,09±5,96 idi. Gruplar arasında cinsiyet, yaş ve vücut kitle indeksi (VKİ) benzer bulundu. DM süresi osteoporoz grubunda anlamlı olarak yüksek saptandı (p<0,005). Laboratuvar paramaretlerinin gruplar arası karşılaştırılmasında glukoz, trigliserid, glikolize hemoglobin (HbA1c), alkalen fosfataz (ALP) ve BNP ortalamaları istatistiksel olarak anlamlı şekilde osteoporoz grubunda daha yüksekti (p<0,05).

Sonuç: Dolaşımdaki BNP, T2DM'li osteoporoz hastaları için bir biyobelirteç olarak kullanılabilir.

Anahtar Kelimeler: Tip 2 diabetes mellitus, osteoporoz, B-tipi natriüretik peptid

ABSTRACT

Objective: The aim of this study was to evaluate the relationship of circulating B-type natriuretic peptide (BNP) with osteoporosis in type 2 diabetes mellitus (T2DM) patients.

Material and Method: 95 patients with T2DM were included in the study. Patients with circulating BNP levels in their patient file systems and whose BMD were measured within 15 days were included in the study. The patients were divided into three groups according to their BMD scores as normal, osteopenia and osteoporosis. The relationship between circulating BNP and diabetic osteoporosis and other parameters was investigated.

Results: A total of 95 patients, 75 female and 20 male, were included in our study. The mean age of the patients was 66.09±5.96 years. Gender, age and BMI were similar between the groups. The duration of DM was found to be significantly higher in the osteoporosis group (p<0.005). In the comparison of laboratory parameters between groups, the averages of glucose, triglyceride, HbA1c, ALP and BNP were statistically significantly higher in the osteoporosis group (p<0.05).

Conclusion: Circulating BNP can be used as a biomarker for osteoporosis patients with T2DM.

Keywords: Type 2 diabetes mellitus, osteoporosis, B-type natriuretic peptide

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GİRİŞ

Diabetes mellitus (DM), insülinin fonksiyonlarında ve salınım mekanizmalarındaki patolojiler sonucu oluşan karbonhidrat, yağ ve protein metabolizmasındaki değişiklikler ve bunların yol açtığı kronik hiperglisemi ile karakterize metabolik bir bozukluktur (1). 2018 ADA kılavuzuna göre tip 1 diabetes mellitus (T1DM), tip 2 diabetes mellitus (T2DM), gestasyonel DM ve diğer nedenlere bağlı spesfik DM olmak üzere dört ana başlıkta sınıflandırılır. T2DM, pankreastan kan glukoz düzeyine yanıt olarak salınan insulin sekresyonunda azalma ve/veya periferik dokularda özellikle kas ve yağ dokusunda oluşan insulin direnci nedeniyle oluşur (2).

DM prevalansı özellikle diyabetle ilişkili renal ve kardiyovasküler komplikasyonlarla birlikte artmakta, bu da sağlık sistemleri üzerinde çok büyük bir yüke neden olmaktadır. Uluslararası Diyabet Federasyonu 20-79 yaş aralığında 425 milyon diyabet hastasının yaşamakta olduğunu ve 2045 yılında bu sayının 629 milyona ulaşacağını bildirmiştir. Ayrıca, bozulmuş glukoz toleransı olan 318 milyon yetişkin olduğu tahmin edilmektedir (3).

DM ve osteoporoz arasındaki ilişki ise karmaşıktır. DM iskeleti de olumsuz etkiler ve kırık riskinin artması diyabetiklerde önemli bir komplikasyondur (4). Kemik kütlesi ve mineralizasyonun bir göstergesi olan kemik mineral yoğunluğu (KMY), kemik gücünün ana belirleyicilerinden biri ve genel popülasyonda osteoporozu saptamak ve kırık riskini tahmin etmek için önemli bir araç olarak kabul edilmektedir. T1DM, dolaşımdaki düşük IGF-1 ve insülin seviyeleri nedeniyle düşük kemik mineral yoğunluğu (KMY) ile karakterizedir. T2DM'de ise KMY azalmış, normal veya artmasına rağmen kırık riski epidemiyolojik çalışmalarda artmış olarak bulunmuştur (5-7). Artmış kırık riski, bozulmuş kemik kalitesi ve kemik dışı faktörlerden kaynaklanabilir (8). Ancak, altta yatan mekanizma net olarak belirlenmemiştir. Bu nedenle, diyabetik osteoporozun erken önlenmesi ve tedavisi için klinik olarak uygun osteoporoz göstergelerinin bulunması büyük önem taşımaktadır.

Kalp yetersizliği (KY), kalbin yeterli venöz dönüşe rağmen istirahat ve egzersiz süresince dokuların metabolik gereksinimlerini karşılayacak kanı pompalayamamasıdır (9). T2DM'nin sık görülen önemli bir kardiyovasküler komplikasyonudur (10). B tipi natriüretik peptit (BNP), KY'de özellikle sol ventrikül yetmezlikli hastalarda ventriküler dilatasyon, aşırı basınç ve iskemik hasara yanıt olarak salgılanan bir nörohormondur (11). Yaş, cinsiyet, renin-anjiyotensin sisteminin (RAS) aktivitesi ve adipokin seviyeleri gibi çeşitli faktörler kemik metabolizmasını etkileyebilir. Natriüretik peptitler(NP), RAS'ı inhibe eden ve KMY'yi etkileyen güçlü lipolitik ajanlardır (12,13). Bununla birlikte BNP'nin KMY değerleri ve osteoporoz ile ilişkili bu bulgular tutarsız ve tartışmalıdır.

Bu çalışmanın amacı, T2DM hastalarında dolaşımdaki BNP'nin osteoporoz ile ilişkisini değerlendirmektir

GEREÇ VE YÖNTEM

Bu çalışma, üniversite/yerel insan araştırmaları etik kurulu tarafından onaylanmış ve insan katılımcıları içeren çalışmalarda gerçekleştirilen tüm prosedürler, kurumsal ve/veya ulusal araştırma komitesinin etik standartlarına, 1964 Helsinki Bildirgesi ve daha sonra yapılan değişikliklere veya karşılaştırılabilir etik standartlara uygun olarak yapılmıştır. Çalışma için Hitit Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan etik kurul onayı alınmıştır (Tarih: 31.01.2022, Karar no: 2022-01).

Çalışmamız retrospektif olarak planlandı 2020 yılında iç hastalıkları polikliniğinimize başvuran en az bir yıldır diyabet tanısı ile takipli hastaların dosyaları hastane otomasyon sisteminden tarandı. Serum BNP bakılmış ve kemik dansitometri yapılmış toplam 390 hastaya ulaşıldı. Dahil edilme ve dışlanma kriterlerini karşılayan toplam 95 hasta çalışmaya dahil edildi. Dahil edilme kiterlerinde 50-75 yaş aralığında olmak, en az bir yıldır DM tanısı ile takipli olmak, serum BNP bakılmış ve 15 gün içersinde kemik dansitometri yapılmış hastalar yer almaktadır. Malignite varlığı, son 3 ayda atriyal fibrilasyon, aort darlığı, miyokard enfarktüsü veya stabil olmayan anjina gibi kardiyak aritmileri, kontrolsüz hipertansiyon (>180/100 mmHg) varlığı, akut solunum yetmezliği öyküsü, tromboemboli öyküsü, hematolojik sistem hastalıkları varlığı, otoimmün hastalıklar ve gebelik dışlanma kriterleri olarak belirlendi.

Klinik ve Biyokimyasal Ölçümler

Tüm hastaların yaş, cinsiyet, vücut kitle indeksleri(V-Kİ), diyabet süreleri , diyabet ilaçları ve mevcut hastalıkları not edildi. Rutin biyokimyasal analizler hastanemiz merkezi laboratuvarında gerçekleştirildi. Açlık kan şekeri, glikolize hemoglobin (HbA1c), total kolesterol (TK), trigliserit (TG), yüksek yoğunluklu lipoprotein kolesterol (HDL-K) ve düşük yoğunluklu lipoprotein kolesterol (LDL-K), serum kreatinin, kalsiyum, alkalen fosfataz (ALP), hemoglobin (Hb), beyaz kan hücresi (WBC), nötrofil ve lenfosit sayıları, nötrofil/lenfosit oranı (NLO), 25 hidroksivitamin-D(25-OH-D) ve dolaşımdaki BNP değerleri kayıt edildi. Dolaşımdaki BNP düzeyleri Roche Cobas e 601 immunoassay cihazı (Roche Diagnostics Avustralya Pty Limited Avustralya) ile uyumlu ticari kitler (Elecsys proBNPII) kullanılarak ölçüldü. Normal aralığı 0-125 pg/ml idi.

KMY Ölçümü ve Osteoporoz Teşhisi

Kalça ve omurganın Dual Enerji X-ray absorbsiyometri (DEXA) ile ölçümü ileride oluşabilecek bir fraktürün önceden tahmini ve takibi için günümüz teknolojisinde kullanılmaktadır. KMY, kemiğin belirli bir alanının santimetrekaresindeki mineralin gram (g/cm^2) cinsinden ifadesidir. Ortaya çıkan sonuç 2 farklı kriter ile bağlantı kurularak değerlendirilir. Standart olarak ölçüm sonuçlarında T-skoru kullanılır ki bu aynı ırk ve cinsteki genç sağlıklı insanların kemik yoğunluğu ile hastanın kemik yoğunluğunun karşılaştırılmasıdır. Z-skoru ise hastayı aynı yaş grubundaki ama yine aynı ırk ve cinsteki bireyler ile karşılaştırır. Dünya Sağlık Örgütü (DSÖ) tanı kriterlerine göre KMY T skoru >-1 ise normal, -1 ile -2,5 arası osteopeni, ≤-2,5 ise osteoporoz, ≤-2,5 ve frajilite kırığı varsa ciddi osteoporoz olarak sınıflandırılmaktadır.

İstatistik Yöntemi

Nominal ve ordinal verilerin tanımlanmasında frekans analizi, ölçüm parametrelerinin tanımlanmasında ortalama ve standart sapma değerleri kullanıldı. Fark analizleri öncesinde, normallik dağılımı için Kolmogorov Smirnov testi yapıldı. Normal dağılan parametreler için One Way ANOVA ve Tukey testleri, normal dağılmayan parametreler için Kruskal Wallis ve Mann Whitney U testleri yapıldı. Nominal ve ordinal verilerin fark analizinde Ki-Kare Benzerlik oranı kullanıldı. İlişkisel tarama analizinde, Spearman's rho korelasyon analizi yapıldı. Tüm analizler %95 güven aralığında ve 0,05 anlamlılık düzeyinde, SPSS 17.0 for Windows programında yapıldı.

BULGULAR

Çalışmamıza 75'i kadın, 20'si erkek olmak üzere toplam 95 hasta dahil edildi. Hastaların yaş ortalaması 66,09±5,96 idi. Gruplar arasında cinsiyet, yaş ve VKİ benzer bulundu. DM süresi osteoporoz grubunda anlamlı olarak yüksek saptandı (**Tablo 1**).

Hastaların laboratuvar paramaretlerinin gruplar arası karşılaştırılmasında glukoz, trigliserid, HbA1c, ALP ve BNP ortalamaları istatistiksel olarak anlamlı şekilde osteoporoz grubunda daha yüksekti (p<0,05) (**Tablo 2**).

İkili grup kıyaslamalarına göre farkı anlamlı çıkan tüm parametrelerin normal ve osteoporoz grubu arasındaki farkı istatistiksel olarak anlamlıydı (p<0,05). Normal grup ile osteopeni arasında ise total lomber T ve femur boyun T skoru düzeyleri farkları anlamlıydı (p<0,05). Osteoporoz ile osteopeni grupları arasında trigliserid dışındaki farkı anlamlı çıkan tüm parametrelerin farkı istatistiksel olarak anlamlıydı (p<0,05) (**Tablo 3**).

Osteoporoz grubunda BNP ile MPV (r=-0,363; p<0,05), PLT (r=0,347; p<0,05), HDL (r=-0,436; p<0,01), ALP (r=0,549; p<0,01), L1-L4 total lomber T skoru (r= -0,489, 0,000) ve femur boyun T (r=-0,383; p<0,05) değerleri arasında istatistiksel olarak anlamlı ilişki vardı.

Tablo 1. Hasta gruplarına göre bazı demografik ve klinik verilerin dağılımı

Grup	Normal (n=35)	Osteoporoz (n=37)	Osteopeni (n=23)	p değeri
Cinsiyet, n (%)				
Kadın	29 (82,9)	27 (73,0)	19 (82,6)	0,527[a]
Erkek	6 (17,1)	10 (27,0)	4 (17,4)	
Yaş	66,03±5,82	66,70±6,44	65,26±5,90	0,670[b]
Vücut kitle indeksi (VKİ)	32,45±5,56	33,92±5,24	33,91±5,43	0,447[b]
Diabetes mellitus (DM) süresi	8,34±5,34	14,05±7,19	8,87±4,60	0,000[b]
DM tedavisi, n (%)				
Metmorfomin	15 (42,9)	6 (16,2)	12 (52,2)	
Pioglizaton	1 (2,9)	-	2 (8,7)	
Empagliflozin	10 (28,6)	7 (18,9)	3 (13,0)	
Vildagliptin	3 (8,6)	2 (5,4)	1 (4,3)	
İnsülin	1 (2,9)	10 (27,0)	2 (8,7)	
Linagliptin	1 (2,9)	1(2,7)	-	
Diğer	4 (11,4)	11 (29,7)	3 (13,0)	
DM komplikasyon, n (%)				
Yok	29 (82,9)	14 (37,8)	18 (78,3)	
Nöropati	4 (11,4)	8 (21,6)	2 (8,7)	
Nefropati	-	1 (2,7)	1 (4,3)	0,002[a]
Retinopati	-	1 (2,7)	1 (4,3)	
Nöropati+Nefropati	1 (2,9)	9 (24,3)	-	
Nöropati+Retinopati	1 (2,9)	1 (2,7)	1 (4,3)	
Nefropati+Retinopati	-	(8,1)	-	

Ki-Kare Benzerlik Oranı, b. One Way ANOVA

Tablo 2. Hastaların laboratuvar paramaretlerinin ve KMY değerlerinin gruplar arası karşılaştırılması

Grup	Normal ORT±SS	Osteoporoz ORT±SS	Osteopeni ORT±SS	p değeri
HbA1c	5,67±1,36	7,64±1,60	6,06±1,43	0,000[b]
WBC	9,55±6,64	9,40±3,43	8,05±1,70	0,367[c]
Hb	13,87±5,14	12,38±3,17	18,06±4,45	0,279[c]
MPV	10,00±1,26	9,9±1,83	9,88±1,07	0,261[c]
Nötrofil	4,59±1,94	15,99±51,41	4,66±1,78	0,391[c]
Lenfosit	3,00±3,54	2,78±1,15	2,36±0,68	0,080[c]
NLO	2,18±2,06	6,38±22,19	2,27±1,51	0,080[c]
PLT	275,52±101,19	271,85±117,78	293,96±97,66	0,724[b]
PLO	113,70±46,04	112,20±68,09	135,04±68,87	0,322[b]
Glukoz	142,26±102,31	192,78±70,31	132,83±49,29	0,000[c]
Trigliserid	148,23±50,27	204,48±90,45	172,87±79,81	0,003[c]
Total kolesterol	187,49±39,87	224,92±48,65	192,87±33,16	0,001[c]
HDL-K	51,40±11,65	47,17±11,82	46,87±9,14	0,193[c]
LDL-K	123,77±30,58	146,47±42,60	119,78±30,09	0,054[c]
Kreatinin	0,90±0,31	0,95±0,20	0,82±0,29	0,209[c]
Kalsiyum	9,32±0,49	10,67±12,05	9,04±0,66	0,350[c]
ALP	83,34±34,80	141,59±77,08	95,13±34,57	0,000[c]
BNP	1248,55±5274,18	1892,71±4734,81	622,02±1415,50	0,000[c]
25-OH-D vitamini	22,71±10,45	13,97±7,71	20,22±10,80	0,000[c]
L1-L4 total lomber T skoru	0,98±1,29	-3,45±0,48	-1,55±0,39	0,000[b]
L1-L4 total lomber Z skoru	0,54±0,89	-1,31±0,99	0,32±0,71	0,000[c]
Femur boyun T skoru	0,62±1,47	-2,96±0,88	-1,37±1,04	0,000[b]
Femur boyun Z skoru	0,55±1,03	-1,21±1,08	0,20±1,09	0,000[b]

Ki-Kare Benzerlik Oranı, b. One Way ANOVA, c. Kruskal Wallis Testi, ORT: Ortalama SS: Standart Sapma.

Tablo 3. Farkı anlamlı çıkan parametreler için Post Hoc ikili kıyaslama sonuçları (p değerleri)

Grup	Normal-Osteoporoz	Normal-Osteopeni	Osteoporoz-Osteopeni
DM süresi	0,000[a]	0,942[a]	0,004[a]
HbA1c	0,000[a]	0,582[a]	0,000[a]
Glukoz	0,000[b]	0,113[b]	0,000[b]
Trigliserid	0,003[b]	0,283[b]	0,115[b]
Total kolesterol	0,001[b]	0,272[b]	0,009[b]
ALP	0,000[b]	0,105[b]	0,013[b]
BNP	0,000[b]	0,349[b]	0,004[b]
L1-L4 total lomber T skoru	0,000[a]	0,000[a]	0,000[a]
L1-L4 total lomber Z skoru	0,000[b]	0,197[b]	0,000[b]
Femur boyun T skoru	0,000[b]	0,000[b]	0,000[b]
Femur boyun Z skoru	0,000[b]	0,136[b]	0,000[b]

Tukey testi, b. Mann Whitney U Testi.

Tablo 4, Osteoporoz grubunda BNP ile diğer parametreler arasındaki ilişki için yapılan Spearman's rho korelasyon analizi sonuçları

BNP	Osteoporoz	
	r	p
Yaş	0,263	0,115
Cinsiyet	0,131	0,439
VKİ	0,172	0,310
DM süresi	0,176	0,298
DM tedavisi	-0,069	0,685
DM komplikasyon	0,127	0,452
ALP	0,549**	0,001
25-OH-D vitamini	-0,007	0,966
L1-L4 total lomber T skoru	-0,489*	0,000
L1-L4 total lomber Z skoru	0,156	0,355
Femur boyun T skoru	-0,383*	0,019
Femur boyun Z skoru	-0,088	0,606

*p<0,05 **p<0,01

TARTIŞMA

Diabetes mellitus tüm toplumlarda yaygın görülen, ciddi morbidite ve mortalite nedeni olan ve prevelansı giderek artan metabolik bir hastalıktır (1,14). Ailede DM öyküsü olması, kadın cinsiyet, ileri yaş, etnik köken, obezite, fiziksel inaktivite, yanlış beslenme, stres, kentsel yaşam, gebelik, gestasyonel DM, intrauterin beslenme bozuklukları DM için predispozan faktörlerdir (14). Bizim çalışmamızda 95 hastanın 75'i kadın hastaydı. Yaş ortalaması 66,09±5,96 olarak saptandı.

T2DM ve osteoporoz esas olarak kronik sonuçları nedeniyle ciddi morbidite, artan mortalite ve önemli sosyal maliyetlerle ilişkilidir (15). Endokrin osteoporoz nedenleri arasında düşünülmesi gereken T2DM'nin kronik komplikasyonları arasında iskelet kırılganlığında artış

mevcuttur. Epidemiyolojik veriler, T2DM'nin artmış kırık riski ile ilişkili olduğunu göstermektedir (16,17).

Özellikle kadın cinsiyet , ileri yaş, düşük VKİ, uzun diyabet süresi ile dislipidemi, hipertansiyon ve hiperglisemi gibi kardiyometabolik risk faktörlerinin diyabetik osteoporozun patogenezinde önemli bir rol oynadığı gösterilmiştir (18,19). Bu çalışmada da bulgularımız, diyabetik osteoporoz ve osteopenisi olan hastalarda önemli ölçüde daha fazla kadın hasta, artmış yaş aralığı, anlamlı şekilde daha uzun diyabet süresi, artmış HbA1c değeri ve dislipidemi mevcuttu.

DM komplikasyonları akut ve kronik komplikasyonlar olmak üzere ikiye ayrılırlar. Nefropati, nöropati ve retinopati diyabetin mikrovasküler kronik komplikasyonlarındandır (14). DM'nin mikrovasküler komplikasyonları sonucu oluşan görme bozukluğunun, vaskülarizasyonun azalmasının, kemik metabolizmasının etkilenmesinin, egzersiz ve kas kitlesinin azalmasının KMY'nin azalmasına ve kırık riskinin artmasına neden olduğunu gösteren çalışmalar mevcuttur (20,21). Yapılan çalışmalarda T2DM ve nöropatisi olan erkeklerde kemik yıkım oranı, nöropatisi olmayan erkeklere göre daha yüksek bulunmuştur. Ayrıca kemik yıkım belirteçlerinden C-telopeptid ve prokollajen tip1 aminoterminal propeptidi değerleri de nöropatili hastalarda anlamlı derecede yüksek saptanmıştır. Bu da T2DM'li hastalarda osteoporozun gelişiminde, nöropatinin rol oynadığını düşündürmektedir. DM'de eklem beslenmesinin bozulması ve nöropati sonucu duysal uyaranların azalmasının sekonder osteoporoz gelişimine zemin hazırladığı düşünülmektedir (22,23). Bizim çalışmamızda mikrovasküler komplikasyonlar osteoporoz grubunda anlamlı olarak yüksek saptandı (p=0,002).

Yapılan son araştırmalarda tam kan sayımından elde edilen nötrofil lenfosit oranı (NLO) ve platelet lenfosit oranı (PLO) sistemik inflamatuvar hastalıkların prognozuyla korelasyon gösteren ucuz, basit hesaplanabilir bir indekstir (24). Diyabeti olmayan postmenopozal kadınlarda yapılan bir çalışmada ve T2DM osteoporozu olan hastalar üzerinde yapılan çalışmalarda düşük KMY ile artmış NLO arasında güçlü bir ilişki bulunmuş, osteoporozun değerlendirilmesinde NLO'nun yardımcı bir biyobelirteç olarak kullanılabileceği sonucuna varılmıştır (25,26). Bu çalışmada NLO ile diyabetik osteoporoz hastalarında anlamlı bir sonuca ulaşılamadı.

BNP ventriküllerden pre-pro-BNP olarak sentezlenip pro-BNP'ye sonrasında ise biyolojik aktif BNP ve inaktif olan N terminal BNP'ye dönüşür. BNP 32 aminoasitten oluşan bir polipeptiddir. BNP ventriküler hacim yükü artışına, vazokonstrüksiyona, sodyum retansiyonuna ve RAS aktivasyonuna karşı regülatör rol üstlenir (27). Natriüretik peptitler, RAS'ı inhibe ederek KMD'nin azalmasına yol açabilir. Wang ve ark. (13) yapmış olduğu bir çalışmada 52 periton diyalizi hastasında artmış serum NT-proBNP değeri ile düşük kemik mineral yoğunluğu arasında anlamlı ilişki saptanmış. Lee ve ark. (28) 69 renal transplantasyon hastasında yapmış oldukları çalışmada da serum NT-proBNP değeri ile lomber T skoru arasında negatif korelasyon bulunmuş. Ayrıca Kajita ve ark. postmenopozal hastalar üzerinde kantitatif lokus analazi yaparak BNP varyasyonunun kemik kaybı mekanizmasına neden olmasından dolayı postmenopozal osteoporozun önemli bir belirleyicisi olabileceğini gösterdi (29). T2DM hastalarında yapılmış, bilinen tek çalışma olan Chen ve ark. (26)'nın çalışmasında dolaşımdaki BNP ve KMY arasında negatif korelasyon saptanmış. Bu çalışmalarla uyumlu olarak bizim çalışmamızda osteoporozlu T2DM hastalarında dolaşımdaki BNP'nin anlamlı olarak daha yüksek olduğunu bulduk.

SONUÇ

Dolaşımdaki BNP, T2DM'li osteoporoz hastaları için potansiyel bir biyobelirteç olabilir. Bununla birlikte, dolaşımdaki BNP'nin diyabetik osteoporoz gelişimindeki potansiyel rolünü doğrulamak ve biyobelirteç olarak belirlemek için daha fazla araştırmaya ihtiyaç vardır.

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Hasta Onamı: Çalışma retrospektif olarak tasarlandığından hastalardan yazılı bilgilendirilmiş onam formu alınmamıştır.

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The significance of haematological parameters and CA 19-9 in assessing vascular invasion and inoperability in pancreatic cancer

Pankreas kanserinde vasküler invazyon ve inoperabilitenin değerlendirilmesinde hematolojik parametrelerin ve CA 19-9'un önemi

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ABSTRACT

Aim: In this study, by comparing resectable and unresectable patients over the laboratory data of patients with pancreatic cancer, the predictive usefulness of haematological parameters and CA19-9 in the evaluation of inoperability was explored.

Material and Method: The study included 147 individuals diagnosed with pancreatic cancer at Hitit Univesity Erol Olçok Training and Research Hospital between 2015 and 2021. Patients were divided into two groups: those who had surgery (group 1) and those who were unable to have surgery (group 2). The platelet/mean platelet volume ratio (P/MPV), platelet/platelet distribution volume ratio (P/PDW), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and C- reactive protein/lymphocyte ratios (CRP/L) were all calculated.

Result: When the patients' NLR, mass size, CRP/L, CRP, and CA-19.9 levels were compared between groups, a significant difference was observed. When the age, NLR, mass size, P/PDW, P/MPV, CRP (C reactive protein), CRP/L, platelet distribution volume (PDW), and CA 19-9 values of patients in Group 2 with superior mesenteric artery (SMA) and superior mesenteric vein (SMV) invasion (n:26) were compared to those in Group I, a statistical difference was detected.

Conclusion: In this study, NLR, CRP, CRP/L, CA 19-9 levels, and tumour mass were revealed to be significantly relevant in determining the chance of resectable surgery. In cases of unresectability or vascular invasion, we anticipate that these values can assist us prevent unnecessary laparotomies.

Keywords: Pancreatic cancer, vascular invasion, unresectability

ÖZ

Amaç: Bu çalışmada, pankreas kanserli hastaların laboratuvar verileri üzerinden rezeke edilebilen ve edilemeyen hastalar karşılaştırılarak, hematolojik parametrelerin ve CA19-9'un inoperabilitenin değerlendirilmesinde prediktif faydası araştırıldı.

Gereç ve Yöntem: Çalışmaya 2015-2021 yılları arasında Hitit Üniversitesi Erol Olçok Eğitim ve Araştırma Hastanesi'nde pankreas kanseri teşhisi konan 147 birey dahil edildi. Hastalar ameliyat olanlar (grup 1) ve ameliyat olamayanlar (grup 2) olmak üzere iki gruba ayrıldı. Trombosit/ortalama trombosit hacim oranı (P/MPV), trombosit/trombosit dağılım hacim oranı (P/PDW), nötrofil/lenfosit oranı (NLR), lenfosit/monosit oranı (LMR) ve C-reaktif protein/lenfosit (CRP/L) oranları hesaplandı.

Bulgular: Hastaların NLO, kitle boyutu, CRP/L, C reaktif protein (CRP) ve Ca-19.9 düzeyleri gruplar arasında karşılaştırıldığında anlamlı fark görüldü. Grup 2'de yer alan ve superior mezenterik arter (SMA), superior mesenteric ven (SMV) invazyonu olan hastalar (n:26) Grup I ile karşılaştırıldığında; yaş, NLR, kitle boyutu, P/PDW, P/MPV, CRP, CRP/L, trombosit dağılım hacim (PDW) ve Ca 19-9 değerleri arasında istatistiksel fark saptandı.

Sonuç: Bu çalışmada, NLR, CRP, CRP/L, CA 19-9 seviyeleri ve tümör kitlesinin, rezektabl cerrahi şansını belirlemede önemli ölçüde ilişkili olduğu ortaya çıktı. Rezektabl olmama veya vasküler invazyon durumlarında, bu değerlerin gereksiz laparotomileri önlememize yardımcı olabileceğini tahmin ediyoruz.

Anahtar Kelimeler: Pankreas kanseri, vasküler invazyon, rezektabl olmama

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INTRODUCTION

Pancreatic cancer has a high propensity for local invasion, hematogenous spread, has a high incidence of recurrence after curative resection, and is the fourth leading cause of cancer-related death in the United States (1). With the recent development of advanced multimodal pancreatic cancer treatments, the overall 5-year survival rate has risen to 8.8% (1). However, the majority of patients are inoperable at the time of diagnosis due to locally advanced or metastatic disease. Patients with metastatic disease have a one-year median survival (2). Surgical resection is the only option for cure, but less than 20% of cases diagnosed with pancreatic cancer are surgically resectable, while the remaining cases have involvement of major abdominal vessels and/or distant metastatic disease and are considered unresectable (3). There is no significant laboratory data studied so far in the evaluation of unresectability. Imaging studies are the most used method in determining unresectability. Multidetector computed tomography is the most widely used imaging modality for assessing local disease spread, vascular involvement, and distant metastases (CT). It has been reported that it predicts resectability 77% accurately and unresectability 93% accurately (4). However, the test has a low positive predictive value, and unresectable lesions develop at laparotomy in approximately 25-50% of patients who were thought to have resectable disease on computed tomography (5). It remains difficult to identify patients who would not benefit from surgical exploration by preoperative imaging (6). As a result, unnecessary laparotomy is applied to patients and this surgical intervention adds extra morbidity and mortality to the patient.

In this study, the predictive value of hematological parameters and CA19-9 were investigated in the evaluation of inoperability by comparing resectable and unresectable patients over the laboratory data of patients with pancreatic cancer.

MATERIAL AND METHOD

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was carried out with the permission of Hitit University Faculty of Medicine Clinical Research Ethics Committee (Date: 02.03.2022, Decision No: 15). With the ethics committee approval, the data were scanned retrospectively using the Hospital Information Management System.

The study examined 147 individuals with pancreatic cancer who were diagnosed at Hitit Univesity Erol Olçok Training and Research Hospital between March 15, 2015, and October 15, 2021. The study included patients over the age of 18 who had been diagnosed with pancreatic cancer. Patients under the age of 18, those with a disease that could affect their blood values (cirrhosis, chronic kidney failure), pregnant and lactating women, patients from a small population (those without mental faculties, soldiers, and convicts), and those whose data could not be obtained were all excluded from the study.

The demographic information of the patients, such as their age and gender, was recorded. The patients were divided into study groups as those who underwent surgery and were resectable (Group 1) and those who were evaluated both radiologically and intraoperatively as unresectable/inoperable (large vessel invasion, presence of metastatic disease) in the perioperative period (Group 2) (**Figure 1**). The clinical archive system was reviewed retrospectively, and patients whose data were fully accessible and who met the study criteria were included.

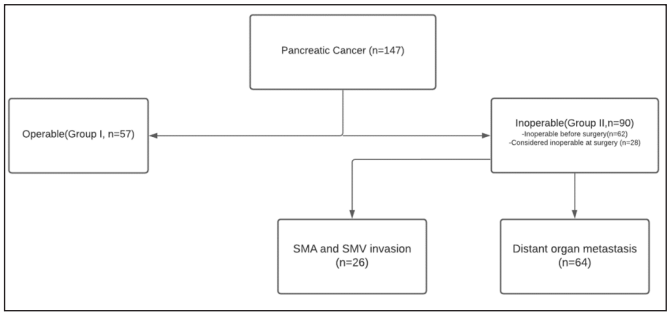

Figure 1. Flowchart of the operable group (Group I) and inoperable group (Group II).

The dimensions of the pancreatic tumor were measured from the triphasic computed tomography data of all patients in the preoperative period. Monocyte (MO), lymphocyte (LY), platelet (P), neutrophil (NE), mean platelet volume (MPV), platelet distribution width (PDW), C-reactive protein (CRP), and cancer antigen 19-9 (CA19-9) values were measured in laboratory samples collected during the patients' preoperative period. Platelet/mean platelet volume ratio (P/MPV), platelet/platelet distribution volume ratio (P/PDW), neutrophile/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and C- reactive protein/lymphocyte values were computed using the information collected.

Statistical Analysis

The SPSS program for Windows version 22.0 was used to assess the data analysis (SPSS Inc., Chicago, Illinois, USA). The mean + standard deviations are used to represent continuous variables having a normally distributed distribution. To demonstrate that the parameters followed a normal distribution, the Kolmogorov-Smirnov test was used. The diagnostic capacity of Laboratory index was evaluated using a receiver operating characteristic (ROC) curve analysis, and ROC curves were generated to analyse the balance between sensitivity and specificity. P value 0.05 was used to determine statistical significance.

RESULTS

The study included 147 patients who had been diagnosed with pancreatic cancer and were being followed up on. The mean age of the patients who took part in the study was determined to be 69.5 (11.3±SD). 47 (31.2%) of the patients included in the study were female and 100 of them (68.8%) were male. There were 57 patients in Group I and 90 patients in Group II. It was seen that 62 patients in Group 2 were considered inoperable as a result of the preoperative evaluations, and 28 patients were evaluated as operable in the preoperative examinations and underwent surgery but were considered unresectable during the operation.

Group I had a mean age of 69.1 (10.6 SD), while group II had a mean age of 69.8 (11.2 SD). There was no statistical difference between the two groups in terms of age and gender distribution (p:0.870, p:756, respectively). The age, gender, and test result characteristics of all patients are shown in **Table 1.**

Table 1. Characteristic of subjects in Group I and Group II

	Total (n=147) (SD)	Group I (n=57)	Group II (n=90)	p value
Age, years	69.8 (11.2)	68.9 (10.6)	69.8 (11.2)	0.870
Sex				0.756
Male	100 (68.8%)	30 (70.2%)	70 (77.7%)	
Female	47 (31.2%)	17 (29.8%)	30 (22.3%)	
NLR	5.4 (8.2)	3.4 (2.7)	6.7 (10.1)	0.001
Mass size,mm	34.4 (14.8)	27.9 (13.9)	38.5 (13.9)	0.001
LMR	3.02 (2.1)	3.1 (1.9)	2.9 (2.2)	0.262
P/PDW	19.4 (11.6)	(20.8 (11.1)	18.6 (11.9)	0.080
P/MPV	24.5 (11.9)	26.1 (11.2)	23.6 (12.2)	0.107
P/RDW	16.2 (7.2)	16.6 (5.6)	16.1 (8.1)	0.218
CRP/L	35.9 (139.4)	11.9 (13.1)	41.2 (176.6)	0.001
CRP	34.1 (50.4)	17.4 (19.2)	44.5 (60.4)	0.001
PDW	13.9 (2.7)	13.4 (2.5)	14.2 (2.8)	0.136
CA 19-9	3801 (15,904)	924 (2796.5)	5624 (20,034)	0.001

NLR:Neutrophil/lymphocyte ratio, LMR:Lymphocyte/monocyte ratio, P/PDW:Platelet/platelet distribution width ratio, P/MPV:Platelet/mean platalet volume ratio, P/RDW:Platelet/red blood cell distribution width, L: Lymphocyte CRP: C-reactive protein, Statistically significant data bolded

When the patients' NLR, mass size, CRP/L, CRP, and Ca-19.9 levels were compared between groups, a significant difference was observed (**Table 1**). According to this, it was determined that as NLR increased and the size of the mass was larger, the probability of patients being inoperable increased. Furthermore, increases in Ca-19.9, CRP, and CRP/L ratio were statistically significant in terms of patient inoperability. Platelet/platelet distribution width ratio (P/PDW) and Platelet/mean platelet volume ratio (P/MPV) values did not differ statistically between groups.

ROC analysis was used to investigate the predictive value of these statistically significant results.

As a result of the study, the tumor size with the highest AUC value was found. It had a sensitivity of 77.8 % and a specificity of 61.4 % at a cut-off value of 29 mm. CA 19-9 also had the second highest AUC value. When the predictive value of the NLR value obtained from the routine laboratory values in separating the groups is examined, it was seen that AUC value was 0.679. Its sensitivity was 64.4% and specificity was 63.2 % in differentiating inoperable patients at a cut-off value of 3.21. (**Table 2**) (**Figure 2**).

Table 2. Sensitivity, specificity and area under the curve of NLR, mass size, CRP/L,CRP and CA 19-9

	AUC	Cut-off value	Sensitivity (%)	Specificity (%)
NLR	0.679	3.21	64.4	63.2
Mass size, mm	0.742	29	77.8	61.4
CRP/L	0.683	10.6	62.2	61.4
CRP	0.674	14.1	61.1	63.2
CA 19-9	0.705	14.5	63.3	63.2

NLR:Neutrophil/lymphocyte ratio, L: Lymphocyte, CRP: C-reactive protein

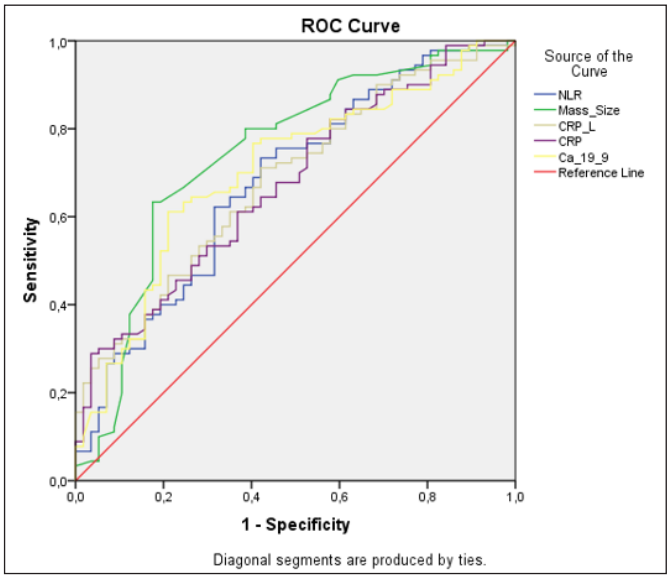

Figure 2. ROC curves for subjects (Group I vs Group II)

When the age, NLR, mass size, P/PDW, P/MPV, CRP, CRP/L, PDW, and CA 19-9 values of patients in Group 2 with SMA and SMV invasion (n:26) were compared to those in Group I, a statistical difference was discovered between age, NLR, mass size, P/PDW, P/MPV, CRP, CRP/L, PDW, and CA 19-9 values were compared. In the ROC analysis, the highest AUC value belonged to mass size. At a cut-off value of 31.1 mm, it had 76.9 % sensitivity and 75.4 % specificity. Following that, at a cut-off value of 3.2, the NLR had 65.4 % sensitivity and 64.9 % specificity. In addition, the CA 19-9 value had a cut-off value of 158.8 with a sensitivity of 69.2% and a specificity of 68.4% (**Table 3**) (**Figure 3**).

Table 3. Sensitivity, specificity and area under the curve of NLR, mass size, CRP/L,CRP ,CA 19-9, P/PDW, P/MPV, PDW and age for SMA/SMV invasion

	AUC	Cut-off value	Sensitivity (%)	Specificity (%)
NLR	0.733	3.2	65.4	64.9
Mass size, mm	0.765	31.1	76.9	75.4
CRP/L	0.686	10.3	61.5	59.6
CRP	0.662	14.1	61.5	61.4
Ca-19-9	0.672	158.8	69.2	68.4
P/PDW	0.362	17.1	46.2	43.9
P/MPV	0.365	21.2	42.3	40.4
PDW	0.641	57.7	57.9	57.9
Age,years	0.650	72.4	57.7	57.9

NLR: Neutrophil/lymphocyte ratio, L: Lymphocyte, CRP: C-reactive protein, P/PDW: Platelet/platelet distribution width ratio, P/MPV:Platelet/mean platelet volume ratio

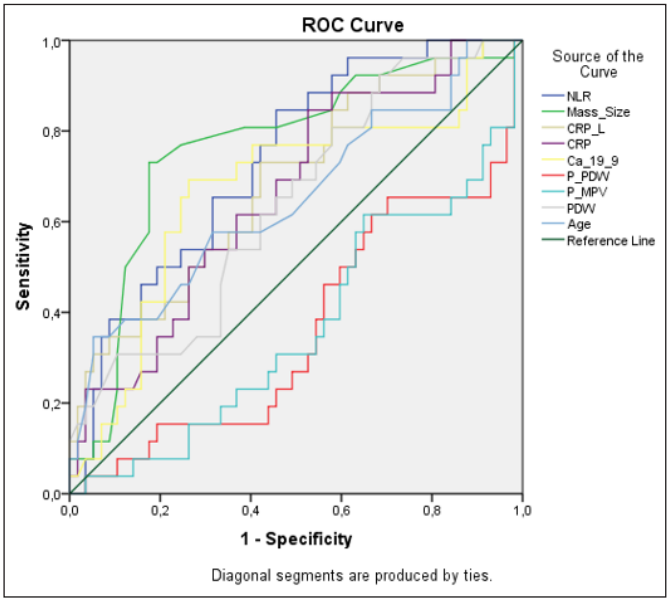

Figure 3. ROC curves for subjects (Group I vs Group II)

DISCUSSION

As a result, pancreatic cancer is the deadliest cancer. Even though surgery is still the primary treatment, most patients have missed out on this opportunity at the time of application. In our study, NLR, CRP, CRP/L, CA 19-9 levels, and tumour mass were found to be extremely important in terms of the possibility of resectable surgery. These values, we believe, can help us avoid unnecessary laparotomies in cases of unresectability or vascular invasion.

Pancreatic cancers are among the types of cancers which have an extremely poor prognosis and a high mortality rate. Late discoveries lead to late diagnosis, resulting in the disease being clinically detected at advanced stages. Pancreatic cancers are cancers with a high risk of vascular invasion due to their anatomical structure. Therefore, the possibility of inoperability is high. Imaging techniques, in particular, are utilized to assess the operability of pancreatic cancer. According to the NCCN guideline, superior mesenteric artery (SMA), celiac artery involvement, unresectable superior mesenteric vein (SMV), portal vein involvement, and distant organ metastases are considered locally advanced pancreatic cancer in imaging methods (7). Locally advanced pancreatic cancer has no place for surgical treatment and adjuvant chemotherapy is planned (8). However, imaging methods reduce the sensitivity to 77%, especially in lesions less than 2 cm (9). As a result, unnecessary laparotomy is performed.

Pancreatic cancer is more common in men than in women. Men are 30% more likely than women to develop pancreatic cancer, according to Shaib's research (10). Pancreatic cancer was found to be 37.6 % more common in men in this study, which was thought to be consistent with previous research.

The increase in mass size in pancreatic cancers adversely affects the risk of vascular involvement and prognosis. According to Phoa et al.'s (11) research, lesions larger than 3 cm increase unresectability and worsen prognosis. According to Chatelain et al. (12), tumours larger than 2 cm in diameter have a poor prognosis. Takahashi et al. (13) discovered that lesions larger than 2 cm in diameter reduced the likelihood of R0 resection. According to our research, the mass size in terms of unresectability had a sensitivity of 77.8 % and a specificity of 61.4 % at a cut-off value of 29 mm. Furthermore, at a cut-off value of 31.1 mm, the mass size demonstrated 76.9 % sensitivity and 75.4 % specificity in terms of large vessel invasion. These findings were determined to be statistically significant and compatible with the literature data.

A high neutrophil count in the blood is frequently the cause of high NLR, which is accompanied by lymphocytopenia. A high neutrophil count may help to form and progress a neoplasia by creating a favourable tumour microenvironment in which many growth factors are released (14). Various studies have demonstrated that NLR predicts the course of disease in many cancer types, including oesophageal, stomach, colorectal, bladder, lung, breast, hepatocellular carcinoma, and pancreas cancer (15). In a study of patients with locally advanced and metastatic pancreatic cancer, Teo et al. (16) found that patients with a high baseline NLR had a shorter survival time. In their study, Stotz et al. (17) revealed that NLR increased in inoperable patients. NLR values between 2.5 and 5 have been linked to metastatic pancreatic cancer and a poor prognosis in various studies. The cut-off value for NLR in our study was 3.21, and it was discovered that the probability of locally progressed and metastatic pancreatic cancer rose over this value, which is consistent with the literature. Moreover, the risk for NLR was found to be elevated at a cut-off value of 3.2 in the vascular invasion evaluation, which was not stated separately in

previous research, and we believe that these findings will contribute to the literature.

Wiese's study (18) found that patients with elevated CRP levels in pancreatic cancer had a considerably lower overall survival. C-reactive protein/lymphocyte ratios greater than 1.8 have recently been linked to poor survival. A ratio greater than 1.8 was also identified as an independent risk factor for death in pancreatic cancer stages II, III, and IV (19). Correspondingly, an increase in CRP before surgery has been linked to invasion and a poor prognosis in pancreatic cancers (20). Similarly, preoperatively evaluated CRP increase has been linked to invasion and poor prognosis in pancreatic cancers (20). Likewise, when the patients were divided into groups based on vascular invasion, it was discovered that those with a high preoperative CRP and CRP/L ratio had more SMA and SMV invasions.

CA 19-9 is the most commonly used serum biomarker for detecting pancreatic cancer. According to Young Choon Kim's (21) research, the possibility of resectability decreased once the cut-off value for CA 19-9 was reached at 92.77. In another study, a cut-off value of 130U/ml was determined for Ca19-9, and it was observed that the probability of unresectability was high above this value (22). In our study, CA 19-9 elevation was observed to be increased in inoperable pancreatic cancers. These studies' findings support the link between tumour stage and CA19-9 level. However, this study emphasizes the relationship between vascular invasion and CA19-9, which has not been mentioned before. As a result, pancreatic cancer with a CA 19-9 cut-off value of 158.8 U/ml was discovered to have a high risk of SMA and SMV invasion.

Although the findings of this study are consistent with previous research, the fact that it is a single-centre study may be a disadvantage. Besides that, the significantly higher proportion of inoperable patients versus operable patients suggests that the patient group may have delayed hospital admission due to their low socioeconomic status. Furthermore, the recent increase in the number of inoperable patients shows that late admission may be linked to the COVID-19 epidemic, which has been going on for nearly two years.

CONCLUSION

The high NLR, CRP, CRP/L, CA 19-9 values in our study enabled us to conclude that they are predictive markers for inoperable pancreatic cancer. In addition, the probability of locally advanced and metastatic pancreatic cancer was found to exceed this value. These values, we believe, can help us avoid unnecessary laparotomies in cases of unresectability or vascular invasion.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Faculty of Medicine Clinical Research Ethics Committee (Date: 02.03.2022, Decision No: 15).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict Of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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Is it possible to treat night eating disorder and sleep quality with surgery? Benefits of obesity surgery

Gece yeme bozukluğu ve uyku kalitesini ameliyat ile tedavi etmek mümkün mü? Obezite cerrahisinin faydaları

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ABSTRACT

Aim: This study was conducted to assess sleep quality and night eating syndrome in patients with morbid obesity after bariatric surgery.

Material and Method: Patients with morbid obesity who underwent sleeve gastrectomy were evaluated. The preoperative and postoperative values of Body Mass Index (BMI), Hamilton Rating Scale for Depression (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Night Eating Questionnaire (NEQ), Pittsburgh Sleep Quality Index (PSQI), and Berlin Sleep Questionnaire (BSQ) were compared.

Results: A total of 82 surgery candidates who were aged between 18 and 65 (36.36±10.37) were planned for bariatric surgery participated in our study. We completed our study with 77 patients since 5 of the patients did not come to their postoperative 6th-month controls for various reasons. Standard psychiatric examinations of the candidates were performed before and after the surgery, and their written consent was obtained after they had been informed about the study. Mean preoperative BMI value was found as 44.53±4.33, HAM-A value as 4.96±6.14, HAM-D value as 3.82±3.84, PSQI value as 4.69±3.64, and NEQ score as 15.94±7.94. In the 6th month evaluations after surgery, the mean BMI value was found as 30.74±3.55, HAM-A value as 2.39±3.47, HAM-D value as 1.57±2.39, PSQI value as 1.48±1.42, and NEQ score as 5.58±3.06. The mean EWL value was found as 61.71±10.58.

Conclusion: In conclusion, morbid obesity may cause anxiety, depression, and night eating syndrome and may impair sleep quality in parallel to them. We observed that these clinical conditions improved after bariatric surgery.

Keywords: Bariatric surgery, sleep, night eating syndrome

ÖZ

Amaç: Bu çalışma, bariatrik cerrahi sonrası morbid obezitesi olan hastalarda uyku kalitesi ve gece yeme sendromunun değerlendirilmesi amacıyla yapılmıştır.

Gereç ve Yöntem: Morbid obezitesi olan ve tüp mide ameliyatı yapılan hastalar değerlendirildi. Vücut Kitle İndeksi (BKİ), Hamilton Depresyon Derecelendirme Ölçeği (HAM-D), Hamilton Anksiyete Derecelendirme Ölçeği (HAM-A), Gece Yeme Anketi (NEQ), Pittsburgh Uyku Kalitesi İndeksi (PSQI) ve ameliyat öncesi ve sonrası değerleri Berlin Uyku Anketi (BSQ) karşılaştırıldı.

Bulgular: Çalışmamıza 18-65 yaşları arasında (36,36±10,37) obezite cerrahisi planlanan toplam 82 cerrahi adayı katıldı. Hastalardan 5'i ameliyat sonrası 6. ay kontrollerine çeşitli nedenlerle gelmediği için 77 hasta ile çalışmamızı tamamladık. Adayların ameliyat öncesi ve sonrası standart psikiyatrik muayeneleri yapıldı ve çalışma hakkında bilgilendirildikten sonra yazılı onamları alındı. Ameliyat öncesi ortalama VKİ değeri 44,53±4,33, HAM-A değeri 4,96±6,14, HAM-D değeri 3,82±3,84, PUKİ değeri 4,69±3,64 ve NEQ puanı 15,94±7,94 olarak bulundu. Ameliyat sonrası 6. ay değerlendirmelerinde ortalama VKİ değeri 30,74±3,55, HAM-A değeri 2,39±3,47, HAM-D değeri 1,57±2,39, PUKİ değeri 1,48±1,42 ve NEQ puanı 5,58±5 olarak bulundu. 3.06. Ortalama EWL değeri 61,71±10,58 olarak bulundu.

Sonuç: Sonuç olarak, morbid obezite anksiyete, depresyon ve gece yeme sendromuna neden olabilir ve bunlara paralel olarak uyku kalitesini bozabilir. Bariatrik cerrahi sonrası bu klinik durumların düzeldiğini gözlemledik.

Anahtar Kelimeler: Uyku, gece yeme sendromu, obezite cerrahisi

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INTRODUCTION

The increase in the prevalence of obesity has brought on many comorbid conditions. Bariatric surgery draws attention as an effective treatment method both in the world and our country since the desired results cannot be achieved in obesity with traditional methods and more effective results are obtained in a short time with this surgery (1,2). Bariatric surgery methods are administered to individuals with a body mass index (BMI) of ≥40 kg/m^2 or those with comorbid diseases, such as hypertension, diabetes, sleep apnea, and a BMI of ≥35 kg/m^2 (3,4). Weight loss after bariatric surgery provides a clinical improvement in many comorbid diseases existing before surgery.

When the effects of sleep on food consumption are considered, the mutual relationship between sleep disorders and obesity gains importance 2. Poor quality sleep and reduced sleep duration contribute to the development and progression of obesity 3. In return, obesity can cause some physical and mental symptoms that may impair sleep quality. Some of these conditions include obstructive sleep apnea syndrome (OSAS), anxiety disorders, and mood disorders (5). Obesity is one of the most common known risk factors in the etiology of OSAS. In most cases, bariatric surgery and the resulting dramatic weight loss provide an improvement in sleep disturbance and OSAS (6,7). In addition, it has been reported that weight loss after bariatric surgery contributes positively to sleep quality regardless of whether it is accompanied by OSAS (7). Disordered sleep is the DSM-5 diagnostic criteria for both anxiety disorders and depressive disorders, and it reduces the quality of life of the patients. Weight loss after bariatric surgery does not only improve sleep quality physiologically but also provides positive effects by contributing to the reduction of psychiatric complaints (8). Another issue that is emphasized in the relationship between sleep and obesity is eating habits. It has been shown that after surgery, eating disorders can improve, eating attitudes can change positively, and preoccupations with weight and body can decrease (9). In this context, night sleep problems and night eating syndrome following excessive eating in the evening can be considered as another condition that may impair sleep quality in people with obesity clinically.

In this study, it was aimed to determine sleep disturbance in individuals with obesity, identify risk factors that may be clinically relevant, and investigate the effect of surgery on sleep quality.

MATERIAL AND METHOD

This study was started after the ethical approval of the study was obtained from Balıkesir University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.04.2021, Decision No: 2021-106). 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 Declaration of Helsinki and its later amendments or comparable ethical standards. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 82 surgery candidates who were between 18 and 65 years old, were admitted to General Surgery outpatient clinic, and were planned for bariatric surgery evaluated in our study. We completed our study with 77 patients (since 5 of the patients did not come to their postoperative 6th-month controls for various reasons). Psychiatric examinations of the candidates were performed before the surgery by a psychiatrist, and then their written informed consent was obtained after they had been informed about the study. Following these procedures, a socio-demographic data form, which was created by us, the Hamilton Anxiety Rating Scale (HAM-A), the Hamilton Rating Scale for Depression (HAM-D), the Night Eating Questionnaire (NEQ), the Pittsburgh Sleep Quality Index (PSQI), and the Berlin Sleep Questionnaire (BSQ) were applied to the candidates. Psychiatric evaluations of the patients were done again in the 6th month after surgery, and the scales were re-administered.

The Sociodemographic Data Form

This form, which was prepared by the researcher, included questions about the candidates' background and their medical information, such as age, gender, height/weight, previous psychiatric illness, chronic illness, and medications used.

The Hamilton Rating Scale for Depression (HAM-D)

It consists of 17 items questioning the symptoms of depression in the last week. The highest score on the scale is 53. The interpretation of the scores is as follows: 0-7, no depression; 8-13, mild depression; 14-18, moderate depression; 19-22, severe depression; and 23 and higher, very severe depression. The Turkish validity and reliability study of the scale was conducted by Akdemir et al. (10).

The Hamilton Anxiety Rating Scale (HAM-A)

It consists of 14 items used to evaluate the somatic and psychic symptoms of anxiety. Each item is scored between 0 and 4 points according to the severity of the symptom. The scores are interpreted as follows: 0-5, normal; 6-14, mild; 15 and higher, severe anxiety. The Turkish reliability and validity study of the scale was conducted by Yazıcı et al. (11).

The Night Eating Questionnaire (NEQ)

The original scale was developed by Allison and collegues for determining the risk of night eating syndrome (12). The questions on the questionnaire are scored between 0 and 4 using a five-point Likert-type scoring system. Total scores on the questionnaire range between 0-52. The cut-off score was stated as 25 in the original study, and a score of 18 and higher was considered clinically significant in the Turkish validity study (13).

The Pittsburgh Sleep Quality Index (PSQI)
This scale was developed by Buysse et al. (14) to assess subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleeping pills, and impairment in daytime work. Each response is scored between 0-3 according to the frequency of the symptom. The global score varies between 0-21, and high values indicate poor sleep quality and high levels of sleep disturbance. A global score of 5 and higher indicates that the clinical sleep quality is significantly poor. The PSQI was adapted to Turkish patients by Agargün et al. (15).

The Berlin Sleep Questionnaire (BSQ)
The BSQ is a questionnaire designed for OSAS population surveys. It consists of 10 questions in 3 categories in total. A score of ≥2 points in categories 1 and 2 and a score of ≥1 point in category 3 are considered significant. Each category is evaluated within itself, and if 2 or more categories are positive, the risk of OSAS is considered high (16).

Statistical Analysis
The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, and minimum and maximum values) were employed, and the distribution of the data was evaluated with the Shapiro-Wilk Test. The Mann-Whitney U test was used to compare quantitative data in groups of two. Wilcoxon rank test was used for comparisons of two periods. Chi-square analysis was used to determine the relationship between qualitative data. Quantative data were given as median ± standart deviation (minimum - maximum)(median), and categorical data were indicated in count (n) and percentages (%). Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

RESULTS

The ages of the patients in our study ranged from 20 to 61, with the mean age being 36.36±10.37 years. Of the participants, 74% (n=57) were female, and 26% (n=20) were male.

In the preoperative evaluations of the participants, the mean value of Body Mass Index (BMI) was found as 44.53±4.33, the Hamilton Anxiety Rating Scale (HAM-A) as 4.96±6.14, the Hamilton Rating Scale for Depression (HAM-D) as 3.82±3.84, the Pittsburgh Sleep Quality Index (PSQI) as 4.69±3.64, and the Night Eating Questionnaire score (NEQ) as 15.94±7.94. On the other hand, the mean postoperative values of the participants were found as follows: BMI, 30.74±3.55; HAM-A, 2.39±3.47; HAM-D, 1.57±2.39; PSQI, 1.48±1.42; and NEQ, 5.58±3.06. The mean EWL value was 61.71±10.58, which supports the success of the surgery. The evaluations of the participants according to BSQ in terms of risk for OSAS indicated that 37 (48.1%) patients had no risk, but that the remaining 40 (51.9%) were in the risk group. It was observed that the risk continued in only 2 of the participants (2.6%) after the surgery.

The participants were divided into two subgroups according to their pre-surgical sleep quality to evaluate the factors affecting their sleep quality. Thirty-two patients (41.5%) who scored 5 or higher from the Pitsburgh Sleep Quality Index were included in the group with poor sleep quality, and forty-five patients (58.5%) with a score of less than 5 were placed in the group with good sleep quality. There was no statistically significant difference between the groups in terms of age and gender ($p=0.225$; $p=0.669$). Patients with poor sleep quality had significantly higher BMI, HAM-A, HAM-D, and NEQ scores compared to the group with good sleep quality. ($p=0.001$; $p<0.05$). Factors that might have affected the participants' sleep quality before surgery are shown in **Table 1**.

Table 1. Comparison of preoperative measurements by sleep status

		n	Mean±Sd	Min.-Max. (Median)	p
Age	PSQI<5	45	37.42±11.05	20-61 (35)	0.226
	PSQI>5	32	34.88±9.29	24-53 (30.5)	
Preop BMI	PSQI<5	45	42.89±2.46	40.39-50.78 (42.28)	0.001**
	PSQI>5	32	46.93±5.31	40.39-58.87 (46.31)	
Ham-A	PSQI<5	45	2.93±3.28	0-14 (2)	0.001**
	PSQI>5	32	7.81±7.93	0-33 (6)	
Ham-D	PSQI<5	45	2.93±3.32	0-11 (2)	0.009**
	PSQI>5	32	5.06±4.21	0-21 (4.5)	
NEQ	PSQI<5	45	13±5.91	5-29 (12)	0.001**
	PSQI>5	32	20.06±8.66	3-34 (20.5)	

Mann Whitney U Test; *p<0.05; **p<0.01

The comparison of the pre-and post-operative scale scores of the participants with good and poor sleep quality is given in **Tables 2 and 3**. There was a statistically significant decrease in scale scores in both groups postoperatively.

Table 2. Comparison of the pre-and post-operative scale scores of the patients with good sleep quality

		Preoperative Measurement	Postoperative Measurement	p
BMI	Mean±Sd Min.-Max. (Median)	42.89±2.46 40.39-50.78 (42.28)	29.65±2.55 26.71-40.39 (28.8)	0.001**
HAM-A	Mean±Sd Min.-Max. (Median)	2.93±3.28 0-14 (2)	1.69±2.57 0-9 (0)	0.001**
HAM-D	Mean±Sd Min.-Max. (Median)	2.93±3.32 0-11 (2)	1.13±1.79 0-8 (1)	0.001**
NEQ	Mean±Sd Min.-Max. (Median)	13±5.91 5-29 (12)	5.29±2.5 1-12 (5)	0.001**

Wilcoxon Rank Test; *p<0.05; **p<0.01

Table 3. Comparison of the pre-and post-operative scale scores of the patients with poor sleep quality

		Preoperative Measurement	Postoperative Measurement	P
BMI	Mean±Sd Min.-Max. (Median)	46.93±5.31 40.39-58.87 (46.31)	32.33±4.21 26.42-40.39 (31.44)	0.001**
Ham-A	Mean±Sd Min.-Max. (Median)	7.81±7.93 0-33 (6)	3.38±4.29 0-15 (1.5)	0.001**
Ham-D	Mean±Sd Min.-Max. (Median)	5.06±4.21 0-21 (4.5)	2.19±2.97 0-12 (1)	0.001**
NEQ	Mean±Sd Min.-Max. (Median)	20.06±8.66 3-34 (20.5)	6±3.72 1-16 (5)	0.001**

Wilcoxon Test; *p<0.05; **p<0.01

DISCUSSION

Many different clinical conditions impair sleep quality. Obesity causes psychiatric situations such as mood disorders and anxiety disorders, which makes it important to determine both physiological and psychological aspects of sleep disorders caused by obesity (17). It is expected that bariatric surgery will improve sleep quality by contributing to both areas. As expected, a significant decrease was found in all post-operative psychiatric total scale scores of the participants in our study. This finding is similar to the findings of other studies showing the positive effects of surgery on sleep disorders, anxiety, depression levels, and eating attitudes (8). However, the fact that the presence of severe psychiatric diseases constituted a surgical contraindication in the pre-operative psychiatric evaluation may have supported the efforts of the patients to not report their symptoms during the interview and to show themselves well. This may explain why the preoperative anxiety and depression scale scores were lower compared to the population with obesity who did not apply for surgery, although a significant decrease was determined in the scale scores postoperatively (18).

When evaluated in terms of OSAS, which is one of the most prominent risk factors for sleep quality, 40 out of 77 patients in our study were found at risk. It was observed that the risk continued in only 2 of the participants (2.6%) after the surgery. In the literature, many studies support that bariatric surgery reduces the risk of OSAS 17. In the study of Dileklitaş et al. (19), a significant improvement was found in sleep quality and daytime sleepiness in the 6th month of surgery, and it was reported that there was a decrease in the risk for OSAS. However, even though it is stated that the risk is reduced, it should also be kept in mind that the Berlin questionnaire is a clinical screening tool for OSAS and that polysomnography is the gold standard for the diagnosis of OSAS.

In our study, 32 (41.5%) of the 77 surgical candidates with obesity were found to have poor quality sleep. Similar to our study, Toor et al. (20) reported deterioration in sleep quality in 78% of bariatric surgery candidates and found a significant increase in sleep quality and sleep duration after surgery. In the 6-month-follow-up study of Ghiasi et al. (21), although an increase in sleep quality and a decrease in daytime sleepiness were determined, the lack of psychiatric evaluation that could affect sleep quality was stated as a limitation of the study. In another study conducted in 2020, a decrease in general sleep quality was found in 65% of bariatric surgery candidates, and clinically significant insomnia findings were found in 35% (22). In our study, increased BMI values and anxiety and depression scores were found to be associated with deterioration in sleep quality. This relationship has been supported by the literature (23).

Another condition that we think may affect sleep quality is night eating syndrome, which is defined as a condition characterized by loss of appetite in the morning, overeating in the evening, and insomnia. Night eating syndrome is defined in oher specified feeding and eating disorder (OSFED) subgroup of eating disorder in DSM-5 and characterized by recurrent episodes of night eating, as manifested by eating after awakening from sleep or by excessive food consumption after the evening meal. The night eating causes significant distress and/or impairment in functioning (24). In night eating syndrome, the biological rhythms of eating and sleep are separated, people's morning eating is suppressed, and their evening and night eating increases. There is a 2 - 6 hours delay between eating and sleep rhythms, which may have consequences that may impair sleep quality (25). In our study, scores on the night eating questionnaire were significantly higher in individuals with poor sleep quality than in individuals who defined their sleep as good. Yeh et al. (26), too, stated that impaired eating attitude contributed to the relationship between decreased sleep quality and weight gain. In surgical candidates with obesity, clinical insomnia and depressive symptoms have been associated with increased daily consumption of junk food, emotional eating, and night-eating behavior (9). In a 6-year follow-up study, it was reported that there was an increase in weight gain and binge eating with the accompanying disinhibited eating behavior in patients with short sleep duration (27). Although we found a significant decrease in scores on the night eating questionnaire in our study, Lawson et al. (28) found the score on the PSQI as 7.58 after bariatric surgery in patients with eating attitude disorder. Poor sleep quality was positively correlated with perceived stress, depression, eating disorder, and night eating in these individuals, and a lower EWL value was found in those with poor sleep quality. The significant decrease observed in postoperative scores in both groups was a finding that supported the effect of bariatric surgery on sleep quality with a decrease in night eating behavior, anxiety, and depression levels. However, the evaluation of sleep disorders and the determination of related factors in individuals with ongoing night-eating syndrome after surgery should be supported by studies.

CONCLUSION

It was observed that morbid obesity might cause anxiety, depression, and night-eating syndrome and that it might impair sleep quality in parallel with them. We observed that these clinical conditions improved after bariatric surgery. We believe that obesity is one of the most important etiological causes of sleep quality disorder, but further studies are needed since there are other causes in the etiology.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was started after the ethical approval of the study was obtained from Balıkesir University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.04.2021, Decision No: 2021-106).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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The relationship between the prognostic nutritional index and the clinical course of COVID-19: a single-center experience

Prognostik nütrisyonel indeks ve COVID-19 klinik seyri arasındaki ilişki: tek merkez deneyimi

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ABSTRACT

Aim: It was aimed to investigate the relationship between the prognostic nutritional index (PNI) and the clinical course in COVID-19 because the nutritional status is important in defense against infection.

Material and Method: 1579 patients who applied to the hospital inpatient clinic between 01/04/2020 and 30/11/2020 were included in the study. The PNI scores of the patients were calculated at the time of admission to the hospital. Comparisons were made between PNI scores of the patients and intensive care unit admission status, treatment results, length of hospital stay, and presence of pneumonia on thorax CT. Moreover, comparisons were made between PNI scores and C-reactive protein (CRP), neutrophil/ymphocyte ratio (NLR), CRP/albumin ratio.

Results: A total of 1579 patients (755 females and 824 males) were included in the study. The rate of admission to the ICU was significantly higher in males. The mortality rate of the study group was 9.4%. PNI scores were found to be significantly lower in patients who died and in patients admitted to the ICU. CRP and CRP/albumin ratio levels were significantly higher in patients with pneumonia on thorax CT, in patients admitted to the intensive care unit, and in patients who died. There were a significant negative correlation between PNI score and CRP/albumin ratio levels.

Conclusion: PNI scores were found to be significantly lower in patients who needed admission to the intensive care unit and died due to severe COVID-19 than the others. In patients with a low PNI score, COVID-19 can be more severe and it may cause worse clinical outcomes.

Keywords: COVID-19, CRP/albumin ratio, neutrophil/lymphocyte ratio, prognostic nutritional index

ÖZ

Amaç: Enfeksiyona karşı savunmada beslenme durumunun önemli olması nedeniyle COVID-19'da prognostik beslenme indeksi (PNI) ile klinik seyir arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntem: 01/04/2020-30/11/2020 tarihleri arasında hastaneye başvuran 1579 hasta çalışmaya dahil edildi. Hastaların hastaneye başvuru anında PNI skorları hesaplandı. Hastaların PNI skorları ile yoğun bakıma yatış durumu, tedavi sonuçları, hastanede kalış süreleri ve toraks BT'de pnömoni varlığı arasında karşılaştırmalar yapıldı. Ayrıca PNI skorları ile C-reaktif protein (CRP), nötrofil/imfosit oranı (NLR), CRP/albumin oranı arasında karşılaştırmalar yapıldı.

Bulgular: Çalışmaya toplam 1579 hasta (755 kadın ve 824 erkek) dahil edildi. Erkeklerde yoğun bakıma kabul oranı anlamlı olarak daha yüksekti. Çalışma grubunun mortalite oranı %9,4'tü. Ölen hastalarda ve yoğun bakım ünitesine kabul edilen hastalarda PNI skorları anlamlı olarak daha düşük bulundu. Toraks BT'sinde pnömoni olan hastalarda, yoğun bakıma yatırılan hastalarda ve ölen hastalarda CRP ve CRP/albümin oranı anlamlı olarak daha yüksekti. PNI skoru ile CRP/albümin oranı arasında anlamlı negatif korelasyon vardı.

Sonuç: Şiddetli COVID-19 nedeniyle yoğun bakım ünitesine yatırılması gereken ve ölen hastalarda PNI skorları anlamlı derecede daha düşük bulundu. PNI skoru düşük olan hastalarda COVID-19 daha şiddetli seyredebilir ve daha kötü klinik sonuçlara neden olabilir.

Anahtar Kelimeler: COVID-19, CRP/albümin oranı, nötrofil/lenfosit oranı, prognostik beslenme indeksi

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious viral disease. The causative agent of COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). SARS-CoV-2 is an enveloped RNA virus (2). In humans beings are the main route of transmission of SARS CoV-2 is virus-carrying respiratory droplets (3). Generally, COVID-19 patients develop symptoms 5-7 days after exposure. Common symptoms are fever, sore throat, cough, myalgia, headache, dyspnea, nausea and diarrhea. SARS-CoV-2 enters the cell by attaching to the angiotensin converting enzyme 2 (ACE2) receptor. The infection process begins with the binding of the viral envelope S protein of SARS CoV-2 to the ACE2 receptor in the cell membrane. The ACE2 receptor is found in the lungs, endothelium, heart, kidneys, brain and intestines (3). Therefore, all these organs can be a target of the virus and complications may occur in these organs.

The nutritional status of a person is important in defense against infection. Individuals with nutritional deficiencies are more susceptible to infectious diseases and worse clinical results may be seen in these individuals (4). Based on this, in studies conducted, malnutrition was found to be an independent risk factor for complications in hospitalized patients and was associated with higher mortality (5). Prognostic nutrition index (PNI) is a new risk score based on serum albumin and lymphocyte values, reflecting the immunological and nutritional status of the person. PNI has proven prognostic value in a variety of diseases, including cardiovascular diseases, infectious diseases and malignancies. It has been shown that low PNI score is associated with poor survival (6,7). It is not difficult to calculate this index as it only requires blood parameters and it is a cost-effective method.

COVID-19 continues to be a widespread public health problem all over the world today, and it also causes major social and economic problems. We think that the nutritional status of patients is very important in the course of infectious diseases. In this study, it was aimed to investigate the relationship between the PNI score of COVID-19 patients and the clinical course of the disease.

MATERIAL AND METHOD

For this study, written consent was obtained from the patients and was carried out with the the permission of Sancaktepe Sehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date:10/03/2021, Decision No: 2020/123). All human studies have been performed under the rules of 1964 Declaration of Helsinki.

The study was conducted on 1724 patients who applied to the inpatient clinic between 01/04/2020 and 30/11/2020. COVID-19 PCR test was performed on these patients who were admitted to the hospital with suspicion of COVID-19, blood was taken for the test, and thorax CT was planned. The diagnose of COVID-19 in patients had been confirmed by a positive result for SARS-CoV-2 RNA in nasopharyngeal swabs by using real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR) before the patients was applied to the inpatient clinic. In all patients, gender, age, medical history, COVID-19 PCR test results, blood test results, thorax CT reports, hospitalization status and treatment results were examined. Patients over 18 years old with positive COVID-19 PCR test were included in the study. Patients under the age of 18, with negative COVID-19 PCR test result, in case of malignancy, pregnancy, and with severe endocrinological, nephrological, gastrointestinal, neurological, psychiatric diseases, hematological disease were excluded from the study. For these reasons, a total of 145 patients were excluded from the study. Finally, a total of 1579 patients were included in the study.

The PNI scores were calculated according to the results of the blood tests of patients at the hospital. For each patient, the PNI score was calculated based on this formula; PNI = [10 x albumin (mg/dL)] + [0.005 x lymphocyte count (per mm^3)] (8). Comparisons were made on whether there was a relationship between PNI scores of the patients and intensive care unit (ICU) admission status, treatment results (exitus/healed), length of hospital stay, and presence of pneumonia on thorax CT. Also, comparisons were made between PNI scores and the results of some other infection parameters such as C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), CRP/albumin ratio.

Statistical analysis: While evaluating the study data, the suitability of the parameters to the normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro Wilks tests and the homogeneity of group variances was assessed by the Levene test. Descriptive statistical methods including percentage and mean±standard deviation (±SD) or median (interquartile range [IQR] were used to provide the basic features of the data, according to the evaluation of distribution for normality. Differences in the values of the variables between the groups were evaluated by the Mann–Whitney U test according to the results of normality tests. Chi-square test was used to analyze qualitative data. Spearman Correlation test was performed to evaluate the correlation between PNI scores and other parameters. The IBM SPSS (Statistical Package for Social Sciences; version 20.0 for windows, Chicago, USA) was used for statistical analyses, and $p<0.05$ was considered significant for all statistical analyses.

RESULTS

A total of 1579 patients (755 females and 824 males) were included in the study. The median age of the whole patient group was 54 [IQR:43-65] years. 85.9% of the patients had pneumonia on thorax CT, 87.9% of males and 83.8% of females had pneumonia on thorax CT. The rate of presence of pneumonia on thorax CT was significantly higher in males (p:0.022). 14.8% of all patients were admitted to the intensive care unit (ICU), 18.8% of males and 10.3% of females were admitted to the ICU. The rate of admission to the ICU was significantly higher in males (p<0.001). The mortality rate in the whole group was 9.4%. The mortality rate was 11.4% in males and 7.2% in females. The The mortality rate was significantly higher in males (p:0.004). There was no significant difference in ICU admission rates according to gender, but total length of hospital stay was significantly longer in males (p=0.006). CRP and CRP/albumin ratio levels were higher in males. There was no significant difference between PNI scores and neutrophil/lymphocyte ratio (NLR) levels according to gender. (**Table 1**)

When we compare according to laboratory parameters and PNI score; PNI scores were found to be significantly lower in patients who died and in patients admitted to the ICU (p=0.005, p<0.001). There was no significant difference between PNI scores and the presence of pneumonia on thorax CT. CRP and CRP/albumin ratio levels were significantly higher in patients with pneumonia on thorax CT, in patients admitted to the ICU, and in patients who died (p=0.022, p=0.042, p<0.001, p<0.001, p<0.001, p<0.001, respectively). (**Table 2**)

When we look at the whole group, there was a significant negative correlation between PNI score and NLR (r=-0.399; p<0.001), and CRP/albumin ratio levels (r=-0.288; p<0.001) (**Table 3**). There was a significant negative correlation between PNI score and length of ICU stay, and length of hospital stay (r=0.170;p=0.009, r=0.274;p<0.001). There was a significant positive correlation between CRP/albumin ratio and NLR values (r=0.202; p<0.001), and between CRP/albumin ratio and length of ICU stay (r=0.134; p=0.041). (**Table 4**) In the ROC curve for the CRP/albumin ratio variable of COVID-19 patients who died, the area under the curve is 0.851, with a standard error of 0.011 (p<0.001). The cut-off point for CRP/albumin ratio is 1.09. The sensitivity of this value was 94.6%, and the sensitivity was 74.1%. (**Table 5**). The ROC curve is shown in **Figure 1.**

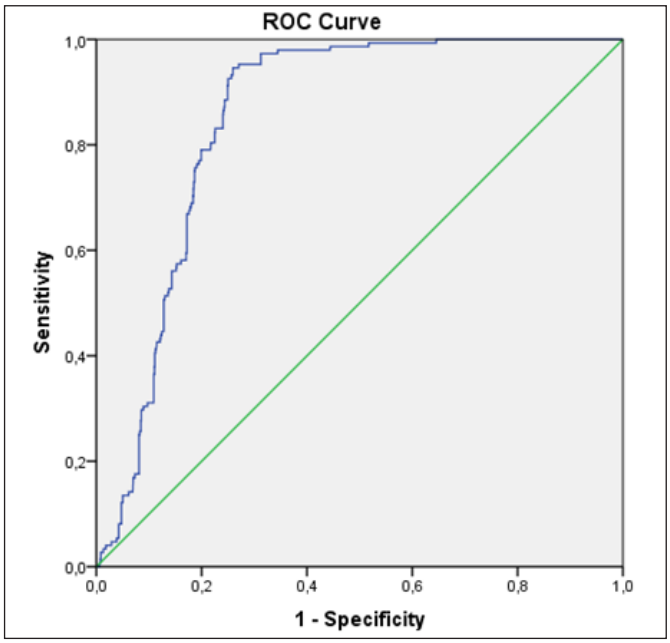

Figure 1. ROC curve analysis of CRP/albumin value variable of COVID-19 patients who died

Table 1. Distribution of selected baseline characteristics and laboratory parameters of whole group and by gender

	All Patients (n=1579)	Females(n=755, %47.8)	Males(n=824, %52.2)	p
Age (Year) (Median)	54 [43-65]	55 [44-66]	53 [41-64]	0.002[a]
Pneumonia on thorax CT				0.022[b]
Yes	1357 (85.9%)	633 (83.8)	724 (87.9%)	
No	222 (14.1%)	122 (16.2)	100 (12.1%)	
Hospitalized in				<0.001[b]
Ward	1346 (85.2%)	677 (89.7)	669 (81.2%)	
ICU	233 (14.8%)	78 (10.3)	155 (18.8%)	
Result				0.004[b]
Heraled	1431 (90.6%)	701 (92.8)	730 (88.6%)	
Exitus	148 (9.4%)	54 (7.2)	94 (11.4%)	
Length of ICU stay (day)	10 [7-16]	10 [7-15.25]	11 [7-17]	0.466[a]
Length of Hospital Stay (day)	7 [6-10]	7 [6-9]	7 [6-11]	0.006[a]
CRP	1.43 [0.29-5.35]	1.21 [0.25-4.85]	1.67 [0.34-5.97]	0.023[a]
Leukocyte	6.15 [4.70-8.00]	6.20 [4.80-8.00]	6.10 [4.62-8.00]	0.872[a]
Neutrophil	3.64 [2.57-5.00]	3.70 [2.59-5.00]	3.56 [2.54-4.99]	0.314[a]
Lymphocyte	1.45 [1.01-1.92]	1.45 [1.04-1.93]	1.43 [0.99-1.92]	0.274[a]
Albumin	3.72 [2.82-4.12]†	3.82 [2.82-4.12]†	3.70 [2.82-4.12]†	0.245[a]
NLR	2.57 [1.72-3.84]	2.63 [1.72-3.76]	2.51 [1.72-3.88]	0.948[a]
CRP / Albumin	0.41 [0.07-1.59]†	0.36 [0.06-1.49]†	0.48 [0.09-1.70]†	0.016[a]
PNI	44.65 [37.35-49.05]†	44.90 [37.45-49.25]†	44.37[37.01-48.85]†	0.346[a]

a Mann-Whitney test, b Chi-Square Test, p<0.05 was considered significant for all statistical analyses. ICU: Intensive care unit, CRP: C-reactive protein, NLR: Neutrophil/Lymphocyte ratio, PNI: Prognostic Nutritional Index.

Table 2. Distribution and comparision of pneumonia on thorax CT, hospitalization status, treatment results according to the Prognostic Nutritional Index and blood test values

	Leu	Neu	Lymp	CRP	Alb	NLR	CRP/Alb	PNI
Pneumonia on Thorax CT								
Yes	6.10 [4.70-8.00]	3.63 [2.59-4.95]	1.45 [1.01-1.94]†	1.50 [0.30-5.69]	3.82 [2.82-4.12]	2.54 [1.74-3.73]	0.43 [0.08-1.62]†	44.50 [35.70-48.16]†
No	6.50 [4.87-8.00]	3.78 [2.35-5.12]	1.39 [1.02-1.83]	0.94 [0.20-4.25]	3.72 [2.82-4.12]	2.79 [1.63-4.24]	0.34 [0.06-1.18]†	44.65 [37.45-49.05]†
p	0.211	0.536	0.468	0.022	0.077	0.406 a	0.042 a	0.256 a
Hospitalised in								
Ward	6.18 [4.80-7.80]	3.64 [2.62-5.01]	1.48 [1.04-1.95]	1.03 [0.20-3.72]	3.82 [2.82-4.12]	2.56 [1.70-3.85]	0.32 [0.05-1.00]†	45.35 [37.73-49.50]†
ICU	6 [4-11]	3.74 [2.00-4.90]	1.27 [0.78-1.74]	6 [4-9]†	3.60 [2.82-4.00]	2.58 [1.80-3.71]	1.92 [1.28-2.84]†	41.25 [33.60-44.92]†
p	0.084	<0.001a	<0.001a	<0.001a	<0.001a	0.606 a	<0.001a	<0.001a
Result								
Healed	6.10 [4.60-7.70]	3.57 [2.48-4.93]	1.44 [1.00-1.91]	1.10 [0.22-4.00]	3.82 [2.82-4.12]	2.57 [1.70-3.84]	0.34 [0.06-1.15]†	45.10 [36.55-49.30]†
Exitus	8 [6-12]	4 [3-5]	1.55 [1.16-1.96]	8 [6-11]	3.80 [3.50-4.00]	2.58 [1.86-3.73]	2.28 [1.67-3.13]†	42.62 [40.46-45.10]†
p	<0.001a	0.001a	0.056	<0.001a	0.522	0.548 a	<0.001a	0.005a

a Mann-Whitney test, p<0.05 was considered significant. ICU: Intensive care unit, CRP: C-reactive protein, NLR: Neutrophil/Lymphocyte ratio, PNI: Prognostic Nutritional Index, Leu: Leukocyte, Neu: Neutrophil, Lymp: Lymphocyte, Alb: Albumin

Table 3. Correlation analysis of PNI scores with other parameters

	Correlation coefficient (r)	P
Spearman's Rho		
NLR	-0.399	<0.001
CRP/Albumin	-0.288	<0.001
Length of ICU stay	0.170	0.009
Length of Hospital Stay	0.274	<0.001

P<0.05 was considered significant. ICU: Intensive care unit, CRP: C-reactive protein, NLR: Neutrophil/Lymphocyte ratio, PNI: Prognostic Nutritional Index

Table 4. Correlation analysis of CRP/albumin ratio levels with other parameters

	Correlation Coefficient	P
Spearman's Rho		
NLR	0.202	<0.001
PNI	-0.288	<0.001
Length of ICU stay	0,134	0.041
Length of Hospital Stay	0.096	<0.001

P<0.05 was considered significant. Neutrophil/Lymphocyte ratio, PNI: Prognostic Nutritional Index, ICU: Intensive care unit.

Table 5. ROC curve analysis of CRP/albumin ratio variable of COVID-19 patients who died

AUC(%95 Confidence Interval)	Cutt-Off	Standard Error	P	Sensitivity (%)	Specificity (%)
0.851 (0.830-0.872)	1.09	0.011	<0.001	94.6	74.1

P<0.05 was considered significant.

DISCUSSION

There is a close relationship between nutrition, immune system and infections. A healthy nutrition is essential for the development of immune response and protection from infections. A healthy diet can prevent viral infections by optimizing the immune response. On the other hand, malnutrition impairs the immune system, suppresses its functions and increases the risk of infection. It is known that malnutrition impairs the immune response, especially by affecting the cell-mediated immune system (9). Therefore, malnutrition leads to decreased immunity, which causes nosocomial infections and increases the morbidity and mortality associated with infections (10). The PNI score, calculated from albumin and lymphocyte levels, is an objective indicator of inflammatory and nutritional status. And the PNI is a parameter that has been confirmed to have prognostic value in cardiovascular diseases, malignancies and some infectious diseases such as infective endocarditis, mycobacterial infections (6,11-14) In this study, we used the PNI score to investigate the effect of nutritional status on the course of the disease in COVID-19 patients. There are not enough studies on COVID-19 and the nutritional status of patients. And there is not enough data in the literature about the relationship between COVID-19 and PNI. To our knowledge, this current study is the most comprehensive study which evaluates relationship between PNI or nutritional status of patients and COVID-19 disease severity.

In our study, which included 1579 patients, we found that the PNI score was statistically significantly lower in COVID-19 patients admitted to the intensive care unit and in patients who died. In other words, the PNI score was found to be lower in patients who needed admission to the intensive care unit and died due to severe COVID-19. In a study by Wang Z et al. (15) on 101 COVID-19 patients in China, the PNI score was found to be significantly lower in patients with severe COVID-19

disease. In a study conducted by Wang R et al. (16) on 450 COVID-19 patients in China, the mortality rate was found to be higher in patients with a low PNI score, and the PNI score was found to be an independent risk factor for mortality. In the study conducted by Yildirim A et al. (17) on 187 COVID-19 patients in Turkey, PNI score was found to be an independent predictor of mortality in hospitalized patients.We found similar results with the studies we mentioned in this current study.

Since the PNI score is calculated according to albumin and lymphocyte levels, we can explain these results over these two parameters as follows. The cytokine storm characterized by the release of large amounts of cytokines, especially interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) is associated with the severity of the disease (18,19). As in those with nutritional deficiencies, there may be a decrease in serum albumin level as a result of suppression of the synthesis ability of hepatocytes due to the increase in inflammatory cytokines such as IL-6 and TNF-α (20). In other words, low albumin level is an indicator of adverse processes such as tissue damage, cytokine storm, consumption due to hypermetabolic effect in COVID-19 patients. Low albumin levels in COVID-19 patients may exacerbate pulmonary edema by causing intravascular fluid exudation and accelerate the development of acute respiratory distress syndrome (ARDS) (21). Another component of the PNI score is the lymphocyte level. In COVID-19 disease, it is thought that there is a decrease in lymphocyte count due to direct attack of the virus on lymphocytes, dysfunction in antigen presenting cells (APC), or apoptosis due to excessive cytokine secretion (22). Lymphopenia was found to be an independent risk factor for mortality in COVID-19 patients (23).

In our study, CRP and CRP/albumin ratio levels were significantly higher in patients with pneumonia on thorax CT, in patients admitted to the intensive care unit, in patients who died. Similarly, in many studies, CRP and CRP/albumin ratio levels were found to be a good prognostic indicator in COVID-19. High levels of CRP and CRP/albumin ratio were associated with higher hospitalization rates, higher ICU admission rates, and higher mortality rates. (24,25) CRP and CRP/albumin are well-known parameters in predicting the prognosis of infections. CRP elevation is already an expected finding in infectious diseases. We have mentioned above the possible causes of low albumin. Based on these, CRP and CRP/albumin ratio can also be used as good parameters to predict the clinical course in COVID-19. Also, in this current study, we found that there was a significant negative correlation between PNI scores and CRP/albumin ratio levels. The increase in the CRP/albumin ratio and the decrease in the PNI score were correlated in demostrating the clinical course. We think that this supports the importance of a low PNI score in predicting poor clinical course in COVID-19 patients.

Using the PNI score in COVID-19 patients, we investigated whether there is a relationship between the nutritional status of the patients and their clinical course. We found a higher mortality rate and higher ICU admission rate in patients with low PNI scores. We also found that patients with higher CRP and CRP/albumin ratios had a worse prognosis. We found a negative correlation between the PNI score and CRP/albumin ratio. PNI score, as a reflection of nutrition and inflammatory status in COVID-19 patients, can be used as a good parameter in showing the clinical course. However, more reliable results can be obtained with multicenter and more comprehensive studies to be conducted in the future.

CONCLUSION

In this study, we used the PNI score to show the nutritional status of the patients, we found that the PNI score was significantly lower in COVID-19 patients admitted to the intensive care unit and in patients who died. In other words, the PNI score was found to be lower in patients who needed admission to the intensive care unit and died due to severe COVID-19. In COVID-19 patients with a low PNI score, COVID-19 may be more severe and the clinical course may be worse. Therefore, patients with poor nutrition or low PNI scores should be followed up more carefully. CRP and CRP/albumin ratio levels were significantly higher in patients with pneumonia on thorax CT, in patients admitted to the intensive care unit, and in patients who died. High CRP and CRP/albumin ratio levels and low PNI scores can be used to predict poor clinical course in COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital Ethics Committee (Date:10/03/2021, Decision No: 2020/123).

Informed Consent: All patients signed the free and informed consent form.

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Relationship between age at menopause and breast ultrasonography results

Menopoz yaşı ile meme ultrasonografi sonuçları arasındaki ilişki

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ABSTRACT

Aim: Menopause, the natural process of women's aging, brings many problems. With menopause, the loss of mammary glandular tissue increases rapidly, and large losses occur in the mammary glands due to atrophy, degeneration, and hyalinization. Ultrasonography (USG) helps to detect these breast changes. This study compared breast USG findings in menopausal cases before and after 40 years.

Material and Method: The files of menopausal patients who applied to the Gynecology and Obstetrics Clinic of Göztepe Prof. Dr. Süleyman Yalçın City Hospital between October 2014 and September 2020 were retrospectively scanned and analyzed. According to the age of patients entering menopause, it was divided into two groups: 1st group under 40 years old and 2nd group over 40 years old. 52 patients in the 1st group (case group) and 67 patients in the 2nd group (control group) were included in the study.

Results: The mean age of the participants in the study was 33.2 in the 1st group and 48.6 in the 2nd group. Body mass indexes (BMI) were 24.8 kg/m² in group 1 and 25.1 kg/m² in group 2. When the breast USG findings were examined, the incidence of cyst formation in the 1st group was found to be statistically significantly higher than in the 2nd group ($p<0.05$), and the incidence of fibroadenoma was found to be significantly higher in the 1st group than in the 2nd group ($p<0.05$).

Conclusion: Menopause is an important period in the life of women. Breast USG can be used as an auxiliary examination for diagnostic purposes. In the present study, the rate of breast masses and malignancies was directly related to menopausal age and especially menopause at older ages.

Keywords: Breast ultrasonography, breast, menopause

ÖZ

Giriş: Kadınların yaşlanmasının doğal süreci olan menopoz, beraberinde pek çok sorunu da getirmektedir. Menopozla birlikte meme bezi dokusu kaybı hızla artar ve meme bezlerinde atrofi, dejenerasyon ve hyalinizasyona bağlı olarak büyük kayıplar meydana gelir. Ultrasonografi (USG) bu meme değişikliklerinin tespit edilmesine yardımcı olur. Bu çalışmada menopozal olgularda 40 yıl öncesi ve sonrası meme USG bulguları karşılaştırıldı.

Gereç ve Yöntem: Göztepe Prof. Dr. Süleyman Yalçın Şehir Hastanesi Kadın Hastalıkları ve Doğum Kliniği'ne Ekim 2014-Eylül 2020 tarihleri arasında başvuran menopozal hastaların dosyaları retrospektif olarak taranarak analiz edildi. Menopoza giren hastaların yaşlarına göre 1. grup 40 yaş altı ve 2. grup 40 yaş üstü olmak üzere iki gruba ayrıldı. 1. grupta (olgu grubu) 52 hasta ve 2. grupta (kontrol grubu) 67 hasta çalışmaya dahil edildi.

Bulgular: Çalışmaya katılanların yaş ortalaması 1. grupta 33.2, 2. grupta 48.6 idi. Vücut kitle indeksleri (BKİ) grup 1'de 24,8 kg/m², grup 2'de 25.1 kg/m² idi. Meme USG bulguları incelendiğinde 1. grupta kist oluşum insidansı istatistiksel olarak anlamlı derecede yüksek bulundu. 2. grup ($p<0.05$) ve fibroadenom insidansı 1. grupta 2. gruba göre anlamlı derecede yüksek bulundu ($p<0.05$).

Sonuç: Menopoz, kadınların hayatında önemli bir dönemdir. Meme USG tanı amaçlı yardımcı muayene olarak kullanılabilir. Bu çalışmada meme kitleleri ve malignite oranları menopoz yaşı ve özellikle ileri yaşlarda menopoz ile doğrudan ilişkilidir.

Anahtar Kelimeler: Meme ultrasonografisi, meme, menopoz

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INTRODUCTION

According to the World Health Organization, menopause is the cessation of menstruation in women that occurs due to the cessation of ovarian follicle activity and ends the pregnancy in women (1). Thus, women are considered menopause when they have at least 12 months of menstrual interruption, unrelated to pregnancy, breastfeeding, or other hormonal disorders (2). Post-menopausal women are projected to increase from 467 million to 1,200 million worldwide by 2030, with the most significant increase in developing countries (3). Menopausal age changes usually occur in the age range of 45-55 years and it changes from country to country (4,5). Hormonal changes during this period lead to post-menopausal women being prone to cardiovascular disease (CVD), bone complications, and an increased risk of developing breast cancer and endometriosis (2,6,7). Among the most important problems for women before and after menopause are breast lumps and cysts, and according to estimates, today, one in six women undergoes a biopsy due to breast problems (3,5,8).Most examinations and biopsies are performed on individual breast masses found by patients, physicians, or mammograms (6). The nature of these masses is often benign, self-limiting, and in some cases, malignant. Among benign cases, the most common causes of breast masses include fibrocystic changes, fibroadenoma, breast trauma, and infections (3). Cases such as mammary duct ectasia are also in the category of benign masses, but in terms of prevalence, they are much lower and less common (9). Malignant breast masses and lesions are much less common than benign cases and include primary breast cancer and cases of breast metastasis (6). Cases of benign breast masses can be divided into groups without hyperplasia, atypical hyperplasia, and non-atypical hyperplasia (5-8). Cases without hyperplasia, such as fibrocystic changes and simple cysts, are not associated with an increased risk of breast cancer (9,10).

Fibrocystic changes are a finding of unknown cause and are very common in adults. The exact prevalence of this disease is not known, but in some studies, this rate has been reported to be more than 50%. Cysts also increase over time until menopause and decrease abruptly (4,6,8). Atypical hyperplasia includes conditions such as intraductal papilloma and fibroadenoma, which slightly increase the risk of breast cancer (7). Fibroadenoma is an often asymptomatic lesion in the examination of rubbery and mobile consistency, with a variable size of about 1 to 10 cm, and after menopause, it increases in size (3,7,8).

Some studies consider menopausal age a health indicator, so understanding its causes may have important epidemiological and clinical implications (10). Identifying the factors associated with early and late menopause is important because menopausal age is related to the risk of developing several chronic diseases such as CVD, breast and uterine cancer, and osteoporosis (11). Women with early menopause are at risk for CVD (4,6,8) and osteoporosis (4,6,9), while women with late menopause are at risk for breast (2,4,5) and uterine cancers (3). Socio-demographic factors and reproductive and behavioral characteristics are known as menopausal-related factors (7-9). Therefore, with the annual increase in the number of post-menopausal women and the problems mentioned, it seems necessary to conduct several studies in this field. Thus, according to the above, the present study aims to investigate the relationship between age at menopause and breast ultrasonography (USG) results.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Researches Ethics Committee (Date:13.01.2021, Decision No:2021/0040). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Due to the study's retrospective nature, the stage of obtaining informed consent from patients was omitted.

A total of 119 patients were enrolled at Gynecology and Obstetrics Clinic Göztepe Prof. Dr. Süleyman Yalçın City Hospital between October 2014 and September 2020. Participants ranged in age from 25 to 54 years. The inclusion criteria were: (1) the woman between the ages of 20 and 55. The exclusion criteria were: (1) pregnant women and women in the breastfeeding period; (2) women who received infertility treatment; (3) having diabetes, thyroid dysfunction, and systemic diseases; (4) smoking and using alcohol.

Patients' data were obtained from their records and analyzed retrospectively. The study participants were divided into two groups. The women who had normal menopause were included in the control group (n:67), and the women with premature menopause were included in the study group (n:52).

Statistical Analysis

Data were analyzed, tabulated, and subjected via the SPSS (version 26). The continuous data were displayed as mean±SD. At the same time, categorical data were illustrated as percentages and numbers. The Kolmogorov-Smirnov test of normality was utilized to test the normality hypothesis. Based on the test results, Man Whitney, Kruskal Wallis, and Chi-square test were used. A p-value of <0.05 was regarded as statistically

significant.

RESULTS

This study sample included 119 participants (52 cases and 67 control). The participants' BMI and mean age were 22.71±1.94 and 41.46 years ±7.41, respectively. The mean age of the first period was 11.24±1.02 years. The mean age at menopause was 38.10±6.74. The breast USG findings showed that no cyst was found in 28 (23.5%) subjects, a cyst was detected in 50 (42%) subjects, and cystic changes were found in 21 (17.6%) subjects. In 11 (9.2%) and 9 (7.5%) subjects, solid lesions and fibroadenoma were detected. **Table 1** shows the explanatory information of the variables.

Table 1. Explanatory information of the variables

Variable	N	Min	Max	Mean	SD
Age(yr)	119	25.00	54.00	41.46	7.41
BMI	119	18.00	28.00	22.71	1.94
The age the first period (yr)	119	9.00	14.00	11.24	1.02
Age at menopause (yr)	119	25.00	46.00	38.10	6.74
Breast USG		**Frequency**			**Percent**
No cyst		28			23.5
Cyst		50			42
Cystic changes		21			17.8
Solid lesion		11			9.2
Fibroadenoma		9			7.5

Min: Minimum, Max: Maximum

Table 2 shows the comparison of research variables for the two groups. It was expected that variables age and age at menopause were significantly different. They are reported only because of the mean information in each group. There was no statistically significant difference between the study group and controls regarding BMI (p value>0.05). A statistically significant difference was observed between the two groups regarding the age of the first period (p value=0.012). The control group had higher age (11.47) than the case group (10.94). The table also shows that 76% had breast-related complications.

Table 2. Distinction of laboratory results of two groups

Variable	Categories	Normal menopause (n=67) (Mean±SD) or n (%)	Premature menopause (n=52) (Mean±SD) or n (%)	P value
Age(yr)		47.47±2.13	33.71±3.56	0.000*
BMI		22.91±1.81	22.46±2.10	0.158
The age the first period (yr)		11.47±1.03	10.94±0.93	0.012*
Age at menopause(yr)		43.62±1.28	31±3.41	0.000*
Number of births				0.000**
	0	5(7.4)	34 (65.3)	
	1	42 (62.6)	14 (26.9)	
	2	17 (20.8)	4 (7.6)	
	3	3 (4.4)	0 (0)	

* Mann–Whitney U test, **Pearson Chi-Square Test

As **Table 2** shows, the number of births in the case group and controls was statistically significantly different (p value<0.05). The information about the subjects' mean age of menopause is shown in **Figure 1**.

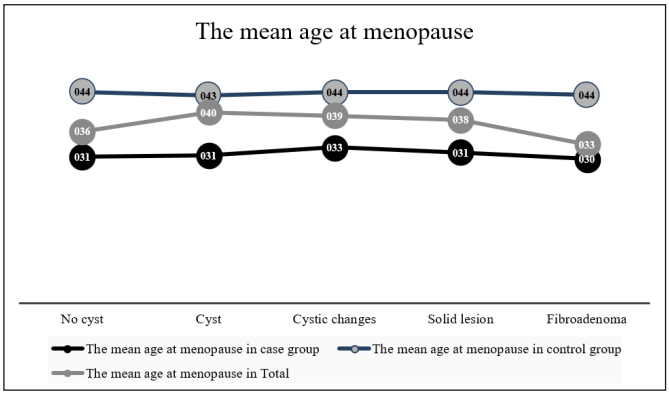

Figure 1. The mean age at menopause in breast USG finding between two groups

Table 3 shows the comparison of groups regarding breast USG results.

Table 3. Relationship between groups and breast USG results

Variable	Categories	Normal menopause (n=67) or n (%)	Premature menopause (n=52) or n (%)	P value	P value
Breast USG					0.014
	No cyst	11(16.4)	17(32.6)	0.038	
	Cyst	36(53.7)	14(26.9)	0.003	
	Cystic changes	12(17.9)	9(17.3)	0.932	
	Solid lesion	6(8.9)	5(9.6)	0.902	
	Fibroadenoma	2(2.9)	7(13.4)	0.032	

*Pearson Chi-Square Test

As shown in **Table 3**, the case group and controls had a statistically significant difference in terms of breast USG findings (p value<0.05). These differences were observed in the normal menopause group having more cyst (p value=0.003) and the premature menopause group having more fibroadenoma (p value=0.032). This information is shown in **Figure 2**.

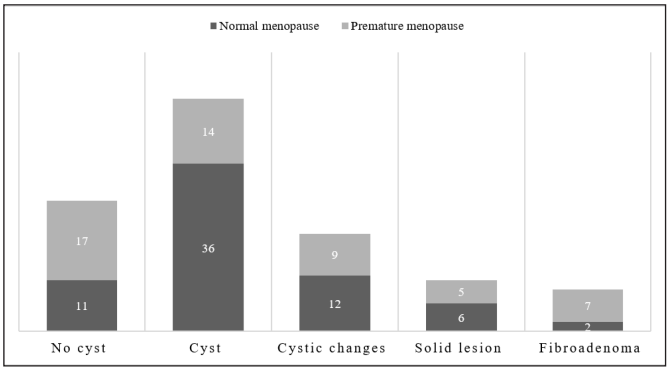

Figure 2. Breast USG finding prevalence in case and control group

DISCUSSION

Breast lumps are common in pre-and post-menopausal ages and are a common complaint among women. About 40% of the reasons for women to go to diagnostic centers are breast diseases (10, 11). Most of these lumps are benign but can be a critical and warning sign of malignancy in some cases. According to previous studies, 11% of people with breast lumps complaints have had breast cancer and malignancy. In general, the prevalence of benign breast pathologies has been reported to be 2 to 8 times higher than malignant cases (6,8,10).

In the present study, 119 records of women referred to our center with various complaints and symptoms were examined to extract breast USG findings and examine these findings' relationship with the prevalence of breast masses in the two groups of early menopause and normal menopause. These results indicate the importance of breast masses, especially in the post-menopausal period, when malignancies are the more common breast complications (10). The results showed that the most common pathological findings in breast USG in the group of early menopause were cyst (26.9%) and cystic changes (17.3%), respectively. For the normal menopausal group, the most common pathologies were also cyst (53.7%) and cystic changes (17.9%). Our results also showed a significantly higher rate of fibroadenoma in women with early menopause (p value=0.032), which is consistent with previous results (12-14).

In this study, the high prevalence of fibroadenoma in women with early menopause was consistent with the results of many studies that indicated that fibroadenoma is the most common breast mass among women with early menopause (14-16). However, fibroadenoma is the second most common post-menopausal woman (17). The most common benign breast masses in previous studies were cysts (13,15,17). In the present study, cystic masses were also at the top of benign masses, consistent with other studies in this field.

It is also important to note that the overall rate of malignant breast masses in post-menopausal women is much higher than in women of childbearing age, which is evidence that hormonal cycles during fertility have a protective effect against malignancies (17,18). The rate of breast cysts in women who have menstrual cycles is significantly higher than in menopausal women due to the high impact of cysts on hormonal cycles (14,15). This phenomenon is significantly reduced in post-menopausal women but remains in early-menopausal women (16,17). Our results are also consistent with these findings.

In the present study, the rate of cystic changes and solid lesions in women were similar between the two groups. However, the number of cysts is more common in the group with normal menopause. The present study results show a significant relationship between the number of cysts and menopausal status in women; Its shows that the cyst prevalence is significantly higher in women with normal menopause than in women with early menopause. It should be noted that fibrocystic changes are a lesion without hyperplasia and an increased risk of malignancy (15,16). This finding can be justified based on related studies because the average age of post-menopausal women is usually high, and according to estimates, age over 50 years is directly related to an increase in breast cancer in women (18-20). Thus, it can be concluded that menopause at a younger age is associated with a lower risk of cysts. These findings are consistent with the results of previous studies (21,22).

It is important to pay attention to the results of this study because over the past few decades, due to the increase in life expectancy and the number of postmenopausal women (14,17), the age parameter, which is one of the most important indicators of breast cancer, has increased significantly. In the present study, the rate of breast masses and malignancies was directly related to menopausal age and especially menopause at older ages. Finally, regular check-ups are recommended at appropriate intervals, especially in women over 50 for cysts and women with early menopause for fibroadenoma. Among the limitations of this study are the small number of samples and the single center of study information. Studying more samples and considering more diverse ethnic factors is necessary to get more comprehensive results.

CONCLUSION

Menopause is an important period in the life of women. Breast USG can be used as an auxiliary examination for diagnostic purposes. In the present study, the rate of breast masses and malignancies was directly related to menopausal age and especially menopause at older ages. Regular check-ups are recommended at appropriate intervals, especially in women over 50 for cysts and women with early menopause for fibroadenoma.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Researches Ethics Committee (Date:13.01.2021, Decision No:2021/0040).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article / Özgün Makale

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Analysis of global publications on tracheostomy between 1980 and 2021, including the impact of COVID-19: a bibliometric overview

COVID-19'un etkisi de dahil olmak üzere 1980 ve 2021 yılları arasında trakeostomi ile ilgili küresel yayınların analizi: bibliyometrik bir bakış

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ABSTRACT

Aim: The usage of tracheostomy and related studies have increased in recent years with the COVID-19 pandemic, however, there is not enough bibliometric study in the literature. This study aims to summarize scientific articles on tracheostomy.

Material and Method: Published articles about tracheostomy between 1980 and 2021 were analyzed using bibliometric and statistical methods. Articles were retrieved from the Web of Science database. Keyword network visualization maps were used to identify trending topics and collaborations. The Exponential Triple Smoothing estimator was used to forecast the possible number of future publications. Spearman's test was used for correlation studies.

Results: A total of 6274 publications were found. 3573 were articles. The top three countries were USA (n=1337), UK (n=361) and Germany (n=298). The top three institutions were Harvard University (n=67), University Michigan (n=50), University of Pennsylvania (n=40). The top three journals with the highest number of publications were Laryngoscope (n=189), International Journal of Pediatric Otorhinolaryngology (n=128), Otolaryngology-Head and Neck Surgery (n=121). According to the average number of citations per article, the top three most influential journals were Chest (70.2), Critical Care Medicine (66.5), and Journal of Trauma-Injury Infection and Critical Care (48.5).

Conclusion: This comprehensive bibliometric study summarized articles on tracheostomy. There is an increasing trend in the number of articles following the COVID-19 pandemic. This study showed that the need for tracheostomy may increase in epidemics which cause respiratory failure. This article can be a useful resource for clinicians and scientists.

Keywords: Bibliometric analysis, citation analysis, coronavirus, COVID-19, tracheostomy, trends

ÖZ

Amaç: Son yıllarda COVID-19 pandemisi ile birlikte trakeostomi kullanımı ve ilgili çalışmalar artmış olmakla birlikte literatürde yeterli bibliyometrik çalışma bulunmamaktadır. Bu çalışma, trakeostomi ile ilgili bilimsel makaleleri özetlemeyi amaçlamaktadır.

Gereç ve Yöntem: 1980-2021 yılları arasında trakeostomi ile ilgili yayınlanmış makaleler bibliyometrik ve istatistiksel yöntemlerle analiz edildi. Makaleler Web of Science veri tabanından alındı. Trend olan konuları ve işbirliklerini belirlemek için anahtar kelime ağ görselleştirme haritaları kullanıldı. Gelecek yıllardaki yayın sayısını tahmin etmek için Exponential Triple Smoothing tahmincisi kullanıldı. Korelasyon araştırma çalışmaları için Spearman's testi kullanıldı.

Bulgular: Toplam 6274 yayın bulundu. Bu yayınlardan 3573 makale idi. İlk üç ülke ABD (n=1337), İngiltere (n=361) ve Almanya (n=298) oldu. En aktif ilk üç kurum Harvard Üniversitesi (n=67), Michigan Üniversitesi (n=50), Pennsylvania Üniversitesi (n=40) oldu. En fazla yayına sahip ilk üç dergi Laryngoscope (n=189), International Journal of Pediatric Otorhinolaryngology (n=128), Otolaryngology-Head and Neck Surgery (n=121) idi. Makale başına ortalama atıf sayısına göre, en etkili üç dergi Chest (70,2), Critical Care Medicine (66,5) ve Journal of Trauma-Injury Infection and Critical Care (48,5) oldu.

Sonuç: Bu kapsamlı bibliyometrik çalışma, trakeostomi hakkındaki makaleleri özetledi. COVID-19 pandemisini takiben makale sayısında artış eğilimi vardı. Bu çalışma, solunum yetmezliğine neden olan salgınlarda trakeostomi ihtiyacının artabileceğini göstermiştir. Bu makale klinisyenler ve bilim adamları için faydalı bir kaynak olabilir.

Anahtar Kelimeler: Bibliyometrik analiz, alıntı analizi, coronavirus, COVID-19, trakeostomi, trendler

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INTRODUCTION

There is a significant increase in the number of patients who require mechanical ventilation. Tracheostomy is a frequently performed technique in critically ill patients who require long mechanical ventilation for acute respiratory failure and airway problems (1-3). Tracheostomy can also be used on traumatic neurological injuries requiring mechanical ventilation, upper airway obstruction, foreign body aspiration, etc (1,4).

Bibliometric is the analysis of scientific outputs in the literature using various statistical methods (5,6). In parallel with the increasing number of publications in the literature, bibliometric research and analyzes have been carried out on different medical subjects (5-12). Bibliometric studies can reveal past and current trends on a topic using citation analysis, bibliometric and statistical methods. Bibliometric studies can allow researchers to understand the literature briefly and can also highlight researches ideas for future studies (8-10).

Although the use of tracheostomy and the number of global studies have increased in recent years with the COVID-19 pandemic, there is not enough bibliometric study in the literature. This study aims to summarize the published scientific articles on tracheostomy between 1980 and 2021 and performs analyses using bibliometric and statistical methods. As a result of the analysis, we want to show the most effective studies on tracheostomy using citation analysis; to identify the most active authors, journals, institutions, and countries; to highlight possible cooperation between countries, and to identify past and current trend issues.

MATERIAL AND METHOD

Ethics committee approval is not required in this bibliometric study.

We have used the Web of Science database (WoS) (by Clarivate Analytics) for the literature review. Publication scanning was done only in the "title" section of the studies. Search keywords related to tracheostomy ("tracheostomy", "tracheotomy", "tracheostomies", "tracheotomies", "tracheostomied", "tracheotomied" etc.) were used for literature review in WoS. With this search method, all articles related to tracheostomy and other usage were obtained and downloaded from WoS. The following search criteria were used: Title: tracheostomy or tracheotomy; timespan: 1980-2021; indexes: SCI-Expanded, SSCI, A&HCI, CPCI-S, CPCI) -SSH, BKCI-S, BKCI-SSH, ESCI) (Access date: 25.10.2021).

VOSviewer (Version 1.6.17, Leiden University's Center for Science and Technology Studies) package program was used for bibliometric network visualizations and citation analysis. VOSviewer gave special importance to the graphical representation of large bibliometric networks. These networks may include journals, researchers, or individual publications. The networks can be constructed based on citation, bibliographic coupling, co-citation, or co-authorship relations (13).

The Exponential Triple Smoothing estimator in the Microsoft Office Excel (Version 2013, Microsoft) program was used to forecast the possible number of publications in the coming years based on past publication trends. The estimator use AAA (additive error, additive trend, and additive seasonality) version of the Exponential Triple Smoothing (ETS) algorithm. Statistical analyzes were performed with the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) package program. The normal distribution of the data was tested with the Kolmogorov-Smirnov test.

The relationship between world publication productivity and economic development on tracheostomy was investigated. Economic development indicators; Gross Domestic Product (GDP) and Gross Domestic Product per capita (GDP per capita) were obtained from the World Bank (14). The correlation between the number of articles produced by countries and their economic development was evaluated with Spearman's correlation coefficient according to data distribution. A p-value of 0.05 or less is considered statistically significant.

RESULTS

As a result of the literature review, a total of 6274 publications on tracheostomy published between 1980 and 2021 were found in the WoS. The types of these publications are article (3573, 56.9%), meeting abstract (1030, 16.4%), letter (946, 15%), proceedings paper (282, 4.5%), review (213, 3.4%), and other types (230, 3.7%) (Editorial material, early access, note, book chapter, correction, news item, book review, discussion, poetry, retracted publication). Bibliometric analyzes were carried out with articles. 92.6% (3307) of these articles were in English, 4.2% (151) in German, 1.6% (58) in French, 0.8% (27) in Spanish, and the rest in other languages (Turkish (14), Portuguese (5), Russian (2), Slovenian (2), Chinese (1), Czech (1), Hungarian (1), Italian (1), Japanese (1), Korean(1), and Polish (1)). The h-index of articles was 91, the average citations per article was 15.22, and the sum of times cited was 54367 (without self-citations: 29275).

Active Research Areas

The top 10 research areas on tracheostomy were otorhinolaryngology (1054, 29.4%), surgery (846, 23.6%), critical care medicine (555, 15.5%), respiratory system (437, 12.2%), pediatrics (352, 9.8%), anesthesiology (340, 9.5%), general internal medicine (274, 7.6%), research in experimental medicine (222, 6.2%), clinical neurology (146, 4%), and cardiac cardiovascular systems (143, 4%)).

Development and Future Trends

The distribution of the number of published articles by year is shown in **Figure 1**. The estimated values of the ETS estimation model, which is used to estimate the number of articles that can be published in 2021 and beyond, are shown in **Figure 1**. The data collection phase was done before the completion of 2021, therefore the number of articles published in 2021 was excluded from the estimation model. According to the estimation model results, it is estimated that 329 (Confidence Interval (CI) %: 283-376) articles will be published in 2021 and 347 (CI%: 295-398) articles will be published in 2025 (**Figure 1**).

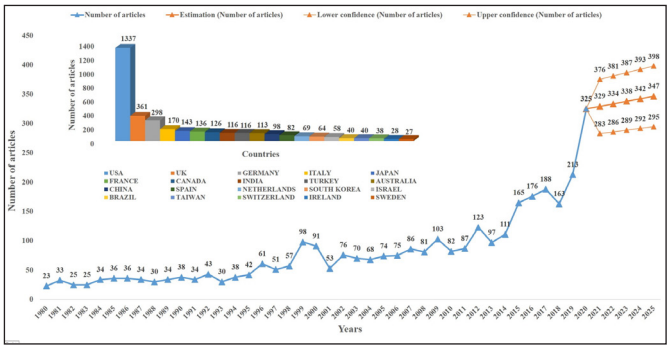

Figure 1. a. Distribution of articles on tracheostomy by years and estimation of articles in the coming years b. Top 20 countries in the world that have published the most articles on tracheostomy

Active Countries

The first 20 countries with the most articles on tracheostomy is shown in the column chart of **Figure 1**. These countries are; USA (1337, 37.4%), UK (361, 8.9%), Germany (298, 7.6%), Italy (170, 4.7%), Japan (143, 4%), France (136, 3.8%), Canada (126, 3.5%), India (116, 3.2%), Turkey (116, 3.2%), Australia (113, 3.1%), China (98, 2.7%), Spain (82, 2.2%), Netherlands (69, 1.9%), South Korea (64, 1.7%), Israel (58, 1.6%), Brazil (40, 1.1%), Taiwan (40, 1.1%), Switzerland (38, 1.0%), Ireland (28, 0.7%), and Sweden (27, 0.7%).

90 countries have produced publications. Among these countries, 44 countries were selected. The selected countries have produced at least 5 articles and had international cooperation among their authors. For the selected countries, the total link strength scores were calculated. The International Collaboration Density map is created based on these scores (**Figure 2.a**). The network visualization map of cluster analysis is shown in **Figure 2.b**. According to the results of the cluster analysis, six different clusters regarding international cooperation were found (Cluster 1: Austria, Canada, Czech Republic, Germany, Israel, Italy, Japan, Netherlands, Norway, South Korea, Sweden, Thailand. Cluster 2: Australia, Belgium, France, Ireland, Portugal, South Africa, Switzerland, Taiwan. Cluster 3: Croatia, Finland, New Zealand, China, Singapore, Turkey, USA. Cluster 4: Argentina, Brazil, Chile, Colombia, Greece, Spain, Venezuela. Cluster 5: Egypt, India, Pakistan, Saudi Arabia, United Arab Emirates. Cluster 6: Denmark, England, Scotland, Wales).

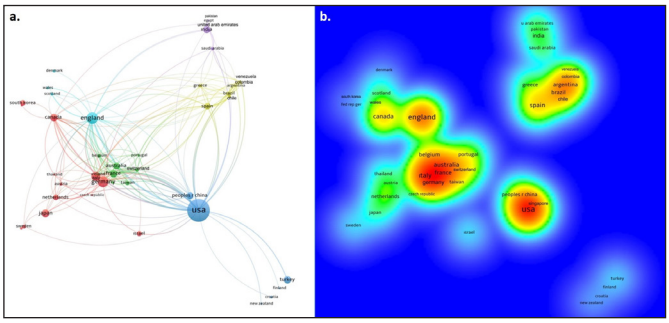

Figure 2. a. Network visualization map of cluster analysis on international collaboration between countries on tracheostomy. **Footnote:** Colors indicate clustering. The size of the circle indicates a large number of articles. **b.** Density map for international collaboration of countries on tracheostomy. **Footnote:** The strength of international collaboration score increases from blue to red (blue-green-yellow-red)

Correlation Analysis

There was a positive and statistically significant high correlation between the GDP and GDP per capita values of the countries and the number of articles (rgdp=0.717, p<0.001; rGDP per capita=0.701, p<0.001).

Active Authors

The top 10 most active authors with the most articles were Pandian V. (20), Leder SB. (19), Brenner MJ. (15), Byhahn C. (15), Johnson RF. (14), Pelosi P. (14), Westphal K. (14), Kluge S. (12), Lischke V. (12), and Mcgrath BA. (12).

Active Institutions

The 15 most active universities that produced the most articles on tracheostomy were determined. These universities were Harvard University (n=67), University Michigan (n=50), University of Pennsylvania (n=40), University Toronto (n=37), Yale University (n=37), University Washington (n=36), Northwestern University (n=34), University Pittsburgh (n=32), Johns Hopkins University (n=29), Boston Children's Hospital (n=27), Children's Hospital of Philadelphia (n=26), University of North Carolina (n=26), Medical College of Wisconsin (n=24), and Stanford University (n=24).

Active Journals

3573 articles on tracheostomy were published in 816 different journals. The first 34 most active journals that have 20 or more articles, the total number of citations received by these journals, and the average number of citations per article are presented in **Table 1**. The citation network visualization map between these journals is presented in **Figure 3.**

Table 1. The 34 most active journals that have published more than 20 articles on tracheostomy

Journals	RC	C	AC	Journals	RC	C	AC
Laryngoscope	189	3752	19.9	American Surgeon	32	706	22.1
International Journal of Pediatric Otorhinolaryngology	128	1497	11.7	Anaesthesia and Intensive Care	32	546	17.1
Otolaryngology-Head and Neck Surgery	121	1572	13.0	Critical Care	30	1218	40.6
Journal of Laryngology and Otology	87	711	8.2	Journal of Oral and Maxillofacial Surgery	30	395	13.2
Respiratory Care	75	1167	15.6	British Journal of Oral & Maxillofacial Surgery	28	360	12.9
Chest	70	4912	70.2	Journal of Trauma-Injury Infection and Critical Care	27	1310	48.5
Annals of Otology Rhinology and Laryngology	63	1547	24.6	Acta Anaesthesiologica Scandinavica	26	499	19.2
Critical Care Medicine	52	3460	66.5	HNO	26	94	3.6
Head and Neck-Journal for the Sciences and Specialties of the Head and Neck	51	782	15.3	Anesthesia and Analgesia	25	644	25.8
European Archives of Oto-Rhino-Laryngology	50	383	7.7	British Journal of Anaesthesia	25	597	23.9
Intensive Care Medicine	48	2162	45.0	JAMA Otolaryngology-Head & Neck Surgery	24	305	12.7
Pediatric Pulmonology	46	468	10.2	Laryngo-Rhino-Otologie	24	79	3.3
Anaesthesia	41	1028	25.1	Journal of Critical Care	22	316	14.4
Archives of Otolaryngology-Head & Neck Surgery	37	819	22.1	American Journal of Surgery	21	324	15.4
Indian Journal of Otolaryngology and Head & Neck Surgery	36	24	0.7	Journal of Otolaryngology	21	294	14.0
American Journal of Otolaryngology	34	295	8.7	Neurocritical Care	21	259	12.3
Annals of Thoracic Surgery	34	1003	29.5	Minerva Anestesiologica	20	240	12.0

RC: Record Count, C: Number of Citation, AC: Average Citation Per Document

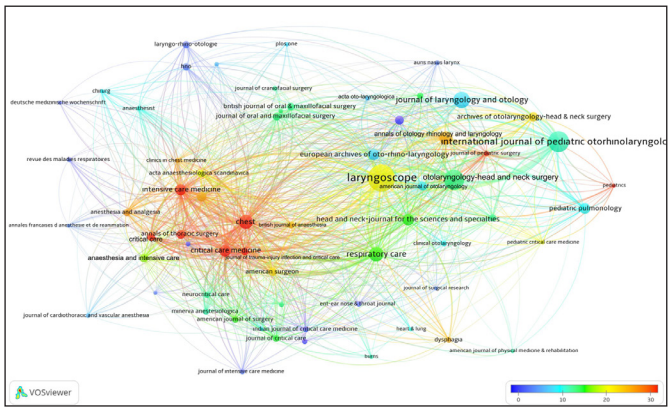

Figure 3. Network visualization map for citation analysis of active journals on tracheostomy. **Footnote:** The average number of citations per article by journals increases from blue to red (blue-green-yellow-red). The size of the circle indicates a large number of articles

Citation Analysis

The first 20 articles with the highest number of citations, out of 3573 articles published between 1980 and 2021, are presented in **Table 2**. The last column of **Table 2** presents the average number of citations per year.

Co-citation Analysis

In the references section of all 3573 articles, there are a total of 29551 studies cited. Among these studies, the first 9 studies that received the most co-citations (more than 150 citations) were Ciaglia (1985) (Number of co-citations (NC): 476), Rumbak (2004), (NC: 215), Griggs (1990) (NC: 196), Freeman (2000) (NC: 184), Stauffer (1981) (NC: 179), Griffiths (2005) (NC: 176), Hazard (1991) (NC: 172), Delaney (2006) (NC: 171) and Young (2013) (NC: 154) (2, 3, 15-21).

Trend Topics

4027 different keywords were used in all 3573 articles published on tracheostomy. Among these keywords, the most used 50 different keywords (used in at least 20 different articles) are shown in **Table 3**. The cluster network visualization map between these keywords is shown in **Figure 4**. The trend visualization network map is presented in **Figure 5** and the citation network visualization map is presented in **Figure 6**.

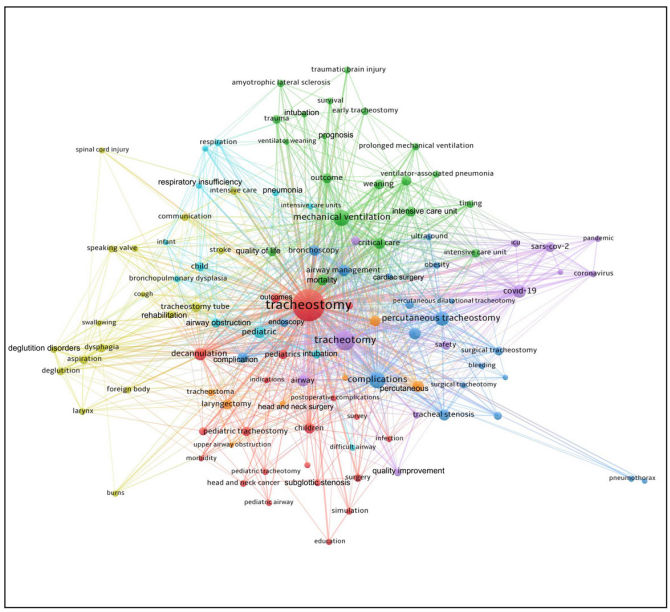

Figure 4. Network visualization map for cluster analysis based on keyword analysis on tracheostomy. **Footnote:** Colors indicate clustering. Keywords in the same cluster are of the same color. The size of the circle indicates the number of uses of the keyword

Table 2. The top 20 most cited articles on tracheostomy by total number of citations

No	Article	Author	Journal	PY	TC	AC
1	Complications and consequences of endotracheal intubation and tracheotomy - a prospective-study of 150 critically ill adult patients	Stauffer JL. et al.	American Journal of Medicine	1981	812	19.8
2	Elective percutaneous dilatational tracheostomy - a new simple bedside procedure - preliminary-report	Ciaglia P. et al.	Chest	1985	700	18.92
3	A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients	Rumbak MJ. et al.	Critical Care Medicine	2004	430	23.89
4	Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure - A different approach to weaning	Bach JR. et al.	Chest	1996	319	12.27
5	Obstructive sleep-apnea syndrome and tracheostomy - long-term follow-up experience	Guilleminault C. et al.	Archives of Internal Medicine	1981	318	7.76
6	Urinary catecholamines before and after tracheostomy in patients with obstructive sleep-apnea and hypertension	Fletcher EC. et al.	Sleep	1987	288	8.23
7	Effect of Early vs Late Tracheostomy Placement on Survival in Patients Receiving Mechanical Ventilation The tracman Randomized Trial	Young D. et al.	JAMA-Journal of the American Medical Association	2013	287	31.89
8	A simple percutaneous tracheostomy technique	Griggs WM. et al.	Surgery Gynecology& Obstetrics	1990	285	8.91
9	Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients a randomized controlled trial	Terragni PP. et al.	JAMA-Journal of the American Medical Association	2010	283	23.58
10	Early tracheostomy for primary airway management in the surgical critical care setting	Rodriguez JL. et al.	Surgery	1990	271	8.47
11	A meta-analysis of prospective trials comparing percutaneous and surgical tracheostomy in critically ill patients	Freeman BD. et al.	Chest	2000	266	12.09
12	Comparative clinical-trial of standard operative tracheostomy with percutaneous tracheostomy	Hazard P. et al.	Critical Care Medicine	1991	243	7.84
13	Comparison of percutaneous and surgical tracheostomies	Friedman Y. et al.	Chest	1996	223	8.58
14	Intermittent positive pressure ventilation via the mouth as an alternative to tracheostomy for 257 ventilator users	Bach JR. et al.	Chest	1993	198	6.83
15	Percutaneous dilatational tracheostomy - results and long-term follow-up	Ciaglia P. et al.	Chest	1992	198	6.6
16	Endoscopic guided percutaneous tracheostomy - early results of a consecutive trial	Marelli D. et al.	Journal of Trauma-Injury Infection and Critical Care	1990	194	6.06
17	Pediatric tracheotomies: Changing indications and outcomes	Carron JD. et al.	Laryngoscope	2000	184	8.36
18	Early tracheostomy versus prolonged endotracheal intubation in severe head injury	Bouderka MA. et al.	Journal of Trauma-Injury Infection and Critical Care	2004	182	10.11
19	Complications in pediatric tracheostomies	Carr MM. et al.	Laryngoscope	2001	178	8.48
20	Clinical predictors and outcomes for patients requiring tracheostomy in the intensive care unit	Kollef MH. et al.	Critical Care Medicine	1999	178	7.74

PY: Publication year, TC: Total citation, AC: Average citations per year

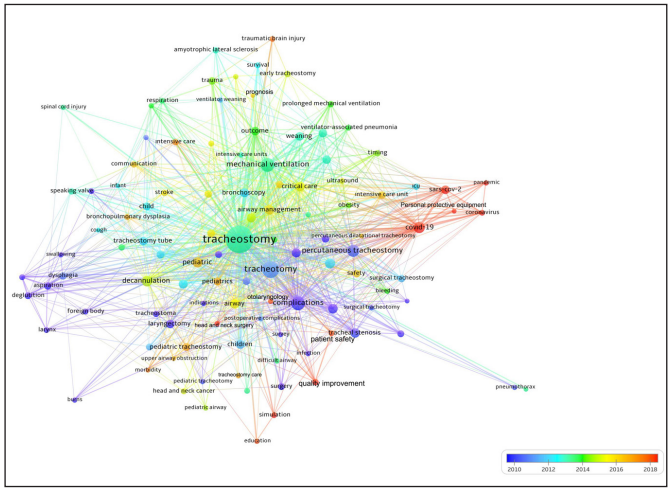

Figure 5. Network visualization map for trends on tracheostomy. **Footnote:** In the indicator given in the lower right corner of the figure, the topicality of the article increases from blue to red (blue-green-yellow-red). The size of the circle indicates the number of uses of the keyword

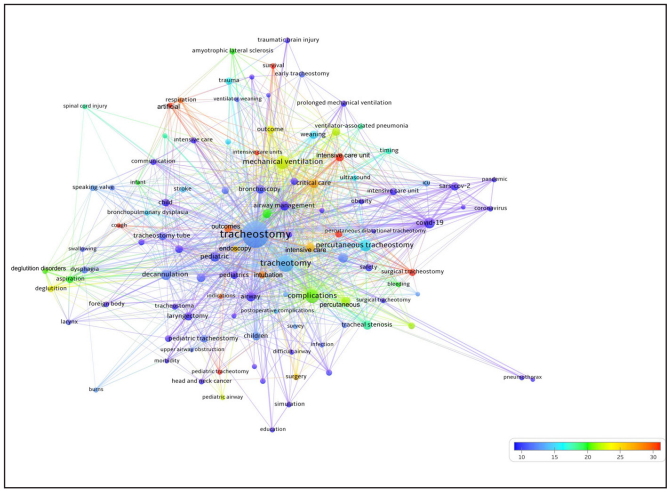

Figure 6. Network visualization map of the most frequently cited topics on tracheostomy. **Footnote:** In the indicator given in the lower right corner of the figure, the number of citations received by the topic increases from blue to red (blue-green-yellow-red). The size of the circle indicates the number of uses of the keyword

Table 3. The 50 most frequently used keywords in articles about tracheostomy

Keywords	Number of uses	Keywords	Number of uses
Tracheostomy	1282	Pediatric tracheostomy	41
Tracheotomy	317	Airway obstruction	39
Complication (s)	237	Aspiration	34
Mechanical ventilation	175	Surgical tracheostomy	34
Percutaneous tracheostomy	129	Intubation	33
Intensive care unit (s) (ICU)	127	Quality of life	33
Pediatric (s)	108	Ventilation	31
COVID-19	104	Dysphagia	30
Child / children	89	Percutaneous dilational tracheostomy	30
Decannulation	86	Safety	29
Outcome (s)	86	Trauma	29
Percutaneous dilatational tracheostomy	79	Endoscopy	25
Intensive care	78	Surgery	25
Airway management	64	Trachea	25
Critical care	64	Deglutition	24
Tracheal stenosis	63	Percutaneous tracheotomy	24
Airway	61	Amyotrophic lateral sclerosis	23
Percutaneous	61	Early tracheostomy	23
Mortality	56	Prolonged mechanical ventilation	23
Bronchoscopy	52	Quality improvement	22
Tracheostomy tube	50	Stroke	22
Weaning	50	Communication	21
Respiratory failure	46	Speaking valve	20
Laryngectomy	45	Timing	20
Sars-cov-2	44	Tracheostoma	20

DISCUSSION

Between 1980 and 1995, in each year the number of published articles on tracheostomy were between 0 and 50 (the average 34). Between 1996 and 2008, the number of articles was 50-100 (average 72). In 2009, the number of articles exceeded 100 and an average of 130 articles were published between 2009 and 2018. A remarkable upward trend was seen in 2019 and 2020, with 212 articles published in 2019 and 325 articles in 2020. When the Exponential Triple Smoothing forecast results are evaluated, it is seen that the number of articles will show an increasing trend.

The significant increase in the number of publications on tracheostomy in 2020 reveals the effect of the COVID-19 pandemic on respiratory failure. Tracheostomy is a frequently performed technique in critically ill patients who require long mechanical ventilation for acute respiratory failure and airway problems (1-3). The need for prolonged ventilation is frequently encountered, especially in COVID-19 patients hospitalized in intensive care (22-24). This bibliometric study reveals that the number of publications on tracheostomy has increased with the increase in COVID-19 cases. This shows that the number of patients who performed tracheostomy has increased with COVID-19.

When the distribution of countries' publications is examined, 16 of the first 20 are most active in article productivity on tracheostomy. These countries are also developed countries, while the other four (India, Turkey, China, Brazil) are developing countries. However, these four countries have relatively large economies. According to the results of the correlation analysis; a highly significant correlation was found between article productivity and economic development indicators. This shows that the economic development of the countries is effective in its productivity. The bibliometric studies carried out on some medical subjects in the literature also stated that economic development is effective in article productivity, similar to our results (5,6,25).

When the International Collaboration Density map based on total link strength scores (**Figure 2a**) was evaluated, the countries with the most intensive cooperation were determined as USA, UK, Italy, Germany, Canada, Australia, Spain, France, Ireland, Switzerland, Belgium, Brazil, Chile, Argentina, Colombia, Venezuela. When the co-authorship cooperation of the countries is examined, it is seen that the collaborations according to the geographical locations of the countries are effective in the production of articles (Germany, Italy, Austria, Netherlands, Czech Republic), (France, Belgium, Switzerland), (Brazil, Argentina, Venezuela, Colombia,

Chile), and (Egypt, Saudi Arabia, United Arab Emirates, Pakistan, India). On the other hand, among the countries that are in the same clusters but do not have geographical proximity (USA, China, Turkey), (Canada, Japan), etc. joint works have been done. Some studies in the literature have stated that geographical proximity is primarily effective in international cooperation (9,10).

The journals that publish the most articles on tracheostomy are Laryngoscope, International Journal of Pediatric Otorhinolaryngology, Otolaryngology-Head and Neck Surgery, Journal of Laryngology and Otology, Respiratory Care, Chest, Annals of Otology Rhinology and Laryngology, Critical Care Medicine, Head and Neck - Journal for the Sciences and Specialties of the Head and Neck, and European Archives of Oto-Rhino-Laryngology. We can suggest that authors who want to publish articles related to tracheostomy can consider these journals.

When the citation analyses of the journals are evaluated, the most effective journals according to the average number of citations per article are Chest, Critical Care Medicine, Journal of Trauma-Injury Infection and Critical Care, Intensive Care Medicine, Critical Care, Pediatrics, Journal of Pediatric Surgery, Annals of Thoracic Surgery, Anesthesia and Analgesia, Clinics in Chest Medicine, and Anaesthesia. We can suggest that researchers who want their articles to be cited more can consider these journals.

According to the total citation count, the average number of citations per year, and the most co-citations numbers; we can suggest that researchers can read the following articles; Stauffer et al. (2), Ciaglia et al. (3), Rumbak et al. (15), Bach et al. (16), Guilleminault et al. (17), McGrath et al. (18), Angel et al. (19), Young et al. (20), Martin-Villares et al. (21), Griggs et al. (26), Freeman et al. (27), Griffiths et al. (28), Hazard et al. (29), Delaney et al. (30).

When the keyword analysis findings are evaluated; the cluster analysis reveals that tracheostomy subjects were divided into 7 different clusters. These clusters are; red (related to pediatric), blue (related to complications), green (related to ventilation), yellow (related to tracheostomy tube), orange (percutaneous tracheostomy), purple (related to COVID-19), and turquoise (related to respiratory insufficiency).

The most cited keywords were intensive care unit, surgical tracheostomy, percutaneous dilational tracheostomy, outcomes, survival, intubation, pediatric tracheotomy, respiration, artificial, indications, and cough. According to trend topics analysis, the keywords studied in recent years are COVID-19, Coronavirus, Sars-Cov-2, pandemic, personal protective equipment, quality improvement, patient safety, education, simulation, head and neck surgery, otolaryngology, traumatic brain injury, and morbidity.

Our bibliometric study has identified the most popular studies, authors, and journals on tracheostomy. Thus, clinicians can have the opportunity to research tracheostomy more quickly and practically. Additionally, this bibliometric study can guide researchers for new articles on tracheostomy by highlighting the points they can focus on.

This study showed that the need for tracheostomy may increase in epidemics that may cause respiratory failure such as clinically COVID-19. Therefore, similar bibliometric analyzes on various pandemics and epidemics can guide clinicians in their approaches to diseases and make a serious contribution to the management of diseases.

As a result of the literature review on tracheostomy, we could not find any bibliometric study. It can be said that this comprehensive study we have done on this subject is the first bibliometric research. Only the WoS database was used in the literature review of our study. Pubmed database was not preferred because citation and co-citation analyzes could not be performed. Scopus database was not preferred, because the database includes journals with low impact levels. The reason why the WoS database is preferred is that Wos indexes the articles published in journals with higher impact factors than the other databases and comprehensive citation analyzes can be performed (10). In recent years, WoS has been preferred more in bibliometric analyzes (7-13). Additionally, if more than one database is used, the same articles in different databases can be included in the analysis more than once, therefore reliability can decrease.

CONCLUSION

This comprehensive bibliometric study on tracheostomy summarizes 3573 articles published between 1980 and 2021. There is an increasing trend in the number of articles following the COVID-19 pandemic. The trend topics in tracheostomy research are COVID-19, Coronavirus, Sars-Cov-2, pandemic, personal protective equipment, quality improvement, patient safety, education, simulation, head and neck surgery, otolaryngology, traumatic brain injury, and morbidity. This study showed that the need for tracheostomy may increase in pandemics such as COVID-19 which cause respiratory failure.

The tracheostomy technique has been applied for many years, as a result, the developments that have occurred over the years have led to different studies on tracheostomy. This article, summarizing the literature history on tracheostomy, can be a useful resource for clinicians and scientists.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval is not required in this bibliometric study.

Informed Consent: Informed Consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Serum albumin and C-reactive protein/albumin ratio in community-acquired pneumonia

Toplum kökenli pnömönide serum albümin ve CRP/albümin oranının hastalık seyrine etkisi

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ABSTRACT

Introduction: Community-acquired pneumonia (CAP) is a common type of respiratory tract infections with high morbidity and mortality. Prognostic role of CRP/Albumin ratio in CAP patients still is unknown. The aim of this study was to investigate the role the CRP/albumin ratio in predicting 30-day mortality and ICU requirement in hospitalized patients with CAP.

Material and Method: The study included patients with CAP.Clinical records and plain radiographic images of the patients were retrieved from hospital database and were reviewed for each patient.

Results: The 179 CAP patients who were hospitalized were included. CRP level and the CRP/albumin ratio were found to have no significant effect on mortality and ICU requirement (p=0.728, p=0.232, and p=0.110, respectively), whereas low albumin level was associated with high mortality and ICU requirement (p<0.001 for both).

Conclusion: Increased albumin concentration was associated with a lower risk of 30-day mortality. The CRP/albumin ratio was found to have no significant role in predicting short-term mortality and morbidity in CAP patients. Further large-scale, multicenter studies are needed to investigate the prognostic value of the CRP/albumin ratio in predicting long-term prognosis in CAP patients.

Keywords: Community-acquired pneumonia, biomarkers, mortality, prognosis

ÖZ

Amaç: Toplum kökenli pnömöni (TKP) solunum yolu enfeksiyonları içinde yüksek mortalite ve morbiditeye sahiptir. Tanı, tedavi, prognoz takibinde çeşitli biokimyasal markerlar kullanılmaktadır. CRP, albümin rutin uygulamada sıklıkla kullanılan biokimyasal markerlardır. İnflamasyon temellli CRP/albümin oranı çeşitli hastalıklarda prognoz tahmininde kullanılmaktadır. Bu çalışmanın amacı TKP nedeniyle hastaneye yatırılan CRP/albümin oranının 30 günlük mortalite tahminindeki rolünü belirlemekti. Çalışmanın ikincil sonlanım noktası ise yoğun bakım ihtiyacı idi.

Gereç ve Yöntem: Göğüs hastalıkları ve yoğun bakım servisine yatırılan TKP'li hastalar çalışmaya dahil edildi. Retrospektif olarak hasta dosyaları, radyolojik incelemeleri ve laboratuvar bulguları tarandı.

Bulgular: Yüz (%55,9)'ü göğüs hastalıkları servisinde 79'u yoğun bakımda yatmakta olan 179 TKP'li hasta çalışmaya dahil edildi. Hastaların yaş ortalaması 72,027±12,88 yıldı; %61,5'i erkek, %38,5'i kadındı. CRP değeri ve CRP/albümin oranı 30 günlük mortalite ve yoğun bakım ihtiyacını tahmin etmede anlamlı bulunmazken (sırasıyla p:0,728, p:0,232, p:0,110), düşük albümin değerlerinin mortalite ve yoğun bakım ihtiyacı riskini anlamlı derecede artırdığı bulundu (p<0,001, p<0,001). CURB-65, PSI ve albümin 30 günlük mortalite ve yoğun bakım ihtiyacını tespit etmede anlamlı bulunan değişkenlerdir.

Sonuç: Albümin değerinin yüksek olması TKP'de 30 günlük mortalite ve yoğun bakım ihtiyacı riskini azaltmaktadır. CRP, CRP/albümin oranının TKP'de kısa dönem mortalite ve morbiditeyi tahmin edememektedir. TKP'li hastalarda serum albümin, CRP düzeyleri ve CRP/albümin oranının uzun dönem prognozu tahmin gücünü ortaya koymak için geniş kohortlarda, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Toplum kökenli pnömöni, biyomarkerlar, mortalite, prognoz

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INTRODUCTION

Community-acquired pneumonia (CAP) is a common type of respiratory tract infections with high morbidity and mortality. CAPis acquired in the community during daily life activities.Chest radiography is commonly used in the diagnosis of CAP patients,often supported bybiochemical parameters such as C-reactive protein (CRP) which is an acute phase protein produced by liver (1,2).

In infection, the decreased albumin synthesis from livermay alter the pharmacokinetic effects of antimicrobial therapies, thereby leading to decreased achievement of pharmacodynamic targets for antimicrobial agents, ultimately resulting in suboptimal treatment. On the other hand, albumin level has also been associated with mortality in diseases including CAP (3,4). CRP/albumin ratio, as a novel parameter, has been shown to be more accurate than albumin and CRP alone in predicting overall prognosis of certain clinical conditions (5,6).

The present study was designed to investigate the role of CRP and albumin levels and the CRP/albumin ratio in predicting 30-day mortality and the requirement of intensive care unit (ICU) admission in hospitalized patients with CAP.

MATERIAL AND METHOD

The retrospective study included a total of 179 patients diagnosed with CAP that were followed up in ICU and in inpatient clinic between 2012 and 2018. This study approved by Ufuk University Non-Interventional Clinical Researches Ethics Committee (Date: 07.03.2019, Decision No: 20190703/10).

Clinical records and plain radiographic images of the patients were retrieved from hospital database. Patients that were grouped based on the Confusion Urea Respiratory Rate Blood Pressure-65 (CURB-65) and pneumonia severity index (PSI) scores, clinically and radiologically diagnosed with CAP, initiated on a therapy based on national or international guidelines, and were followed up for a minimum of one month, and patients that underwent chest radiography within the first 24 h after admission, underwent complete blood count and biochemical analysis including CRP and albumin were included to the study (1,7-9).The guidelines recommend ICU admission in the presence of at least one major criterion or three minor criteria (7-9).Exclusion criteria were as follows: <18 years, pregnancy, active infection other than CAP, hospital-acquired pneumonia and ventilator-associated pneumonia, myocardial infarction, chronic kidney disease, malignancies, a history of connective tissue disease, and immunosuppressive drug use within one month. Based on the chest radiographs, the patients were divided as having bilateral, unilateral, reticular,and bronchoalveolar infiltration. For the patients hospitalized in ICU, the Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores and the predicted mortality rates were recorded retrospectively (10).Based on arterial blood gas analysis at room air performed on admission, patients with partial pressure of oxygen (PaO_2) <60 mmHg and partial pressure of carbon dioxide ($PaCO_2$) <45 mmHg were accepted as hypoxic and patients with PaO_2<60 mmHg and $PaCO_2$>45 mmHg were accepted ashaving hypercapnic respiratory failure. CRP and albumin levels were measured spectrophotometrically using an Abbott Architect C8000 apparatus. The normal reference ranges used for CRP and albumin levels were 0.01-5 mg/L and 2.5-5 g/dL, respectively.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows version 23.0 (IBM SPSS Inc., Armonk, NY, USA). Descriptives were expressed as frequencies, percentages, mean±standard deviation (SD), and median (minimum-maximum). Normal distribution of data was tested using Kolmogorov-Smirnov and Shapiro Wilk tests. Homogeneity of variances was tested by Levene's test. Continuous variables were compared using Student's t-test or Mann-Whitney U test and categorical variables were compared using Chi-square test. Correlations between variables were determined using Spearman's Rank Correlation Coefficient. Univariate and multivariate analyses of logistic regression were performed to determine the factors affecting ICU requirement, and mortality ROC curves were constructed to compare the diagnostic values of parameters including CRP/albumin ratio, PSI, CURB-65, APACHE II, predicted mortality rate, and ICU requirement. Sensitivity, specificity and area under the ROC curve (AUC) were determined based on 95% confidence interval (CI). A p value of <0.05 was considered significant.

RESULTS

The patients included 110 (61.5%) men and 69 (38.5%) women with a mean age of 72.027±12.88 years.Of these, 131 (73.2%) patients were present with comorbidities. **Table 1** presents the demographic characteristics of the patients.

All the patients (100%) had hypoxic respiratory failure and 32 (17.9%) patients had hypercapnic respiratory failure. The one-month mortality rate was 31.3%. **Table 2** presents the radiological findings, lengths of ICU stay,

mortality rates, and CURB-65 and PSI scores. In the 79 patients admitted to ICU, mean APACHE-II score was 28.25±6.73and the mean predicted mortality rate was 60.96%±21.19%.

The CRP level was higher in 176 (98.3%) and lower in 3 (1.7%) patients compared to the normal range. The albumin level was normal in 127 (70.9%) and higher in 52 (29.1%) patients compared to the normal range. Mean CRP and albumin levels were 111.18±95.32 mg/L and 2.9±0.69 g/L, respectively, and the mean CRP/albumin ratio was 42.29±39.8. In the multivariate logistic regression analysis, PSI, CURB-65, and serum albumin level were found to be effective factors for mortality and ICU requirement (**Table 3**).

In the ROC analysis, PSI score, CURB-65 score, and albumin level were found to be significant predictors of mortality and ICU requirement ($p<0.001$ for both) (**Figure 1, 2**) and increased albumin level were found to be protective factors for mortality and ICU requirement. However, the CRP/albumin ratio was found to have no significant effect on mortality and ICU requirement ($p=0.232$ and $p=0.110$, respectively).

The CRP/albumin ratio was significantly lower in PSI I-III patients compared to PSI IV-V patients (33.84±32.35 vs. 49.132 ±43.911;$p=0.014$); however, no significant difference was found between patients with a CURB-65 score ≤2 and >2 with regard to the CRP/albumin ratio (40.244±34.937 vs. 43.186±41.832; $p=0.883$). On the other hand, the CRP/albumin ratio was significantly higher in patients detected with bilateral infiltrates compared to patients detected with unilateral infiltrates on chest radiography (51.863±42.896 vs. 36.438±36.766;$p=0.007$).In contrast, no significant difference was found between patients with reticular infiltrates compared to patients bronchoalveolar infiltrates with regard to the CRP/albumin ratio (43.488±41.587 and 41.620± 38.921, respectively) ($p=0.935$).

Table 1. Demographic characteristics of the study group

Age (years)	**Mean±SD**	**Median (D.Gen)**	**N**
	72.027±12.88	75 (74)	179
Variables		**N**	**%**
Gender	Male	110	61.5
	Female	69	38.5
Comorbidities	No	48	26.8
	Yes	131	73.2
COPD	No	117	65.4
	Yes	62	34.6
DM	No	137	76.5
	Yes	42	23.5
CAD	No	136	76
	Yes	43	24
CKD	No	168	65.4
	Yes	11	6.1

COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CAD: Coronary artery disease, CKD: Chronic kidney disease

Table 2. Clinical characteristics of the patients

Variables		**N**	**%**
CURB-65	2	54	30.2
	3	75	41.9
	4	32	17.9
	5	18	10.1
PSI	2	23	12.8
	3	57	31.8
	4	55	30.7
	5	44	24.6
ICU admission	No	100	55.9
	Yes	79	44.1
Mortality	No	123	68.7
	Yes	56	31.3
Infiltration	Unilateral	111	62
	Bilateral	65	38
Infiltration type	Bronchoalveolar	114	63.7
	Reticular	65	36.3
NIV	No	147	82.1
	Yes	32	17.9
IMV	No	109	60.9
	Yes	70	39.1
WBC	Normal	66	37.9
	High	108	62.1
HB/HCT	Low	69	38.5
	Normal	101	56.4
	High	0	5
Creatinine	Low	0	0
	Normal	139	77.7
	High	40	22.3
BUN	Low	0	0
	Normal	139	77.7
	High	40	22.3

NIV: Noninvasive ventilation, IMV: Invasive mechanical ventilation, ICU: Intensive care unit, CURB-65: Confusion Urea Respiratory Rate Blood Pressure-65, PSI: Pneumonia Severity Index, WBC: White blood cell, BUN: Blood urea nitrogen, HB: Hemoglobin, HCT: Hematocrit

Table 3. Multivariate analysis of factors affecting 30-day mortality (I) and ICU requirement (II)

Variables	**B**		**Standard Error**		**O.R.**		**95% CI**				**p**	
							Lower bound		**Upper bound**			
	I	**II**	**I**	**II**	**I**	**II**	**I**	**II**	**I**	**II**	**I**	**II**
PSI score												
(3)	-0.978	0.086	1.344	1.199	0.376	1.090	0.027	0.104	5.236	11.437	0.467	0.943
(4)	1.192	1.818	1.200	1.151	3.294	6.158	0.313	0.645	34.626	58.786	0.321	0.114
(5)	4.127	4.127	1.307	1.557	11.543	62.009	1.010	2.930	149.638	1312.130	0.041	0.008
CURB-65 score												
(3)	1.086	1.086	0.887	0.657	3.587	2.964	0.631	0.817	20.405	10.747	0.150	0.098
(4)	2.697	2.697	0.977	0.921	14.120	14.837	2.079	2.441	95.887	90.185	0.007	0.003
(5)	1.504	1.504	1.199	1.623	12.520	4.502	1.193	0.187	131.390	108.378	0.035	0.354
Albumin*	1.177	1.177	0.323	0.459	4.694	3.246	2.493	1.319	8.849	8.000	<0.001	0.010

PSI:Pneumonia Severity Index, CURB-65: Confusion Urea Respiratory Rate Blood Pressure-65, ICU: Intensive care unit, *Albumin was found to be a protective factor. Lower albumin levels indicate a higher risk.

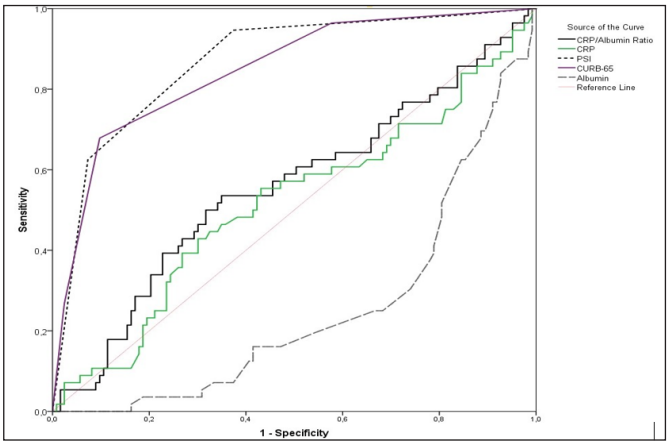

Figure 1. Predictive value of CRP/albumin ratio, PSI, CURB-65, CRP, and albumin for mortality

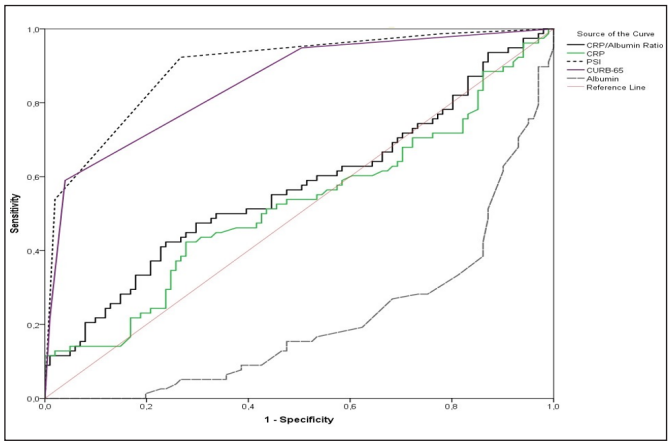

Figure 2. Predictive value of CRP/albumin ratio, PSI, CURB-65, CRP, and albumin for ICU requirement

DISCUSSION

CAP is a significant cause of mortality and morbidity. Despite the recent advancements in treatment methods, CAP still has high complication and mortality rates (8). Similarly, despite optimal treatments, the 30-day mortality rate is 10-12% (11). In the present study, the patients had a higher mortality rate (31.3%) compared to those reported in the literature, which could be attributed to the inclusion of patients hospitalized in both the general ward and ICU and to the high mean age of the patients.

The severity of CAP can be assessed by numerous scoring systems such as PSI and CURB-65 and also by inflammatory markers including CRP, PCT, and albumin (1,12). CRP and albumin, in particular, are commonly used in the evaluation of critical patients (13).

Serum albumin level which is a sensitive indicator of patients' nutritional status is closely associated with mortality in infection-related diseases (14). In the elderly population, low albumin levels on admission are associated with high mortality (15).Charles et al. (16) reported that albumin level was an independent risk factor for vasopressor support and mechanical ventilation and ICU requirement. Another study found that hypoalbuminemia was a significant predictor of mortality in patients with sepsis and septic shock associated with CAP (14). Similarly, in our study, increased serum albumin level was found to be a protective factor for mortality and ICU requirement ($p<0.01$ for both).

In the presence of an infection or inflammation, CRP level increases by about 6 h and peaks at around 48 h (2,17-18). In CAP patients, however, the prognostic value of serum CRP level remains controversial. Lee et al. (12) found that CRP and albumin were independently associated with 28-day mortality when combined with a PSI score >3. Charles et al. (16) found that the failure of CRP to fall by 50% or more within 4 days of admission was an independent risk factor for worse outcomes. Similarly, Nair et al. (19) found a significant association betweena decrease of less than 25% in CRP levels at the second day and mortality in hospitalized patients with severe CAP.

On the other hand, Lee et al. (12) also noted that baseline CRP and albumin levels were significant independent factors for 28-day mortality and that low albumin and high CRP levels were associated with high mortality in hospitalized patients with severe CAP. In our study, although baseline CRP level was not found as a significant factor for predicting mortality and ICU requirement, baseline albumin level had a significant prognostic value in hospitalized patients with CAP, as consistent with the study by Lee et al. (12). This finding could be attributed to the fact the CRP levels in our patients were measured only within the first 24 h after admission and, unlike in previous studies, no serial measurement was performed (2,12,19).

Literature indicates that CRP, albumin, or CRP/albumin ratio can be used as a useful prognostic factor for inflammatory or nutritional status and the CRP/albumin ratio, in particular, can be a strong indicator of inflammatory response (17). A previous study evaluated patients admitted to the emergency department who were older than 65 years and reported that high-sensitivity CRP/albumin ratio was associated with all-cause mortality. Although the authors did not evaluate the scores, changes in mental state, and vital findings of the patients, the causes of mortality were examined in detail (15). Another study evaluated patients admitted to ICU and found that the CRP/albumin ratio was an independent risk factor for 30-day and 12-month mortality. In the same study, the cut-off values for 30-day and 12-month mortality were 1.58 and 1.75, respectively (13). Kim et al. (14) evaluated patients with sepsis and septic shock and suggested that the CRP/albumin ratio could be used for predicting 3-month mortality. The

authors calculated the CRP/albumin ratio based on serially measured CRP levels (14). The present study is the first study in the literature to investigate the prognostic value of the CRP/albumin ratio and to show that baseline CRP/albumin levels are not significant predictors of one-month mortality and ICU requirement in hospitalized patients with CAP. Nevertheless, we could not compare this finding with literature data since, to the best of our knowledge, there has been no study investigating the prognostic value of CRP/albumin ratio for mortality in CAP patients. It is commonly known that there is no standard time interval for the measurement of albumin levels and a single measurement is often adequate for the analysis. However, it is recommended that CRP levels should be measured at appropriate time intervals by serial measurements. In our study, the CRP/albumin ratio was found to have no significant prognostic value for mortality in CAP patients, which could be attributed to the single measurement of CRP levels performed within the first 24 h after admission.

Both PSI and CURB-65 scores are used in the treatment and management of CAP, particularly in making decisions related to outpatient, inpatient, and ICU hospitalization and predicting disease severity and prognosis. In both of these scoring systems, higher scores indicate increased mortality and disease severity (20). Literature also indicates that these two methods have a role in predicting short-term mortality in CAP patients (21). In the study by Lee et al. (12), the CRP/albumin ratio was correlated with PSI scores in predicting mortality although it showed no correlation with CURB-65 scores. Similarly, in our study, no significant difference was found between the patients with low and high CURB-65 scores with regard to the CRP/albumin ratio although the CRP/albumin ratio was significantly higher in patients with high PSI scores compared to patients with low PSI scores.

Pneumonia may present with a wide variety of radiological patterns on chest radiography (22,23). A previous study evaluated the radiological features of CAP and detected alveolar opacities, interstitial opacities, and borderline diffuse infiltrates. This wide variety of features was attributed to advanced age of the patients and the underlying chronic cardiorespiratory diseases (21). Additionally, it is also suggested that the radiological pattern of CAP may vary according to the cause of pneumonia (24, 25).In the present study, all the radiographic examinations were performed by a chest specialist (D.H). However, as the study had a retrospective design, no microbiological sampling that could lead to differences was performed during radiographic examinations. On the other hand, the CRP/albumin ratio was significantly higher in patients that were radiologically detected with bilateral infiltrates, which could be ascribed to the greater number of ICU patients with high APACHE-II scores.

Our study was limited in several ways. First, clinical data of patients were retrieved from electronic databases as the study had a retrospective design. Second, the results of the study may not represent all the CAP patients as the study was a single-center study and only included hospitalized patients. Third, no information was available regarding the specific causes of death in the nonsurviving patients and the mortality records were limited to a one-month period. Finally, no analysis was performed for microbiological factors that could have a significant role in the severity of pneumonia.

CONCLUSION

The CAP that requires hospitalization or ICU admission is a significant cause of morbidity and mortality. In the present study, albumin level as well as PSI and CURB-65 scores had a significant predictive value for mortality and ICU requirement in CAP patients while CRP and the CRP/albumin ratio had no significant role in predicting the prognosis. Further prospective, multicenter studies performing microbiological analyses and serial CRP measurements are needed to investigate the prognostic value of the CRP/albumin ratio in predicting long-term prognosis in CAP patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Ufuk University Non-Interventional Clinical Research approved by the Ethics Committee (Date: 07.03.2019, Decision No: 20190703/10).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review / Derleme

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Systemic sclerosis related interstitial lung disease and nintedanib

Sistemik skleroz ilişkili interstisyel akciğer hastalığı ve nintedanib

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ABSTRACT

Although many mechanisms leading to lung fibrosis in systemic sclerosis-associated interstitial lung disease (SSc-ILD) have been suggested, this issue has not been fully understood yet. Recently, there has been increased evidence that the mediators and pathological mechanisms responsible for idiopathic pulmonary fibrosis (IPF) are similar to those in SSc-ILD. Accordingly, studies have been conducted to support that antifibrotic agents used in the treatment of IPF may also be useful in SSc-ILD. There are currently two antifibrotic agents on the market, namely nintedanib and pirfenidon. Although studies on the use of pirfenidone in SSc-ILD are not satisfactory, nintedanib studies have yielded positive results. The SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) study is the first and most comprehensive Phase III study on this subject. In 2019, the results of SENSCIS trial showed that, nintedanib significantly reduced the annual decline in lung function in SSc-ILD. After this trial, which did not include SSc-ILD patients with severe lung function loss, nintedanib licenced for the treatment of SSc-ILD worldwide. However, the currently available literature data lacks information about long-term effects and side effects of nintedanibe on SSc-ILD an also about the advanced SSc-ILD. The aim of this study is to review SSc-ILD patients treated with nintedanib, by also mentioning the pathogenesis of this disease according to the current literature.

Keywords: Sistemik skleroz, nintedanib, akciğer, fibrozis

ÖZ

Sistemik skleroz ile ilişkili interstisyel akciğer hastalığında (SSc-İAH) akciğer fibrozisine yol açan birçok mekanizma öne sürülmesine rağmen, bu konu henüz tam olarak anlaşılamamıştır. Son zamanlarda, idiyopatik pulmoner fibrozdan (İPF) sorumlu aracıların ve patolojik mekanizmaların SSc-İAH'dekilere benzer olduğuna dair kanıtlar artmıştır. Buna göre, İPF tedavisinde kullanılan antifibrotik ajanların SSc-İLD'de de faydalı olabileceğini destekleyen çalışmalar mevcuttur. Şu anda piyasada nintedanib ve pirfenidon olmak üzere iki antifibrotik ajan bulunmaktadır. SSc-İAH'de pirfenidon kullanımına ilişkin çalışmalar tatmin edici olmasa da, nintedanib çalışmaları olumlu sonuçlar vermiştir. SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) çalışması bu konudaki ilk ve en kapsamlı Faz III çalışmasıdır 2019'da SENSCIS çalışmasının sonuçları, nintedanib'in SSc-İAH'de akciğer fonksiyonundaki yıllık düşüşü önemli ölçüde azalttığını göstermiştir. Şiddetli akciğer fonksiyon kaybı olan SSc-İAH hastalarını içermeyen bu çalışmadan sonra, nintedanib dünya çapında SSc-İAH tedavisi için lisans almıştır. Bununla birlikte, şu anda mevcut olan literatür verileri, nintedanibin SSc-İAH üzerindeki uzun vadeli etkileri ve yan etkileri ve ayrıca ileri evre SSc-İAH üzerine etkilerinden yoksundur. Bu çalışmanın amacı, SSc-İAH'de nintedanib kullanımını güncel literatür eşliğinde, bu hastalığın patogenezinden de bahsederek gözden geçirmektir.

Anahtar Kelimeler: Sistemik skleroz, nintedanib, akciğer, fibrozis

INTRODUCTION

Systemic sclerosis (SSc) is a rarely seen connective tissue disease causing fibrosis of various internal organs, including kidneys, heart, lungs, musculoskeletal system and gastrointestinal tract and skin (1,2). Interstitial lung disease (ILD), develops in approximately 50% of patients within five years of being diagnosed with SSc (3). The high mortality rate is the reason, why many randomized controlled trials (RCTs) have been performed for the management of the disease in SSc-associated interstitial lung disease (SSc-ILD) patient group (4).

Evidence-based therapies used in clinical practice are immunomodulatory drugs such as mycophenolate mofetil (MMF) and cyclophosphamide (CYC) (4,5).

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Despite immunomodulatory therapy, SSc-ILDs may show rapid deterioration of lung function, termed as 'progressive fibrotic phenotype'.

The widespread use of nintedanib to treat a similar fibrotic condition as idiopathic pulmonary fibrosis (IPF) has led to increased interest in exploring its role in SSc-ILD. The use of nintedanib treatment seems beneficial in this patient group resistant to immunomodulatory therapy.

Since the use of nintedanib in SSc-ILD is a current issue, we reviewed the literature on this subject. We searched in PubMed database to find relevant studies for our review. The literature search was conducted on March 12, 2022 and the keywords "systemic sclerosis AND scleroderma AND nintedanib were searched in titles and abstracts. First we found 35 results and the first study was published in 2015. Most of the articles were published after 2019. This is likely because the SENSCIS study was resulted in 2019. We selected 20 articles from the search results which were relevant to our review topic.

PATHOGENESIS OF FIBROSIS IN SSC-ILD

It is believed that, all ILDs are triggered by recurrent chronic vascular or epithelial injuries, or by granulomatous inflammation, which causing to cell destruction and in the case of fibrotic disease, to unregulated repair (6,7). Recurren micro-injuries causes damage of alveolar epithelium and basement membrane as a result cells in this area, causes the secretion of proinflammatory cytokines and chemokines such as TNF-α (tumor necrosis factor-alpha), IL-1 (interleukin-1) and MCP-1 (monocyte chemoattractant protein-1). These secreted mediators located in the interstitium or migrate here from the circulation activating other cells, especially fibroblasts, causes continued tissue damage (8,9). Fibroblasts are the keystone cells in fibrosing ILDs and attack the injury site from different areas.

DIFFERENCES OF PATHOGENESIS BETWEEN SSC-ILD AND IPF

Although pathogenesis of fibrosis basically similar in SSc-ILD and IPF, there are some differences. For example in SSc-ILD endothelium is the first to be damaged, while epithelial damage develops later. On the other hand, in IPF damage begins in the epithelium first. Immune dysregulation which develops following the epithelial and/or endothelial damage is, more prominent in SSc-ILD. In the last stage of pathogenesis, fibroblast activation and increased extracellular matrix production occurs in both IPF and SSc-ILD. Transformation of cells such as epithelium, endothelium, pericyte, adipocyte, into fibroblastic cells, and transformation of cells into myofibroblasts is similar in both diseases. MUC1 and KL-6 (Krebs von den Lungen-6) are markers of epithelial damage and correlate with the degree of lung fibrosis. The factors responsible for epithelial damage are genetic predisposition and environmental factors (smoking, aspiration, infections). The effect of smoking as a triggering agent in IPF is more pronounced, while, gastro-oesophageal reflux degree was associated with the degree of fibrosis in SSc-ILD. In pathogenesis, following epithelial and/or endothelial damage, the resulting immune dysregulation is more prominent in SSc-ILD. However, since the role of inflammatory cells in IPF is limited, inflammatory process active in SSc-ILD targeted therapies do not show efficacy in IPF.

Despite the fact that the pathophysiology mechanism of fibrosis in SSc-ILD is not well known, clinical trials have shown that nintedanib, an antifibrotic agent seems to inhibit this fibrotic process.

Nintedanib

Nintedanib is a potent inhibitor of intracellular tyrosine kinase and targets the Vascular endothelial growth factor (VEGF), Platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) receptors (10). It was first used as a cancer drug. Because of its potential to slow down and perhaps inhibit the fibrosis process, it was studied to reduce respiratory pulmonary function decline, reduce exacerbations, and improve quality of life in patients with IPF (11). The pathophysiology of IPF causing pulmonary fibrosis is very similar to that of SSc-ILD.

In these diseases, fibrotic cascade begins with epithelial and/or endothelial cell damage and cell death (12). Also, the final common pathway causing lung fibrosis in IPF and SSc-ILD is believed to be occured by the recruitment and activation of myofibroblasts caused by aberrant transformation growth factor-beta (TGF-B) signaling (12). Consequently, myofibroblasts, which are specialized fibroblasts, cause fibrosis in both IPF and SSc-ILD through excessive extracellular matrix deposition (13).

Nintedanib experience in SSc-ILD: first case report

In 2018 the first case report demonstrating the clinical benefit of nintedanib in a patient with SSc-ILD published by Duarte et al. (14). This female patient was diagnosed with SSc at the age of 41 and ILD developed within seven years. Unfortunately, immunosuppressive agents could not prevent progression in lung fibrosis. Nintedanib treatment, which was only indicated for IPF at that time, was started at a dose of 2X150 mg/day with the consent of the patient. One year after starting nintedanib, the need for supplemental oxygen therapy was decreased, forced vital capacity (FVC) was slightly increased and the patient was clinically improved.

SENSCIS TRIAL: FIRST RANDOMIZED CLINICAL TRIAL IN SSC-ILD

In 2019 the results of the SENSCIS (ClinicalTrials.gov identifier: NCT02597933) trial were announced. This was a double-blinded, large-scale, phase III randomized clinical trial. A total of 576 patients (placebo 288, nintedanib 288) from 32 countries participated to this study. Fibrosis over 10% on high-resolution computed tomographic (HRCT) scan was accepted as ILD. Patients with mild or moderate ILD, whose diffusing lung capacity for carbon monoxide (DLCO) over than 30% and FVC was over than 40% of the predicted value were included to the study. The primary end-point of the trial was the yearly decline of FVC, which was assessed over 52 weeks. At the end of 52 weeks, the primary end-point analysis showed that the annual decline of FVC was 93.3 mL in placebo group and 52.4 mL in nintedanib group.

The most common adverse event in placebo and nintedanib group was non-severe diarrhea (75.7% vs 31.6%), that occurs within the first 3 months of treatment. Most patients were treated symptomatically, although some patients required temporary discontinuation and/or dose reduction of the drug. Elevations in aspartate aminotransferase, alanine aminotransferase level, to at least three times the upper limit of the normal range, were reported in 0.7% of patients in the placebo group and 4.9% of patients in the nintedanib group. There wasn't any difference between the placebo and nintedanib groups in terms of newly developing digital ulcers (DU). Because these results were statistically significant, nintedanib was approved as the first drug to slow the decline in respiratory function in SSc-ILD patients (15).

Subgroup Analyse of SENSCIS in Asians

In 2021 Azuma et al. (16) examined the subgroup analysis of the SENSCIS trial in Asian race. They compared the non-Asians (placebo 207, nintedanib 226) with Asians (placebo 81, nintedanib 62). FVC decline over 52 weeks was similar between non-Asian and Asian patients both in the placebo group, (-99.9 mL versus -90.6 mL) and in the nintedanib group (-39.0 mL vs - 44.3 mL). The most common side effect was diarrhea and was reported with similar frequency of non-Asians and Asians; in the placebo group (32.9% vs 28.4%) and nintedanib group (74.3% vs 80.6%).

As a result, this study also proved that, nintedanib showed significant benefit in slowing progression of SSc-ILD in non-Asians and Asians with a similar adverse event profile.

Subgroup Analyse of SENSCIS in Japanese

In 2021 Kuwanaa et al. (17) examined the subgroup analysis of the SENSCIS trial in Japanese patients with SSc-ILD. They compared the non-Japanese (placebo 252, nintedanib 254) with japanese (placebo 36, nintedanib 34). FVC decline over 52 weeks in Japanese patients was similar between placebo and nintedanib group (-90.9 mL versus -86.2 mL). For non-Japanese patients annual FVC decline in placebo group was higher than nintedanib group (-93.6 mL vs 47.9 mL). In the nintedanib group, asymptomatic liver enzym elevations were reported in 6 patients. Diarrhea was reported in 28 patients in the nintedanib group. But none of them were serious. In placebo group mild diarrhea reported in 11 patients. Although skin ulcers reported as adverse events were more frequent in the nintedanib group than in the placebo group (8 vs 3), the number of patients in each group were rare overall.

UNANSWERED QUESTIONS

Pneumothorax and Nintedanib

Pneumothorax has not been reported in SENSCIS trial. However, this clinical trial was conducted in patients with relatively good lung function. Data in the literatüre on the use of nintedanib in severe SSc ILD is insufficient. Sumi et al. (18) reported two patients with severe SSc-ILD, who developed spontaneous pneumothorax during nintedanib therapy. In a post-marketing survey in Japan, the frequency of pneumothorax in patients with IPF treated with nintedanib was low at 0.33% (17). Sumi et al (18) explained this situation as; fibrosis increases the fragility of the lungs, nintedanib, on the other hand, may increase fragility even more due to its anti-VEGF effect.

Digital Ulcer and Nintedanib

Although the pathophysiology of DU development in SSc is not known exactly, it is thought to result from decreased circulation due to the Raynaud phenomenon in distal areas like fingers. DU management is important in SSc as it can result in serious infections, gangrene and autoamputation. Currently available treatment is calcium channel blockers, antiaggregants, prostaglandin I2 (PGI2) analogues, endothelin receptor antagonists (ERA), phosphodiesterase-5 (PDE-5) inhibitors. Since SSc skin involvement occurs due to microvascular changes and fibrosis-related changes, long-term data are needed on the effect of nintedanib in skin involvement with DU.

In the SENSCIS study, no difference was found between nintedanib and placebo groups in terms of newly developing DU. But patients with more than three DU at baseline were excluded. There is not enough data in the current literature on the results of nintedanib use in patients with a large number of digital ulcers or severe skin involvement. Although there is general agreement that nintedanib can potentially impair angiogenesis and wound healing, more RCTs are needed in this area.

Nintedanib in Severe Progressive Fibrotic SSc-ILD

According to the extent of skin involvement in SSc, there are two clinical patterns, diffuse and limited. The diffuse pattern progresses more rapidly than the limited pattern, and its mortality is higher. Severe SSc-ILD is more common in diffuse pattern. Since the progression is rapid and mortality is high in this patient group, long-term follow-up is not possible. Therefore, the number of large case series published in this field is insufficient.

Bordas-Martinez et al. (19) hypothesized that patients with severe progressive fibrotic SSc- ILD (FVC <40% predicted or DLCO <30% of predicted) who are candidates for lung transplant may also benefit from nintedanib therapy. In this limited series of 4 cases with progressive fibrosing SSc- ILD, patients were treated with mycophenolate (2x720 mg/day) and nintedanib (2x150 mg/day). However, three of them also received corticosteroids less than 10 mg/day. Long-term oxygen therapy was started in one patient just before antifibrotic therapy. In two patients, a significant FVC improvement was observed, and in other two DLCO and FVC decline slowed down. Three patients reported digestive system complaints, 1/4 asthenia, 1/4 presented liver function elevation and 2/4 weight loss. All adverse events that developed were mild and none of the patients discontinued treatment for this reason. Lung transplantation was performed in one patient 249 days after the start of antifibrotic therapy.

300 mg/day or 200 mg/day?

The standard treatment dose of Nintedanib is 300mg/day. The level of efficacy at doses lower than the standard treatment dose is not exactly known.

Nishino et al. (20) reported a 73-year-old female patient with a diagnosis of SSc-ILD who had significant improvement in HRCT images following nintedanib treatment. Due to increase in ground glass areas on HRCT 26 months after the first visit, and deterioration in general condition, nintedanib was started as 2×100 mg/day. At the first month of nintedanib treatment, the patient reported an improvement in her dyspnea and cough. There were no side effects such as nausea or loss of appetite. Diarrhea did not develop, but the patient was using codeine phosphate as an antitussive. In the HRCT performed at the eighth month of nintedanib treatment, it was determined that the ground glass opacities significantly regressed. Radiological regression on HRCT was accompanied by a decline in dyspnea on exertion and dry cough. This case report is very meaningful as it shows that there is significant radiological improvement after the initiation of 200 mg/day nintedanib treatment.

Respiratory Tract Infection

The development of pneumonia was reported as a serious adverse event in the SENSCIS study. Pneumonia was much less common in the placebo group compared to the nintedanib group (0.3% vs 2.8%) (15). In patients with advanced ILD, concomitant use of mycophenolate and/or corticosteroids, clearly increases the incidence of pneumonia. A potential risk of infection due to the effect of nintedanib on macrophage function remained unanswered.

CONCLUSION

Clinical studies have proven that nintedanib has clinical benefits in the management of SSc-ILD. On the other hand, there is a need for long-term case-control series in this area. We hope that in the near future a large number of case series including nintedanib experiences in advanced SSc-ILD and the effects and side effects in SSc-ILD patients treated with nintedanib will be published.

ETHICAL DECLARATIONS

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Review / Derleme

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Gestasyonel hipertansiyon ve güncel tedavi yaklaşımları

Gestational hypertension and current treatment approaches

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ÖZ

Gebelikte optimal kan basıncının idame edilmesi sağlıklı fetüs gelişimi için vazgeçilmez bir unsurdur. Gebeliğin 20. haftasından sonra proteinüri benzeri sistemik bulguların eşlik etmediği, kan basıncının 140/90 mmHg ve üzerinde olmasına 'gestasyonel hipertansiyon' denir. Hamilelik sırasındaki hipertansif bozukluklar, uzun vadede kardiyovasküler hastalık riskini attırdığı için bu hastalara ömür boyu takip önerilmelidir. Anne ölümlerine ilişkin araştırmalar preeklampsi ve eklampsiye bu konuda göz ardı edilmemesi gereken nedenler olduğunu ortaya koymuştur. Gebelik döneminde tedavi edilmeyen hipertansiyon hem anne hem de bebek için maternal kardiyovasküler çeşitli morbiditelere yol açabilir. İlave olarak gebelik sonrası yaşamda kardiyovasküler hastalıklar da gestasyonel hipertansiyon tanısı konulmuş annelerde daha sık görülür. Bu derlemede gestasyonel hipertansiyon ve yeni tedavi yaklaşımları ele alınmıştır.

Anahtar Kelimeler: Gestasyonel hipertansiyon, gebelikte hipertansiyon, preeklampsi, gebelikte antihipertansifler

ABSTRACT

Maintaining optimal blood pressure during pregnancy is an essential element for healthy fetal development. Gestational hypertension is defined as a blood pressure of 140/90 mmHg and above without accompanying systemic findings such as proteinuria after the 20th week of pregnancy. Because hypertensive disorders during pregnancy increase the long-term risk of cardiovascular disease, these patients should be offered lifelong follow-up. Studies on maternal deaths have revealed that preeclampsia and eclampsia are causes that should not be ignored in this regard. Untreated hypertension during pregnancy can lead to various maternal cardiovascular morbidities for both mother and baby. In addition, cardiovascular diseases are more common in mothers diagnosed with gestational hypertension in the post-pregnancy life. In this review, gestational hypertension and new treatment approaches are discussed.

Keywords: Gestational hypertension, hypertension in pregnancy, preeclampsia, antihypertensives in pregnancy

GEBELİK VE HİPERTANSİYON

Gebeliğin 20. haftasından sonra proteinüri benzeri sistemik bulguların eşlik etmediği, kan basıncının 140/90 mmHg ve üzerinde olmasına 'gestasyonel hipertansiyon' denir. Kronik hipertansiyon ise gebeliğin 20. haftasından önce ortaya çıkan hipertansiyondur. Vakaların çoğu ailede hipertansiyon öyküsü ile ilişkili olabilen esansiyel hipertansiyona atfedilebilir (2). Sekonder nedenler genellikle daha azdır. 24 saat boyunca ayaktan kan basıncı izlenmesi kronik hipertansiyonu doğrulayabilir. Beyaz önlük hipertansiyonu (hastane ortamında tansiyonu yüksek ölçülen, ancak evdeki ölçümleri normal) olan kadınların yarısında gestasyonel hipertansiyon veya preeklampsi gelişir (1,2).

Gestasyonel hipertansiyon, preeklampsinin herhangi bir özelliği olmaksızın 20. gebelik haftasından sonra gelişen yeni başlangıçlı hipertansiyondur. Kan basıncı yüksekliği özellikle 33. gebelik haftasından önce tespit edilmişse, gestasyonel hipertansiyon veya preeklampsi gelişme riski %40 civarındadır (2). Gerçek gebelik hipertansiyonu veya kronik hipertansiyonu olan kadınların %25'inde preeklampsi gelişir. Bu nedenle, bu hastalar gebelikleri boyunca takip edilmelidir (3).

Preeklampsi

Uluslararası Gebelikte Hipertansiyon Çalışması Derneği (ISSHP), preeklampsiyi, 20. gebelik haftasından sonra aşağıdaki özelliklerden bir veya daha fazlasının

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eşlik ettiği yeni başlangıçlı hipertansiyon (TA≥140/90 mmHg) olarak tanımlamıştır (4).

1. Proteinüri varlığı (ciddi proteinüri idrar proteini/kreatinin oranının ≥30 mg/mmol, albümin/kreatinin oranının ≥8 mg/mmol veya her ikisinin birlikte olması) olarak tanımlanmıştır. Preeklampsi, proteinüri olmadan da ortaya çıkabilir) (5).
2. Uteroplasental disfonksiyon (umblikal arteryal Doppler ultrasonografi incelemesinde anormal dalga formu analizi, fetal büyümede gerilik veya ölü doğum) (3).
3. Diğer organlarda disfonksiyon (akut böbrek hasarı, karaciğer tutulumu, nörolojik komplikasyonlar (eklamptik nöbetler, şiddetli baş ağrıları, görme bozuklukları, klonus, mental durum değişikliği veya inme), hematolojik komplikasyonlar (hemoliz, DIK, trombositopeni) (3).

Preeklampsi, potansiyel olarak ilerleyici bir klinik durumu temsil eder. ACOG, preeklampsiyi şiddetli özellikleri olan veya olmayan olarak tanımlar (**Tablo 1**) (6).

Tablo 1. Şiddetli preeklampsi bulguları

Kan basıncının≥160/110 mmHg olması
Trombositopeni (≤100.000 μl^{-1})
Karaciğer fonksiyon bozukluğu (Aspartat aminotransferaz veya alanin aminotransferazın normal üst sınırın 2 kat ve üzerinde olması veya açıklanamayan sağ üst kadran ağrısı, epigastrik ağrı)
Böbrek yetmezliği (başka neden olmaksızın kreatinin 2 kat artışı)
Pulmoner ödem varlığı
Görme bozukluğu
Yeni başlayan, başka sebeplerle açıklanamayan, medikal tedaviye yanıtsız baş ağrısı

ISSHP tanı kriterleri klonusu içerir ancak hiperrefleksiyi içermez; çünkü bu oldukça sübjektif bir bulgudur ve sağlıklı kadınlarda da bulunabilir (4,7). HELLP sendromu (hemoliz, karaciğer enzimlerinde yükseklik ve trombositopeni) hem anne hem de bebek için potansiyel olarak yaşamı tehdit eder ve şiddetli preeklampsiyi gösterir. Plasental abruption veya DIK ile başvuran hastaların durumu kritik seyredebilir (8).

Preeklampsi gelişimi için çok sayıda risk faktörü tanımlanmıştır (**Tablo 2**) (9). Plasental biyobelirteçler, uterin arteryal doppler ölçümleri ve maternal risk faktörleri dahil olmak üzere birden fazla özelliği içeren risk tahminleri, daha erken tanıya ve daha iyi sonuçlara katkı sağlayabilir. Plasental büyüme faktörü (PlGF), 26. ve 30. gebelik haftaları arasında pik yapan ve terme doğru seviyesi azalan plasental bir biyobelirteçtir. PlGF, özellikle şiddetli preeklampside azalır (10). PlGF testi %96 sensitivite ve %98 spesifiteye sahiptir (10,11).

Tablo 2. Preeklampsi gelişimi için güçlü ve orta risk faktörleri

Güçlü Risk Faktörleri	Orta Risk Faktörleri
Preeklampsi öyküsü	Primiparite
Kronik hipertansiyon	İki gebelik arasının 5 yıldan fazla olması
Vücut kitle indeksi >30 kg/m^2	Anne yaşı ≥40 yıl
Pregestasyonel diabetes mellitus	Ailede preeklampsi öyküsü
Antifosfolipid antikor sendromu/SLE	Multipl gebelik
Yardımcı üreme tedavileri	Kronik böbrek yetmezliği

Diğer bir plasental biyobelirteç olan, soluble fms-like tirozin kinaz 1 (sFlt-1), vazokonstriksiyona ve endotelyal hasara neden olan ve preeklampside artan bir PlGF antagonistidir. sFlt-1/PlGF oranı yüksek olan kadınlarda preeklampsi riski yüksektir. sFlt-1/PlGF oranı %80 sensitivite ve %99,3 negatif predictivite oranına sahiptir (12). Genel olarak, anjiyojenik biyobelirteçler preeklampsiyi ekarte etmeye ve preeklampsili kadınlarda tanıyı hızlandırmaya yardımcı olabilir (12). NICE, 20. hafta ile 35. gebelik haftası arasında preeklampsi olan kadınların ekarte edilmesine yardımcı olmak için standart klinik değerlendirmeyle birlikte PlGF testi ve Elecsys immünoassay sFlt-1:PlGF oranının kullanılmasını önermektedir (13).

Şiddetli preeklampsili hastalarda oksidatif stres parametreleri ve seruloplazmin seviyelerinin incelendiği çalışmada, preeklampsili hastalarda hem oksidatif stres hem de seruloplazmin düzeylerinin arttığı ve artan seruloplazmin düzeylerinin oksidatif stresin bir sonucu olduğu gösterilmiştir(14). Nötrofil jelatinaz ilişkili lipokalin ve prokalsitonin düzeylerinin preeklampsinin varlığı ve şiddeti ile ilişkisi incelendiğinde, preeklampside seviyelerinin arttığı ve hastalığın şiddeti ile ilişkili olduğu gösterilmiş(15).

Hem PREP-S (erken başlangıçlı pre-eklampsi [hayatta kalma analizi modeli])'de hem de fullPIERS (pre-eklampsi entegre risk tahmini)'de gebelik yaşı, vital bulgular ve biyokimyasal belirteçler risk tahmin modelleridir. PREP-S gebeliğin 34. haftasına kadar kullanılabilirken, fullPIERS gebeliğin herhangi bir döneminde kullanılabilir. Bu risk tahmin modelleri NICE tarafından tavsiye edilmektedir ve özellikle bir hastanın hospitalizasyonuyla ilgili karar vermede yol gösterici olabilir; fakat bu modellerin hiçbirisi fetal sonuçları tahmin edemez (13,16).

Preeklempsi Ayırıcı Tanısı

Kronik hipertansiyon, kronik böbrek yetmezliği, primer nöbet bozuklukları (epilepsi), safra kesesi ve pankreas hastalıkları, immün trombositopeni, trombotik trombositopenik purpura ve hemolitik sendrom ayırıcı tanıda yer almalıdır. Tedaviye dirençli hipertansif semptom ve bulguların olduğu 20 hafta üstü her gebede öncelikle preeklampsi akla gelmelidir. Çoğunlukla 3.trimesterda ortaya çıksa da kronik hipertansiyon, böbrek hastalığı ve sistemik lupus eritematozus gibi eşlik eden hastalıkları

olanlarda daha erken gelişebilir. Persistan bir hipertansiyon varlığında tanı koymak gerçekten güç olabilir (17).

Preeklempsi Önleme

Tüm gebelere sağlıklı bir diyet ve egzersizin sürdürülmesiyle ilgili genel yaşam tarzı tavsiyeleri verilmelidir. Gebelik sırasında düzenli aerobik egzersiz yapan kadınlarda hipertansif bozukluklar ve gestasyonel diyabet oranı daha düşüktür (18). ASPRE (Kanıta Dayalı Preeklampsi Önleme Aspirin) Denemesi, 11-14 haftadan 36 haftaya kadar günde 150 mg aspirin alan kadınlarda plaseboya kıyasla daha düşük preterm- preeklampsi oranı olduğu sonucuna varmıştır (%1,6'ya karşı %4,3) (19). NICE, preeklampsi riski yüksek olan gebelere 12 haftadan bebeğin doğumuna kadar, günde 75-150 mg aspirin verilmesini önerir (13). İki veya daha fazla orta risk faktörü olan gebelere de aspirin önerilmelidir (13,19). Kalsiyumun diyetle alımının düşük olduğu durumlarda, takviye alınması (>1 gr/gün) preeklampsi gelişme riskini azaltabilir ancak etkinliği kanıtlanmamıştır (20). Folik asit etkinliği ise kanıtlanmamıştır. Yakın zamanda yayınlanan preeklampsi (FACT) çalışmasında yüksek riskli hastalarda ilk trimesterden sonra yüksek doz folik asit (4 mg/gün) takviyesinin preeklampsiyi önlemediği gösterilmiştir (20,21).

Gestasyonel Hipertansiyona Yaklaşım

Gebelikte tüm hipertansif bozukluklar için antihipertansif tedaviye başlama eşiği düşürülmüştür 2019 NICE Klavuzuna göre kan basıncı 140/90 mmHg ve üzerinde tedavi verilir, 135/85 mmHg ve altına düşürmek hedeflenir (5) 2017 AHA/ACC Klavuzuna göre gebelikte kan basıncı 140/90 mmHg ve üzerinde tedavi başlanması önerilmiş olup, kan basıncı 130/80 mmHg iken tedavi başlanmasının şiddetli hipertansiyona ilerlemeyi önlediği fakat anne ve bebek sonuçlarına etkisi olmadığı bildirilmiştir.

Maternal tansiyonu kontrol etmenin temel amacı, intraserebral kanama ve inmenin önlenmesidir. Preeklampsili kadınlarda peripartum dönemde inme oranı 100.000'de 133'tür ve hemorajik inme, iskemik inmeden daha yaygındır (22). NICE, başlangıç tedavisi olarak oral labetalol, ardından alternatif olarak nifedipin ve ardından metildopa önermektedir (5). İkinci ve üçüncü sıra ajanlar arasında hidralazin ve prazosin bulunur (4). Şiddetli hipertansiyonu olan preeklampsili kadınlar (≥160/110 mmHg), takip ve tedavi için hastaneye yatırılmalıdır. Hastaya antihipertansif tedavi ve profilaktik antikonvülsan tedavi (magnezyum sülfat) başlanmalıdır.Labetalol, non-selective bir beta blokerdir ve gebelikte en sık kullanılan beta blokerdir. Bisoprolol ve metoprolol gibi diğer β1 selektif ilaçlar da kullanılabilir ancak atenololden kaçınılmalıdır. Beta bloker kullanırken astımı olan hastalarda dikkatli olunmalıdır (23).

Nifedipin gibi dihidropiridin kalsiyum kanal blokerleri de hamilelik sırasında kullanılabilir. Doğrudan salınan oral nifedipin, magnezyum sülfat ile birlikte kullanımında derin hipotansiyona neden olabilir. Sinerjik etki göstererek doğabilecek fetal risklerinden dolayı bu iki ilaç birlikte kullanılmamalıdır. Bu durumda modifiye salınımlı nifedipin daha uygun olabilir. Tiyazid diüretikleri, anjiyotensin dönüştürücü enzim (ACE) inhibitörleri veya anjiyotensin II reseptör blokerleri (ARB'ler) kullananlarda gebe kaldıklarında konjenital anomali riski nedeniyle bu ilaçlar kesilip, daha güvenli bir antihipertansif ilaç başlanmalıdır (5,23).

Hastalar, belirli sıklıkta kan basıncı takibi, idrar tahlili ve kan tetkikleri yaptırmalıdır. Ultrason ile fetal değerlendirme, klinik olarak belirtildiği gibi her 2-4 haftada bir yapılmalıdır (5). Şiddetli preeklampsili kadınlarda 37.haftadan önce doğum planlanmalıdır (**Tablo 3**). 37.haftadan sonra 24-48 saat içinde doğum başlatılmalıdır (5).

Tablo 3. 37. gebelik haftasından önce erken doğumun planlanmasını gerektiren şiddetli preeklampsi ile ilişkili özellikler

Maternal kan basınıcının, uygun dozlarda 3 veya daha fazla sınıf antihipertansif kullanılmasına rağmen kontrol altına alınamaması
Karaciğer fonksiyonu, böbrek fonksiyonu, hemoliz veya trombosit sayısında progresif bozulma
Maternal spO2 <90% (oda havasında)
Şiddetli baş ağrısı, tekrarlayan görme bozukluğu veya eklampsi gibi devam eden nörolojik hadiseler
Plasental abrupsiyon
Umbilikal arter dopplerde ters diyastol sonu akışı, güven vermeyen bir kardiyotokograf (Non Stress Test) veya ölü doğum

Kısaltmalar: spO2: Puls oksimetre ile ölçülen oksijen saturasyonu

Doğumdan sonra hipertansiyon devam eden hastalarda beta blokerler ve kalsiyum kanal blokerleri kullanılabilir. Bu ilaçlar anne sütüne geçer ancak bebek için güvenlidir(24). Propranolol , metoprolol ve labetalol ,beta blokerler içinde anne sütüne en düşük geçişe sahiptir. Bebeklerde advers olaylarla ilişkilendirilmemiştir. Buna karşılık, atenolol ve asebutolol anne sütüne daha fazla geçer ve bebeklerde beta blokajı bildirilmiştir(25,26). Bu nedenle, bu ilaçları yüksek dozda alan, üç aylıktan küçük bir bebeği veya erken doğmuş bir bebeği emziren hastalar için diğer beta blokerler tercih edilmelidir. Emzirme sırasında karvedilol veya bisoprolol ile ilgili çalışmalar yeterli olmadığı için kullanımı önerilmemektedir. Kalsiyum kanal blokerlerinden diltiazem , nifedipin , nikardipin ve verapamil , kabul edilebilir olan yüzde 2'den daha az süte geçiş oranı nedeniyle tedavinin devamında tercih edilebilir. ACE inhibitörleri çok düşük seviyelerde süte geçer. Emziren hastalarda kaptopril ve enalapril kullanılabilir. Ancak yenidoğanlar, bu ilaçların hipotansiyon gibi hemodinamik etkilerine, oligüri ve nöbet gibi sekellere daha duyarlı olabilir. Bu nedenle, bu ilaçlar tercih edilmeden önce bebeğin hemodinamik durumunun göz önünde bulundurulması önerilmektedir. Emzirme döne-

minde anjiyotensin II reseptör blokerlerinin (ARB'ler) kullanımına ilişkin bilgi yoktur. Diüretikler, süt hacmini azaltabilir. Hidroklorotiyazid <50 mg/gün emzirme döneminde yenidoğan için güvenli kabul edilir. Metildopa ve hidralazin yenidoğan için güvenlidir. Metildopa uygulamasını takiben maternal depresyon rapor edildiğinden ve hastalar zaten doğum sonrası depresyon riski altında olduğundan, ACOG doğum sonrası hastalarda metildopa kullanımından kaçınılmasını önermektedir(27).

HİPERTANSİF ACİL DURUMLAR

Şiddetli hipertansiyon; akut başlangıçlı kan basıncı yüksekliği ve kan basıncının ≥160/110 mmHg olarak 15 dakika boyunca devam etmesi olarak tanımlanmıştır (6). Hipertansif acil durum, miyokard enfarktüsü, pulmoner ödem, solunum yetmezliği veya stroke gibi uç organ hasarı ile ortaya çıkabilir. Gebelikte hipertansif acil durumlar için risk faktörleri **Tablo 4**'te listelenmiştir (28).

Tablo 4. Gebelikte hipertansif acil durumlar için risk faktörleri

Preeklampsi
Kronik böbrek yetmezliği
Kardiyak hastalıklar
Antihipertansif ilaçlara uyumsuzluk
Doğum sonu kanamanın önlenmesi ve tedavisi için uterotonik ilaçların kullanımı
Bağımlılık yapan madde kullanımı
Düşük sosyoekonomik durum
Non-Hispanik siyahi nüfus

Gebelikte şüpheli hipertansif acil durumlar için ilk tetkikler; kan testleri (tam kan, üre, kreatinin, elektrolitler, laktat dehidrojenaz, fibrinojen, haptoglobin), tam idrar tetkiki, EKG ve fundoskopiyi içermelidir. Klinik tabloya bağlı olarak ek spesifik testler düşünülebilir ve bunlar arasında ekokardiyografi (iskemi veya kalp yetmezliği); beyin veya toraks görüntüleme (stroke veya aort diseksiyonu); böbrek ultrasonu (böbrek parankimal hastalığı); idrarda uyuşturucu taraması (şüpheli kokain veya amfetamin kullanımı); serum kardiyak troponin (akut miyokardiyal iskemi), B tipi natriüretik peptit (kalp yetmezliği) bakılabilir. Fetal iyilik halinin ve fetal büyümenin değerlendirilmesi yapılmalıdır. Bunun için ultrason muayenesi, doppler usg ve kardiyotokografi (NST) yapılabilir (23).

Hipertansif acil durumlar, invaziv kardiyak monitörizasyona gerek kalmadan intravenöz labetalol, hidralazin ve hızlı salınımlı oral nifedipin ile tedavi edilebilir. Labetalol 20 mg IV olarak 2 dakikada uygulanabilir ve kademeli olarak 80 mg'ye kadar arttırılabilir (29). Kan basıncı yüksek kalırsa hidralazin gibi başka bir antihipertansif ajan eklenebilir.(Labetalol ve hidralazin ülkemizde bulunmamaktadır fakat lüzum halinde yurt dışından temini yapılmaktadır, oral nifedipin ülkemizde mevcuttur.) Hidralazin direkt bir vazodilatördür ve titrasyon yapılmadan büyük bolus dozlarında kullanıldığında yan etkilere neden olabilir. Bunlar, annede hipotansiyon, artan acil sezaryen riski, plasenta dekolmanı ve fetal taşikardiyi içerir. Akut başlangıçlı şiddetli hipertansiyonu olan hastalar için doğru sıvı uygulaması önerilir, ancak IV hidralazin ile birlikte 500 ml'ye kadar kristalloid sıvı infüzyonu gerekebilir. Kan basıncı yüksek kalırsa, 2 dakika boyunca 5-10 mg hidralazin IV verilebilir, başlangıç dozunu takiben 20 dakika sonra 10 mg daha IV uygulanabilir (30). Hızlı salınımlı oral nifedipin için önerilen başlangıç dozu 10 mg'dir, 20 dakika sonra kan basıncı hala yüksekse 20 mg daha uygulanır (30,31). Gliserol trinitrat (GTN) infüzyonu, şiddetli hipertansiyon ve preeklampsi ile ilişkili akut pulmoner ödem için kullanılabilir (32). Furosemid (20-60 mg IV) gibi diüretikler de güvenli kabul edilir (33). İlave olarak şiddetli preeklampsi hastalarında, devam eden başka sıvı kayıpları yoksa idame sıvıları 80 ml/saat ile sınırlandırılmalı ve sıvı dengesinin takip edilmesi gerekir (5,34,35).

Eklampsi

Eklamptik nöbetler genellikle kendi kendini sınırlar ancak pulmoner aspirasyona ve maternal hipoksiye neden olabilir. Eklampsili kadınlarda stroke riski preeklampsili kadınlara göre yaklaşık 10 kat daha fazladır (22).Preeklampsili bir kadın kalıcı nörolojik semptomlar veya belirtiler (şiddetli inatçı baş ağrısı, serebral irritabilite, klonus veya görme bozukluğu belirtileri) ile başvurduğunda, eklamptik nöbetlerin önlenmesi için magnezyum sülfat birinci basamak tedavi olarak kullanılmalıdır (36). Genellikle 4-6 gr IV 20-30 dakikada yükleme dozu olarak verilir, ardından 24 saat boyunca doğuma kadar 1-2 gr/saat sürekli IV infüzyon yapılır (6). Tekrarlayan nöbetler için ayrıca 2-4 gr bolus verilebilir. Magnezyum sülfat ayrıca bilateral gluteal kas içine IM uygulanabilir (6). Magnezyum toksisitesi nedeniyle derin tendon refleksleri azaldığı için tedavi boyunca izlenmelidir. Yetersiz böbrek fonksiyonunda magnezyum toksisitesi riski artar ve solunum frekansının azalmasına, spO2 düşüşüne ve progresif kas paralizisine yol açabilir (37). Hedeflenen serum magnezyum terapötik aralığı 2-4 mmol/L'dir. Magnezyum toksisitesi, kalsiyum glukonat ile tedavi edilir (10 ml'lik %10'luk Ca-glukonat 10 dakika boyunca IV verilir) (37). NICE, eklamptik nöbetleri olan gebelerde magnezyum sülfata alternatif olarak benzodiazepinler veya diğer standart antikonvülzanların kullanılmasını önermez (5).

Analjezi ve Anestezi İçin Akılda Tutulması Gerekenler

Şiddetli preeklampsili kadınlar, ağrıyı azaltmaya ve kardiyovasküler stabiliteyi kolaylaştırmaya yardımcı olabileceğinden doğum sırasında nöroaksiyel analjeziden fayda gö-

rebilir (38). Epidural hematom riskinin artması nedeniyle koagülopati veya trombositopeni varlığında nöroaksiyel teknikler kontrendikedir. Nöroaksiyel blok uygulamadan önce yeni bir trombosit sayımı ve koagülasyon faktörleri çalışılmalıdır (38,39). Şiddetli preeklampsili gebelerde trombositopeni ve daha nadiren DIK aniden ortaya çıkabilir. Trombosit sayımı, bölgesel analjezi uygulandıktan sonraki 6 saat içinde veya daha erken alınmalıdır (39). Trombosit sayısı $>70\times10^9$ ise epidural hematom riski son derece düşüktür (<%0,2) (40). Bölgesel analjezi kontrendike olduğunda inhalasyon ve parenteral analjezi kullanılabilir. Remifentanil hasta kontrollü analjezi (PCA), bölgesel analjeziye iyi bir alternatiftir (41,42).

Ameliyatla doğum gerektiğinde, preeklampsili çoğu hasta için genel anestezi yerine nöroaksiyel anestezi tercih edilir. Spinal, epidural veya kombine spinal/epidural anestezi uygulanabilir. Genel anestezi, laringoskopi sırasında serebrovasküler kanamaya yol açabilen hava yolu problemleri ve artan sistemik ve serebral kan basınçları ile ilişkilidir. Laringoskopiye verilen hipertansif yanıt, IV alfentanil 25 mg/kg veya remifentanil 1 mg/kg gibi opioidler veya labetalol 0,25 mg/kg veya esmolol 500 mg/kg IV bolus olarak uygulanabilecek diğer antihipertansif ilaçlardır (43). Kan basıncını indüksiyon öncesi değerlerde tutmayı ve ortalama arter basınçlarının 110 mmHg'nın altında tutmayı hedefleyin. Anesteziye bağlı gelişen herhangi bir hipotansiyon, fenilefrin veya metaraminol gibi bir alfa agonistinin etki gösterecek şekilde titre edilmiş intravenöz bolusları veya infüzyonları ile tedavi edilebilir (38). Nöbet riskini azaltmak için magnezyum sülfat infüzyonlarına devam etmek önemlidir ve laringoskopiye hipertansif yanıtı azaltmak için oran geçici olarak artırılabilir. Magnezyum sülfat, depolarizan olmayan tüm nöromüsküler bloke edici ajanların etkisini güçlendirir, bu nedenle daha küçük dozlar gerekir (36,38). Alternatif olarak, entübasyon dozunda 1,2 mg/kg roküronyum kullanılabilir ve sugammadeks kullanılarak rezidüel blok tersine çevrilebilir. Magnezyum, suksametonyumu ve sugammadeksi etkilemez (38).

Preeklempside Takip

Preeklampsili hastalarda oksijen satürasyonları, solunum frekansı, kalp hızı ve noninvaziv arter basıncı düzenli olarak izlenmelidir. İnvaziv arteriyel ve santral venöz basınç takibi rutin olarak gerekli değildir ancak dirençli hipertansiyonu ve kalp yetmezliği olan yüksek riskli hastalarda düşünülmelidir. Doğru sıvı dengesi değerlendirmesinin bir parçası olarak ve pulmoner ödem riskini azaltmak için, böbrek fonksiyonunda akut bozulma meydana gelebileceğinden idrar çıkışı sürekli olarak izlenmelidir. Preeklampsili kadınlar, semptomların şiddetine bağlı olarak doğum veya doğum sonrası serviste veya yoğun bakım ünitesinde yönetilebilir ve alınacak kararlar multidisipliner bir ekip tarafından verilmelidir (28,44).

Olası solunum desteği ihtiyacı (entübasyon dahil), taşipne (>35 nefes/dk), bradikardi (<40 atım/dk) veya taşikardi (>150 atım/dk), vazopressör ihtiyacı, invaziv monitorizasyon ihtiyacı, daha fazla müdahale gerektiren anormal EKG (örn; kardiyoversiyon), ilave IV antihipertansif ilaç ihtiyacı, asit baz bozukluğu veya ciddi elektrolit anormallikleri durumunda hastanın yoğun bakım ünitesine transfer düşünülmelidir (28).

Doğum sonrası hipertansiyon 6-8 haftaya kadar devam edebilir, bu nedenle tüm hastalara doğumdan sonra 6-8 hafta boyunca takip önerilmelidir (45). Hamilelik sırasındaki hipertansif hastalığın etiyolojisi ne olursa olsun, doğum sonrası tüm hastalar, normotansif gebelikleri olan kadınlara kıyasla, doğum sonrası kardiyovasküler hastalık, inme, diyabet, kronik böbrek hastalığı ve venöz tromboembolizm riskinde artışa sahiptir. Bu nedenle, tüm hastaların aile hekimleri tarafından yaşam boyu takipleri yapılmalıdır (45,46).

SONUÇ

Gebelikte hipertansiyon, hem anne hem de fetüs için önemli bir morbidite ve mortalite nedeni olmaya devam etmektedir. Kılavuzlar son yıllarda güncellenmiştir ve preeklampsili gebelerde karar vermede yol göstermek için kullanılabilecek yeni risk tahmin araçları bulunmaktadır. Erken tanı, tedavi ve komplikasyonların yönetimi, sağlıklı anneler ve sağlıklı bebekler için hayati önem taşımaktadır.

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Case Report / Olgu Sunumu

MEDICINE PALLIATIVE CARE

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An adolescent case with unexplained ecchymosis: Munchausen syndrome

Açıklanamayan ekimozları olan bir ergen olgusu: Munchausen sendromu

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ABSTRACT

Munchausen syndrome (MS) is a condition in which a patient deliberately mimics signs and symptoms of health problems to gain attention from their close circle and healthcare professionals. Symptoms can be self-induced or fabricated. The paper aimed to discuss MS detected in an adolescent girl who presented with hematological findings and shift the interest to factitious disorders that may be confronted in pediatric practice. A thirteen-year-old girl was admitted to the pediatric hematology outpatient clinic with bruises spread throughout the body, predominantly localized on the arms, persisting for three months and disappearing every two weeks. She had complaints of fatigue and loss of appetite, emerging simultaneously with the occurrence of bruises. Following elaborative examinations, we discovered that the patient was painting bruises on her skin using an eye shadow. MS needs to be considered in differential diagnoses among patients with long-term, inconsistent, and irrational complaints, no underlying causes, and normal laboratory findings. Overall, we presented the case to underline that MS is likely to be confronted in pediatric practice.

Keywords: Munchausen syndrome, adolescent, ecchymosis

ÖZ

Munchausen sendromu (MS), çevresinden ve sağlık görevlilerinden ilgi görmek adına kasıtlı olarak hastalık belirti ve semptomlarını taklit etmesidir. Semptomlar kendi kendine indüklenebilir veya uydurulabilir. Yazımızda hematolojik bulgularla başvuran ergen bir kız çocuğunda saptanan Munchausen sendromunu tartışarak pediatri pratiğinde karşılaşılabilecek yapay bozukluklara dikkat çekmeyi amaçladık. On üç yaşındaki kız hasta, çocuk hematoloji polikliniğine 3 aydır devam eden ortaya çıktığında 2 haftada kaybolan ekimoz şikayeti ile başvurdu. Bu bulgunun eşliğinde halsizlik ve iştahsızlık şikayetleri de mevcuttu. Yapılan tıbbi inceleme ve alınan ayrıntılı öyküden hastanın göz farı ile cildinde ekimozlar çizdiği belirlendi. Tutarsız ve mantıksız şikayet ve bulgular ile başvuran hastalarda , altta yatan herhangi bir patolojik neden yoksa Munchausen sendromu ayırıcı tanıda mutlaka düşünülmelidir. Bu vaka, pediatrik pratikte de Munchausen sendromuyla karşılaşılabileceğine dikkat çekmek için için paylaşılmıştır.

Anahtar Kelimeler: Munchausen sendromu, adölesan, ekimoz

INTRODUCTION

Munchausen syndrome (MS), also known as factitious disorder imposed on self, is a condition in which a patient deliberately mimics medical or psychiatric symptoms. Symptoms can be self-induced or fabricated. It is a psychiatric disorder where patients manufacture a picture of illness or disability knowingly and willingly, although they have no apparent interest in it (1).

In pediatric practice, MS, which may be fabricated by parents or caregivers and is also considered a type of child abuse, comes to mind in children followed up for a long time, with inconsistent and non-diagnostic complaints, symptoms, or laboratory findings (2).

Children and adolescents may also make up a disease themselves beyond the knowledge of parents or caregivers; yet, this situation is frequently ignored. It is often claimed in the literature that almost half of adult cases with factitious disorders begin to develop disease symptoms in adolescence (3).

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The paper aimed to discuss MS detected in an adolescent girl who presented with hematological findings and shift the interest to factitious disorders that may be confronted in pediatric practice.

CASE

A thirteen-year-old girl was admitted to the pediatric hematology outpatient clinic with bruises spread throughout the body, predominantly localized on the arms, persisting for three months and disappearing every two weeks. She had complaints of fatigue and loss of appetite, emerging simultaneously with the occurrence of bruises. The patient reported that her bruises used to get worse in the evening hours. There was no complaint of fever and weight loss. The patient had not attended school for a month because she felt pretty exhausted due to her bruises getting worse on the way to school. Besides, she claimed to show good performance in her lessons other than mathematics. Her parents was also worried because of these complaints. She applied to the adult hematology outpatient clinic in another center two months ago; however, no pathology was detected in her examinations. She was also seen in the pediatric hematology outpatient clinic in another center a month ago, and her blood tests yielded no abnormality. The patient persistently claimed that the staff suspected 'leukemia' in the external center evaluations. We were also informed that the patient was diagnosed with iron deficiency anemia and prescribed relevant treatment. Yet, the patient discontinued the treatment upon the belief that it might be associated with the onset of bruises. She had been using a proton pump inhibitor and antacid for a year due to gastritis and reflux symptoms. Thinking that it might cause bruises, her treatment was interrupted for the last month, again by the patient.

In her physical examination, we detected purple and gray ecchymosis-like areas on her arms and legs, which were about to fade. Ecchymosis-like areas localized on the extremities were especially more in numbers and larger on the left arm and leg. All areas defined as bruises were black-purple (**Figure 1-4**). Besides, other system examinations resulted in regular findings. Complete blood count, peripheral smear findings, and reticulocyte count were also normal. There was no pathological finding in previous bleeding susceptibility tests.

When the patient's forearm was wiped using alcohol wipes to check bleeding time, we surprisingly discovered that the area with the so-called bruise immediately disappeared. Other gray-black and purple areas were also cleaned with moisturizing cream. Then, we considered that the patient made bruise-like coloring using make-up material.

It should be noted that we avoided accusatory and humiliating behaviors during examinations. Her parents were appropriately informed about the situation. Overall, the patient was considered to develop MS and referred to the child psychiatry clinic.

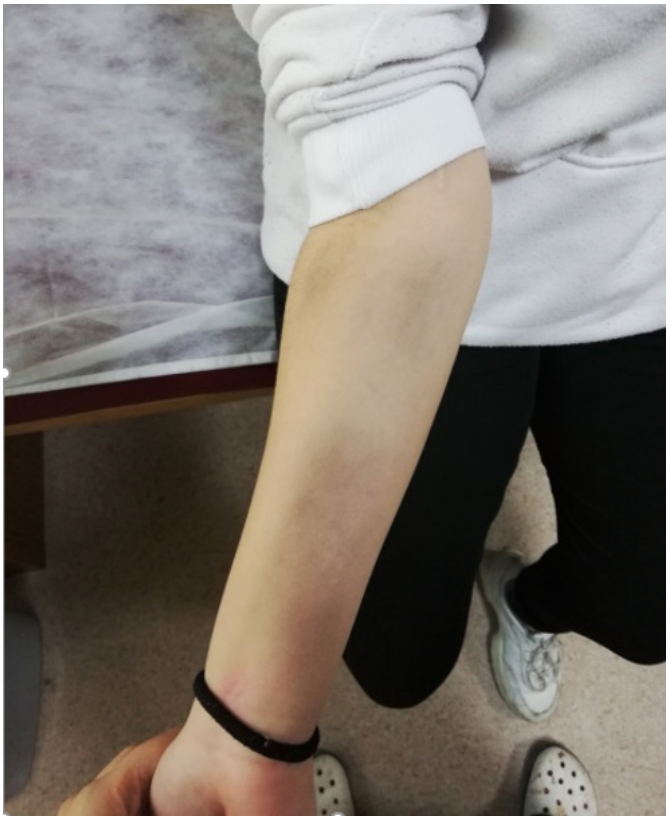

Figure 1. Ecchymosis on the patient's right forearm

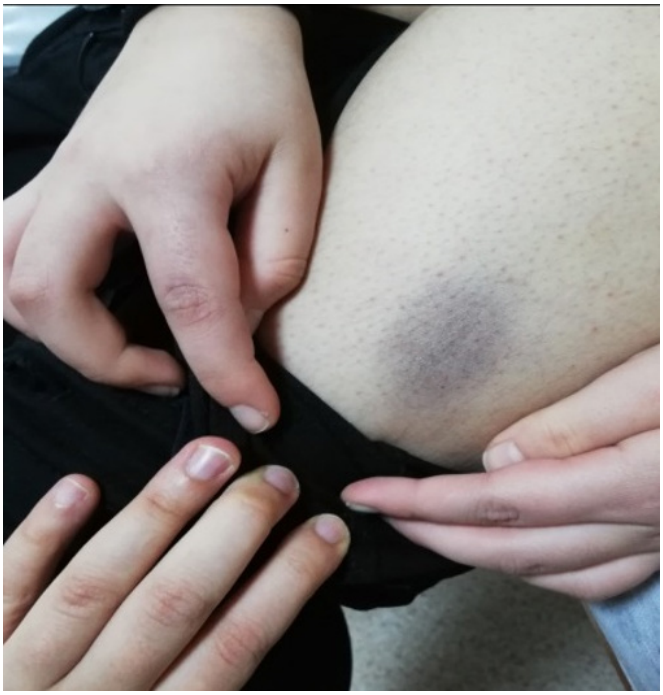

Figure 2. Single large-scale ecchymosis on the patient's left upper leg

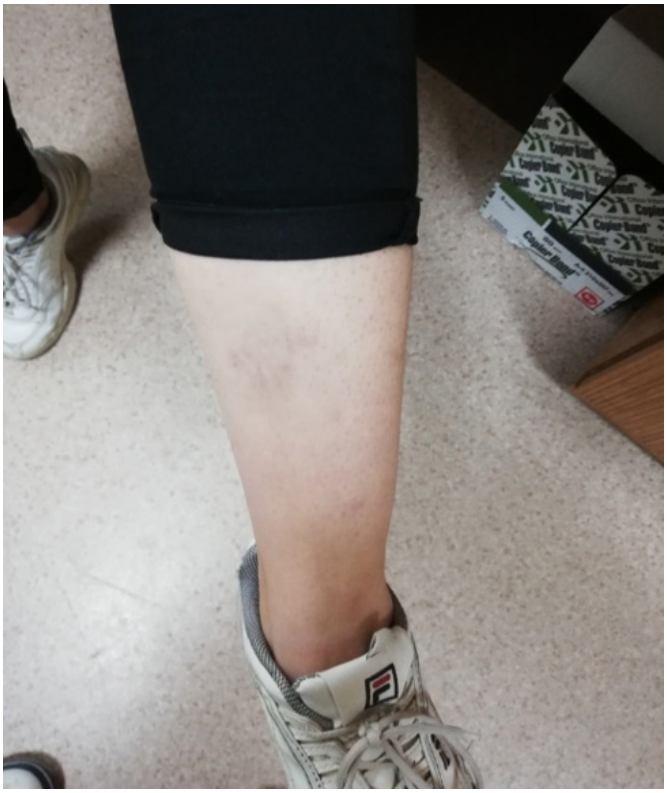

Figure 3. Ecchymosis on the patient's left leg

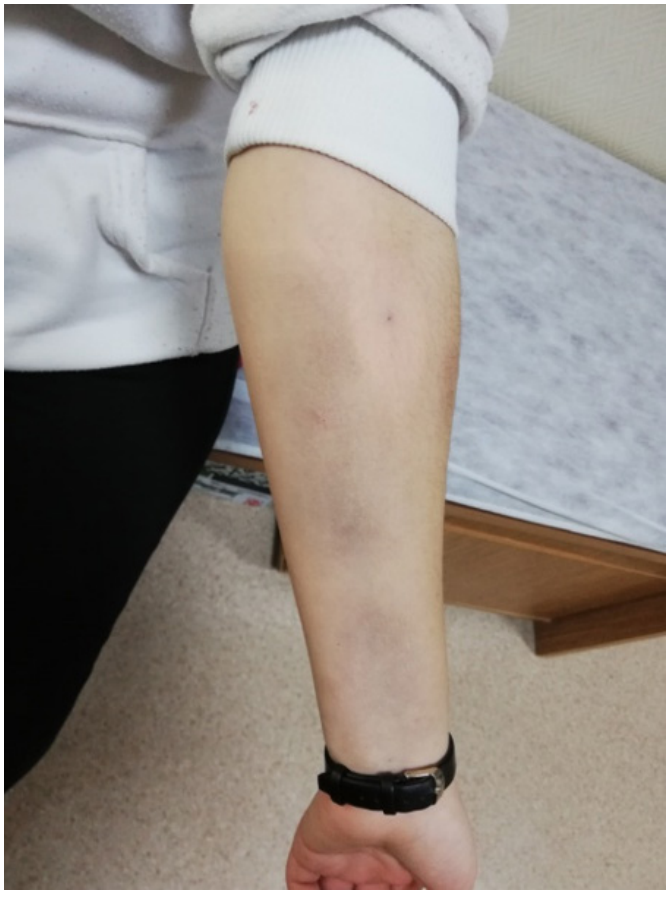

Figure 4. Ecchymoses on the patient's left forearm

DISCUSSION

MS is rare and difficult to detect in pediatric patients, and the knowledge on this subject in the literature is limited chiefly to case reports.

There are a few important points to consider to understand whether the situation is a factitious disorder or not. Patients are generally hesitant to communicate their condition with family members, friends, and physicians. Atypical presentation of diseases, repetitive applications in different hospitals, mastery of medical terminology, and accepting all kinds of interventional medical procedures, including surgery, are among the findings raising suspicion for factitious disorders (4). The inconsistencies in the anamnesis reported by our case made it easier for us to diagnose MS. Besides, nobody witnessed the formation of her lesions. Moreover, lesions appeared in the areas where her hands could reach but not on her face and back. The symptoms and her calm behaviors in diagnostic or therapeutic interventions were unusual. We also thought that our patient attempted to imitate leukemia with false ecchymoses. Eventually, we found out that she manufactured the bruises on her own using make-up materials. It was previously reported in the literature that one-third of adult MS patients have hematological symptoms at admission (5). Similarly, in their review, Libow et al. reported seven patients with purpura out of 42 MS patients (6). In another study, hematologic symptoms were found in two-thirds of the pediatric patients with MS (7).

It takes an average of 18.9 months to diagnose factitious disorders in adolescent patients (6). Our patient had a history of applying to more than one health center with similar complaints for three months. Diagnostic tests in different centers resulted in normal findings. Despite discovering that ecchymoses were due to MS at the end of three months, we thought that the beginning of the process might go back further, considering that she had been using medication for dyspeptic-gastric complaints for up to a year. Yet, although the medications were abandoned simultaneously with ecchymoses, peptic complaints were no longer mentioned.

MS can be rather dangerous, particularly among children with a chronic illness or close contact with such people in their immediate environment. In the literature, a 12-year-old diabetic patient who underwent subtotal pancreatectomy due to recurrent episodes of diabetic ketoacidosis admitted after the operation that he did not knowingly take an insulin dose (8). Moreover, the literature hosts case reports about adolescents who self-injected steroids to create Cushing's syndrome, self-injected subcutaneous air to manufacture facial emphysema, and used hydrofluoric acid to create toe

necrosis (6). These dramatic examples in the literature demonstrate that patients can display potentially fatal, self-destructive behaviors. Therefore, the importance of early diagnosis and support is clear to prevent worse outcomes in patients with suspected MS. In addition, the cost of this condition, which is often associated with morbidity and mortality, to the health system is too high to ignore (9). Some other case reports mentioned patients costing healthcare systems hundreds of thousands of dollars (10).

CONCLUSION

MS needs to be considered in differential diagnoses among patients with long-term, inconsistent, and irrational complaints, no underlying causes, and normal laboratory findings. The early diagnosis of this condition seems to be critical to be able to offer an early solution to the underlying problems. Overall, we presented the case to underline that MS is likely to be confronted in pediatric practice.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

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Case Report / Olgu Sunumu

MEDICINE PALLIATIVE CARE

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A rare breast tumor; Adenomyoepithelioma: a case report and review of the literature

Memenin nadir bir tümörü; Adenomiyoepitelyoma: olgu sunumu ve literatürün gözden geçirilmesi

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ABSTRACT

Adenomyoepithelioma is rare benign breast neoplasia characterized by the proliferation of both epithelial and myoepithelial cells of the mammary lobules and ducts. This tumour, which does not have specific risk factors and radiological findings, is mostly seen in advanced ages. This tumour, which occurs with the biphasic proliferation of epithelial and myoepithelial cells, also contains normal breast lobules and ducts. This tumour is very difficult to diagnose and includes many radiological and pathological pitfalls. Although malignant degeneration has been reported in the literature, it is a rare condition. In this study, we present a rare case with radiologically suspicious findings and pathologically reported as adenomyoepithelioma.

Keywords: Adenomyoepithelioma, breast, stromal tumour

ÖZ

Adenomiyoepitelyoma, meme lobül ve kanallarının hem epitel hem de miyoepitelyal hücrelerin proliferasyonu ile karakterize, nadir görülen benign bir meme neoplazisidir. Kendine özgü risk faktörleri ve radyolojik bulguları olmayan bu tümör çoğunlukla ileri yaşlarda görülür. Epitelyal ve miyoepitelyal hücrelerin bifazik proliferasyonu ile meydana gelir ve içerisinde normal meme lobülleri ve duktuslarını da barındırır. Bu tümör tanı açısından oldukça zordur ve radyolojik ve patolojik olarak birçok tuzakları içerir. Malign dejenerasyon literatürde bildirilmekle beraber nadir bir durumdur. Bu çalışmada radyolojik olarak şüpheli bulgular gösteren ve patolojik olarak adenomiyoepitelyoma olarak raporlanan nadir bir olgu sunduk.

Anahtar Kelimeler: Adenomiyoepitelyoma, meme, stromal tümör

INTRODUCTION

Adenomyoepithelioma of the breast (AME) is a very rare benign breast tumour that was first described in 1970. It is generally seen in the fifth and sixth decades (1-3). While AME is frequently encountered in the salivary glands and skin appendages, it is very rare in the breast. Clinically, it presents as a single nodule with a rounded shape, irregular contours, and a hard differential diagnosis with breast cancer (4,5). Histopathologically, AME may exhibit different growth patterns such as tubular, papillary, solid, or more often a combination of these patterns (5). Although benign, local recurrence rates are high in this tumour and wide surgical excision is mandatory for diagnosis and treatment. Various metaplasias and some degree of atypia can be seen in the myoepithelial component of AME (6,7). Malignant transformation may be limited to the epithelial or myoepithelial component, or it can be seen in both components, it has been reported very rarely in the literature and is called malignant AME (7). Here, we present a rare case of AMI presenting with radiologically suspicious findings.

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CASE

In the physical examination of a 55-year-old female patient who applied to the outpatient clinic with the complaint of a right breast mass, a firm mass of approximately 2 cm in size was palpated in the right breast at the 3 o'clock position. In the localization described in the radiological images, a 20x15 mm sized, lobulated contour, hypoechoic, solid mass was observed and was considered suspicious and histopathological verification was recommended. There was no history of breast cancer in the patient's first-degree relatives and there was no other disease in his history. After the tru-cut biopsy result showed sclerosing adenosis, lumpectomy was decided and the mass was excised with wide surgical margins. Histopathological examination revealed that the tumour consisted of small epithelial cells and glands with eosinophilic cytoplasm surrounded by clear cell myoepithelial cells (**Figure**). A diagnosis of adenomyoepithelioma was made in the presence of clinical, radiological and pathological findings. No recurrence or metastasis was observed in the 24-month follow-up of the case.

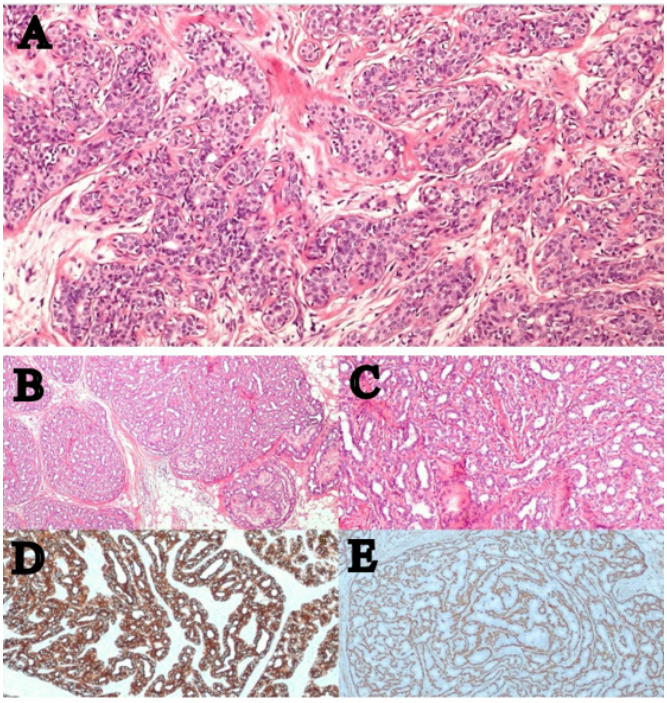

Figure . General view of Adenomyoepithelioma. A-B-C: The tumour consisted of gland structures with eosinophilic cytoplasm surrounded by myoepithelial cells in a loose edematous stroma (x10-x20, H&E). D: Positive staining with CK7 was observed in the epithelial layer of tumoral cells (x10). E: Positive staining with p63 was observed in the myoepithelial layer of tumoral cells (x10).

DISCUSSION

Breast-localized AME was first described by Hamperl in 1970 and is an extremely rare neoplasm, with approximately 150 cases described in the literature (1-3). The age range is wide (26-81), and the incidence increases with age. AME presents as a palpable, well-circumscribed, firm mass (mean 1–2 cm) that can reach up to 8 cm in size (4,5). It is usually localized in the middle of the breast and very rarely presents as satellite nodules, multiple breast masses, or bilateral involvement (6,7). Rarely, the male breast may also be affected (7). In our case, the lesion was presented as a single, well-circumscribed mass of 2 cm in the middle-outer part.

AME is characterized by the proliferation of epithelial and myoepithelial cells of the chest lobules and ducts (8). Myoepithelial cells form part of the normal microscopic anatomy of the breast and are commonly found in the breast. The radiological appearance of this tumour varies considerably and its differential diagnosis from other breast tumours is difficult (8,9). In the US, they are usually seen as a well-circumscribed, hypoechoic, solid lesion. On MRI, they are observed as a well-defined, lobulated contoured density. On mammography, it is usually in the form of an oval or round isodense mass with shaded edges, but it may not allow visualization of the tumour in dense breast tissue (9,10). Microcalcifications can sometimes be detected in the mass in imaging methods. There are also cases in the literature showing homogeneously increasing masses in patients with benign AMI with a dynamic progressive enhancement curve on MR (10). In our case, the lesion was evaluated as suspicious in imaging methods and a definitive diagnosis was made by histopathological examination.

Fine needle aspiration is often not diagnostic for the diagnosis of AMI. Core needle biopsy is ineffective due to the heterogeneity of AMEs (11). Therefore, the definitive diagnosis is excisional biopsy and histopathological examination of the mass. The histopathology of AME is macroscopical as a well-circumscribed, encapsulated and mobile mass (11,12). Microscopically, it is characterized by the proliferation of epithelial cells and glans with eosinophilic cytoplasm surrounded by myoepithelial cells (12). In epithelial cells, immunoreactions are detected with various keratins, especially CK7 and CK19, and EMA, and in myoepithelial cells with p63, SMA, S100, CK14, and calponin. Estrogen and/or progesterone receptors may also be positive (11-13). In our case, positive staining was observed with CK7 in epithelial cells and with p63 in myoepithelial cells.

AME tumours of the breast are rare tumours with variable behaviour. Benign AME is classified according to its growth pattern as tubular, lobulated, and spindle cell variant (14). Malignant transformation is possible and in this case, the tumour should be treated as breast carcinoma. The radiological findings are not specific and significant on their own and do not allow to distinguish the benign or malignant nature of the lesion (14,15). Morphological and hemodynamic features on MRI provide additional information, but no definitive information. Evidence of malignant development relies on histopathologically

detecting findings such as increased mitotic activity, necrosis, cellular pleomorphism, cytological atypia, and infiltrative margins of the tumour nodules that form the lesion (16,17). Malignant changes may involve mostly epithelial cells and rarely both. The role of immunohistochemistry in the diagnosis of malignant AME is limited (17). Nuclear atypia, nuclear pleomorphism, mitosis, necrosis and infiltration of surrounding tissues were not observed in our case.

Adenosis, intraductal papilloma, nipple adenoma and fibroadenoma should be considered in the differential diagnosis when diagnosing AMI (9). The above-mentioned radiological, morphological and immunohistochemical features of the case are very helpful in avoiding these diagnostic pitfalls (9,10). While malignant cases are frequently described in the literature, benign AMI cases have been reported rarely. Therefore, there are no guidelines to distinguish between benign and malignant cases of AMI, and there is no clear consensus on their treatment (14,15). In our case, typical morphological and immunohistochemical findings were very helpful in the differential diagnosis.

In cases of AMI, the distinction between benign and malignant should be made carefully. Although the prognosis is good for benign AMI, the prognosis is poor in malignant cases due to high recurrence and metastasis (15). Malignant AMEs metastasize to organs such as the lung, brain, and liver by hematogenous rather than lymphatic route. Tubular variants and some lobular variants with high mitosis (>3 mitoses/10 HPF) are associated with a high incidence of recurrence (15,16). Given the uncertain and unpredictable tendency for malignant transformation and the risk of local recurrence, conservative excision with negative margins seems to be the appropriate surgical treatment at present. In the case of malignant AMI, mastectomy and analysis of the sentinel lymph node are recommended. Chemotherapy has not had much success (16,17). No recurrence or metastasis was detected in the 2-year follow-up of our case.

CONCLUSION

AME is a rare breast tumour with a mostly benign prognosis and should be kept in mind in the differential diagnosis with other solid lesions of the breast. Imaging features are not pathognomonic and definitive diagnosis is only possible with histopathological examination. Surgical excision with a solid margin is the optimal therapeutic method because of the high recurrence rate in benign and aggressiveness in malignant ones.

ETHICAL DECLARATIONS

Informed Consent: Written consent was obtained from the patient participating in this study.

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Conflict of Interest Status: The authors declared that there was no conflict of interest in this study.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All authors; declared that they participated in the design, execution and analysis of the article and approved the final version.

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Manuscripts are double-spaced with Microsoft Word, and title titles (Abstract, Abstract, Introduction, Materials and Methods, Results, Discussion, References, etc.) are written in 12 pt. 2.5 cm space should be written at the top and bottom. The writing style should be Times New Roman. "System International" (SI) units should be used. Figures, tables and graphs should be referenced in the text. Abbreviations should be given in parentheses where the word first appears. Turkish articles should be 50% contiguous, and English should be 50% contiguous. A comma should be used in decimal numbers in Turkish (55.78) and a period (55.78) should be used in English manuscripts. Review articles and research articles should not exceed 4000 words, case reports 2000 words, letters to the editor should not exceed 500 words (This limits to all article types are excluding Abstract and References section). Pages should be numbered from the abstract page.

SECTIONS OF MANUSCRIPT

1. Presentation to the Editor

This is the article that the author of the article sends to the editor of the journal. In this section, it should be noted that part or all of the article is not published elsewhere and is not in the process of being evaluated in another journal at the same time, "**Material Support and Interest Relationship**" status, language and statistical checks are made.

2. Title Page

The category of the article submitted at the beginning of the page should be indicated (clinical analysis, research article, experimental study, case report, review, etc.). The names and surnames of all authors should be numbered after the superscript and numbered from 1, and they should be added under the names of the institutions, clinics, cities and countries. On the title page, each author's **Orcid ID** should be his/her e-mail address. This page should include the Authorized Author (s), name, full address, telephone and **e-mail** (address information should be indicated in Turkish if the language of the article is Turkish and English if it is English). Oral or Poster presentations presented at congresses should be indicated on the title page by giving the name, place and date of the congress.

3. Article File

There should be no names of authors and institutions, only this information should be on the title page.

Title: There should be a short and clear title. It should not contain abbreviations and should be written in Turkish and English. Abstract: Turkish and English abstracts should be written. In research articles; It should be divided into sections of Aim/Introduction, Material and Method, Results/Findings and Conclusion and should not exceed 400 words. In the review, case reports and the like, Öz; it should be short and one paragraph, and should not exceed 300 words in reviews and 250 words in case reports.

Keywords: Turkish Abstract and English should be found at the end of the abstract. A minimum of 3 and a maximum of 6 should be written. Words should be separated by semicolons. Keywords should be submitted in accordance with Subject **Medical Subject Headings (MESH)** (www.nlm.nih.gov/mesh/MBrowser.html). Turkish Keywords "Turkey Science Terms' what should be in accordance with (www.bilimterimleri.com). If not, a one-to-one Turkish translation should be provided.

Figures, Photographs, Tables and Graphics: It should be indicated at the end of the sentence where it is mentioned in the text, should not be placed in the text, and should be added to the end of the text after the references. Abbreviations used should be indicated in the description below. If previously printed figures, pictures, tables and graphics are used, written permission must be obtained and this permission should be stated in the description of figures, pictures, tables and graphics. The article should be passed by the authors for academic plagiarism prevention program. The picture/photo should be in jpeg and at least 300 dpi resolution.

Text Sections: The text samples to be sent for publication are as follows.

Editorial Comment/Discussion: It is the evaluation of the original research articles published by the expert other than the authors. It is published before the articles in the journal.

Research Article: Prospective-retrospective and all kinds of experimental studies can be published. Abstract (approximately 400 words; aim/introduction, material and method, results/findings and conclusion sections in Turkish and English), Introduction, Material and Method, Results, Discussion, Conclusion, References.

Review: Can be prepared by invited authors or directly. It can be prepared to include the latest medical literature for any subject that has medical characteristics. Abstract (about 300 words, unpartitioned, Turkish and English), titles, references.

Case Report: These are rare or different articles in diagnosis and treatment. It should be supported with sufficient number of photographs and diagrams. Abstract (about 250 words; no section; Turkish and English), Introduction, case report, discussion, conclusion.

Letter to the Editor: The articles that are published in the journal within the last year include a maximum of 500 words containing various opinions, experiences and questions of the readers. There are no Title and Abstract sections. The number of references is limited to 5 (max. 10). It should be indicated which article (number, date) is dedicated and at the end there should be the name, institution and address of the author. The answer to the letter is given by the editor or the author (s) of the article and published in the journal.

Education: Scientific articles supported by the latest clinical and laboratory applications that send messages to readers on current issues within the scope of the journal. Abstract (about 250 words; no section; Turkish and English), related titles, references.

Book Evaluations: Evaluations of national or internationally accepted books of current value within the scope of the journal.

WHAT SHOULD BE INDICATED BEFORE THE RESOURCES

ETHICAL DECLERATIONS

Ethics Committee Approval: The study was carried out with the permission of ..... Ethics Committee (Date:....., Decision No. .....).

Informed Consent: Written informed consent was obtained from all participants who participated in this ....study (If study retrospective: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgements: If any, it should be written before references.

References: References should be written according to the order of arrival. If the number of authors in the source is 6 or less, all authors (surname and first name should be the first letter, the names of the authors should be separated by commas) should be specified; ("et al "), the name of the article (only the first letter of the sentence and the first letter of the special names will be capitalized), short journal name, year, volume, short page number (15-8, not 15-18) and a space between the punctuation marks. The format used for the manuscript submission should be as specified in Index Medicus (www.icmje.org). The list of references should only include studies that have been published or accepted for publication or have a Doi number. Journal abbreviations should follow the style used in **Cumulated Index Medicus** (http://www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng.). The number of references should be limited to 40 in research articles, 60 in reviews, 20 in case reports and 5 (max. 10) in letter to the editor. References should be given in parentheses at the end of the sentence just before the period. For example (4,5). The author (s) is responsible for the accuracy of the references. Importance should be given to the synthesis of domestic and foreign sources.

4. Figures and Table Titles

Titles should be written after the references. Each must be submitted as a separate image file (at least 300 dpi resolution, jpg).

After the article is accepted for publication, the first copy of the string will be sent to the responsible author by e-mail. In this text, only the spelling errors will be corrected and no additions or substitutions will be made. The responsible author will notify the editorial center by e-mail of the corrections within 2 days.

SOURCE WRITING EXAMPLES

Excerpt from journals;

Cesur S, Aslan T, Hoca NT, Cimen F, Tarhan G, Cifci A. Clinical importance of serum neopterin level in patients with pulmonary tuberculosis. Int J Mycobacteriol 2014; 3: 15-8 (not 15-18).

Excerpt from the book;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Excerpt from the book, which is the only author and editor;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams & Wilkins; 1996: 46-60.

Excerpt from the book with multiple authors and editors;

Schulz JE, Parran T Jr.: Principles of identification and intervention. In: Principles of Addicton Medicine, Graem AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams & Wilkins; 1998: 1-10.

If the editor is also the author of the chapter in the book;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Excerpt from PhD/Undergraduate Thesis;

Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Excerpt from an internet site;

Site name, URL address, author names, access date should be given in detail.

Giving a Doi number;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into the family market in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

For other reference styles, see "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References".

Eder I hereby declare that all or part of the material in this study has not previously been published in any place and is not currently being evaluated elsewhere for publication. electronic submissions and all kinds of pre-declarations.

Sponsorship Statement

Authors should declare, if any, the roles of sponsors of the study:

1. Design of the study 2. Data collection, analysis and interpretation of the results 3. Writing the report

CHECKLIST/CONTROL LIST

The checklist must be complete.

What should be in the article;

—Editor to Presentation Page

—Title Page

- Ethical Status,
- "Conflict of Interest"
- Orcid numbers and author information should be on this page.

—Main Text

—Copyright Transfer Form

1. **Presentation page to the Editor:** It should be written by the responsible author addressed to the editor. Phone and E-mail must be added. The title, short name of the submitted article, mamış Unpublished previously, has not been sent to any journal for review and is the original work of the authors "should include a Conflict of Interest Statement".
2. **Title page:** Turkish and English Article titles/Short titles, Authors and Institutions, Corresponding Author's postal address and telephone, **Orcid no** (mandatory since 2019) and **E-mail** addresses of all authors. **Special names and lowercase letters should be used in the title.**
3. **Main pages of the article:** Turkish and English Article Titles/Short Titles, Turkish and English Abstract and Keywords, Article Text, References, Table and Figure Titles, Tables. **This page will not contain author names or institution information.**
4. **Font:** Titles should be "Times New Roman 12 and 12 pt, with 11 pt, double-spaced line spacing and 2.5 cm indentation in all areas.
5. **Abstract**: Turkish abstract should start with ÖZ; "**Giriş/Amaç, Gereç ve Yöntem, Bulgular ve Sonuç**". The English abstract should begin with the title ABSTRACT and include the sections "**Introduction/Aim, Material and Method, Findings/Results, Conclusion"**.
6. **Keywords** should be added under the abstract in "**Keywords**", under "**Abstract**". Keywords should be at least 3, at most 6 words/words, separated by commas, and should be MeSH-compliant.
7. **M**aterial and Method section should indicate the approval of the **Ethics Committee** (it is recommended to include the place, date, ethics committee number). In articles that do not require Ethics Committee Approval, it should be stated that the Approval/Permission of the Institution has been obtained (in order to avoid Conflict of Interest). Related documents should be sent on request. It should be noted that the author (s) is responsible for ethical problems.
8. **S**tatistical terms (such as p, r, α) should **not** be used in the discussion.
9. **"Financial Support/Conflict of Interest Status";** should be stated before the bibliography and "***Acknowledgment***" should be written before the bibliography.
10. **References Representation;** should be as detailed in the spelling rules. Journal's number number "(2)" **is not** in bibliography. In articles with up to six authors, the names of all authors should be written (with the first letter of surname and first name), and for articles with seven or more authors, the first three authors should be cited as et al (et al.). The name of the manuscript should be in the form of sentence usage (**except for special names and first letter**). **The journal should be given a short name.** A space must be left between the punctuation marks after the journal name.
11. **T**ables, Graphs, Pictures and Figures should be placed under a separate title after the bibliography. **Figures/ Images** (at least 300 dpi resolution, must be **jpeg** file) and **Table**s should be submitted as one or more separate files.
12. **Copyright Transfer Form:** Must be filled in the original language of the manuscript. It must be signed by all authors. In the absence of the signature of all authors, the **Corresponding Author** may take responsibility and sign on behalf of all authors.

YAYIN KURALLARI, YAYIN POLİTİKASI, GENEL İLKELER VE GÖNDERME KURALLARI

YAZARLARA BİLGİ

Journal of Medicine and Palliative Care (JOMPAC) hakemli, açık erişimli, periyodik olarak çıkan bir dergidir. Dergi yazım kurallarına göre düzenlenmiş makaleler **DergiPark** sistemi üzerinden kabul edilmektedir. https://dergipark.org.tr/tr/pub/jompac/archive web adresinden ve **Dergipark** web sayfasından tüm sayılara ücretsiz olarak erişilebilmektedir. Amacımız uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayımlamak ve bilime katkı sağlamaktır. Yılda dört kez (**Mart, Haziran, Eylül, Aralık**) yayımlanmaktadır. Hakemli bir dergi olarak gelen yazılar biyomedikal makalelere ait **Uluslararası Tıp Dergileri Editörleri Komitesi** (www.icmje.org) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilmektedir. Dergimizde yayımlanmış makalelerin tamamına elektronik ortamdan ulaşabilir, **DergiPark** web sitemizden (https://dergipark.org.tr/en/pub/jompac) okuyabilir, indirebilirsiniz. Amacımız siz meslektaşlarımızın göndermiş olduğu yayınların karar ve yayımlanma sürecini en kısa sürede sonuca ulaştırmaktır. Dergimizin kalitesini yükseltmek için her zaman önerilere ve yapıcı eleştirilere açık olduğumuzu ve bu konudaki bildirimlere gereken hassasiyeti göstereceğimizi belirtmek isteriz. Makale işletim sisteminde ve atıflarda derginin İngilizce adı kullanılacaktır.

Journal of Medicine and Palliative Care (JOMPAC) kapsam olarak tıbbın ve tıpla ilgili sağlık bilimlerinin her branşı ile ilgili retrospektif/prospektif klinik ve laboratuvar çalışmaları, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve teknik yazıları yayımlayan bilimsel, hakemli bir dergidir. Derginin dili **İngilizce** ve **Türkçe**'dir. Makaleler hem Türkçe hem de İngilizce olarak kabul edilmektedir. Türkçe gönderilen makalelerde ayrıca İngilizce Başlık, Abstract, Keywords olmalı, İngilizce olarak gönderilen makalelerde de ayrıca Türkçe Başlık, Öz, Anahtar Kelimeler olmalıdır. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez. Editör, yardımcı editör ve yayıncı dergide yayımlanan yazılar için herhangi bir sorumluluk kabul etmez. Dergimizde yayımlanmış makalelerin tamamına elektronik ortamdan ulaşabilir, https://dergipark.org.tr/tr/pub/jompac web sitemizden okuyabilir, indirebilirsiniz. Yazıların tüm bilimsel sorumluluğu yazar(lar)a aittir.

DERGİ ADI

Journal of Medicine and Palliative Care

DERGİ ADININ KISALTMASI

J Med Palliat Care/JOMPAC/jompac

YAZIŞMA ADRESİ

Yazılar e-posta yoluyla sorumlu yazar tarafından, **DergiPark**'a kayıt olunduktan sonra **DergiPark** üzerinden https://dergipark.org.tr/tr/journal/3258/submission/step/manuscript/new linkine girilerek gönderilmelidir.

MAKALE GENEL YAZIM KURALLARI

Yazıların tüm bilimsel sorumluluğu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayımlanan yazılar için herhangi bir sorumluluk kabul etmez.

EDİTÖRİYEL ÖN KONTROL DEĞERLENDİRMESİ

Journal of Medicine and Palliative Care (JOMPAC)'e gönderilen yazılar format ve intihal açısından değerlendirilir. Formata uygun olmayan yazılar değerlendirilmeden sorumlu yazara geri gönderilir. Bu tarz bir zaman kaybının olmaması için yazım kuralları gözden geçirilmelidir. Basım için gönderilen tüm yazılar iki veya daha fazla yerli/yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayıma kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya yayıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

BİLİMSEL VE ETİK SORUMLULUK

Journal of Medicine and Palliative Care (JOMPAC)'in yayın ve yayın süreçleri, Dünya Tıbbi Editörler Derneği (World Association of Medical Editors (**WAME**)), Yayın Etiği Komitesi (Committee on Publication Ethics (**COPE**)), Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (**ICMJE**)), Bilim Editörleri Konseyi (Council of Science Editors (**CSE**)), Avrupa Bilim Editörleri Birliği (**EASE**) ve Ulusal Bilgi Standartları Organizasyonu (National Information Standards Organization (NISO)) kurallarına uygun olarak şekillendirilmiştir. Dergi, Bilimsel Yayıncılıkta Şeffaflık ve En İyi Uygulama İlkeleri'ne (Principles of Transparency and Best Practice in Scholarly Publishing (**doaj.org/bestpractice**)) uygundur.

Klinik araştırma makalelerinin protokolü Etik Komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda "**Gereç ve Yöntem**" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın **Helsinki İlkeler Deklarasyonu**'na (**https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/**) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm kişilerin **Bilgilendirilmiş Onam Formu'**nu imzaladığı metin içinde belirtilmelidir. **Journal of Medicine and Palliative Care (JOMPAC)'**e gönderilen makalelerdeki çalışmaların **Helsinki İlkeler Deklarasyonu'**na uygun olarak yapıldığı, kurumsal etik ve yasal izinlerin alındığı varsayılacak ve bu konuda sorumluluk kabul edilmeyecektir. Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntem bölümünde hayvan haklarını **Guide for the Care and Use of Laboratory Animals** (**https://www.nap.edu/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals**) prensipleri doğrultusunda koruduklarını, çalışmalarında ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır. Olgu sunumlarında hastanın kimliğinin ortaya çıkmasına bakılmaksızın hastalardan "Bilgilendirilmiş rıza" alınmalıdır. Makalede Etik Kurul Onayı alınması gerekli ise; alınan belge makale ile birlikte gönderilmelidir. Makale yazarlar tarafından **akademik intihal önleme programı**ndan geçirilmelidir. Makalenin etik kurallara uygunluğu yazarların sorumluluğundadır.

Tüm makale başvuruları intihal araştırılması için taranmalı ve sonrasında dergi sistemine yüklenmelidir. İntihal, atıf manipülasyonu ve gerçek olmayan verilerden şüphelenilmesi veya araştırmaların kötüye kullanılması durumunda, yayın kurulu **COPE** yönergelerine uygun olarak hareket eder. Bakınız: **Guidance from the Committee on Publication Ethics** (**COPE**).

Yazar olarak listelenen her bireyin **Uluslararası Tıp Dergisi Editörleri Komitesi** (**ICMJE - www.icmje.org**) tarafından önerilen yazarlık kriterlerini karşılaması gerekir. **ICMJE** yazarlığın aşağıdaki 4 kritere dayanmasını önerir: (1) Çalışmanın tasarımı, verilerin elde edilmesi, analizi veya yorumlanması (2) Dergiye gönderilecek kopyanın hazırlanması veya bu kopyanın içeriğini bilimsel olarak etkileyecek ve ileriye götürecek şekilde katkı sağlanması (3) Yayımlanacak kopyanın son onayı (4) Çalışmanın tüm bölümleri hakkında bilgi sahibi olma ve tüm bölümleri hakkında sorumluluğu alma.

Bir yazar, yaptığı çalışmanın bölümlerinden sorumlu olmanın yanı sıra, çalışmanın diğer belirli bölümlerinden hangi ortak yazarların sorumlu olduğunu bilmeli ayrıca yazarlar, ortak yazarlarının katkılarının bütünlüğüne güvenmelidir. Yazar olarak atananların tümü yazarlık için dört kriteri de karşılamalı ve dört kriteri karşılayanlar yazar olarak tanımlanmalıdır. Dört kriterin tümünü karşılamayanlara makalenin başlık sayfasında teşekkür edilmelidir. Yayın kurulu yazarlık şartlarını karşılamayan bir kişinin yazar olarak eklendiğinden şüphe ederse yazı daha fazla incelenmeksizin reddedilecektir.

Journal of Medicine and Palliative Care (JOMPAC)'e gönderilen bir çalışma için bireylerden veya kurumlardan alınan mali hibeler veya diğer destekler Editör Kurulu'na bildirilmelidir. Potansiyel bir çıkar çatışmasını bildirmek için, **ICMJE Potansiyel Çıkar Çatışması Bildirim Formu**, katkıda bulunan tüm yazarlar tarafından imzalanmalı ve gönderilmelidir. Editörlerin, yazarların veya hakemlerin çıkar çatışması olasılığı, derginin Editör Kurulu tarafından **COPE** ve **ICMJE** yönergeleri kapsamında çözümlenecektir. Derginin Editör Kurulu, tüm itiraz durumlarını **COPE** kılavuzları kapsamında ele almaktadır. Bu gibi durumlarda, yazarların itirazları ile ilgili olarak yazı işleri bürosu ile doğrudan temasa geçmeleri gerekmektedir. Gerektiğinde, dergi içinde çözülemeyen olayları çözmek için bir kamu denetçisi atanabilir. Baş editör itiraz durumlarında karar alma sürecinde alınacak kararlarla ilgili nihai otoritedir. Yazarlar, dergiye bir makale gönderirken, yazıların telif haklarını **Journal of Medicine and Palliative Care (JOMPAC)**'e devretmiş olmayı kabul ederler. Yazı yayımlanmamak üzere reddedilirse veya herhangi bir sebepten geri çekilirse telif hakkı yazarlara geri verilir.Şekiller, tablolar veya diğer basılı materyaller de dahil olmak üzere basılı ve elektronik formatta daha önce yayımlanmış içerik kullanılıyorsa yazarlar telif hakları sahiplerinden gerekli izinleri almalıdır. Bu konudaki hukuki, finansal ve cezai yükümlülükler yazarlara aittir. **Journal of Medicine and Palliative Care'de (JOMPAC)** yayımlanan makalelerde belirtilen ifade veya görüşler, editörlerin, yayın kurulunun veya yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmez. Yayınlanan içerikle ilgili nihai sorumluluk yazarlara aittir.

MAKALE "BAŞKA BİR YERDE YAYIMLANMAMIŞTIR" İBARESİ

Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

YAYIN HAKKI DEVİR FORMU

Telif Hakkı Devir Formu (https://dergipark.org.tr/tr/journal/3258/file/3177/show) linkinden temin edilebilir. Makalenin ana dilinde (makalenin dili İngilizce ise, İngilizce olmalıdır, makalenin dili Türkçe ise, Türkçe olmalıdır) doldurulmalı, makale (https://dergipark.org.tr/tr/journal/3258/submission/step/manuscript/new) adresi üzerinden yüklenirken on-line olarak gönderilmelidir 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

YAZIM DİLİ KONTROLÜ

Derginin yayın dili **Türkçe** ve **İngilizce**'dir, makaleler hem Türkçe hem de İngilizce olarak kabul edilmektedir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu nedenle Türk Dil Kurumu'nun Türkçe sözlüğü veya www.tdk.org.tr adresi ayrıca Türk tıbbi derneklerinin kendi branşlarına ait terimler sözlüğü esas alınmalıdır. İngilizce makaleler ve İngilizce Abstract gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanımız ve redaksiyon komitemiz tarafından düzeltilmektedir.

İSTATİSTİK DEĞERLENDİRMESİ

Tüm prospektif, deneysel ve retrospektif araştırma makaleleri istatistik yönünden (gerekirse istatistik uzmanı tarafından) değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir.

YAYIMA KABUL EDİLMESİ

Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak yayım sırasına alınır. Her yazı için bir **Doi** numarası alınır.

MAKALE YAZIM KURALLARI

Yazılar Microsoft Word programı ile çift satır aralıklı ve başlık yazıları (Makale Adı, Öz, Abstract, Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Kaynaklar vs.) 12 punto olarak, makalenin diğer kısımları 11 punto olacak şekilde, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New Roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil, tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçe'de ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Araştırma makalesi ve derleme 4000, olgu sunumu 2500, editöre mektup 500 kelimeyi (ABSTRACT/ÖZ ve REFERENCES/KAYNAKLAR hariç olmak üzere) geçmemelidir. Öz sayfasından itibaren sayfalar numaralandırılmalıdır.

Yazının Bölümleri

1. Editöre Sunum Sayfası

Journal of Medicine and Palliative Care (Tıp ve Palyatif Bakım Dergisi)'de yayımlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığı ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığı, "**Maddi Destek ve Çıkar İlişkisi**" durumu, dil ve istatistik kontrolünün yapıldığı belirtilmelidir.

2. Başlık Sayfası

Sayfa başında gönderilen makalenin kategorisi belirtilmedir (klinik analiz, araştırma makalesi, deneysel çalışma, olgu sunumu, derleme vs). Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, çalıştıkları kurum, klinik, şehir ve ülke yazar isimleri altına eklenmelidir. Başlık sayfasında her yazarın **Orcid no** bilgisi, **e-posta** adresi olmalıdır. Bu sayfada Sorumlu Yazar belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir (Dergimizin formatı gereği adres bilgileri, kurumları makale dili Türkçe ise Türkçe olarak, İngilizce ise İngilizce olarak belirtilmelidir). Kongrelerde sunulan Sözlü veya Poster bildiriler başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmelidir.

3. Makale Dosyası

Yazar ve kurum isimleri bulunmamalıdır, bu bilgiler sadece başlık sayfasında olmalıdır.

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemeli, Türkçe ve İngilizce olarak yazılmalıdır. Öz: Türkçe ve İngilizce (Abstract) yazılmalıdır. Araştırma makalelerinde Öz; Amaç, Gereç, Yöntem, Bulgular ve Sonuç bölümlerine ayrılmalı ve 400 kelimeyi geçmemelidir. Derleme, olgu sunumları ve benzerlerinde Öz; kısa ve tek paragraflık olmalı, derlemelerde 300, olgu sunumlarında 250 kelimeyi geçmemelidir.

Anahtar Kelimeler: Türkçe Öz'ün ve İngilizce Abstract'ın sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce Anahtar Kelimeler (Keywords) "**Medical Subject Headings (MESH)**"e uygun (www.nlm.nih.gov/mesh/MBrowser.html) olarak verilmelidir. Türkçe Anahtar Kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda bire bir Türkçe tercümesi verilmelidir.

Şekil, Fotoğraf, Tablo ve Grafikler: Metin içinde geçtiği yerlerde ilgili cümlenin sonunda belirtilmeli, metin içine yerleştirilmemeli, kaynaklardan sonra metin sonuna eklenmelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Makale yazarlar tarafından akademik intihal önleme programından geçirilmelidir. Resim/fotoğraf jpeg ve en az 300 dpi çözünürlükte olmalıdır.

Metin Bölümleri: Yayımlanmak üzere gönderilecek yazı örnekleri şu şekildedir.

Editöriyel Yorum/Tartışma: Yayınlanan orijinal araştırma makaleleri ile ilgili, araştırmanın yazarları dışındaki, o konunun uzmanı tarafından değerlendirilmesidir. Dergide makalelerden önce yayımlanır.

Araştırma Makalesi: Prospektif-retrospektif ve her türlü deneysel çalışmalar yayımlanabilmektedir. Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç olarak düzenlenmelidir. Öz (yaklaşık 400 kelime; amaç, gereç ve yöntem, bulgular ve sonuç bölümlerinden oluşan Türkçe ve İngilizce), Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Kaynaklar.

Derleme: Davet edilen yazarlar tarafından veya doğrudan hazırlanabilir. Tıbbi özellik gösteren her türlü konu için son tıp literatürünü de içine alacak şekilde hazırlanabilir. Öz (yaklaşık 300 kelime, bölümsüz, Türkçe ve İngilizce), konu ile ilgili Başlıklar, Kaynaklar.

Olgu Sunumu: Tanı ve tedavide farklılık gösteren veya nadir görülen makalelerdir. Yeterli sayıda fotoğraflarla ve şemalarla desteklenmiş olmalıdır. Öz (yaklaşık 250 kelime; bölümsüz; Türkçe ve İngilizce), Giriş, Olgu sunumu, Tartışma, Sonuç olarak düzenlenmelidir.

Editöre Mektup: Dergide son bir yıl içinde yayımlanan makaleler ile ilgili okuyucuların değişik görüş, tecrübe ve sorularını içeren en fazla 500 kelimelik yazılardır. Başlık ve Öz bölümleri yoktur. Kaynak sayısı 5 (en fazla 10) ile sınırlıdır. Hangi makaleye (sayı, tarih verilerek) ithaf olunduğu belirtilmeli ve sonunda yazarın ismi, kurumu, adresi bulunmalıdır. Mektuba cevap, editör veya makalenin yazar(lar)ı tarafından, yine dergide yayımlanarak verilir.

Eğitim: Derginin kapsamı içinde güncel konularda okuyucuya mesaj veren son klinik ve laboratuvar uygulamaların da desteklediği bilimsel makalelerdir. Öz (yaklaşık 250 kelime; bölümsüz; Türkçe ve İngilizce), konu ile ilgili Başlıklar, Kaynaklar.

Kitap Değerlendirmeleri: Derginin kapsamı içinde güncel değeri olan ulusal veya uluslararası kabul görmüş kitapların değerlendirmeleridir.

KAYNAKLARDAN HEMEN ÖNCE BELİRTİLMESİ GEREKENLER

ETİK BEYANLAR

Etik Kurul Onayı (Eğer gerekiyorsa): "Çalışma için …….. Etik Kurulu'ndan .....tarih ve ..... sayı /karar no ile etik kurul onayı alınmıştır." ifadesiyle yazarlar tarafından belirtilmelidir.

Aydınlatılmış Onam: Bu çalışmaya katılan hasta(lar)dan yazılı onam alınmıştır (Olgu sunumlarında ve kişilerle yapılan prospektif çalışmalarda mutlaka olmalıdır. Eğer çalışma retrospektif ise: "Aydınlatılmış Onam: Çalışma retrospektif olarak dizayn edildiği için hastalardan aydınlatılmış onam alınmamıştır." ifadesiyle yazarlar tarafından belirtilmelidir.

Hakem Değerlendirme Süreci: "Harici çift kör hakem değerlendirmesi" ifadesiyle yazarlar tarafından belirtilmelidir.

Çıkar Çatışması: "Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir." ifadesiyle yazarlar tarafından belirtilmelidir.

Finansal Destek: "Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir" ifadesiyle yazarlar tarafından belirtilmelidir.

Yazar Katkıları: "Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir." ifadesiyle yazarlar tarafından belirtilmelidir.

Teşekkür Yazısı: Varsa kaynaklardan önce yazılmalıdır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar (soyadı ve adının ilk harfi olacak şekilde olmalı, yazar isimleri birbirinden virgül ile ayırılmalı) belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmeli, makale ismi (Tümce şeklinde sadece cümlenin ilk harfi ve özel isimlerin ilk harfi büyük olacak), kısa dergi adı, yıl, cilt, kısa sayfa no (15-8. şeklinde olacak, 15-18 olmayacak) eklenmeli ve noktalama işaretleri arasında birer boşluk bırakılmalıdır. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www. icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya Doi numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları **Cumulated Index Medicus**'ta kullanılan stile uymalıdır (http://www2.bg.am.poznan.pl/czasopisma/ medicus.php?lang=eng.). Kaynak sayısının araştırma makalelerinde 40, derlemelerde 60, olgu sunumlarında 20, editöre mektupta 5 (en fazla 10) ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce parantez kullanılarak belirtilmelidir. Örneğin (4,5). Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

4. Şekil, Grafik, Resim ve Tablo Başlıkları

Başlıklar kaynaklardan sonra yazılmalıdır. Her biri ayrı bir görüntü dosyası (en az 300 dpi çözünürlükte, jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra Dizginin ilk düzeltme nüshası sorumlu yazara e-posta yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-posta ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı;

Cesur S, Aslan T, Hoca NT, Çimen F, Tarhan G, Çifci A. Clinical importance of serum neopterin level in patients with pulmonary tuberculosis. Int J Mycobacteriol 2014; 3: 15-8 (15-18 değil).

Kitaptan yapılan alıntı;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı;

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998: 1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Doktora/lisans tezinden alıntı;

Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı;

Sitenin adı, URL adresi, yazar adları, erişim tarihi detaylı olarak verilmelidir.

Doi numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into family prac- tice in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi:10.1093/ecam/nep019).

Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

"Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayımlanmadığını ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim." Bu 400 kelimeye kadar olan özler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir.

Sponsorluk Beyanı

Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

1. Çalışmanın dizaynı 2. Veri toplanması, analizi ve sonuçların yorumlanması 3. Raporun yazılması

KONTROL LİSTESİ

Kontrol listesindekiler eksiksiz yapılmalıdır.

Makalede mutlaka olması gerekenler;

—Editöre Sunum Sayfası

—Başlık Sayfası

- Etik Durum,
- "Çıkar Çatışması Durumu" belirtir cümle,
- Orcid numaraları ve yazar bilgileri bu sayfada olmalıdır.

—Ana Metin

—Telif Hakkı Devri Formu

1. **Editöre Sunum Sayfası:** Sorumlu Yazar tarafından editöre hitaben yazılmış olmalıdır. Telefon ve E-posta eklenmelidir. Gönderilen makalenin adı, kısa adı, "Daha önceden yayımlanmamış, şu an herhangi bir dergiye değerlendirilmek üzere gönderilmemiştir ve yazarların kendi orijinal çalışmasıdır" ibaresi, "Çıkar Çatışması Beyanı" içermelidir.
2. **Başlık sayfası:** Türkçe ve İngilizce Makale başlıkları/Kısa başlıklar, Yazarlar ve Kurumları, Sorumlu Yazar posta adresi ve telefon, tüm yazarların **Orcid no** (2019 yılından itibaren zorunludur) ve **E-posta** adresleri. **Başlıkta özel isimler ve ilk harf dışında küçük harf kullanılmalıdır**.
3. **Makalenin Ana Metin sayfaları:** Türkçe ve İngilizce Makale Başlıkları/Kısa Başlıklar, Türkçe ve İngilizce Öz/Abstract ve Anahtar Kelimeler/Keywords, Makale Metni, Kaynaklar, Tablo ve Şekil Başlıkları, Tablolar. **Bu sayfada yazar isimleri, kurum bilgileri olmayacaktır.**
4. **Yazı tipi:** Başlıklarda "Times New Roman" ve 12 punto olmalı, makalenin diğer kısımlarında 11 punto, çift boşluklu satır arası ve tüm alanlarda 2,5 cm girinti ayarıyla yazılmalıdır.
5. **Öz/Abstract:** Türkçe özet **ÖZ** ile başlamalı; "**Giriş/Amaç, Gereç ve Yöntem, Bulgular ve Sonuç**" kısımlarını içermelidir. İngilizce özet **ABSTRACT** başlığıyla başlamalı "**Introduction/Aim, Material and Method, Findings/Results, Conclusion**" kısımlarını içermelidir.
6. **Anahtar Kelimeler/Keywords:** Türkçe Öz kısmının altına "**Anahtar Kelimeler**", İngilizce "Abstract" kısmının altında "**Keywords**" (birleşik) halde eklenmelidir. Anahtar kelimeler en az 3, en çok 6 kelime/sözcük olmalı, birbirlerinden virgülle ayırılmalı ve MeSH'e uygun olmalıdır.
7. **G**ereç ve Yöntem kısmında **Etik Kurul Onayı** alındığı (Alındığı yer, tarih, etik kurul no olacak şekilde yazılması önerilir) belirtilmelidir. Etik Kurul Onayı gerektirmeyen makalelerde Kurum Onayı/İzni alındığı (Çıkar Çatışması olmaması için) belirtilmelidir. İlgili belgeler talep edildiğinde gönderilmelidir. Etik problemlerde sorumluluğun yazar(lar)da olduğu unutulmamalıdır.
8. **T**artışmada istatistiksel terimler (p, r, α gibi) **kullanılmamalıdır.**
9. **"Maddi Destek/Çıkar Çatışması Durumu"** kaynakçadan önce belirtilmeli, "***Teşekkür Yazısı***" varsa kaynakçadan önce yazılmalıdır.
10. **Kaynak Gösterimi;** yazım kurallarında detaylı anlatıldığı gibi olmalıdır. Derginin sayı numarası "(2)" parantez içinde olacak şekilde bizim kaynakça gösterimimizde **bulunmamaktadır.** Altı yazara kadar yazarı olan makalelerde bütün yazarların adı yazılmalı (Soyadı ve Adının ilk harfi olacak şekilde), yedi ve daha üstü yazarlı makalelerde ilk üç yazar, et al. (ve ark.) şeklinde kaynak gösterilmelidir. Makalenin adı Tümce kullanımı şeklinde (**özel isimler ve ilk harf dışında küçük harf kullanılmalıdır**) olmalıdır. **Derginin kısa adı verilmelidir.** Dergi adından sonraki noktalama işaretleri arasında birer boşluk bırakılmalıdır.
11. **T**ablo, Şekil ve Resimler ayrı bir başlık altında kaynakçadan sonra yerleştirilmelidir. **Şekil/Resim** (En az 300 dpi çözünürlükte, **jpeg** dosyası olmalıdır) ve **Tablo**lar ayrı bir veya daha fazla dosya halinde gönderilmelidir.
12. **Telif Hakkı Devri Formu:** Makalenin asıl dilinde doldurulmalıdır. Tüm yazarlar tarafından imzalanmalıdır. Tüm yazarların imzasının olmadığı durumlarda **Sorumlu Yazar** tüm yazarlar adına sorumluluğu alarak imzalayabilir.