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Phone: +90 362 408 25 15

Fax: +90 362 408 25 15

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Araştırma Makalesi (Research Article)
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DULOKSETİN HİDROKLORÜRÜN DU-145 İNSAN PROSTAT KANSER HÜCRELERİ ÜZERİNE SİTOTOKSİK ETKİSİNİN ARAŞTIRILMASI

Özge KESGİN[1], Serap ŞAHİN[1]*

[1]*Afyonkarahisar Health Sciences University, Faculty of Pharmacy, Department of Biochemistry, 03030, Afyonkarhisar, Türkiye*

Özet: Prostat kanseri (PKa), dünya çapında en yaygın kanserlerden birisi olup kansere bağlı ölümlerin büyük bir kısmını oluşturmaktadır. Bir serotonin-nöradrenalin geri alım inhibitörü (SNGI) olan duloksetin, hem norepinefrin hem de serotoninin geri alımının inhibisyonu yoluyla antidepresan bir rol oynamaktadır. Duloksetin hidroklorürün insan prostat kanser hücresi (DU-145) üzerine sitotoksik etkisi ile ilgili çalışma bulunmamaktadır. Çalışmamızda, duloksetin hidroklorür ve sisplatinin DU-145 prostat kanseri ve sağlıklı fare fibroblast hücreleri (L-929) üzerine sitotoksik etkileri 3-[4,5-Dimetiltiyazol-2-İl]-2,5-Difenil-Tetrazolyum Bromür (MTT) yöntemi ile araştırılmıştır. Sisplatinin hem DU-145 prostat kanser hücrelerinde hem de L-929 sağlıklı hücrelerde 24 saat uygulama süresi için IC_{50} değerleri; >50 µM olarak hesaplanmıştır. Duloksetin hidroklorürün 24 saat uygulama süresinde DU-145 ve L-929 hücreleri için IC_{50} değerleri sırasıyla; 28,76 ± 0,012 µM ve 34,92 ± 0,012 µM olarak hesaplanmıştır. Hücrelere, duloksetin hidroklorür ve sisplatinin birlikte uygulanması sonucunda IC_{50} değerleri; DU-145 hücre hattı için 30,51 ± 0,010 µM ve L-929 hücre hattı için 36,92 ± 0,013 µM olarak hesaplanmıştır. Düşük IC_{50} değeri yüksek antikanser aktiviteye işaret etmektedir. Sonuçlarımız DU-145 hücrelerine karşı, duloksetin hidroklorürün sisplatine göre daha yüksek sitotoksik etkinliğe sahip olduğunu, duloksetin hidroklorürün sisplatin ile birlikte uygulanmasının sisplatin ve duloksetin hidroklorürün ayrı ayrı uygulanması ile benzer sitotoksik etkinliğe sahip olduğunu göstermiştir.

Anahtar kelimeler: Duloksetin hidroklorür, Hücre kültürü, Prostat kanseri, Sitotoksisite, MTT

Investigation of the Cytotoxic Effect of Duloxetine Hydrochloride on DU-145 Human Prostate Cancer Cells

Abstract: Prostate cancer (PCa) is one of the most common cancers worldwide and accounts for a significant proportion of cancer-related deaths. Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), exerts an antidepressant role by inhibiting the reuptake of both norepinephrine and serotonin. There is no study on the cytotoxic effect of duloxetine hydrochloride on human prostate cancer cells (DU-145). In our study, the cytotoxic effects of duloxetine hydrochloride and cisplatin on DU-145 prostate cancer cells and healthy mouse fibroblast cells (L-929) were investigated using the 3-[4,5-Dimethylthiazol-2-Yl]-2,5-Diphenyl-Tetrazolium Bromide (MTT) assay. For cisplatin, the IC_{50} values for both DU-145 prostate cancer cells and L-929 healthy cell after 24-hour exposure were calculated as >50 µM. For duloxetine hydrochloride, the IC_{50} values after 24-hour exposure were calculated as 28.76 ± 0.012 µM for DU-145 cells and 34.92 ± 0.012 µM for L-929 cells. When duloxetine hydrochloride and cisplatin were applied together, the IC_{50} values were calculated as 30.51 ± 0.010 µM for DU-145 cells and 36.92 ± 0.013 µM for L-929 cells. A lower IC_{50} value indicates higher anticancer activity. Our results suggest that duloxetine hydrochloride exhibits higher cytotoxic activity against DU-145 cells compared to cisplatin. Additionally, the combined application of duloxetine hydrochloride and cisplatin showed a similar cytotoxic effect compared to that of the individual applications of cisplatin and duloxetine hydrochloride.

Keywords: Duloxetine hydrochloride, Cell culture, Prostate cancer, Cytotoxicity, MTT

***Sorumlu yazar (Corresponding author):** Afyonkarahisar Health Sciences University, Faculty of Pharmacy, Department of Biochemistry, 03030, Afyonkarhisar, Türkiye
E mail: wserap@yahoo.com (S. ŞAHİN)
Özge KESGİN https://orcid.org/0009-0001-8601-4221
Serap ŞAHİN https://orcid.org/0000-0003-1057-2558

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1. Giriş

Kanser tüm dünyada çok sayıda ölüme neden olan bir hastalık olup, en son istatistikler, kötü huylu tümörlerden (kanser) ölümlerin tüm ölümlerin %20'sinden fazlasını oluşturduğunu ve kanserin, insan sağlığına yönelik en önemli halk sağlığı tehditlerinden biri haline geldiğini göstermektedir (Zheng vd., 2023). Uygun tedavi seçeneklerinin olmaması durumunda 2030 yılına gelindiğinde, 26 milyon yeni kanser tanısının ve 17 milyon kansere bağlı ölümün yaşanacağı öngörülmektedir (Torre vd., 2016). Prostat kanseri erkekler arasında ölüme neden olan önemli kanser türleri arasında yer almakta olup tedavisi için yeni stratejilerin geliştirilmesi önem arz etmektedir. Dünya Sağlık Örgütü (DSÖ) 2022 yılı kanser verilerine göre, prostat kanserinin; tüm kanser vakaları arasında 4. sırada en yaygın görülen (1.467.854 kişi; %7,3), erkeklerde ise 2. sırada en yagın görülen (1.467.854 kişi, % 14,2) kanser türü olduğu ve erkeklerde 5. sırada en çok ölüme neden olan (397.430 kişi, %7,3) kanser türü

olduğu bildirilmiştir (WHO, 2022).

Duloksetin (CYMBALTA), ağızdan alınan CYMBALTA®30 mg ve CYMBALTA® 60 mg gastro-rezistan sert kapsülün etkin maddesi olup, her gastro-rezistan sert kapsül 30 mg ve 60 mg duloksetine eşdeğer miktarda enterik kaplı duloksetin hidroklorür pelletleri içermektedir. CYMBALTA merkezi sinir sisteminde ağrı iletimini azaltan serotonin-nöradrenalin geri alım intibitörü (SNGI) grubu bir antidepresandır. Nöradrenerjik etkileri ağrılı fiziksel belirtilerin tedavisine katkı sağlamaktadır (Bymaster vd., 2001). Bu nedenle kanser hastalarında ağrıyı önleme ve genel anksiyite bozukluğu için reçete edilen ilaçlar arasında yer almaktadır (Pergolizzi vd., 2013). Adjuvanların etkisinin araştırılması, tümör büyümesini arttırmayan ilaçların seçilmesi açısından önemlidir. Sisplatin, en etkili kemoterapi ilaçlarından birisi olup akciğer kanseri, yumurtalık kanseri, meme kanseri ve prostat kanseri dahil olmak üzere birçok farklı kanser türünün tedavisinde yaygın olarak kullanılmaktadır (Dasari ve Tchounwou, 2014; Hager vd., 2016; Rottenberg vd., 2021). Duloksetin hidroklorürün DU-145 prostat kanser hücre hattında tek başına ve sisplatin ile birlikte uygulanmasının sitotoksik etkinliği ile ilgili herhangi bir çalışma bulunmamaktadır. Bu çalışmada, duloksetin hidroklorürün hem tek başına hem de sisplatin ile birlikte DU-145 insan prostat kanser hücreleri üzerine sitotoksik etkinliği ilk defa araştırılmıştır. Ayrıca duloksetin hidroklorürün, L-929 sağlıklı fare fibroblast hücreleri üzerine sitotoksik etkinliği araştırılarak kanser ve sağlıklı hücreler arasındaki seçicilik özelliği de belirlenmiştir.

2. Materyal ve Yöntem

2.1. Materyal

İnsan prostat kanser hücre hattı (DU-145, ATCC ® HTB-81™), %10 (v/v) fetal bovine serum (FBS, Gibco, USA), 100 Unit/ml penicillin ve 100 µg/ml streptomycin (Sigma, GA) içeren DMEM besiyeri (Sigma, GA), sağlıklı fare fibroblast hücreleri (L-929, ECACC (NCTC), RPMI 1640 besiyeri (Sigma, GA) ilgili firmalardan ticari olarak satın alındı.

2.2. Yöntem

2.2.1. MTT analizi

DU-145, %10 (v/v) FBS, 100 Unit/ml penicillin ve 100 µg/ml streptomycin içeren DMEM besiyerinde, L-929 ise %10 (v/v) FBS, 100 Unit/ml penicillin ve 100 µg/ml streptomycin içeren RPMI 1640 besiyerinde %95 nem ve %5 CO_2 içeren 37 °C inkübatörde kültüre edildi. DU-145 ve L-929 hücreleri pasajlanarak 96-kuyulu plakalara ekildi ($1x10^4$ hücre/kuyu) ve uygulamadan önce hücrelerin plakalarda büyümeleri için 24 saat inkübe edilmiştir. Duloksetin hidroklorür ve sisplatinin farklı derişimlerdeki (0–50 µM) çözeltileri dimetilsülfoksitte (DMSO) (Sigma, GA) çözülerek hazırlanmıştır. Farklı derişimlerde duloksetin hidroklorür ve sisplatin uygulanan DU-145 ve L-929 hücreleri 24 saat inkübe edilmiştir. 24 saatin sonunda her bir kuyucuğa MTT (Sigma, GA) çözeltisinden (pH 7,4 PBS içerisinde) 10 µL eklenmiş ve hücreler tekrar inkübatörde 3 saat süreyle inkübe edilmiştir. 3 saatin sonunda MTT içeren besi yeri aspire edildikten sonra her bir kuyuya 100 µL DMSO eklendi ve 15 dk boyunca oda sıcaklığında karıştırıcı üzerinde inkübe edilmiştir. Absorbans değerleri 570 nm dalga boyunda ELISA mikroplaka okuyucu BioTek (Epoch, USA) kullanılarak okunmuştur [Mossman 1983]. Sisplatinin IC_{50} derişimi ile farklı derişimlerde duloksetin hidroklorürün birlikte uygulandığı hücreler için yukarıdaki deney tekrarlanarak ve sitotoksik aktivitede değişiklik olup olmadığı belirlenmiştir.

Negatif kontrol olarak DMSO uygulanan hücreler kullanılmış ve % hücre canlılığı aşağıdaki denklemden (denklem 1) hesaplamıştır.

$$\%\ \text{Hücre canlılığı} = (\text{Örnek absorbansı}/\text{Negatif Kontrol absorbansı}) \times 100 \quad (1)$$

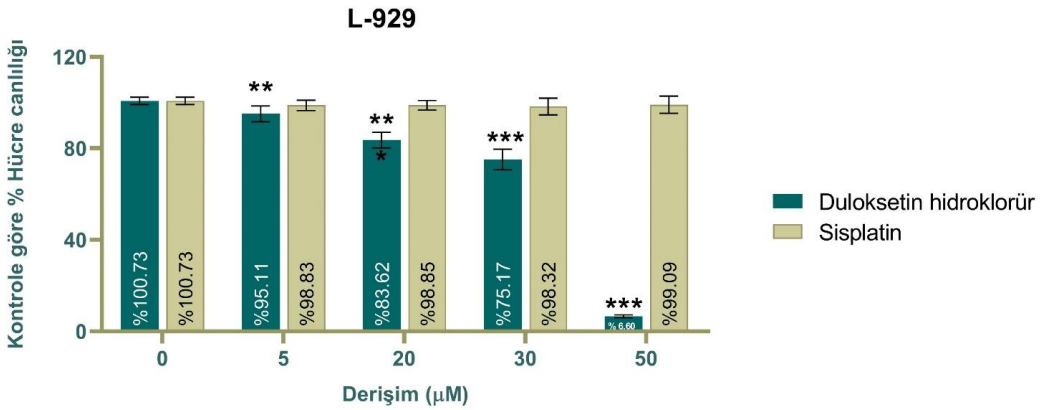
2.3. İstatistiksel Analiz

Sitotoksik aktivite deneylerindeki tüm ölçümler altı tekrarlı olarak yapılmış (n=6) ve sonuçlar standart sapmalarıyla (± SS) verilmiştir. Veri analizleri GraphPad Prism8 programı (GraphPad Software, San Diego, CA, ABD) kullanılarak yapılmış ve hücrelerinin % 50'sini öldürdükleri derişim değerleri (IC_{50}) değerleri hesaplanmıştır. Tüm veriler normallik açısından test edilmiştir. Normal dağılım gösteren verilerde grupların karşılaştırılmasında tek yönlü varyans analizi ve gruplar arası fark saptandığında posthoc Dunnett çoklu karşılaştırma testi uygulanmıştır (Genç ve Soysal, 2018). İstatistik anlamlılık sınır değeri *P<0,05, **P<0,005 ve ***P<0.0001 olarak kabul edilmiştir.

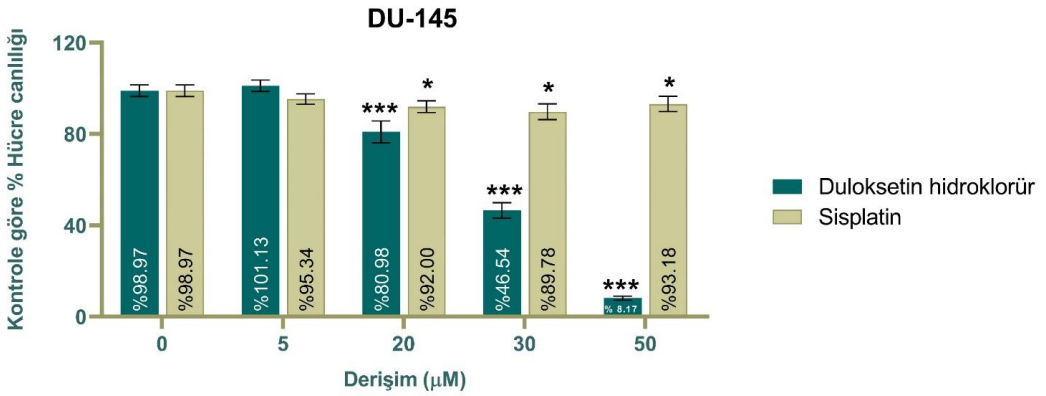
3. Bulgular

Deneyin ilk aşamasında, duloksetin hidroklorür ve sisplatinin farklı derişimlerinin (0-50 µM), 24 saat uygulama süresi için, L-929 sağlıklı fare fibroblast hücreleri ve DU-145 insan prostat kanser hücrelerinin canlılığı üzerine MTT kolorimetrik yöntemi ile belirlenen etkileri Şekil 1 ve Şekil 2'de gösterilmiştir. Şekil 1, ve Şekil 2'de x ekseni sisplatin ve duloksetin hidroklorür derişimlerini (0-50 µM), y ekseni ise kanser ve sağlıklı hücrelerin kontrole göre canlılık oranlarını göstermektedir. Sisplatin ve duloksetin hidroklorürün artan derişimlerine bağlı olarak sağlıklı ve kanser hücrelerinin canlılık oranlarında azalma gözlenmiştir. Sisplatin ve duloksetin hidroklorürün hücre canlılığı üzerine etkinliği karşılaştırıldığında, duloksetin hidroklorürün sisplatine göre daha yüksek hücre ölümüne neden olduğu ve daha yüksek toksik etki gösterdiği belirlenmiştir (Şekil 1, ve Şekil 2).

Şekil 1 ve Şekil 2'de elde edilmiş verilerden yararlanılarak sisplatin ve duloksetin hidroklorürün L-929 ve DU-145 hücreleri için IC_{50} hesaplanmıştır (Tablo 1). Sisplatin hem DU-145 prostat kanser hücrelerinde hem de L-929 sağlıklı hücrelerde 24 saat uygulama süresi için IC_{50} değerleri; >50 µM olarak hesaplanmıştır.



Şekil 1. Duloksetin hidroklorür ve sisplatinin L-929 sağlıklı fare fibroblast hücreleri üzerine sitotoksik etkisi (24 saat). Deneyler 6 tekrarlı yapılmıştır (n=6) ve sonuçlar ±SS olarak verilmiştir. (Kontrole göre anlamlılık **P<0,005, ***P<0,0001).



Şekil 2. Duloksetin hidroklorür ve sisplatinin DU-145 insan prostat kanser hücreleri üzerine sitotoksik etkisi (24 saat). Deneyler 6 tekrarlı yapılmıştır (n=6) ve sonuçlar ±SS olarak verilmiştir. (Kontrole göre anlamlılık *P<0,05, ***P<0,0001).

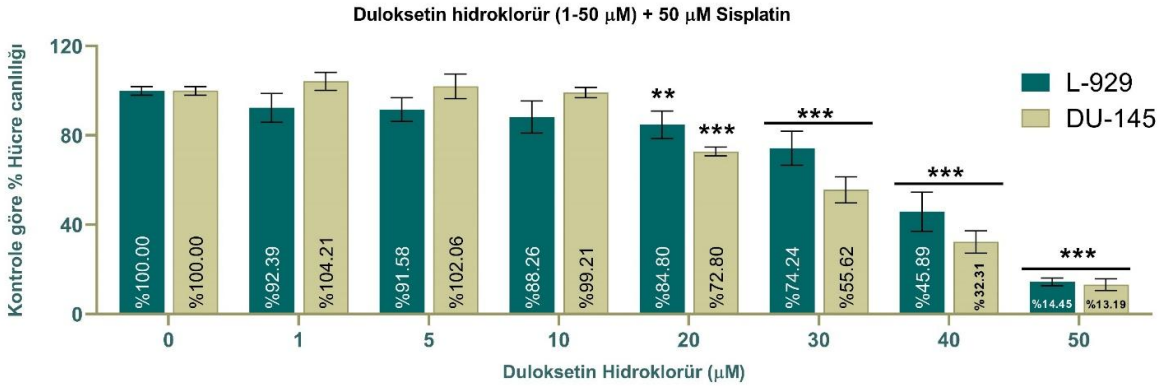
Tablo 1. Sisplatin ve duloksetin hidroklorür'ün ayrı ayrı ve bir arada, L-929 sağlıklı fare fibroblast hücreleri ve DU-145 insan prostat kanser hücreleri için 24 saat ugulama süresi için IC_{50} (µM)

Hücre Hattı	Duloksetin Hidroklorür	Sisplatin	Duloksetin Hidroklorür + Sisplatin
DU-145	28,76 ± 0,012	>50	30,51 ± 0,010
L-929 [a]	34,92 ± 0,012	>50	36,92 ± 0,013

* IC_{50} değerleri MTT yöntemi ile 24 saat inkübasyon süreleri için hesaplanmıştır. Değerler ortalama ± SS olarak verilmiştir (n=6), [a]Sağlıklı hücre.

Vizcarra-Ramos vd. (2024)'nın yaptığı çalışmada $1x10^4$ DU-145/GFP hücresi, sisplatinin farklı derişimleri (10, 30 ve 50 µM) ile 24 ve 48 saat inkübe edilmiş ve sisplatinin IC_{50} değerleri 42 µM ve 20 µM olarak hesaplanmıştır. Li vd. (2010) tarafından yapılan çalışmada, $5x10^3$ DU-145 hücresi sisplatinin farlı derişimleri (0 -512 µM) ile 24, 48 ve 72 saat inkübe edilmiş ve sisplatinin IC_{50} değerleri 192 µM, 96 µM ve 4 µM olarak hesaplanmıştır. Başka bir çalışmada $5x10^5$ DU-145 hücresi sisplatinin farlı derişimleri (0 -250 µM) ile 24, 48 ve 72 saat inkübe edilmiş ve sisplatinin IC_{50} değerleri her üç inkübasyon süresi için de > 250 µM olarak hesaplanmıştır (Zhu vd., 2015). Lazarova vd. (2024) tarafından yapılan çalışmada, $1x10^4$ DU-145 hücresine sisplatin uygulanarak 24 saat inkübe edilmiş ve sisplatinin IC_{50} değeri 22,41 µM olarak hesaplanmıştır. Sitotoksisite test sonuçlarını etkileyen birçok parametre (hücre sayısı, hücre hattının kalitesi, laboratuvar sarf orjinleri, tercih edilen yöntem vb.) bulunduğundan, sisplatin için farklı IC_{50} değerleri belirlenmiştir. Bu nedenle, deney sonucu elde edilen değerlerin, sisplatinin yayımlanmış IC_{50} değerleri ile karşılaştırılması güvenilir bir yaklaşım olmayıp her yeni deney için ayrı bir referans kontrolü gerçekleştirilmesi ve mevcut literatür verilerine IC_{50} için tek başına güvenilmemesi önerilmektedir (Ćwiklińska-Jurkowska vd., 2023). 5 µM, 10 µM, 20 µM, 30 µM ve 50 µM duloksetin hidroklorürün L-929 hücrelerine uygulamaları sonucunda hücre canlılık yüzdeleri sırasıyla; %95,11, %83,62, %75,17 ve %6,60 olarak hesaplanmıştır. 5 µM, 10 µM, 20 µM, 30 µM ve 50 µM

sisplatin uygulamaları sonucunda hücre canlılık yüzdeleri sırasıyla; %99,83, %99,85, %98,32 ve %99,09 olarak hesaplanmıştır. 5 µM, 10 µM, 20 µM, 30 µM ve 50 µM duloksetin hidroklorürün DU-145 hücrelerine uygulamaları sonucunda hücre canlılık yüzdeleri sırasıyla; %101,13, %80,98, %46,54 ve %8,17 olarak hesaplanmıştır. 5 µM, 10 µM, 20 µM, 30 µM ve 50 µM sisplatin uygulamaları sonucunda hücre canlılık yüzdeleri sırasıyla; %95,34, %92,00, %89,78 ve %93,18 olarak hesaplanmıştır. Duloksetin hidroklorürün 24 saat uygulama süresi için DU-145 ve L-929 hücreleri için IC_{50} değerleri sırasıyla; 28,76 ± 0,012 µM ve 34,92 ± 0,012 µM olarak hesaplanmıştır. Düşük IC_{50} değeri yüksek antikanser aktiviteye işaret etmektedir (Meyer vd., 2019; Berrouet vd, 2020). Bu nedenle; duloksetin hidroklorür DU-145 ve L-929 hücrelerine sisplatine göre daha yüsek sitotoksik etki göstermiştir. Deneyin ikinci aşamasında ise sisplatin (50 µM) ve farklı derişimlerde duloksetin hidroklorürün (1-50 µM), 24 saat uygulama süresi için, L-929 sağlıklı fare fibroblast hücreleri ve DU-145 insan prostat kanser hücreleri canlılığı MTT kolorimetrik test yöntemi ile belirlenen etkileri gösterilmiştir (Şekil 3). 1 µM, 5 µM, 10 µM, 20 µM, 30 µM, 40 µM ve 50 µM duloksetin hidroklorür ve 50 µM sisplatinin L-929 hücrelerine uygulamaları sonucunda hücre canlılık yüzdeleri sırasıyla; %92,39, %91,58 %88,26, %84,80, %74,24, %45,89 ve %14,45 olarak hesaplanmıştır. DU-145 hücrelerine uygulamaları sonucunda hücre canlılık yüzdeleri sırasıyla; %104,21, %102,06, %99,21, %72,80, %55,62, %32,31 ve %13,19 olarak hesaplanmıştır. Duloksetin hidroklorür ve sisplatinin birlikte 24 saat uygulama süresi için DU-145 ve L-929 hücreleri için IC_{50} değerleri sırasıyla 30,51 ± 0,010 µM ve 36,92 ± 0,013 µM olarak hesaplanmıştır. Hücrelere, Duloksetin hidroklorür ve sisplatinin birlikte uygulanması sonucunda IC_{50} olarak hesaplanmıştır (Tablo 1). Sonuçlar sisplatin ve duloksetin hidroklorürün birlikte kullanılmasının sisplatin ve duloksetin hidroklorürün ayrı ayrı kullanılması ile benzer sitotoksik aktivite gösterdiğine işaret etmektedir.



Şekil 3. Sisplatin (50 µM) ve farklı derişimlerde Duloksetin hidroklorürün (1- 50 µM), L-929 sağlıklı fare fibroblast hücreleri ve DU-145 insan prostat kanser hücreleri üzerine sitotoksik etkisi (24 saat). Deneyler 6 tekrarlı yapılmıştır (n=6) ve sonuçlar ±SS olarak verilmiştir. (Kontrole göre anlamlılık **P<0,005, ***P<0,0001).

4. Tartışma

Antidepresanlar, esas olarak depresif ruh hali ile karakterize edilen zihinsel bozuklukları tedavi etmek için kullanılan ve somatik semptomları, kaygıyı ve sinirliliği hafifletebilen bir psikotrop ilaç sınıfıdır. Antidepresanlar; trisiklik antidepresanlar (TSA) (amitriptilin vb.), monoamin oksidaz (MAOI) inhibitörleri (fenelzin, moklobemid vb.), seçici seratonin (5-HT) geri alım inhibitörleri (SSGI) (paroksetin, fluoksetin, sertralin vb.), 5-HT, norepinefrin geri alım inhibitörleri (SNGI) (duloksetin, venlafaksin vb.); tetrasiklik antidepresanlar (mirtazapin vb.) ve bitkisel ilaçlar (St John's Wort vb.) gibi farklı sınıflara ayrılmaktadırlar (Alvano ve Zieher, 2020; Sheffler vd., 2025).

Apoptoz ve tümör metabolizma mekanizmaları kanser tedavisinde önemli hedeflerdir. Antidepresanların, mitokondri ve Ca^{2+} aracılı hücre apoptozu, sinir büyüme faktörleri reseptörü/NGF reseptörü aracılı hücre apoptozu, Fas ölümü reseptörü aracılı hücre apoptozu, (JNK)/c-Jun mekanizması, hücre döngüsü düzenleyicileri olan PI3K/AKT/mTOR, NK-kappa B ve ERK sinyal yolları ile ilişkili farklı mekanizmalar yoluyla antitümör etkiler gösterebildikleri saptanmıştır (Zhang vd., 2013; Pula vd., 2013; Jahchan vd., 2013; Yuan vd., 2015). Antidepresanların, bağışıklık tepkisini veya kanser hücrelerinin mikro ortamını değiştirerek tümörleri inhibe edebildikleri bulunmuştur (Stopper vd., 2014). Antidepresanların insan vücudu üzerinde olası düşük olumsuz etkileri onları, kanser tedavisinde geçerli bir seçenek haline getirdiği belirtilmiştir (Zheng vd., 2023). Bazı antidepresanların farklı kanser hücre dizilerine karşı antiproliferatif aktiviteye sahip oldukları ve antipsikotik etkilerine ek olarak güçlü anti-kanser aktiviteye sahip oldukları bildirilmiştir (Bavadekar vd., 2014; Huang vd., 2018). Duloksetinin MCF-7 meme kanseri ve HepG2 karaciğer kanserini de içeren farklı kanser hücreleri üzerinde doza bağımlı sitotoksisite gösterdiği bildirilmiştir (Hill vd., 1994; Yoo vd., 1998; Bailly vd., 1999; Shao vd., 2005; Bavadekar vd., 2014; Kuwahara vd., 2015). Bu nedenle duloksetinin, tümör hücreleri üzerinde potansiyel inhibitör etkinliği kabul edilmiştir. Kuwahara vd (2015) bazı SSGI ve SNGI grubu

ajanların; (Sertralin (0,03-3 µM), Paroxetine (1-10 µM), Fluvaxamine (20-60 µM), Escitaloprom (10-1000 µM), Duloxetine (1-100 µM) ve Milnacipran (1-100 µM)) hepatoselüler karsinoma (HepG2) hücreleri üzerinde anti-tümör etkinliklerini 2-(2-metoksi-4-nitrofenil)-3-(4-nitrofenil)-5-(2,4-disülfofenil)-2H-tetrazolyum monosodyum tuzu (WST-8) kullanarak karşılaştırmışlardır. Bu çalışma sonucunda SSGI grubu ajanların ve duloksetinin doza bağlı olarak hücre canlılığını azalttığı; Milnacipran'ın ise hücre canlılığı üzerinde herhangi bir etkisi olmadığı görülmüştür. SSGI'lar; Sertralin, Paroxetine, Fluvaxamine ve Escitaloprom'ın IC_{50} değerleri sırasıyla 1,24 µM, 7,34 µM, 31,0 µM ve 94,8 µM olarak hesaplanmıştır. SNRI Duloxetine'in IC_{50} değeri 8,95 µM ve Milnacipran'ın IC_{50} değeri >100 µM olarak belirlenmiştir HepG2 hücrelerine 2 µM Sertraline uygulamasından 12 saat ve 24 saat sonra kaspaz3/7 aktivitesinde anlamlı artış gözlenmiştir. Bu sonuçlar, bu çalışmada denenen ajanlar arasında sertralinin HepG2 hücrelerine karşı en yüksek duyarlılığa sahip olduğunu ve sertralinin HepG2 hücrelerine karşı antitümör etkili olduğunu göstermektedir. Duloksetinin, MKN45 kanser hücrelerine karşı antikanser etkinliğe sahip olduğu gösterilmiştir ancak tipik antikarsinojenlere göre daha az antikanser etkiye sahip olduğundan belirlenmiştir (Hassani vd., 2019). Kajiwara vd. (2020) duloksetinin, bağışıklık ve inflamatuar koşulları düzenleyerek pankreas adenokarsinom hücrelerinde anti-proliferatif etki gösterdiğini bildirmiştir. Pankreas yıldız hücreleri (PYH), hücre çoğalmasını ve metastazı teşvik ederek pankreas kanser hücrelerinin (PKH) hayatta kalmasını destekleyen koşulları sağlamaktadır. Duloksetinin PYH'ların aktivasyonunu baskıladığı ve tümör-stroma etkileşimini bozduğu belirlenmiştir (Sagara vd., 2021). Duloksetin hidroklorürün apoptotik mekanizmalarda rol alan genler üzerindeki etkileri araştırılarak, toksik etki mekanizmasın aydınlatılması üzerine çalışmalar planlanmaktadır. Jang vd. (2024), küçük hücreli olmayan akciğer kanser hücrelerine (NSCLC) (H1299, H460 ve A549), 5 µM lapatinib, gefitinib, erlotinibe gibi epidermal büyüme faktörü reseptörü-tirozin kinaz inhibitörlerini (EGFR-TKIs) uygulayarak 48 saat inkübe etmişler ve hücrelerin canlılığının %30'dan daha az bir oranda azaldığını belirlemişlerdir. H1299, H460 ve A549 hücreleri 10 µM duloksetin + 5 µM lapatinib, gefitinib veya erlotinib ile birlikte 48 saat inkübe edilmiş ve duloksetin ile birlikte uygulama yapılmasının her bir ajanın tek başına uygulanmasına göre hücre canlılığında daha fazla düşüşe neden olduğu gözlenmiştir. Duloksetin hidrokolorürün H1299, H460 ve A549 hücreleri üzerine etkisinin araştırılması amacıyla, hücreler 48 saat boyunca farklı derişimlerde duloksetin ile inkübe edilerek hücre canlılığı araştırılmıştır. Duloksetinin, NSCLC hücrelerinin canlılığını doz bağımlı olarak azalttığı ve hücre canlılığı üzerindeki etkisinin hücre hattına göre farklılık gösterdiği belirlenmiştir. NSCLC hücrelerinde, 20 µM duloksetinin hücre canlılığını %20'den fazla azalttığı bulunmuştur. Milnasipran, venlafaksin veya dezvenlafaksinin, NSCLC hücrelerine 100 µM'a kadar uygulanmasına rağmen hücre canlılığında %20'nin altında bir azalma gözlenmiştir. Milnasipran, venlafaksin veya dezvenlafaksin ile 5 µM lapatinib ile kombinasyonlarının, duloksetin ile kombinasyona kıyasla NSCLC hücrelerinin lapatinibe olan duyarlılığını daha fazla artırmadığı belirlenmiştir. Duloksetin ve lapatinib kombinasyonunun, her bir ajanın tek başına uygulanmasına göre daha etkili bir şekilde hücre ölümünü indüklediği gözlenmiştir. Bu sonuçlar, duloksetinin NSCLC hücrelerinin EGFR-TKI'lara olan duyarlılığını artırdığını önermektedir. Kim vd. (2024), paklitaksel dirençli over kanser hücrelerinde (HEYA8-MDR), duloksetin, venlafaksin, desvenlafaksin ve milnasipran gibi SNGIEların hücre canlılığı üzerine etkilerini araştırmışlardır. Test edilen dört farklı antidepresan arasında, duloksetinin HEYA8-MDR hücre canlılığını etkili bir şekilde azaltığı ve hücreleri paklitaksele duyarlı hale getirdiği belirlenmiştir. Ayrıca paklitaksel ve duloksetinin kombine uygulanmasının, HEYA8-MDR hücrelerinde hücre ölümünü tetiklediği, erken ve geç apoptozda bulunan hücrelerin oranının önemli ölçüde arttığı gözlenmiştir.

5. Sonuç

Duloksetin hidroklorürün tek başına ve prostat kanserinde kullanılan kemoterapötik ajan olan sisplatin ile birlikte kullanımının DU-145 prostat kanser hücreleri üzerine sitotoksik etkinliği ile ilgili ilk sonuçlar elde edilmiştir. Duloksetin hidroklorürün sisplatine göre DU-145 prostat kanser hücreleri üzerinde daha yüksek sitotoksik etkinliğe sahip olduğu, sağlıklı hücreler üzerine ise sisplatinden daha düşük toksik etki gösterdiği belirlenmiştir.

Katkı Oranı Beyanı

Yazarların katkı yüzdesi aşağıda verilmiştir. Tüm yazarlar makaleyi incelemiş ve onaylamıştır.

	Ö.K.	Ş.Ş.
K	50	50
T	40	60
Y	50	50
VTI	40	60
VAY	30	70
KT	40	60
YZ	40	60
KI	40	60
GR	40	60
PY	50	50
FA	60	40

K= kavram, T= tasarım, Y= yönetim, VTI= veri toplama ve/veya işleme, VAY= veri analizi ve/veya yorumlama, KT= kaynak tarama, YZ= Yazım, KI= kritik inceleme, GR= gönderim ve revizyon, PY= proje yönetimi, FA= fon alımı.

Çatışma Beyanı

Yazarlar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

Etik Onay/Hasta Onamı

B Hayvanlar veya insanlar üzerinde bir çalışma olmadığı için bu çalışma için etik komite onayı gerekmemiştir.

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EVALUATION OF HEP-2 CELL PATTERNS: HOW OFTEN DO WE REPORT CYTOPLASMIC AND MITOTIC PATTERNS?

Melahat GÜRBÜZ[1]*

[1]*Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Medical Microbiology, 03030, Afyonkarahisar, Türkiye*

Abstract: The indirect immunofluorescence (IIF) method for anti-nuclear antibody (ANA) testing is pivotal in the diagnosis of autoimmune diseases. Despite extensive research on nuclear staining patterns, cytoplasmic and mitotic patterns remain less understood. This study retrospectively analyzed 12,674 ANA test results from a tertiary medical microbiology laboratory over three years to assess the prevalence and diagnostic implications of these patterns. ANA positivity was observed in 24.2% of samples, with cytoplasmic and mitotic patterns accounting for 9.2%. Notably, these patterns were predominantly found in ANA-negative samples, with intercellular bridge (AC-27) emerging as the most frequent pattern. While a substantial proportion of cytoplasmic and mitotic patterns were detected among rheumatology patients, no significant correlation was identified between specific patterns and autoimmune diagnoses. These findings underscore the importance of consistent reporting of cytoplasmic and mitotic patterns, as recommended by the International Consensus on ANA Patterns (ICAP). The incorporation of these patterns into routine diagnostic reports has the potential to enhance diagnostic accuracy, particularly in cases ANA-negative. Further research is essential to elucidate their clinical significance and optimize laboratory practices.

Keywords: Indirect immunoflorescence, Anti-nuclear antibody, Cytoplasmic pattern, Mitotic pattern, Autoimmune diseases

***Corresponding author:** Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Medical Microbiology, 03030, Afyonkarahisar, Türkiye
E mail: drmelahatgrbz@hotmail.com (M. GÜRBÜZ)
Melahat GÜRBÜZ https://orcid.org/0000-0001-6290-1216

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1. Introduction

Detection of staining patterns of autoantibodies against different antigens in cells is still the most widely used diagnostic tool for the diagnosis and monitoring of autoimmune diseases (Aringer et al., 2019). With the indirect immunofluorescence (IIF) method, various staining patterns of antibodies developed against different antigens can be observed in HEp-2 cells. This method is considered as the most sensitive and gold standard method for the detection of Anti-nuclear Antibodies (ANA) that develop against antigens in the nucleus, especially in the screening of autoimmune diseases (Meroni et al., 2010). However, in ANA tests, autoantibodies against cytoplasmic and mitotic structures can also be observed in addition to the presence of ANA (Brito Fde et al., 2014, Damoiseaux et al.,2016).

The identification of cytoplasmic and mitotic patterns is also of great importance. Cytoplasmic patterns are usually associated with antibodies against ribosomal, mitochondrial or actin filament antigens, whereas mitotic patterns are associated with autoantibodies against structures such as chromosomal kinetochores, centrosomes or mitotic braids. These antibodies are also important in the differential diagnosis of autoimmune diseases such as systemic lupus erythematosus (SLE), systemic sclerosis and various overlap syndromes (Betancur et al., 2018).

The reporting of cytoplasmic and mitotic patterns in HEp-2 cells is often given less attention in laboratory practice than ANA patterns. The underlying reason for this discrepancy is that cytoplasmic and mitotic patterns are observed less frequently and the clinical correlation of these patterns is less well understood in comparison to cellular patterns (Nanda et al., 2021). However, the identification of specific clinical conditions in individuals with cytoplasmic and mitotic autoantibodies is of great importance in terms of both diagnosis and prognosis.

The International Consensus on ANA Patterns (ICAP) is an international collaborative effort to provide standardisation in the description and reporting of ANA patterns detected by the IIF method. The primary objective of ICAP is to ensure harmonisation between laboratories by providing detailed descriptions of nuclear, cytoplasmic and mitotic patterns. This system not only takes into account the morphological characteristics of the patterns but also their potential clinical implications. The application of ICAP-standardised definitions of nuclear, cytoplasmic and mitotic patterns ensures consistency in the reporting of these patterns and provides clinicians with more reliable information (Chan et al., 2015a, Chan et al., 2015b)

This study aims to determine how often cytoplasmic and mitotic patterns detected in HEp-2 cells are reported using the IIF method by retrospectively analyzing ANA

tests. The data obtained were evaluated to improve the reporting practices of laboratories and to create a better roadmap for clinical interpretation.

2. Materials and Methods

In this study, ANA tests performed in the Medical Microbiology laboratory of Afyonkarahisar Health Sciences University, Faculty of Medicine, Medical Microbiology laboratory over a 3-year period between 01 January 2020 and 31 December 2022 were retrospectively evaluated. A total of 12,674 test results were analysed, which did not belong to a specific patient group and were sent to the laboratory only for ANA test request without preliminary diagnosis or diagnostic criteria. During the study period, samples were tested at 1/100 dilution using HEp-20-10/Liver (Monkey) Mosaic IIF kit (Euroimmun, Germany) in accordance with the manufacturer's recommendations. The tests were visually evaluated using an immunofluorescence microscope (Olympus BX53) after staining procedures performed according to standard protocols.

Fluorescent staining patterns of each sample were determined and reported by the same experienced expert. Detected nuclear, cytoplasmic and mitotic patterns were categorized according to the ICAP classification guidelines. Cytoplasmic and mitotic patterns are reported when positivity is detected at levels of 2+ or higher. The ICAP classification provided a standard reference for assessing the clinical significance of the detected patterns. All data were analyzed retrospectively and records were verified using the hospital information system and laboratory information system (LIS).

2.1. Statistical Analysis

The obtained data were statistically analyzed using SPSS 20.0 (IBM Corp., Armonk, NY, USA) software. Descriptive statistics presented percentage distributions and frequencies for categorical variables. The mean age and gender distributions were assessed. The chi-square test and Fisher's Exact test were utilized to compare categorical variables between groups. A p value less than 0.05 was considered statistically significant.

3. Results

A total of 12,674 samples were analysed in the present study. ANA positivity was detected in 3,070 (24.2%) samples at 1:100 titer. Cytoplasmic patterns that are specific to autoimmune diseases, including AMA, ASMA, anti-Jo-1, and anti-ribosomal P-protein were excluded from the evaluation. Following this exclusion, the number of samples with cytoplasmic and mitotic patterns was 1,173, representing 9.2% of all samples. The cytoplasmic pattern positivity rate was found to be 0.6%, while the mitotic pattern positivity rate was 8.6% in all samples examined. Of these, 996 (84.9%) were isolated cytoplasmic and mitotic pattern positive and reported as ANA negative. Concurrent ANA positivity was observed in 177 samples. The cytoplasmic/mitotic pattern was identified in a total of 5.7% of patients who were concurrently ANA positive, in contrast to a rate of 10.98% observed in ANA-negative patients. The numbers and ratios of cytoplasmic and mitotic cell patterns are presented in Figure 1. Mitotic pattern positivity was predominantly observed in both the group with ANA positivity and in the group with isolated cytoplasmic/mitotic patterns. The most frequently detected patterns in the whole study group were intercellular bridge (AC-27), centrosome (AC-24) and spindle fibres (AC-25), respectively.

The present study was conducted with the objective of investigating the clinical significance of the cytoplasmic and mitotic patterns detected in the ANA negative group, and this group was analysed in more detail. Of the patients with isolated cytoplasmic and mitotic patterns, 658 (66.1%) were female and 338 (33.9%) were male. The mean age of these patients was 46.7 years. The distribution of patients across various clinical specialties is as follows: 456 (45.8%) were referred from rheumatology clinics, 57 (5.7%) from paediatric clinics, and 483 (48.5%) from other non-specific clinics (Table 1). A statistically significant difference was not observed between the age, gender, and clinic of the patients and the detection of cytoplasmic/mitotic pattern ($P>0.05$).

The results of patients admitted to rheumatology were analysed separately, given that a group of patients with more specific complaints of autoimmune diseases were admitted. The isolated cytoplasmic and mitotic patterns observed in rheumatology patients are shown in detail in Table 2. The most prevalent pattern was identified as AC-27, followed by AC-24 and AC-25, aligning with the observations made in the overall group. When the diagnoses of these patients were analyzed (Table 3), no statistically significant difference was found between the diagnoses and patterns.

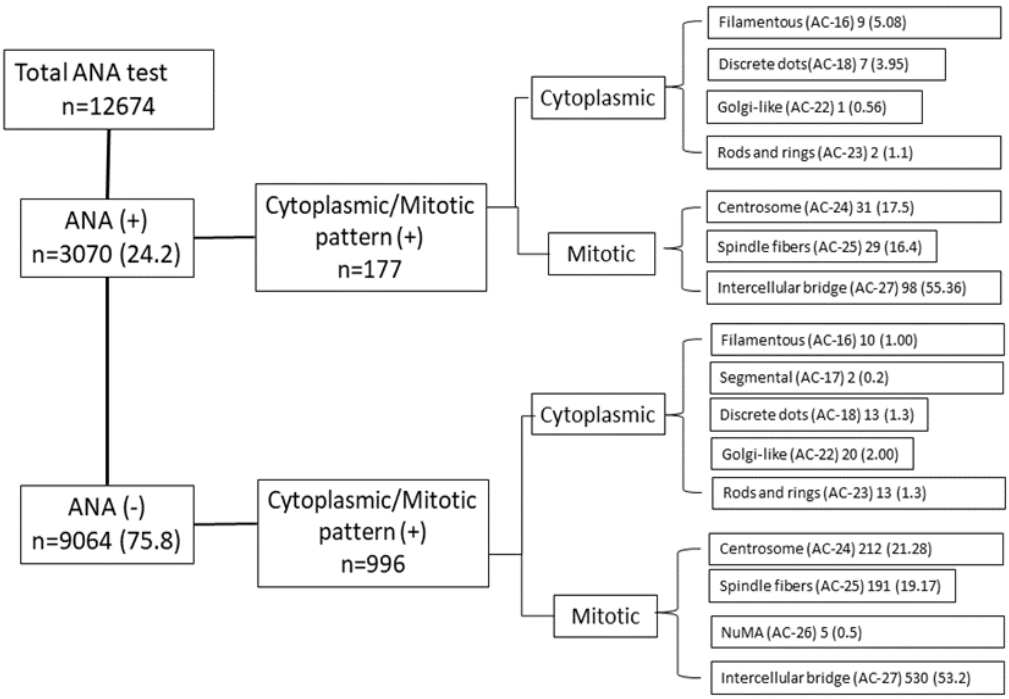

Figure 1. ANA positivity and cytoplasmic/Mitotic pattern prevalence n (%).

Table 1. Demographic data of patients with isolated cytoplasmic-mitotic patterns

		n	%
Age (Mean ± Std)	46.7 ± 16.4		
Gender	Female	658	66.1
	Male	338	33.9
The clinic where the test is requested	Rheumatology	456	45.8
	Internal medicine	242	24.3
	Physical therapy and rehabilitation	80	8.03
	Neurology	62	6.22
	Other non-specific clinics	69	6.93
	Paediatric clinics	57	5.72
	Surgical clinics	30	3.0

Table 2. Distribution of isolated cytoplasmic-mitotic patterns observed in rheumatology patients

Cytoplasmic-mitotic patterns (AC codes)	n (%)
Intercellular bridge (AC-27)	266 (58.4)
Centrosome (AC-24)	94 (20.6)
Spindle fibers (AC-25)	78 (17.1)
Rods and rings (AC-23)	7 (1.5)
Cytoplasmic polar/Golgi-like (AC-22)	5 (1,1)
Cytoplasmic discrete dots (AC-18)	2 (0,43)
Cytoplasmic fibrillar filamentous (AC-16)	2 (0.43)
Cytoplasmic fibrillar segmental (AC-17)	1 (0.22)
NuMA-like (AC-26)	1 (0.22)
Total	456 (100)

Table 3. Diagnoses of rheumatology patients with isolated cytoplasmic-mitotic pattern

	EA	RA	SNRA	AS	HFA	OA	SS	WG	BD	RS	P	Total
AC-16	1			1								2
AC-17	1											1
AC-18	2											2
AC-22	5											5
AC-23	7											7
AC-24	81	4		3	5						1	94
AC-25	68	4		2					2	2		78
AC-26	1											1
AC-27	212	18	3	14	8	3	2	1	4		1	266
Total	378	26	3	20	13	3	2	1	6	2	2	456

EA = Joint pain, RA = Rheumatoid arthritis, SNRA = Seronegative rheumatoid arthritis, AS = Ankylosing spondylitis, HFA = Hereditary familial amyloidosis, OA = Osteoarthritis, SS = Sjögren's syndrome, WG = Wegener's granulomatosis, BD = Behçet's disease, RS = Raynaud syndrome, P = Psoriasis.

4. Discussion

It is known that the prevalence of autoimmune diseases has increased over the years and the prevalence is reported to be approximately 4.5% (Lerner et al., 2015, Dinse et al., 2020). Although the detection of antinuclear antibodies is the gold standard method used in the diagnosis of autoimmune diseases, ANA test positivity can be detected in various infections, inflammatory or neoplastic processes and even in healthy individuals (Betancur et al., 2018).

The relationship between IIF ANA patterns and nuclear autoantibodies is well known and helps in the diagnosis of autoimmune diseases. The association of different staining patterns with certain diseases has been proven. Especially nuclear and certain cytoplasmic pattern positivity stand out in this context and their diagnostic role varies according to diseases (Infantino et al., 2018, Stinton et al. 2004). The ANA test shows high sensitivity but low specificity in certain diseases; SLE (90-95%), Sjögren's syndrome (75%), scleroderma (85-90%) and mixed connective tissue disease (MCTD) (100%) (Damoiseaux et al., 2019).

The International Consensus on ANA Patterns emphasizes the importance of reporting cytoplasmic and mitotic HEp-2 staining patterns as well as nuclear patterns and recommends further monospecific testing to confirm findings (Chan et al., 2015b, Mahler et al., 2019). Cytoplasmic and mitotic patterns in HEp-2 cells are becoming increasingly important clinically, but there remains disagreement over whether they should be reported as ANA-positive or negative.

However, due to the low prevalence of uncommon ANA patterns and inconsistencies in their reporting, their relationship with the clinic cannot be clearly established. Another reason for this is that in the current approach, clinical correlation is based on antigen-specific immunoassays, not Hep-2 patterns. In accordance ICAP recommendations and as stated in the KLIMUD guidelines, we report ANA positive in the presence of nuclear staining patterns in our laboratory and negative otherwise. However, if detected, we also include cytoplasmic and mitotic patterns in our report (Klimud, 2020, von Mühlen et al., 2021).

There are various studies examining the frequency of these staining patterns in routine ANA tests under the name of cytoplasmic, mitotic or nuclear patterns. In the literature, there are studies indicating that cytoplasmic patterns are reported at a rate of 6.4-21.8%, as well as studies reporting lower rates of 3.13% (Infantino et al., 2018, Stinton et al. 2004, Bilgin and Baklacıoğlu, 2023).

In the present study, ANA positivity was observed at a rate of 24.2%, cytoplasmic patterns at a rate of 0.6%, and mitotic patterns at a rate of 8.6%. The relatively low positivity rate of cytoplasmic patterns in our study compared to other studies can be attributed to the exclusion of certain antibodies, such as AMA, ASMA, anti-Jo-1, and anti-ribosomal P-protein, which are known to be specific cytoplasmic patterns for autoimmune diseases. A parallel exclusion study, as reported by Kaşifoğlu et al. (Kaşifoğlu et al., 2022), yielded a positivity rate of 0.7% for cytoplasmic patterns and 1.3% for mitotic patterns.

In the present study, mitotic patterns were identified most frequently. The most prevalent pattern was identified as AC-27, followed by AC-24 and AC-25, respectively. Betancur et al. in their study evaluating 113,491 serum samples, found 53% ANA positivity and 1.3% uncommon pattern positivity, among which mitotic apparatus antigens (NuMA, midbody, centrosome) were predominantly observed. The medical records of the patients in whom mitotic patterns were detected were examined in detail in relation to systemic, organ-specific autoimmune diseases and other diseases. Cytoplasmic patterns were associated with autoantibodies such as anti-Jo-1 associated with anti-synthetase syndrome or anti-ribosomal P associated with SLE. Mitotic patterns are less common than cytoplasmic patterns but are diagnostically important. In different studies, it has been pointed out that patterns such as nuclear centrosome, intercellular bridge and spindle strands may help the diagnosis of SLE, RA and PBC, but many laboratories do not report these patterns consistently. There are also studies showing that patterns such as NuMA and intercellular bridges are associated with conditions such

as idiopathic urticaria, SS, RA and neurofibromatosis (Vermeersch and Bossuyt, 2013, Szalat et al., 2010, Pascual et al., 2015). Cytoplasmic and mitotic patterns at high titers (≥1:160) have been associated with SLE. As a new approach, they advocate the inclusion of these patterns in routine diagnostic reports to improve patient stratification and diagnostic accuracy (Betancur et al., 2018, Nanda et al., 2021).

In our study, cytoplasmic and mitotic pattern positivity was found quite frequently in ANA-negative as well as ANA-positive samples (5.7% vs 10.98%). The frequent presence of cytoplasmic and mitotic patterns in ANA-negative samples suggests that such patterns may be a marker for early stages or specific subgroups of autoimmune diseases (Mahler et al., 2014; Wiik et al., 2010). However, the question of whether these patterns are coincidental or clinically significant suggests the need for further studies.

Despite the existence of publications in the literature which demonstrate an association between uncommon autoantibodies and their Hep-2 patterns with detection and clinical presentation, a clinical correlation could not be detected in this study due to limitations in time and patient numbers (Staruszkiewicz et al., 2023). The finding that cytoplasmic and mitotic patterns were detected more frequently in samples obtained from the rheumatology clinic lends support to the hypothesis that these patterns may be related to autoimmune diseases.

In our study, specific antibodies such as AMA, ASMA, anti-Jo-1, and anti-ribosomal P-protein, which are known as specific cytoplasmic patterns for autoimmune diseases, were excluded and not evaluated. This can be considered a limitation; however, the primary aim of the study was to determine the frequency of reporting of patterns that are not clearly specific for autoimmune diseases and to investigate whether they can assist in indicating the presence of autoimmune disease. Additionally, the lack of evaluation of the relationship between weak and strong positivity and ANA results in our study can also be considered a limitation.

Nevertheless, the absence of a substantial correlation between the prevalence of patterns and diagnoses in rheumatology patients suggests that these patterns alone may lack the diagnostic sensitivity required for determining clinical significance. The retrospective design of the study and the inability to examine all clinical data in detail limit the generalizability of the results. It is therefore recommended that further studies be conducted to provide a more comprehensive and prospective evaluation of these findings.

5. Conclusion

It is evident that identifying potential clinical associations for rare cytoplasmic and mitotic patterns poses a significant challenge. Regular reporting of cytoplasmic and mitotic patterns and categorization of these patterns in accordance with with ICAP recommendations may improve both the diagnostic process and clinical guidance. Integration of ICAP guidelines into broader laboratory practice and widespread validation with monospecific tests may increase the clinical value of these patterns. Despite the limitations of the present study in reaching this conclusion, a substantial corpus of supporting literature suggests that such patterns should not be disregarded, as they may potentially have clinical significance. Future prospective studies will contribute to a clearer determination of the relationship of these patterns with autoimmune and other diseases. Furthermore, more rationalization of test ordering and reduction of unnecessary test orders may improve both the economic and diagnostic efficiency of laboratories.

Author Contributions

The percentages of the author' contributions are presented below. The author reviewed and approved the final version of the manuscript.

	M.G.
C	100
D	100
S	100
DCP	100
DAI	100
L	100
W	100
CR	100
SR	100
PM	100
FA	100

C= concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest

The author declared that there is no conflict of interest.

Ethical Consideration

The study was conducted in accordance with the principles of the Declaration of Helsinki. Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University approved this study (approval date: June 02, 2023, protocol code: 258).

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Research Article
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INVESTIGATION OF THE MORPHOLOGY OF PSOAS MAJOR AND QUADRATUS LUMBORUM MUSCLES IN SACRALIZED INDIVIDUALS

Gamze Nur KOÇER KAHRIMAN[1], Fatih ÇANKAL[2], İlyas UÇAR[1]*

[1]Erciyes University, Faculty of Medicine, Department of Anatomy, 38100, Kayseri, Türkiye
[2]Pursaklar Public Hospital, Department of Radiology, 06145, Ankara, Türkiye

Abstract: This study aimed to evaluate the morphological characteristics of the Psoas Major (PMa) and Quadratus Lumborum (QL) muscles in individuals with lumbosacral transitional vertebra (LSTV) anomalies and to compare the muscle cross-sectional areas (CSA) of these individuals with a control group without LSTV. In this retrospective study, computed tomography (CT) images of 108 individuals aged between 18 and 65 years were analyzed. Participants were divided into two groups based on the presence of sacralization: 54 individuals with sacralization formed the "sacralization group," and 54 individuals without LSTV comprised the control group. Sacralization cases were subclassified according to the Castellvi classification. PMa and QL muscle CSAs were measured bilaterally at the L4 vertebral level using ImageJ software. Data were analyzed with SPSS version 22.0. The sacralization group exhibited significantly larger left PMa CSA (12.56 cm^2, P=0.001), left QL CSA (6.25 cm^2, P=0.004), and right QL CSA (6.48 cm^2, P=0.026) compared to the control group. Male participants had significantly larger PMa and QL CSAs than females (P<0.05). No significant relationship was found between Body Mass Index (BMI) and muscle CSA (p>0.05). However, a weak negative correlation was observed between age and PMa CSA (right PMa: P=0.013, r=-0.237; left PMa: P=0.007, r=-0.257). The observed increase in CSA of PMa and QL muscles in individuals with sacralization suggests that this anatomical variation may influence muscle morphology. These morphological changes could impact lumbar and pelvic function and should be considered during clinical evaluations.

Keywords: Sacralization, Lumbosacral transition, Muscle morphology, Psoas major, Quadratus lumborum

***Corresponding author:** Erciyes University, Faculty of Medicine, Department of Anatomy, 38100, Kayseri, Türkiye
E mail: ilyas.ucar@erciyes.edu.tr (İ. UÇAR)
Gamze Nur KOÇER KAHRIMAN https://orcid.org/0009-0005-4380-3270
Fatih ÇANKAL https://orcid.org/0000-0003-1066-353X
İlyas UÇAR https://orcid.org/0000-0003-3646-5320

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1. Introduction

Lumbosacral transitional vertebrae (LSTV) are among the most common congenital variants of the spine, with a prevalence ranging from 4% to 36% in the population (Matson et al., 2020). LSTV is defined as sacralization, where there is partial or complete fusion between the lowest lumbar vertebra (L5) and the sacrum, and as lumbarization, where the first sacral segment (S1) takes on a lumbar appearance (Castellvi et al., 1984; Türk et al., 2023). The classification system proposed by Castellvi et al. in 1984 categorizes LSTV into four types (I to IV) based on the degree of fusion or articulation (Castellvi et al., 1984; Konin and Walz, 2010).

The presence of LSTV limits the range of motion of the L5-S1 segment, leading to compensatory load increases in the upper segments. This predisposes individuals to disc degeneration, facet joint arthritis, and chronic low back pain (Luoma et al., 2004; Hanhivaara et al., 2020). However, it has also been reported that LSTV causes adaptive changes not only in the bony anatomy but also in the morphological and functional properties of the surrounding muscle tissue (Crane et al., 2021). The Psoas Major (PMa) and Quadratus Lumborum (QL) muscles, which play a critical role in spinal stability, directly contribute to the load-bearing and movement control mechanisms of the lumbar-pelvic region (Penning, 2001). The three-dimensional geometric structure of the PMa indicates a dynamic design that allows the muscle to apply different forces and moments at each lumbar level (Bogduk et al., 1992; Phillips et al., 2008).

Computed Tomography (CT) is commonly used for imaging many body regions, particularly the brain, lungs, abdomen, and pelvis. It plays a vital role in diagnosing conditions such as cancer, trauma, infections, and vascular diseases. It is also used as a guide before and during surgical procedures (Feldkamp et al., 1984). Among the significant advantages of CT are its rapid imaging time, high-resolution detailed images, and the ability to perform three-dimensional reconstructions (Brenner and Hall, 2007). Recent advancements in CT technology include multi-slice scanners that offer faster scan times and higher resolution. Additionally, low-dose CT protocols and iterative reconstruction techniques have made significant progress in reducing radiation

doses while maintaining or improving image quality. Innovations in CT imaging technologies, including multi-slice scanners, low-dose protocols, and iterative reconstruction techniques, provide high accuracy and reliability in muscle cross-sectional area and volumetric analysis (Hanhivaara et al., 2020; Becker et al., 2021).

However, there are a limited number of CT-based studies systematically examining the PMa and QL muscle morphology in individuals with LSTV in the literature. Most existing studies have focused on the morphology of paraspinal muscles such as the multifidus and erector spinae (Dar and Peled, 2017; Çankal et al., 2024). Furthermore, these studies are often limited by small sample sizes and do not comprehensively address the morphological adaptations along the PMa-QL axis.

To fill this gap, our study assessed the cross-sectional areas of the PMa and QL muscles in individuals with sacralization, using a comparative statistical analysis based on the Castellvi classification. The goal was to better understand the biomechanics of the lumbar spine by comparing the cross-sectional areas of the PMa and QL muscles in individuals with sacralization to a control group.

2. Materials and Methods

2.1. Study Population

CT images were retrospectively collected from the PACS system of the Radiology Department for 108 individuals aged 18–65, scanned between January 2020 and January 2022 for abdominal or urinary pathology. All procedures were conducted in accordance with the Declaration of Helsinki.

2.2. Study Groups

Participants were categorized into two groups based on the presence of sacralization on CT. The control group included 54 individuals (26 male, 28 female) without LSTV, while the sacralization group included 54 individuals (34 male, 20 female) diagnosed with sacralization per Castellvi classification by a radiologist.

Exclusion criteria were spinal surgery history, spinal or pelvic trauma, systemic inflammatory/infectious diseases, and poor image quality. Demographic data (age, sex, BMI) were recorded.

2.3. CT Imaging and Classification

Non-contrast abdominal-pelvic CT scans were acquired in the supine position using a GE IQ™ 32-slice MSCT scanner (parameters: 200–320 mAS, 120 kV, 350 mm FOV, 1.25 mm slice thickness). Sacralization types were classified based on the Castellvi system (Figure 2):

- Type I: Dysplastic transverse processes (Ia: unilateral, Ib: bilateral)
- Type II: Articulating transverse processes (IIa: unilateral, IIb: bilateral)
- Type III: Complete osseous fusion (IIIa: unilateral, IIIb: bilateral)
- Type IV: Mixed type (III on one side, II on the other).

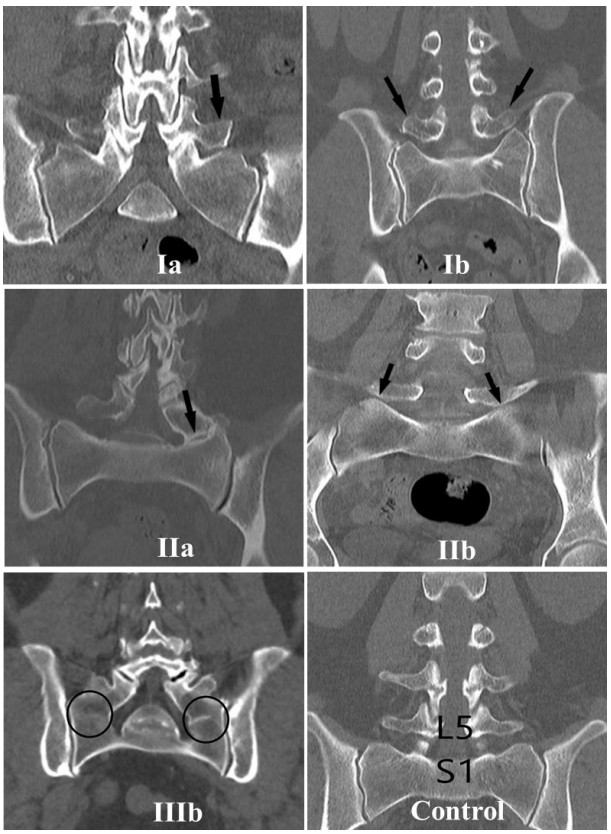

Figure 2. Castellvi classification. Ia= castellvi Type Ia transitional vertebra coronal reformat CT image. Arrow= dysplastic left transverse process; Ib= castellvi Type Ib transitional vertebra coronal reformat CT image. Arrow= dysplastic transverse processes; IIa= castellvi Type IIa transitional vertebra coronal reformat CT image. Arrow= joint between the left transverse process of L5 and the transverse process of S1 vertebra; IIb= castellvi Type IIb transitional vertebra coronal reformat CT image. Arrow= hoint between the transverse processes of L5 and S1 vertebrae on both sides; IIIb= castellvi Type IIIb transitional vertebra coronal reformat CT image. Circle= fusion between the transverse processes of L5 and S1 vertebrae on both sides; Control= normal lumbosacral vertebrae coronal reformat CT image.

2.4. Measurement of Muscle Cross-Sectional Area

CT images were analyzed using RadiAnt DICOM Viewer. Muscle CSAs were measured bilaterally at the L4 vertebral level using ImageJ software (Figure 1). Images were saved as JPEG files, calibrated, and manually traced using the "Free Hand" tool. Measurements were recorded in cm^2 for each side.

2.5. Statistical Analysis

SPSS version 22.0 was used for data analysis. Normality was assessed via visual (histograms, probability plots) and analytical tests (Kolmogorov–Smirnov, Shapiro–Wilk). Independent t-tests and χ^2 tests were used for between-group comparisons. A 2×2 repeated measures ANCOVA was used to analyze CSA data, with Bonferroni post hoc tests for pairwise comparisons. Partial eta squared ($\eta^2 p$) was used for effect size; significance was set at $P<0.05$.

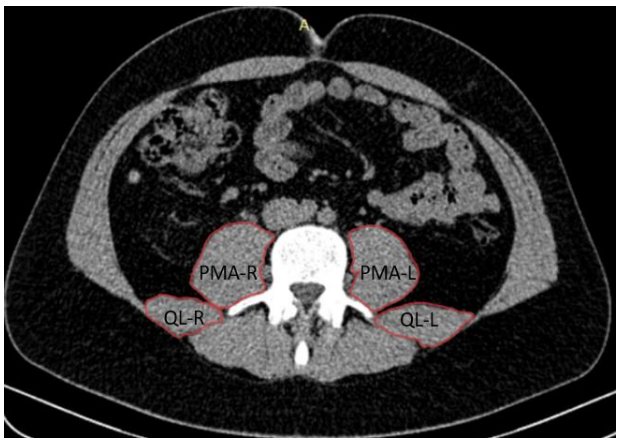

Figure 1. Measurement of muscle size. Axial CT image at the L4 level. PMa-R= right psoas major muscle, PMa-L= left psoas major muscle, QL-R= right quadratus lumborum muscle, QL-L= left quadratus lumborum muscle.

3. Results

A total of 108 participants were analyzed (54 in each group). No significant differences were found between groups in age, BMI, or gender distribution (p>0.05), although the sacralization group had a higher proportion of males (62.96%) compared to controls (48.15%). The most common sacralization type was Type IIb (46.30%), while Type IIIa was the least frequent (1.85%).

Significant increases in CSA were found for the left PMa and bilateral QL muscles in the sacralization group. Conversely, the right PMa CSA was larger in the control group. Male participants had larger muscle CSAs than females across all measures (P<0.05). A weak negative correlation was found between age and PMa CSA; no significant correlation was observed with BMI.

Table 1. Distribution of demographic characteristics by groups

Variable	Participants with sacralization (n=85)	Asymptomatic participants (n=56)	P
Age	45.72±14.28	48.69±9.09	0.200
Body mass index (kg/m²)	25.54±2.69	25.84±2.28	0.536
Female (%)	28 (51.85)	20 (37.04)	0.087
Castelvi type (%)			
1a	8 (14.81)	-	-
1b	8 (14.81)	-	-
2a	7 (12.96)	-	-
2b	25 (46.30)	-	-
3a	1 (1.85)	-	-
3b	5 (9.26)	-	-

Independent samples t test or χ2 test.

Table 2. Independent 2 group t-test comparison of muscle cross-sectional areas as control group and sacralization group

Variable	Group				t test		
	Control Group		Sacralization Group				
	Mean (cm²)	SD	Mean (cm²)	SD	t-statistic	Degrees of Freedom	p-value
Right PMa	10.91	3.76	10.81	4.63	-2.400	106	0.018*
Left PMa	10.81	3.22	12.56	4.64	-2.263	106	0.026*
Right QL	5.12	1.82	6.48	2.48	-3.240	106	0.002*
Left QL	5.50	1.64	6.25	2.09	-2.075	106	0.040*

*P<0.05. PMa= psoas major muscle, QL= quadratus lumborum muscle, SD= standard deviation.

Table 3. Comparison of muscle cross-sectional areas according to gender by independent 2 group t-test

Variable	Gender				t test		
	Male		Female				
	Mean (cm²)	SD	Mean (cm²)	SD	t-statistic	Degrees of Freedom	p-value
Right PMa	14.64	3.51	8.45	2.26	-10.567	106	0.000*
Left PMa	14.16	3.50	8.59	2.20	-9.579	106	0.000*
Right QL	6.99	1.90	4.32	1.77	-7.454	106	0.000*
Left QL	6.94	1.70	4.54	1.18	8.253	106	0.000*

*P<0.05. PMa= psoas major muscle, QL= quadratus lumborum muscle, SD= standard deviation.

Table 4. Association of muscle cross-sectional area with age and BMI

Variable		Age	BMI
Right PMa	r	-0.237	0.131
	p	0.013*	0.177
Left PMa	r	-0.257	0.098
	p	0.007*	0.311
Right QL	r	-0.147	0.088
	p	0.130	0.366
Left QL	r	-0.173	0.021
	p	0.073	0.827

*P<0.05; r= Pearson correlation coefficient, PMa= psoas major muscle, QL= quadratus lumborum muscle, SD= standard deviation, BMI= body mass index.

4. Discussion

This study revealed that individuals with sacralization exhibited significantly larger cross-sectional areas (CSA) in the left Psoas Major (PMa) and both Quadratus Lumborum (QL) muscles compared to controls, whereas the right PMa CSA was found to be greater in the control group. Additionally, male participants showed higher CSA values in both muscles than females, and a weak negative correlation was observed between age and PMa CSA.

Becket et al. (2021) reported that in CT analyses of 46 patients with LSTV and matched controls, the presence of LSTV was associated with decreased volume and increased degeneration in lumbar and trunk muscles. The observed reduction in right PMa CSA in our study supports these findings. However, the increased CSA in the left PMa and both QL muscles may suggest compensatory hypertrophic adaptations developed in response to sacralization.

CT-based morphological assessments of the multifidus muscles have shown notable changes and asymmetry in paraspinal muscles in the presence of sacralization (Dar and Peled, 2017). Moreover, evidence of asymmetry in the multifidus, erector spinae, and psoas muscles in LSTV patients with low back pain highlights the structural and functional adaptations of muscle tissue. In line with this literature, the current study demonstrates that sacralization affects not only bony structures but also muscle morphology. The observed increases in QL and left PMa CSA may be related to localized hypertrophy of muscle fibers and collateral load distribution mechanisms that contribute to spinal stability.

The weak negative correlation between age and PMa CSA observed in this study supports previous findings suggesting a gradual annual decline in PMa CSA after the age of 30 (Nakagawa et al., 2017). Additionally, sex-based differences are consistent with earlier observations indicating that muscle CSA indices obtained from CT imaging are generally higher in males than females (Vu et al., 2024).

Although the clinical impact of LSTV remains controversial, Types II and IV have been significantly associated with lumbar and hip pain (Nardo et al., 2012). Moreover, previous studies have demonstrated a link between LSTV subtypes and degenerative changes in transitional and adjacent spinal segments (Farshad-Amacker et al., 2015). Our findings contribute a new perspective to the existing literature by showing that LSTV affects not only skeletal anatomy but also the muscle tissue responsible for maintaining spinal stability. Recent advances in CT and image processing technologies—such as three-dimensional automatic segmentation and low-dose protocols—have increased the accuracy and reproducibility of muscle morphology analyses. For instance, deep learning–based psoas segmentation models have demonstrated high reliability (Choi et al., 2024). Additionally, PMa morphology and QL positioning have been reported to influence surgical safety and the risk of nerve injury during lateral surgical approaches (Louie et al., 2017). Therefore, morphological changes in the PMa–QL axis in patients with LSTV should be considered during surgical planning, rehabilitation, and long-term functional follow-up.

This study is one of the few CT-based investigations to quantitatively evaluate the asymmetric morphological changes in PMa and QL muscles associated with LSTV. The findings underscore the need for future research to include symptomatology, functional assessments, muscle fat infiltration, and microstructural analyses. Furthermore, prospective cohort studies could provide clearer insights into how these morphological changes impact clinical outcomes and treatment responses.

Our study has some limitations. First, due to its retrospective design, clinical data such as pain, movement limitations, and muscle spasms could not be analyzed, preventing differentiation between symptomatic and asymptomatic individuals. Second, structural changes such as facet joint or disc degeneration and muscle fat infiltration were not evaluated. Lastly, the relatively small sample size may have influenced the statistical significance of certain findings.

5. Conclusion

This study demonstrates that sacralization significantly affects the morphology of stabilizing trunk muscles. These changes should be accounted for in clinical

assessments, surgical planning, and future research. Prospective studies incorporating symptomatic evaluation and tissue composition analysis will further clarify the clinical implications of these findings.

Author Contributions

The percentages of each author's contributions are presented below. The authors reviewed and approved the final version of the manuscript.

	G.N.K.K.	F.Ç.	İ.U.
C	40	20	40
D	30	30	40
S	30	40	30
DCP	30	40	30
DAI	30	20	50
L	40	20	40
W	40	20	40
CR	20	50	30
SR	20	20	60
PM	40	20	40

C= concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management.

Conflict of Interest:

The authors declare no conflict of interest.

Ethical Consideration

This study was approved by the Erciyes University Clinical Research Ethics Committee on May 10, 2023 (approval date: February 14, 2023, protocol code: 2023/330).

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KONJENİTAL KALP HASTALIĞI OLAN HASTALARDA D VİTAMİNİ DÜZEYLERİ: TEK MERKEZ DENEYİMİ

Gül TRABZON[1]*, Osman Fırat ÇALIŞKAN[2], Ufuk Utku GÜLLÜ[3]

[1]*Hatay Mustafa Kemal University, Faculty of Medicine, Department of Internal Medicine, Division of Pediatrics, Unit of Pediatric Endocrinology, 31040, Hatay, Türkiye*
[2]*Hatay Mustafa Kemal University, Faculty of Medicine, Department of Internal Medicine, Division of Pediatrics, 31040, Hatay, Türkiye*
[3]*Hatay Mustafa Kemal University, Faculty of Medicine, Department of Internal Medicine, Division of Pediatrics, Unit of Pediatric Cardiology, 31040, Hatay, Türkiye*

Özet: Bu çalışma, doğumsal kalp hastalığı olan çocuklarda D vitamini düzeylerini değerlendirmeyi ve bu düzeylerin klinik durum üzerindeki olası etkilerini incelemeyi amaçlamaktadır. Nisan 2022 ile Ağustos 2024 tarihleri arasında hastanemize başvuran ve 25-hidroksivitamin D düzeyleri ölçülen 32 çocuk retrospektif olarak incelenmiştir. Karşılaştırma grubu olarak, yaş ve cinsiyet açısından benzer özellikler gösteren ve sağlıklı olduğu bilinen 42 çocuk dahil edilmiştir. Her iki grubun D vitamini, kalsiyum, fosfor ve diğer biyokimyasal parametreleri analiz edilmiştir. Çalışmada, doğumsal kalp hastalığı olan çocukların D vitamini düzeylerinin anlamlı şekilde daha düşük olduğu gözlenmiştir (18,65±8,11 ng/mL'ye karşı 23,80±9,47 ng/mL, P=0.016). Ayrıca bu çocukların yüzde 59,4'ünde D vitamini eksikliği veya yetersizliği saptanırken, sağlıklı grupta bu oran yüzde 28,6 olarak belirlenmiştir (P=0.029). Kalsiyum ve fosfor düzeyleri açısından gruplar arasında anlamlı bir fark bulunmamıştır. D vitamini eksikliğinin, bu hastalarda güneş ışığına yetersiz maruz kalma, beslenme bozuklukları, sık enfeksiyon geçirme ve bazı ilaçların kullanımı gibi faktörlere bağlı olabileceği düşünülmektedir. D vitamini bağışıklık sisteminin dengelenmesinde, iltihabi süreçlerin düzenlenmesinde ve kalp-damar sağlığının korunmasında önemli bir role sahiptir. Bu nedenle eksikliğinin bu hasta grubunda ciddi klinik sonuçlara yol açabileceği düşünülmektedir. Çalışmamız, bu çocuklarda D vitamini düzeylerinin düzenli olarak değerlendirilmesinin ve eksiklik durumlarında uygun destek tedavilerinin planlanmasının, genel sağlık durumlarını ve hastalık süreçlerini olumlu etkileyebileceğini göstermektedir.

Anahtar Kelimeler: Konjenital kalp hastalığı, D vitamini, Çocuk, Kalp anomalileri

Vitamin D Levels in Patients with Congenital Heart Disease: Single-center Experience

Abstract: This study aims to evaluate vitamin D levels in children diagnosed with congenital heart disease and to examine the potential impact of these levels on clinical outcomes. Between April 2022 and August 2024, a retrospective evaluation was conducted on 32 children who were admitted to our institution and had their serum 25-hydroxyvitamin D levels measured. The control group consisted of 42 healthy children with similar age and gender characteristics. Vitamin D, calcium, phosphorus, and other biochemical parameters were compared between the two groups using appropriate statistical methods. The findings showed that children with congenital heart disease had significantly lower vitamin D levels compared to healthy children (18.65±8.11 ng/mL versus 23.80±9.47 ng/mL, P=0.016). Vitamin D deficiency or insufficiency was observed in 59.4 percent of children with congenital heart disease, whereas this rate was 28.6 percent in the control group (P=0.029). There were no significant differences between the groups in terms of calcium and phosphorus levels. The higher prevalence of vitamin D deficiency in children with congenital heart disease may be associated with factors such as limited exposure to sunlight, inadequate nutritional intake, frequent infections, and use of medications that may interfere with vitamin D metabolism. Since vitamin D plays a role in regulating the immune system, modulating inflammatory processes, and supporting cardiovascular function, its deficiency may contribute to adverse clinical outcomes in this patient population. Our study highlights the importance of regularly monitoring vitamin D levels in children with congenital heart disease and implementing timely supplementation or therapeutic interventions when deficiency is detected, to support overall health and disease management.

Key words: Congenital heart disease, Vitamin D, Children, Heart abnormalities

***Corresponding author:** Hatay Mustafa Kemal University, Faculty of Medicine, Department of Internal Medicine, Division of Pediatrics, Unit of Pediatric Endocrinology, 31040, Hatay, Türkiye
E mail: gldirekk@gmail.com (G. TRABZON)
Gül TRABZON https://orcid.org/0000-0002-9262-5678
Osman Fırat ÇALIŞKAN https://orcid.org/0009-0007-4991-1955
Ufuk Utku GÜL https://orcid.org/0000-0002-5561-3598

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1. Giriş

Konjenital kalp hastalıkları (KKH), çocukluk çağında en sık karşılaşılan doğumsal anomalilerdir ve dünya genelinde önemli bir sağlık sorunu olarak kabul edilmektedir. Bu hastalıkların neden olduğu komplikasyonlar ve morbidite oranları, hastaların yaşam kalitesini olumsuz etkileyebilir (Meller vd., 2020). Son yıllarda, D vitamininin kardiyovasküler sağlık üzerindeki

etkileri yoğun bir şekilde araştırılmaktadır (Gökalp vd., 2022). D vitamini, kalsiyum ve fosfor metabolizmasının düzenlenmesinde kritik bir rol oynar ve bu nedenle kemik sağlığının yanı sıra kalp ve damar sağlığı üzerinde de önemli etkileri bulunmaktadır (de la Guía-Galipienso vd., 2021).

D vitamini eksikliği, genel popülasyonda yaygın olup, çeşitli kardiyovasküler hastalıklarla ilişkilendirilmiştir (Jorge vd., 2018). Kardiyak fonksiyonlar, sol ventrikül hipertrofisi, endotel disfonksiyonu ve hipertansiyon gibi durumlarla ilişkili olduğu gösterilmiştir (de la Guía-Galipienso vd., 2021). D vitamini, renin-anjiyotensin-aldosteron sisteminin baskılanmasında rol oynayarak kan basıncının düzenlenmesine yardımcı olur (Huang vd., 2023). Ayrıca, kardiyomiyositlerde ve vasküler düz kas hücrelerinde D vitamini reseptörlerinin bulunması, bu vitaminin doğrudan kardiyak yapı ve işlevler üzerinde etkili olabileceğini düşündürmektedir. Eksikliği durumunda, miyokardiyal kontraktilite azalabilir, ventriküler remodelling hızlanabilir ve kardiyak disritmiler gelişebilir (Crescioli, 2021; Wong vd., 2014) . D vitamini, endotelyal nitrik oksit sentezini artırarak damar genişlemesini destekler (Mahmoud vd., 2019). Endotel disfonksiyonu gibi erken ateroskleroz bulgularında koruyucu rol üstlenir. Ayrıca antiinflamatuar ve antioksidan etkilerle damar sertliği gelişimini yavaşlatır (Levin vd., 2017). Bununla birlikte, KKH olan çocuklarda D vitamini düzeyleri ve bu düzeylerin hastalığın seyri üzerindeki potansiyel etkileri henüz tam olarak anlaşılmamıştır (Dohain vd., 2020). KKH'li çocukların, özellikle hastalığın doğası gereği artmış metabolik ihtiyaçlar ve sınırlı güneş ışığına maruziyet gibi faktörler nedeniyle D vitamini eksikliği açısından daha fazla risk altında olabileceği düşünülmektedir. Bu durum, KKH olan çocuklarda kemik sağlığı ve genel büyüme gelişme süreçleri üzerinde olumsuz etkiler yaratabilir (McNally and Menon, 2013).

Bu çalışma, KKH olan çocuklarda D vitamini düzeylerini değerlendirmeyi incelemeyi amaçlamaktadır. Ayrıca, elde edilen bulguların, KKH olan çocuklarda D vitamini takviyesi gereksiniminin belirlenmesine katkı sağlayacağı düşünülmektedir. Bu bağlamda, çalışma, KKH'li çocuklarda D vitamini düzeylerinin düşük olabileceği hipotezini test edecek ve bu durumun klinik önemini tartışacaktır.

2. Materyal ve Yöntem

2.1. Hasta Seçimi

Bu çalışmada, Nisan 2022 ile Ağustos 2024 tarihleri arasında hastanemize başvuran konjenital kalp hastalığı (KKH) bulunan hastalar retrospektif olarak incelenmiştir. Çalışmaya dahil edilen örneklem, laboratuvar sisteminde 25-hidroksi D vitamini düzeyi kaydı olan ve tanı bilgileri net olarak belirlenmiş çocuk hastalardan oluşmaktadır. Örneklem seçiminde sistematik rasgele bir örnekleme yapılmamış, mevcut hasta kayıtları taranarak uygun vakalar belirlenmiştir. Konjenital kalp hastalıkları alt tipleri açısından siyanotik ve asiyanotik ayrımı yapılmamıştır; bunun temel nedeni, bazı alt gruplarda örneklem sayısının analiz yapmaya yeterli olmamasıdır. Ancak çalışmada yer alan her bir hastanın tanı bilgileri Tablo 3'te detaylandırılmıştır. Kontrol grubu olarak, yaş ve cinsiyet açısından benzer özellikler gösteren ve 25-hidroksi D vitamini düzeyleri ölçülmüş 42 sağlıklı çocuk çalışmaya dahil edilmiştir. Tüm bireylerin yaş, cinsiyet, boy, kilo gibi demografik verileri ile 25-hidroksi D vitamini, kalsiyum ve fosfor seviyeleri kaydedilmiş ve bu veriler karşılaştırmalı olarak analiz edilmiştir. Çalışmaya dahil edilen hastaların seçiminde bazı dışlama kriterleri uygulanmıştır. Dışlama kriterleri; kronik böbrek veya karaciğer hastalığı, bilinen malabsorpsiyon sendromları, D vitamini metabolizmasını etkileyen ilaçların kullanımı, aktif herhangi bir enfeksiyon varlığı gibi durumları içermektedir. Ayrıca, vitamin kullanımı ile ilgili olarak, son 6 ay içinde D vitamini takviyesi aldığı bilinen 3 hasta dışlanmış, kalan 32 hastanın bu tür bir takviyeyi kullanmadığı doğrulanmıştır. Bu bilgiler çalışmanın kısıtlılıkları dikkate alınarak eklenmiştir.

2.2. İstatistiksel Analiz

Verilerin analizi SPSS 27,0 (IBM Corporation, Armonk, NY) yazılımı kullanılarak gerçekleştirildi. Cinsiyet dağılımı için Pearson Ki-Kare testi uygulandı. Yaş ve antropometrik ölçümler için Mann-Whitney U testi kullanıldı. Vaka ve kontrol grupları arasındaki vitamin D, kreatinin, AST, ALT, kalsiyum ve fosfor düzeylerinin karşılaştırılması bağımsız gruplarda t-testi ve Mann-Whitney U testi ile değerlendirildi. İstatistiksel anlamlılık sınırı $p<0.05$ olarak kabul edildi. Ayrıca 25 hidroksi D vitamin düzeyi 12 ng/ml altında olanlar düşük, 12-20 ng/ml arasında olanlar yetersiz, 20 üzerinde olanlar yeterli düzey olarak kabul edildi (Munns vd., 2016).

3. Bulgular

Vaka ve kontrol gruplarının cinsiyet dağılımları arasında istatistiksel olarak anlamlı bir fark bulunmamıştır (P=0.253). Vaka grubunda 18 erkek (%56,3) ve 14 kadın (%43,7) yer alırken, kontrol grubunda 18 erkek (%42,9) ve 24 kadın (%57,1) bulunmaktadır. Bu sonuçlar, her iki grubun cinsiyet açısından homojen olduğunu ve karşılaştırmaların cinsiyet dağılımından etkilenmediğini göstermektedir (Tablo 1).

Vaka ve kontrol gruplarının yaş ve antropometrik ölçümleri detaylı olarak bakıldığında yaş, boy, kilo ve vücut kitle indeksi (VKİ) gibi parametreler açısından gruplar arasında istatistiksel olarak anlamlı bir fark saptanmamıştır. Vaka grubunun yaş ortalaması 8,5±5,16 yıl iken, kontrol grubunun yaş ortalaması 7,57±4,77 yıl olarak belirlenmiştir (P=0.623) (Tablo 2). Bu bulgular, vaka ve kontrol gruplarının yaş ve temel antropometrik özellikler bakımından benzer profillere sahip olduğunu ve bu parametrelerin diğer sonuçları etkilemediğini göstermektedir. Vaka grubundaki konjenital kalp hastalıklarının çeşitliliği Tablo 3'te detaylandırılmıştır.

Tablo 1.Vaka ve kontrol gruplarında cinsiyete göre dağılım

	Grup				Total		P
	Vaka		Kontrol				
	N	%	N	%	N	%	
Erkek	18	56,3%	18	42,9%	36	48,6%	0,253
Kadın	14	43,7%	24	57,1%	38	51,4%	
Total	32	100,0%	42	100,0%	74	100,0%	

Tablo 2. Vaka ve kontrol gruplarında antropometrik ölçümlerin karşılaştırılması

	Grup				P
	Vaka		Kontrol		
	Mean	SD	Mean	SD	
Yaş(yıl)	8,5	5,168	7,57	4,769	0,623
Boy(cm)	128,6	27,924	122,6	31,472	0,612
Boy ZS	-0,37	1,555	-0,36	0,801	0,682
Kilo(kg)	33,02	19,930	30,55	19,109	0,772
Kilo ZS	-0,46	1,783	-0,07	0,977	0,230
VKİ	17,78	4,711	18,02	3,558	0,478
VKİ ZS	-0,48	1,882	0,08	1,090	0,178

VKİ=Vücut Kitle İndeksi, ZS=Z skoru, Ort=Ortalama, SD=Standart Deviasyon

Tablo 3. Vaka grubundaki kardiyak patolojilerin dağılımı

Kardiyak Patoloji Türü	n	%
İzole VSD veya VSD kombinasyonları	7	21,9%
İzole ASD veya ASD kombinasyonları	5	15,6%
Pulmoner Stenoz	3	9,4%
Aort Koarktasyonu (± diğer lezyonlar)	4	12,5%
TOF ve TOF-benzeri lezyonlar	3	9,4%
Kompleks Doğumsal Kalp Hastalıkları (AVSD, Noonan, vs,)	5	15,6%
Diğer (MVR, AVR, PDA, endokardit, vs,)	5	15,6%
Total	32	100,000%

VSD = Ventriküler Septal Defekt, ASD = Atrial Septal Defekt, TOF = Fallot Tetralojisi, AVSD = Atrioventriküler Septal Defekt, MVR = Mitral Valv Replasmanı, AVR = Aort Valv Replasmanı, PDA = Patent Duktus Arteriosus.

Vaka ve kontrol gruplarının D vitamini, kreatinin, AST, ALT, kalsiyum ve fosfor düzeyleri karşılaştırılmıştır. D vitamini vaka grubunda ortalama 18,22±8,51 ng/mL, kontrol grubunda ise 23,80±9,47 ng/mL olarak ölçülmüştür. Aradaki fark istatistiksel olarak anlamlıydı (P=0.016). Bu, KKH olan çocuklar ile sağlıklı çocuklar arasında D vitamini düzeyleri açısından önemli bir farklılık olduğunu göstermektedir. Kalsiyum vaka grubunda ortalama 9,77±0,52 mg/dL, kontrol grubunda ise 9,74±0,43 mg/dL olarak belirlenmiş ve aradaki fark anlamlı değildir (P=0.530). Fosfor vaka grubunda ortalama 4,61±0,56 mg/dL, kontrol grubunda ise 4,87± 0,674 mg/dL olarak saptanmış ve fark istatistiksel olarak anlamlı bulunmamıştır (P=0.157). Aynı şekilde kreatinin, AST ve ALT düzeyinde değerler iki grup için benzerdir (Tablo 4).

Bu bulgular genel olarak KKH olan çocukların D vitamini ve diğer temel biyokimyasal parametreler açısından sağlıklı çocuklarla benzer düzeylere sahip olduğunu göstermektedir.

Hastalar 25 hidroksi D vitamini düzeyinin eksikliği açısından değerlendirildiğinde konjenital kalp hastalığı olan hastaların %59,4'nde eksiklik ve yetersizlik var iken, kontrol grubunda %28,6'sında eksiklik ve yetersizlik saptandı (Tablo 5). Yapılan istatistiksel analiz sonucunda, gruplar arasında anlamlı bir fark bulunmuştur. Konjenital kalp hastalığı olan hastaların %40,6'sında D vitamini seviyeleri normal iken kontrol vakaların %74'ünde D vitamini seviyeleri normaldir, istatiksel olarak konjenital kalp hastalığı ve kontrol grupta anlamlı bir fark vardır (P=0.028).

Tablo 4. Vaka ve kontrol gruplarında biyokimyasal parametrelerin karşılaştırılması

	Grup								P
	Vaka				Kontrol				
	Min	Maks	Ort	SD	Min	Maks	Ort	SD	
D VİT (ng/ml)	4,30	38,49	18,22	8,511	8,51	44,41	23,80	9,461	0,011*
KRE (mg/dl)	0,23	0,64	0,43	0,111	0,18	0,79	0,40	0,133	0,489*
AST (U/L)	3,0	63,0	31,3	11,923	19,0	52,0	30,38	7,330	0,410*
ALT (U/L)	9,0	34,0	17,8	6,234	11,0	39,0	19,8	5,588	0,070**
CA (mg/dl)	8,52	10,77	9,77	0,522	8,81	11,28	9,74	0,427	0,530**
P (mg/dl)	3,20	5,50	4,61	0,558	2,38	6,30	4,87	0,674	0,157**

D VİT=D vitamini, Kre=Kreatinin, AST=spartat aminotransferaz, ALT=Alanin aminotransferaz, Min=Minumum, Mean=Ortalma, Maks=Maksimum, SD=Standart deviasyon, *=Bağımsız Gruplarda t testi, **=Mann Whitney U testi

Tablo 5. Vaka ve kontrol gruplarında D vitamini düzeylerinin dağılımı

	Grup				P
	Vaka		Kontrol		
	N	%	N	%	
D Vitamini Eksikliği	9	28,1%	5	11,9%	0,028
D Vitamini Yetersizliği	10	31,3%	7	16,7%	
Normal	13	40,6%	30	71,4%	
Toplam	32	100%	42	100%	

4. Tartışma

Bu çalışmada, konjenital kalp hastalığı olan hastalar ve kontrol grubu olan hastalarda D vitamini, kreatinin, AST, ALT, kalsiyum ve fosfor düzeyleri karşılaştırılmıştır. D vitamini seviyelerinde gözlemlenen anlamlı fark, konjenital kalp hastalığı (KKH) olan çocukların, sağlıklı çocuklara kıyasla daha düşük D vitamini seviyelerine sahip olduğunu göstermektedir. Konjenital kalp hastalığı (KKH) olan çocuklarda daha düşük D vitamini seviyelerinin birkaç sebebi olabilir. İlk olarak, KKH'li çocuklar, hastalıklarına bağlı olarak daha az güneşe maruz kalabilirler. Uzun süreli hastane yatışları, ameliyatlar ve fiziksel aktivitenin kısıtlanması bu durumu artırabilir. Ayrıca, bu çocuklar hastalıkları nedeniyle daha az besin tüketebilir veya D vitamini açısından yetersiz beslenebilirler (McNally and Menon, 2013). KKH tedavisinde kullanılan bazı ilaçlar da D vitamini metabolizmasını olumsuz etkileyebilir (Nordqvist vd., 2019). Kardiyopulmoner baypas (CPB) gibi cerrahi işlemler, vücutta büyük sıvı değişimlerine yol açarak D vitamini bağlayıcı proteinlerin kaybına ve D vitamini seviyelerinin düşmesine neden olabilir (Dohain vd., 2020). Sonuç olarak, KKH'li çocuklar D vitamini eksikliği açısından daha yüksek risk altındadır ve bu durum, kardiyovasküler fonksiyonlar üzerinde olumsuz etkiler yaratabilir. D vitamini eksikliği, immün sistemin zayıflamasına, inflamatuvar süreçlerin artmasına ve kardiyovasküler fonksiyonların bozulmasına yol açabileceğinden, bu hastalarda D vitamini eksikliği KKH'nin klinik yönetimi açısından dikkate alınmalıdır (Gökalp vd., 2022; McNally and Menon, 2013).

Bu çalışmada, konjenital kalp hastalığı (KKH) olan çocuklarda düşük D vitamini seviyelerinin belirlenmesi ve bu durumun potansiyel sebeplerinin ortaya konması, klinik yaklaşımlar ve tedavi planlaması açısından uzun vadeli faydalar sunabilir. Yine çalışmamızla benzer şekilde Crescioli vd. (2021), ve Wong vd. (2014), D vitamini eksikliğinin vasküler rejenerasyonu olumsuz etkilediğini ve kalp yetmezliği riskini artırabileceğini vurgulamıştır. Özellikle D vitamini eksikliğinin, KKH'nin ilerleyişi ve tedavi sürecine olan etkileri dikkate alındığında, hastaların izlenmesinde ve tedavi edilmesinde önemli değişiklikler yapılabilir. Bizim çalışmamızda olduğu gibi konjenital kalp hastalığı olan çocuklarda yaygın D vitamini eksikliği saptandığında, bu eksikliğin tespit edilmesi ve tedavi edilmesi, kardiyovasküler fonksiyonların korunmasında kritik rol oynayabilir (Gökalp vd., 2022). D vitamini, kemik ve kas sağlığıyla doğrudan ilişkili olduğu gibi, bağışıklık sistemi ve inflamatuvar süreçler üzerinde de önemli etkilere sahiptir. Delrue ve Speeckaert (2023), D vitamini bağlayıcı proteinlerin biyolojik rolünün sadece taşıma değil, aynı zamanda immün modülasyonla ilişkili olduğunu ortaya koymuştur. Bu nedenle, KKH'li çocuklarda D vitamini düzeylerinin düzenli olarak izlenmesi, eksiklik durumunda erken müdahale edilmesi, uzun vadeli komplikasyonların önlenmesine yardımcı olabilir.

Konjenital kalp hastalıklarında yapılan cerrahi müdahalelerin D vitamini seviyelerinde ani düşüşlere yol açabildiği göz önüne alındığında, bu çocuklarda cerrahi öncesi ve sonrası dönemde D vitamini seviyelerinin optimize edilmesi önem arz etmektedir. Cerrahi sonrası dönemde hızlı bir şekilde düşen D vitamini seviyelerinin kontrol altına alınması, iyileşme sürecini hızlandırabilir ve postoperatif komplikasyonları azaltabilir (Dohain vd., 2020; McNally and Menon, 2013).

Konjenital kalp hastalığı tedavisinde ve komplikasyonlarında kullanılan glukokortikoidler, antikonvülzanlar ve diüretikler gibi ilaçlar, D vitamini metabolizmasını olumsuz etkileyebilir. Bu ilaçlar, D vitamini reseptörlerini bloke ederek veya D vitamini metabolizmasını hızlandırarak vücuttaki D vitamini seviyelerini düşürebilir. KKH'li çocuklarda bu tür ilaçlar

kullanıldığında, D vitamini seviyelerinin daha yakından izlenmesi ve gerektiğinde takviye edilmesi gereklidir (Nordqvist vd., 2019).

KKH'li çocuklar, uzun süreli hastane yatışları ve fiziksel aktivite kısıtlamaları nedeniyle yeterli güneş ışığı alamayabilir. Ayrıca, yetersiz beslenme veya D vitamini açısından zengin gıdaların tüketiminin az olması, bu çocuklarda D vitamini eksikliğine yol açabilir. Bu nedenle, D vitamini eksikliği riski altında olan KKH'li çocuklar için beslenme düzenlemeleri yapılmalı ve güneşe maruz kalma süresi artırılmalıdır(McNally and Menon, 2013; Uday and Högler, 2020).

KKH'li çocuklarda düşük D vitamini seviyeleri kardiyovasküler sistem üzerinde uzun vadeli olumsuz etkilere sahip olabilir. D vitamini eksikliği, inflamasyonun artmasına, kalp fonksiyonlarının bozulmasına ve komplikasyon risklerinin artmasına neden olabilir. Bu nedenle, bu çocukların uzun vadede D vitamini düzeylerinin izlenmesi, sadece kemik sağlığı açısından değil, aynı zamanda kardiyovasküler sağlık açısından da önemli olabilir (Gökalp vd., 2022). Buna ek olarak, konjenital kalp hastalığı olan çocuklarda sık görülen tekrarlayan solunum yolu enfeksiyonlarının da D vitamini eksikliği üzerinde etkili olabileceği düşünülmektedir. D vitamini, bağışıklık sistemi hücreleri üzerinde immün modülatör bir etkiye sahiptir ve özellikle antimikrobiyal peptitlerin (örneğin katelisidin) sentezini uyararak enfeksiyonlara karşı savunmayı artırır. Eksikliği durumunda, bu savunma mekanizmaları zayıflar ve solunum yolu enfeksiyonlarına yatkınlık artabilir (Coşar, 2023). Öte yandan, enfeksiyon varlığında sitokin düzeylerindeki artış ve sistemik inflamasyon D vitamini metabolizmasını bozabilir ve 25-hidroksi D vitamini düzeylerinde azalmaya neden olabilir. Bu durum, enfeksiyon ve D vitamini eksikliği arasında çift yönlü bir ilişki olduğunu göstermektedir (Karkeni vd., 2018). Bu nedenle, KKH'li çocuklarda D vitamini düzeylerinin değerlendirilmesinde solunum yolu enfeksiyon öyküsü ve inflamatuvar durum da göz önünde bulundurulmalıdır.

Öte yandan, kalsiyum ve fosfor düzeylerinde vaka ve kontrol grupları arasında anlamlı fark bulunmaması, bu parametrelerin KKH'li çocuklar ile sağlıklı çocuklar arasında belirgin bir değişiklik göstermediğini işaret etmektedir. Kalsiyum ve fosfor, kemik sağlığı ve genel metabolik işlevler için kritik öneme sahip olmalarına rağmen, çalışmadaki iki grup arasında fark bulunmaması, henüz D vitamini eksikliğinin ağır olmamasından kaynaklı olabilir. Bununla birlikte, bu sonuçların D vitamini eksikliğinin ağırlığı ve süresine, hastalığın seyrine göre değişebileceği göz önünde bulundurulmalıdır (Uday and Högler, 2020). Noonan veya Williams sendromu gibi sendromik tanı almış hastaların dahil edilmesi D vitamini düzeylerini potansiyel olarak etkileyebilir. Ancak bu olguların nadirliği ve çalışmada yer alan hasta sayısının sınırlı olması nedeniyle dışlanmamış, bunun yerine çalışmanın bir kısıtlılığı olarak değerlendirilmiştir. Ayrıca, bu sendromlara sahip hastalarda D vitamini düzeylerini spesifik olarak etkileyen güçlü ve tutarlı kanıtların literatürde sınırlı olması ve çalışmamızda kalsiyum ve fosfor seviyelerinin normal sınırlar içinde bulunması nedeniyle bu hastalar çalışmadan çıkarılmamıştır.

Kreatinin, AST ve ALT gibi karaciğer ve böbrek fonksiyonlarını yansıtan biyokimyasal parametrelerde gruplar arasında istatistiksel olarak anlamlı fark bulunmaması, KKH'li çocukların karaciğer ve böbrek fonksiyonlarının sağlıklı çocuklara benzer olduğunu göstermektedir. Bu bulgu, KKH'nin bu organlar üzerindeki doğrudan etkisinin sınırlı olabileceğini düşündürse de, daha ileri araştırmalara ihtiyaç duyulmaktadır. Özellikle AST ve ALT gibi enzim seviyeleri, uzun vadede kardiyak ameliyatlar ya da medikal tedavilerle ilişkili olarak değişiklik gösterebilir (Egbe vd., 2022). Bu bulgular şuan normal olsa da uzun vadede bu hastalar böbrek ve karaciğer fonksiyon testleri açısından mutlaka izlenmelidir.

5. Sonuç

KKH'li çocuklarda D vitamini düzeylerinin düşük olması, bu hastaların klinik yönetiminde dikkate alınması gereken önemli bir bulgu olarak değerlendirilmiştir. D vitamini eksikliği, yalnızca kemik sağlığını değil, bağışıklık sistemi işlevleri ve kardiyovasküler performansı da olumsuz etkileyebilir. Bu nedenle, D vitamini eksikliğinin tespiti ve uygun tedavi yaklaşımlarının planlanması, hem kısa vadeli sağlık kazanımları hem de uzun vadeli klinik sonuçlar açısından büyük önem taşımaktadır. Ayrıca, çalışmamız Türkiye'de bu konuda yapılan sınırlı sayıda araştırmadan biri olması bakımından literatüre yerel düzeyde önemli bir katkı sunmaktadır. Çalışma bulguları, bu hasta grubunun izlemi sırasında D vitamini düzeylerinin düzenli olarak değerlendirilmesi gerektiğini ortaya koymakta ve multidisipliner bir yaklaşımın önemini vurgulamaktadır. Bu nedenle, D vitamini düzeylerinin KKH'li çocuklarda düzenli aralıklarla izlenmesi önerilmektedir. Özellikle ilk tanı anında ve yılda en az bir kez olacak şekilde serum 25(OH)D düzeylerinin kontrol edilmesi, eksiklik saptanan bireylerde ise yaşa uygun D vitamini replasmanı başlanması önem arz etmektedir. Klinik pratiğe yansıtılacak şekilde, 12 ng/mL altı "eksiklik", 12–20 ng/mL arası "yetersizlik" olarak değerlendirilerek, eksik/yetersiz gruba 1000–2000 IU/gün D vitamini desteği planlanması uygun olacaktır. Bu tarama ve destek protokolü, hem kemik sağlığı hem de kardiyovasküler sistemin korunması açısından önemli bir basamak olabilir. Ayrıca, cerrahi geçirecek hastalarda preoperatif D vitamini düzeylerinin değerlendirilmesi ve gerekirse hızlı replasman yapılması postoperatif iyileşmeyi olumlu etkileyebilir. Örneklem büyüklüğünün nispeten küçük olması bir sınırlamadır, ancak çalışma gelecekteki çok merkezli prospektif çalışmalara bilgi sağlayabilecek ilk verileri sunmaktadır.

6. Kısıtlılıklar

Örneklem büyüklüğünün nispeten küçük olması bir sınırlamadır, ancak çalışma gelecekteki çok merkezli prospektif çalışmalara bilgi sağlayabilecek ilk verileri sunmaktadır. Hasta sayısının sınırlı olması ve retrospektif tasarım nedeniyle siyanotik ve asiyanotik KKH tiplerini karşılaştıran alt grup analizi mümkün olmamıştır ancak gelecekteki çalışmalarda ele alınmalıdır. Sendromlarla ilişkili D vitamini eksikliğinin verileri net olmadığı için, çalışmadan çıkarılmamıştır.

Katkı Oranı Beyanı

Yazarların katkı yüzdeleri aşağıda verilmiştir. Yazarlar makaleyi incelemiş ve onaylamıştır.

	G.T.	O.F.Ç.	U.U.G.
K	70	10	20
T	70	25	5
Y	10	5	85
VTI	20	70	10
VAY	40	40	20
KT	60	20	20
YZ	90	5	5
KI	40	30	30
GR	40	30	30
PY	40	30	30

K= kavram, T= tasarım, Y= yönetim, VTI= veri toplama ve/veya işleme, VAY= veri analizi ve/veya yorumlama, KT= kaynak tarama, YZ= Yazım, KI= kritik inceleme, GR= gönderim ve revizyon, PY= proje yönetimi.

Çıkar Çatışması Beyanı

Yazarlar arasında herhangi bir çıkar çatışması bulunmamaktadır.

Etik Onay/Hasta Onamı

Çalışmamız için Hatay Mustafa Kemal Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan (onay tarihi: 02/10/2024, protokol kodu: 30) etik onay alınmıştır. Çalışma retrospektif olarak tasarlanmış olup herhangi bir müdahale içermemektedir. Araştırma, Helsinki Bildirgesi ilkelerine ve Uluslararası Tıp Dergisi Editörleri Komitesi'nin (ICMJE) etik yayın ilkelerine uygun olarak yürütülmüştür.

Teşekkür Beyanı

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EFFECT OF THYMOQUINONE AND BUTYLATED HYDROXYTOLUENE ON BEHAVIOR AND OXIDATIVE STRESS LEVEL IN RATS CHRONICALLY EXPOSED TO ETHANOL

Dilek KUZAY AKSOY[1]*

[1]*Kırşehir Ahi Evran University, Faculty of Medicine, Department of Physiology, 40100, Kırşehir, Türkiye*

Abstract: The objective of this study is to examine the antioxidant activity of Thymoquinone (TQ) and Butylated Hydroxytoluene (BHT) and its effect on behavioral tests in rats chronically exposed to ethanol. The experimental groups were determined as Control, Sham, Ethanol, Ethanol+BHT, Ethanol+TQ and Ethanol+BHT+TQ. In order to create a chronic alcohol exposure model in rats, 7 g/kg ethanol was given for 4 weeks. BHT and TQ were given at a dose of 10 mg/kg for 4 weeks. Glutathione, malondylaldehyde and total nitric oxide levels were analyzed to evaluate oxidative stress in brain, stomach, liver and kidney tissue. Open field test and forced swim test were used to examine anxiety disorder and depression-like behaviors in rats. Compared with the control group, ethanol exposure increased malondylaldehyde and total nitric oxide levels and decreased glutathione levels in all tissues ($P<0.05$). BHT, TQ and BHT+TQ treatment increased glutathione levels and decreased malondylaldehyde levels in all tissues ($P<0.05$). In the ethanol-exposed group, swimming time decreased and immobility time increased, and it was determined that there was a decrease in the time spent in the center of the open field and an increase in the time spent in the periphery ($P<0.05$). BHT and TQ treatment increased swimming time, decreased immobility time and caused an increase in the time spent in the center of the open field ($P<0.05$). Our findings showed that BHT and TQ contributed critically to the protection against ethanol-induced oxidative stress in tissues. BHT and TQ treatment improved behavioral tests after ethanol exposure. The most significant improvement was seen in the group that was given BHT+TQ simultaneously after ethanol exposure.

Keywords: Ethanol, Behavior, Oxidatıve Stress, Antioxidants, Rats, Nigella sativa

***Corresponding author:** Kırşehir Ahi Evran University, Faculty of Medicine, Department of Physiology, 40100, Kırşehir, Türkiye
E mail: dilekkuzay@gmail.com (D. KUZAY AKSOY)
Dilek KUZAY AKSOY https://orcid.org/0000-0002-1460-9883

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1. Introduction

Ethanol is a greatly consumed organic solvent with toxic properties both the central nervous system and other systems such as the liver, kidneys and gastrointestinal tract. Around two billion people in the world consume ethanol and around eighty million people have been diagnosed with ethanol-related illnesses.

Chronic ethanol use raises the production of reactive oxygen species (ROS) in cells (Zhang et al., 2012; Reddy et al., 2014). ROS are the major mediators of oxidative stress. They reduce enzymatic antioxidants and non-enzymatic antioxidants (such as glutathione (GSH)). In addition, ROS oxidize lipids in the cell structure. Many by-products are formed as a result of lipid peroxidation and the most important of these is Malondylaldehyde (MDA). MDA reacts with many molecules in the cell and causes negative effects due to disruption of the structure (Sanpinit et al., 2022). Nitric Oxide (NO) is another biological molecule that can cause an increase in oxidative stress like ROS. At high concentrations, NO rapidly reacts with superoxide radicals and forms peroxynitrite. Peroxynitrite is cytotoxic (Şener et al., 2015).

There are studies showing that ethanol rises NO and MDA levels and reduces GSH levels in cells (Li et al., 2015; Park et al., 2021; Sanpinit et al., 2022). In addition, chronic ethanol exposure causes oxidative stress, edema, excitotoxicity, neuroinflammation, glial scarring and neurodegeneration in brain cells (Duncan et al., 2016). Oxidative stress has also been shown to accelerate telomere shortening, inflammation excitotoxicity and mitochondrial dysfunction. Oxidative stress is also considered to be included in the etiology of neuropsychiatric disorders, such as behavioral disorders associated with chronic alcohol use. The most common behavioral disorders in chronic alcohol users are depression and anxiety disorders (Tsermpini et al., 2022.) Open field tests and forced swimming tests are used to demonstrate anxiety disorder and depression-like behaviours in experimental animals (Brocardo et al., 2012).

Oxidative stress caused by ethanol can be prevented by antioxidants. With respect to the World Health Organization, about 70% to 80% of the world's

population trust traditional medicine. Herbal treatments have been the most utilized form of traditional medicine. Thymoquinone (TQ) is the very important component of the essential oil of Nigella sativa seeds. Previous studies indicate TQ has neuroprotective, anti-inflammatory and antioxidant effects (Kanter et al., 2005; Hosseini et al., 2017; Mehanna et al., 2021; Sanpinit et al., 2022).

Butylated hydroxytoluene (BHT) is a phenol-derived lipophilic organic compound used as an antioxidant. Its antioxidant activity has been proven and is a product used in the food industry to extend the life of packaged foods. However, its effect on cells in biological systems is still being studied (Hamelink et al., 2005).

When we look at the literature, although there are a few studies showing that TQ has antioxidant effects in ethanol exposure, there are no studies examining the antioxidant effect of BHT in ethanol exposure. Additionally, there is no study examining the effects of TQ and BHT on behavior during ethanol exposure.

Therefore, the objective of this study was to examine the impacts of TQ and BHT on oxidative stress levels in the brain, stomach, liver and kidney tissues and behavioral tests of rats exposed to chronic ethanol.

2. Materials and Methods

2.1. Animals

In the study, 36 adult male Wistar Albino rats weighing between 250±20 g were used. Each rat was housed in separate cages in a 12-hour light-dark cycle at 24±2 ºC and fed with standard rat chow and tap water ad libitum.

2.2. Experimental Design

The study design is given in Table 1. All treatments were performed 5 days a week for 4 weeks. The control group was fed with normal rat feed and tap water in the cage. No treatment was performed. The sham group was created to study gavage-induced stress.

Table 1. Experimental design

Group	Number of rats	Explanations
C	n=6	No treatment was performed
S	n=6	Received tap water
E	n=6	Received ethanol
E+B	n=6	Received ethanol and BHT
E+T	n=6	Received ethanol and TQ
E+B+T	n=6	Received ethanol and BHT and TQ

C= control, S= sham, E= etanol, E+B= etanol+BHT, E+T= etanol + TQ, E+B+T= etanol+BHT+TQ

2.3. Chronic Alcohol Exposure

In light of the information obtained from the literature, ethanol given at doses of 3 g/kg and higher causes chronic effects. In this study, in order to create a chronic alcohol exposure model, rats were given approximately 40% ethanol (Sigma Aldrich, USA) at a dose of 7 g/kg by intragastric gavage 5 days a week for 4 weeks (Özcan and Mengi, 1998; Pal et al., 2022).

2.4. Treatment

10 mg/kg BHT (ZAG Chemistry, Türkiye) dissolved in ethanol and 10 mg/kg TQ (CAYMAN Chemical, USA) dissolved in tap water were given by intragastric gavage immediately after ethanol administration for 4 weeks, 5 days a week (Aksoy et al., 2015; Fouad and Jresat, 2015; Hosseini et al., 2017). The drugs were make ready newly every day. It was injected in a volume of 1 ml/kg. Experiments were carried out at 8:00 - 10:00 in the morning.

2.5. Behavioral Studies

Forced swimming test (Fst): To examine the severity of depression, we made a changed Fst, according to the already defined method. A 15-minute pre-test was performed on the rats to prevent acute stress. One day after the pre-test, each rat was floated separately in a 30 cm water-filled container at 25°C±1°C for 5 minutes. (In cylindrical containers with a diameter of 15 cm and a height of 50 cm). Along the test period swimming, climbing and immobility time was registered by a video camera (Kuzay et al., 2022).

Open field test (Oft): To evaluate the spontaneous locomotor activity of the rats, the individual movements of each were registered with a video camera for 5 minutes in a white plexiglass arena with a diameter of 90 cm x 35 cm, whose floor was seperated into 24 units with black stripe. The strips that animals crossed with their four paws were recorded as the number of crossings. The time spent in the center and periphery the open area was also recorded (Brocardo et al., 2012). Two hours after the treatment, behavioral tests of each rat was measured. Figure 1 presents the timeline of behavioral testing.

Figure 1. Timeline depicting the sequence of experimental events. D indicates day of experiment. Rats were tested in the Forced swim test (Fst) on day 28 and in the open field test on day 29. Body weight (BW) was taken on day 0 and day 30.

2.6. Determination of Oxidative Stress Levels

At the end of 1 month, all rats were sacrificed under intra muscular Rompun (5mg/kg) + Ketamine (45mg/kg) anesthesia by removing blood from their hearts. Brain, stomach, liver and kidney tissues were frozen in liquid nitrogen and stored at -80 °C until the day of the study. GSH, MDA and total NO levels were investigated to evaluate oxidative stress. GSH levels were determined by the Modified Ellman method, MDA levels by

Thiobarbituric acid reactive substance formation, and NOx levels by the Griess method (Ayka et al., 1985; Gilbert, 2000; Miranda et al., 2001; Hassanien et al., 2015).

2.7. Statistical Analysis

Data were examined using the Statistical Package for Social Sciences 15.0 software program and offered as mean±standard deviation (SD). Comparisons between groups were made using one-way analysis of variance followed by post hoc Tukey tests. Paired Samples T test was utilized for the assessment of body weight.

3. Results

3.1. Forced Swimming Test (Fst)

In comparison to the control group, the ethanol group displayed a characteristic depressive-like behavior such as less climbing, less swimming, and prolonged immobility in Fst (P<0.05). TQ and TQ+BHT cure caused an important decrease in immobility time and a rise in climbing time and swimming time in Fst compared to the rats receiving only ethanol (P<0.05). BHT treatment caused an important decrease in immobility time and a rise in swimming time in Fst compared to the rats receiving only ethanol (P<0.05) but climbing time was not statistically significant (P>0.05) (Figure 2, 3, 4).

3.2. Open Field Test (Oft)

There was an increase time spent in the periphery and a decrease in the number of crossings and time spent in the center in the Ethanol group when compared to the control group (P<0.05). BHT cure induced reduction time spent in the periphery and an increase time spent in the center compared to the rats receiving only ethanol (P<0.05). BHT treatment did not produce a statistically important change in the number of crossings (P>0.05). TQ and TQ+BHT cure caused a significant decrease time spent in the periphery and a rise in the number of crossings and time spent in the center compared to the ethanol group (P<0.05) (Figure 5, 6, 7).

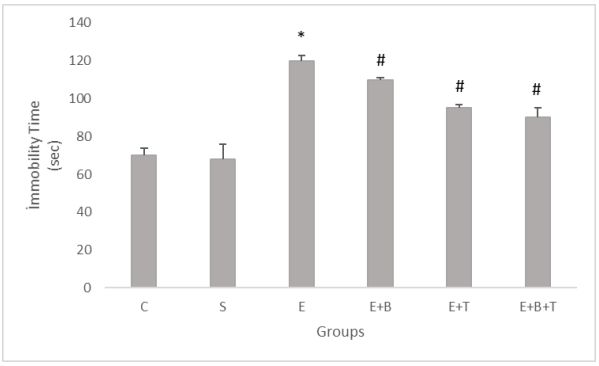

Figure 2. Immobility time (sec). The values are means±SD; n = 6, * P<0.05 Significant differences with C and S groups; # P<0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T: received ethanol and TQ, E+B+T=received ethanol and BHT and TQ.

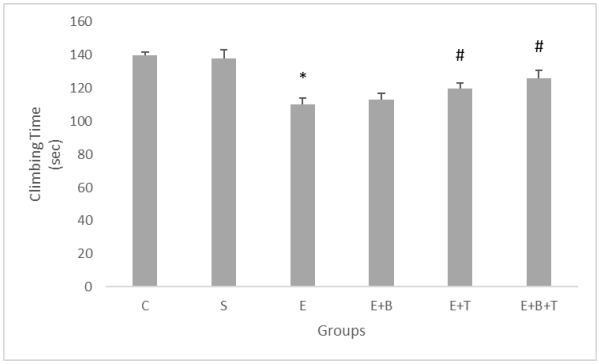

Figure 3. Climbing time (sec). The values are means±SD; n = 6, * P< 0.05 Significant differences with C and S groups; # P<0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

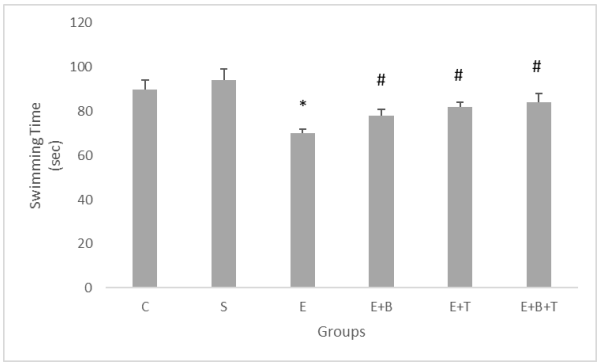

Figure 4. Swimming time (sec). The values are means±SD; n = 6, * P<0.05 Significant differences with C and S groups; # P<0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

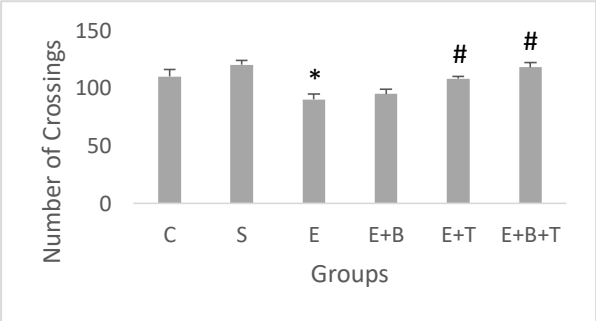

Figure 5. Number of crossings. The values are means±SD; n = 6, * P<0.05 Significant differences with C group; # P<0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

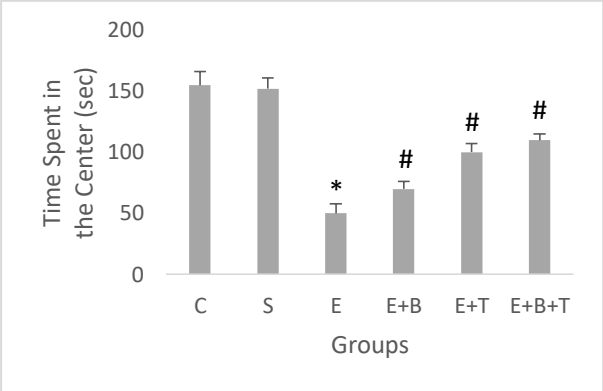

Figure 6. Time spent in the center (sec). The values are means±SD; n = 6, * P<0.05 Significant differences with C and S groups; # P<0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

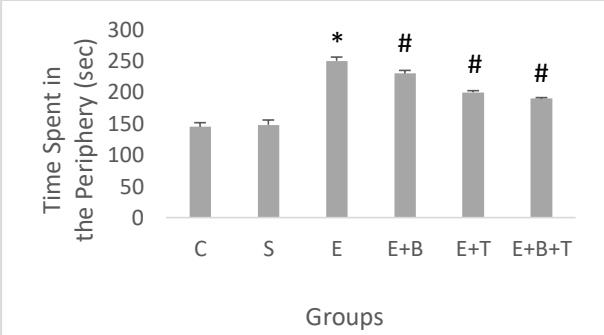

Figure 7. Time spent in the periphery (sec). The values are means±SD; n = 6, * P<0.05 Significant differences with C and S groups; # P<0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

3.3. Body Weight

At the end of the 30th day, there was a rise in body weight in the control and sham groups (P<0.05). Additionally, it was determined that there was a statistically important rise in body weight of groups TQ and TQ+BHT treatment (P<0.05). There were no important alteration in body weight in Ethanol group and BHT cure group (P>0.05) (Figure 8).

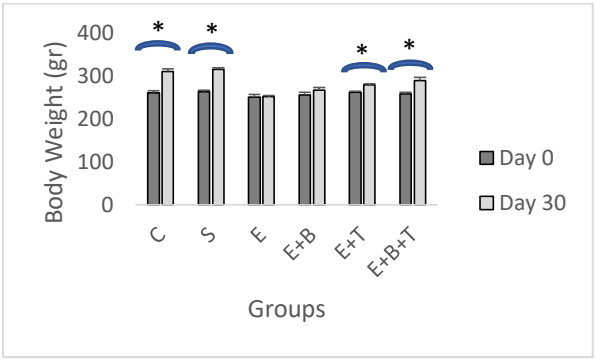

Figure 8. Measured body weight on the 0th day and the30th day. The values are means±SD; n = 6. * P< 0.05. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

3.4. Oxidative Stress

Compared with the control group, it was determined that MDA and NOx levels rised and GSH levels reduced in the ethanol group's brain, stomach, liver and kidney tissues (P<0.05). In the brain tissue, when compared with the Ethanol group, there was a decrease in MDA and NOx levels and an increase in GSH levels in the BHT and BHT+TQ treatment groups (P<0.05). In the brain tissue, when compared with the Ethanol group, it was defined that there was a reduce in MDA levels and a rise in GSH levels in the TQ cure group (P<0.05), but the decrease in NOx levels was not important (p>0.05). In the stomach tissue, there was a reduce in MDA and NOx levels and an increase in GSH levels in the BHT, TQ and BHT+TQ treatment groups compared to the Ethanol group (P<0.05). In liver and kidney tissue, when compared with the ethanol group, there was a decrease in MDA and NOx levels and an increase in GSH levels in the TQ and BHT+TQ treatment groups (P<0.05). In liver and kidney tissue, when compared with the Ethanol group, it was defined that there was a reduce in MDA levels and a rise in GSH levels in the BHT cure group (P<0.05), but the decrease in NOx levels was not important (p>0.05). In the brain, stomach, liver and kidney tissues, the highest reduce in MDA and NOx levels and the highest rise in GSH levels were determened in the BHT+TQ cure group (P<0.05). The findings are given in Table 2, 3, 4, 5.

Table 2. The results of stomach tissue MDA, NO ve GSH levels

	Group (n=6)	MDA Levels (nmol/g)	NO Levels (µmol/g)	GSH Levels (nmol/g)
Stomach Tissue	C	3.7±0.1	8.2±0.6	9.4±0.6
	S	3.2±0.9	7.9±0.9	8.3±1.2
	E	8.6±0.15*	12.3±0.1*	5.6±0.9*
	E+B	6.5±0.7 #	9.6±0.7#	7.1±0.8 #
	E+T	5.33±0.9 #	10.2±0.2#	6.8±0.3 #
	E+B+T	5.21±0.7 #	9.1±0.8 #	7.2±0.1 #

The values are means±SD; n = 6. * P< 0.05 Significant differences with C group; # p <0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

Table 3. The results of liver tissue MDA, NO ve GSH levels

	Group (n=6)	MDA Levels (nmol/g)	NO Levels (µmol/g)	GSH Levels (nmol/g)
Liver Tissue	C	2.84±0.22	9.11±0.7	10.2±0.6
	S	2.76±0.3	9.3±0.4	9.8±1.3
	E	7.9±0.2*	11.9±0.7*	7.4±0.5*
	E+B	5.3±0.1 #	11.1±0.2	8.1±0.8#
	E+T	5.9±0.24 #	10.1±0.4#	8.6±0.7#
	E+B+T	5.1±0.1 #	9.8±0.1#	9.0±0.1#

The values are means±SD; n = 6. * P< 0.05 Significant differences with C group; # p <0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

Table 4. The results of brain tissue MDA, NO ve GSH levels

	Group (n=6)	MDA Levels (nmol/g)	NO Levels (µmol/g)	GSH Levels (nmol/g)
Brain Tissue	C	4.35±0.16	0.31±0.08	4.1±0.2
	S	4.6±0.26±0.20	0.33±0.07	3.9±0.05
	E	6.22±0.21 *±0.21*	0.46±0.02 *	2.6±0.08 *
	E+B	5.03±0.2 #03±0.8#	0.38±0.03 #	3.8±0.12 #
	E+T	5.42±0.15 #.42±0#	0.42±0.06	4.02±0.09 #
	E+B+T	4.85±0.46 #85±0.46	0.36±0.01 #	4.3±0.12 #

The values are means±SD; n = 6. * P<0.05 Significant differences with C group; # P<0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

Table 5. The results of kidney tissue MDA, NO ve GSH levels

	Group (n=6)	MDA Levels (nmol/g)	NO Levels (µmol/g)	GSH Levels (nmol/g)
Kidney Tissue	C	4.4±0.6	10.3±1.8	2.3±0.2
	S	4.6±0.4	10.4±0.9	2.1±0.1
	E	6.84±0.8*	12.7±0.7*	1.5±0.6*
	E+B	5.3±0.3 #	12.1±0.6	1.8±0.4#
	E+T	5.6±0.6 #	11.6±0.2#	1.7±0.7#
	E+B+T	5.2±0.5 #	11.2±1.1#	1.9±0.6#

The values are means±SD; n = 6. * P<0.05 Significant differences with C group; # P<0.05 Significant differences with E group. C= no treatment was performed, S= received tap water, E= received ethanol, E+B= received ethanol and BHT, E+T= received ethanol and TQ, E+B+T= received ethanol and BHT and TQ.

4. Discussion

In this study, the impacts of TQ and BHT on oxidative stress and behaviour were examined in rats chronically exposed to ethanol. Exposure to 7 g/kg of ethanol 5 days a week for 4 weeks importantly rised immobility time and reduced climbing and swimming time in the Fst. In the Oft, it was observed that ethanol exposure caused a rise in the time spent in the periphery and a decrease number of crossings and in the time spent in the center. There was no change in the body weight of the rats in the

measurements made after 30 days. Our results are appropriate with the results of studies in the literature. Exposure to 6.5 g/kg 22.5% ethanol once a day for 55 days in 35-day-old rats caused a decrease the number of crossings in the Oft. Researchers have reported that long-term alcohol exposure may cause damage to the cerebellar, neocortex, and motor cortex due to increased oxidative stress and inflammation (Teixeira et al., 2014). Puppies exposed to 5 g/kg 22.66% ethanol on days 4-9 after birth, It has been reported that the number of crossings decreases in the Oft and the immobility time increases in the Fst (Mazurek et al., 2021). Behavioral tests were performed on the offspring of mother rats exposed to 36% 4.3 g/kg ethanol on the 1st and 22nd days of pregnancy, on the 60th day after birth. There was a rise in the time spent in the periphery and a reduce in the time spent in the center in Oft. It was observed that there was an increase immobility time in Fst. It was stated that the body weight of pups exposed to ethanol did not differ (Brocardo et al., 2012). It has been reported that exposure to 4.8 g/kg of ethanol twice a day for 3 days caused a decrease in the number of crossings in 75–84-day old adult rats and no change in 30–37-day old adolescent rats in the Oft (Sarkar et al., 2013).

According to the Oft results in our study, 30-day cure with BHT at doses of 10 mg/kg treatment caused a rise in the time spent in the center and a decline in the time spent in the periphery. It was seen to increase the number of crossings slightly, but it was not found to be statistically significant. According to Fst, BHT treatment caused a decline in immobility time and a rise in swimming time. There was no important alteration in the body weight of the rats in the measurements made after 30 days. There is no study in the literature examining the effect of BHT treatment on behaviour. However, in a study examining the effects of BHT on locomotion and anxiety-like behaviours of zebrafish larvae. It was determined that BHT increased locomotor activity. Researchers suggest that BHT, in addition to its antioxidant activity, increases Dopamine signaling through Dopamine 2 and 3 receptors (Liang et al., 2020).

30-day cure with TQ at doses of 10 mg/kg importantly cured ethanol-induced alterations. TQ reduced the immobility time and rised the climbing and swimming time in the Fst. According to the Oft results in our study, TQ caused an increase the number of crossings and in the time spent in the center and a decline in the time spent in the periphery. It caused an increase in weight gain at the end of the 30th day. In the literature, there are no studies regarding the impacts treatment of TQ on behavioral tests in the ethanol exposure. However, there are a few studies examining the impact of TQ on behavioral tests. Our results are appropriate with the results of studies in the literature. A one dose of 40 mg/kg TQ reduced immobility time in Fst in rats induced by lipopolysaccharide stress. According to the results of Oft, it caused a decline in the time spent in the periphery and a rise in the time spent in the center. However, it did not induce any alteration in the number of crossings (Hosseini et al., 2012). In cisplatin-induced toxicity, 20 mg/kg TQ caused a rise in the time spent in the central region and the number of crossings and a decline in the time spent in the peripheral region in the Oft (Kandeil, et al., 2020). In a reserpine-induced depression model 20 mg/kg TQ treatment resulted in a rise in the number of crossings in the Oft, a decline in immobility time and a rise in swimming time in the Fst (Fahmy et al., 2020).

In our study, TQ and BHT+TQ cure indicated better healing in comparison to BHT cure in behavioral tests. We can say that the best recovery is in the BHT+TQ cure group. There is no study in the literature on the effect of TQ+BHT combined treatment on behavioral tests.

Alcohol intake has been found to be associated with altered oxidant-antioxidant balance and cell functions. Chronic ethanol exposure has been found to cause toxic effects through ROS production and lipid peroxidation in various tissues and cells of humans and mammals (Hosseini et al., 2017). In this study, a chronic exposure model was established with 7 g/kg ethanol 5 days a week for 4 weeks. At the end of 1 month, an elevate in NOx and MDA levels and a decline in GSH levels were observed in brain, stomach, liver and kidney tissues. Our results are appropriate with the results of studies in the literature. Studies show that alcohol quickly diffuses through the blood-brain barrier and changes neurotransmission. Alcohol exposure is reported to increase MDA levels and reduce GSH levels in brain tissue. It causes impaired regeneration and neurodegeneration by activation of microglia and astrocytes (Tsermpini et al., 2022). In the study by Carol et al., it was shown that there was a large amount of neuron loss in the hippocampal cortical circuits in the coronal sections taken from the brains of rats given ethanol by gavage at a dose of 9-15 gr/kg for 4 days. The most affected regions were found to be the olfactory bulb and dentate gyrus granular cell layer. It was also found that the perirhinal, piriform and entorhinal cortex were affected (Hamelink et al., 2005).

Ethanol causes deterioration of the gastric mucosa, increasing mucosal permeability and bleeding. This leads to gastric ulcers. Leaking white blood cells (such as neutrophils) from the disrupted mucosa cause ROS production and overproduction of other inflammatory mediators. This leads to oxidative damage and cellular damage. In rats given 1 ml/kg of 80% ethanol orally for 7 days, GSH levels decreased, ROS, MDA and induced nitric oxide synthase levels increased in the stomach tissue (Sanpinit et al., 2022). Kanter et al. showed that MDA levels rised and GSH levels reduced in the stomach tissue samples of rats with gastric mucosa damage induced with 1 ml pure ethanol (Kanter et al., 2005). Furthermore, increased free radicals and ROS due to chronic ethanol use destroy gastric mucus, and increase gastric acidity and inflammatory cell infiltration. As a result, gastric ulcers are formed (Sanpinit et al., 2022; Kanter et al., 2005). When 6 mL/kg of 56% ethanol once a day for the first 4 weeks and 8 mL/kg of 56% ethanol

once a day for the next 12 weeks were given by gavage for a total of 16 weeks, MDA and ROS levels in serum and liver tissue rised and GSH levels declined (Xue et al., 2022). In the liver tissue of rats given 7 gr/kg ethanol orally for 28 days, a rise in MDA levels and a decline in GSH levels were determined (Pal et al., 2022).

The liver is the most important organ metabolizing alcohol. Alcohol metabolism in the liver disrupts lipid metabolism. It causes the production of metabolites and by-products that increase inflammatory reactions. Alcohol metabolized by cytochrome P450 2E1 in the liver cause ROS overproduction and induction of endoplasmic reticulum stress. This impairs lysosomal function and autophagy. This results in mitochondrial damage and hepatocellular death. Researchers have reported that oxidative stress triggers the CD14/TLR4 pathway in alcoholic liver disease, which causes cellular damage through the activation of macrophages and the production of inflammatory mediators such as IL1, IL-6 and TNF-. They also reported that these inflammatory factors further accelerate oxidative stress and reduce the antioxidant enzyme capacity of cells. In the liver tissue of rats given 3 and 5 mg/kg 70% ethanol daily by intragastric gavage for 28 days, an elevate in MDA levels and a decline in GSH levels were observed. Researchers suggest that antioxidants in cells are over-consumed to prevent oxidative stress caused by accelerated inflammation (Mehanna et al., 2021). In liver tissues of rats, 3 mg/kg/day ethanol exposure by gavage for 4 weeks induced an elevate in MDA levels and a decline in GSH levels (Hamelink et al., 2005). Increased oxidative stress in liver cells in chronic ethanol use causes cell membrane and mitochondrial damage, acetaldehyde accumulation, hypoxia, impairment of the immune system and iron mobilization. In alcohol-induced liver disease, steatosis, fatty liver and alcoholic hepatitis develop in the early stages. Further progression of the disease can lead to irreversible fibrosis, cirrhosis, and liver cancer (Xue et al., 2022).

Chronic ethanol exposure rises oxidative stress in the kidneys by causing hyperacetylation of mitochondrial proteins. This leads to metabolic dysregulation and disrupted renal function. The TLR4/NF-kB signaling pathway is an important mediator of inflammation and fibrosis in kidney injury. Researchers have reported that oxidative stress is associated with this signaling pathway (Mehanna et al., 2021). In kidney tissues of rats, 3 mg/kg/day ethanol exposure by gavage for 4 weeks induced an elevate in MDA levels and a decline in GSH levels (Hamelink et al., 2005). Kidney cells are also significantly affected by ethanol. Increased oxidative stress as a result of chronic ethanol exposure inhibits tubular reabsorption. Increased cell proliferation and inflammation in the cells of the renal tubules induce abnormal thickening of the basement membrane of the glomeruli. Therefore, the ability of the kidney to regulate body fluid volume and electrolyte balance is impaired in chronic ethanol exposure (Mehanna et al., 2021).

In our study, it was determined that rats given 10 mg/kg BHT with chronic ethanol exposure decreased MDA and NO levels and rised GSH levels in the brain, stomach, liver and kidney tissues. There are studies in the literature showing the antioxidant activity of BHT (Miranda et al., 2001). However, only one study has examined the effects of BHT as a result of direct ethanol exposure. Carol et al. showed that intraperitoneal injection of 40 mg/kg BHT twice daily on days 2 to 4 of 4-day ethanol-exposed rats greatly decreased neuronal loss in the hippocampus and entorhinal cortex. Stating that the mechanisms by which alcohol causes neuronal oxidative damage are unknown and potentially involve acetaldehyde-derived alkaloidal metabolite formation or inflammatory mechanisms, the researchers reported that BHT may reduce inflammation and associated oxidative stress by blocking TNF-α activation. The researchers also measured the oxidation or reduction potential of BHT in vitro by cyclic voltammetry and showed that BHT exhibits an irreversible oxidation potential and is an antioxidant (Hosseini et al., 2017).

In our study, it was determined that rats given 10 mg/kg TQ with chronic ethanol exposure had decreased MDA and NO levels and rised GSH levels in brain, stomach, liver and kidney tissues. The studies in the literature were found to be compatible with our results. Intraperitoneal 10 mg/kg TQ treatment decreased the increased MDA levels and rised the reduced GSH levels in the kidney and liver tissues of rats exposed to 3 mg/kg/day ethanol by gavage for 4 weeks (Hamelink et al., 2005). In rats given 10 mg/kg TQ 1 hour before ingestion of 1 ml pure ethanol, it was defined that MDA levels decreased in the stomach tissue. However, there was no alteration in GSH levels (Kanter et al., 2005).

In this study, it was determined that the highest decline in MDA and NO levels and the highest rise in GSH levels in brain, stomach, liver and kidney tissues as a result of chronic ethanol exposure were found in the group in which TQ+BHT was given together. There is no study in the literature examining how TQ+BHT coadministration affects oxidative stress levels in ethanol exposure.

Our results support that TQ and BHT, which have antioxidant properties, may reduce oxidative stress caused by ethanol exposure in the brain, stomach, liver and kidney tissue. Compared to TQ alone and BHT alone, the combined use of TQ+BHT may reduce oxidative stress more. Additionally, TQ and BHT+TQ treatment against ethanol toxicity gave better results in behavioral tests. However, further research is recommended to explain the antioxidant activity of TQ and BHT and their effects on behavioral tests.

5. Conclusion

Our findings suggest that BHT and TQ critically contribute to the protection against alcohol-induced oxidative stress in brain, stomach, liver and kidney tissue. 30-day TQ and BHT treatment rised antioxidant capacity and caused healing in behavioral tests. The most

significant improvement was observed in the group in which BHT and TQ were given simultaneously after ethanol exposure. Investigating the mechanisms responsible for the antioxidant activity of BHT and TQ that may be protective against ethanol exposure will be the focus of our future research.

Author Contributions

The percentages of the author' contributions are presented below. The author reviewed and approved the final version of the manuscript.

	D.K.
C	100
D	100
S	100
DCP	100
DAI	100
L	100
W	100
CR	100
SR	100
PM	100
FA	100

C= concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest

The author declared that there is no conflict of interest.

Ethical Consideration

The study was initiated after ethical approval was obtained from Animal Experiments Local Ethics Committee at its meeting (approval date: January 11, 2023, protocol code: 68429034/01).

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AN EVALUATION OF HEALTHCARE INSTITUTIONS' EFFICIENCY IN TÜRKIYE USING THE PABON LASSO MODEL: AN INSTITUTION-TYPE BASED ANALYSIS FOR THE PERIOD 2002–2023

Melek YAĞCI ÖZEN[1]*

[1]*Osmaniye Korkut Ata University, Faculty of Health Sciences, Department of Gerontology, 80000, Osmaniye, Türkiye*

Abstract: This study aims to analyze the efficiency of Ministry of Health, university, and private hospitals in Türkiye between 2002 and 2023 using the Pabon Lasso Model. To evaluate hospital efficiency, the indicators of Bed Occupancy Rate (BOR), Bed Turnover Rate (BTR), and Average Length of Stay (ALOS) were utilized. Data were obtained from the Ministry of Health's Health Statistics Yearbook (2023). The collected data were organized using Excel software, and the Pabon Lasso Graph was applied during the analysis process. Three different hospital types were assessed by dividing the period into phases within the framework of the Pabon Lasso Model. It was determined that the efficiency of Ministry of Health hospitals improved between 2007 and 2019 with the implementation of the Health Transformation Program, but performance declined during the 2020–2023 period due to the impact of the COVID-19 pandemic. University hospitals were generally positioned in Region IV throughout the analysis period, characterized by high bed occupancy rates and low turnover rates. Private hospitals, on the other hand, demonstrated a stable efficiency profile within the boundaries of Region II after 2005, achieving rapid patient turnover through agreements with the Social Security Institution despite low bed occupancy rates. Hospital efficiency in Türkiye exhibits significant variation across hospital types. The Health Transformation Program substantially improved efficiency, particularly in Ministry of Health and private hospitals, while the COVID-19 pandemic led to temporary setbacks. These findings underscore the necessity for institution-specific strategic planning and the development of flexible and adaptive health policies.

Keywords: Pabon lasso model, Hospital efficiency, Health transformation program, COVID-19, Health policies, Türkiye

***Corresponding author:** Osmaniye Korkut Ata University, Faculty of Health Sciences, Department of Gerontology, 80000, Osmaniye, Türkiye
E mail: melekyagciozen@hotmail.com (M. YAĞCI ÖZEN)
Melek YAĞCI ÖZEN https://orcid.org/0000-0003-0314-247X

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1. Introduction

Performance and efficiency are two fundamental concepts at the core of contemporary health policies. Particularly in developing countries, rising hospital costs, increasing demand for healthcare services, and rapid advancements in medical technologies pose significant challenges in planning and resource management for healthcare administrators and policymakers (Mehrtak et al., 2014; Kalhor et al., 2014). Hospitals, as the most expensive and critical components of health systems, account for 60% to 80% of total healthcare expenditures, thereby playing a decisive role in the financial sustainability of these systems (Shaqura et al., 2021).

The efficient utilization of healthcare resources has become not only an economic imperative but also an ethical responsibility. Inefficiencies such as unnecessary hospital admissions, prolonged lengths of stay, and low bed turnover rates undermine hospital performance, weaken the quality of healthcare services, and escalate costs (Dopeykar and Meskarpour Amiri, 2020). Therefore, monitoring and evaluating hospital performance is not merely a managerial necessity but also a strategic obligation for protecting public health.

Various methods have been developed in the literature to measure hospital performance. The Balanced Scorecard, pyramid models, regulatory audits, third-party evaluations, and several statistical approaches are among these methods (Kaplan and Norton, 2001; Mehrtak et al., 2014). These models are widely used to establish managerial control mechanisms and to rationalize resource allocation. However, many of these approaches have limited multidimensional analysis capabilities, making them insufficient for simultaneously evaluating resource efficiency.

At this point, the Pabon Lasso Model, developed by Pabon Lasso in 1986, stands out by offering the ability to assess hospital performance through three key indicators simultaneously: Bed Occupancy Rate (BOR), Bed Turnover Rate (BTR), and Average Length of Stay (ALOS). The model integrates these three indicators into a two-

dimensional graph, positioning each hospital within one of four regions, thereby providing both a visual and analytical representation of performance (Goshtasebi et al., 2009; Mohammadkarim et al., 2011; Moradi et al., 2017). This framework enables comparative evaluations between hospitals, analysis of strengths and weaknesses, and supports strategic decision-making processes.

The advantage of the Pabon Lasso Model lies not only in monitoring performance but also in offering managers a more holistic and structural perspective on healthcare service delivery. Especially in developing countries, where resources are limited and needs are high, this model has become a highly practical tool for decision-makers (Mohammadkarim et al., 2011; Khalilabad et al., 2020).

This study aims to analyze the performance of different types of healthcare institutions (Ministry of Health, university, and private hospitals) in Türkiye between 2002 and 2023 using the Pabon Lasso Model. Through a long-term data analysis applying the Pabon Lasso Model, this research seeks to provide original contributions at both empirical and managerial levels. It is particularly significant in demonstrating how this model, often limited to single-year or short-term applications in the literature, can be strategically utilized with multi-year datasets.

2. Materials and Methods

This descriptive-analytical study evaluated the service efficiency of different types of hospitals (Ministry of Health, university, and private hospitals) providing healthcare services in Türkiye between 2002 and 2023, based on three key indicators: Bed Occupancy Rate (BOR), Bed Turnover Rate (BTR), and Average Length of Stay (ALOS). The Pabon Lasso Model applied in this study integrates these three fundamental indicators and positions the resulting data on a two-dimensional graph, categorizing each hospital's performance into one of four regions.

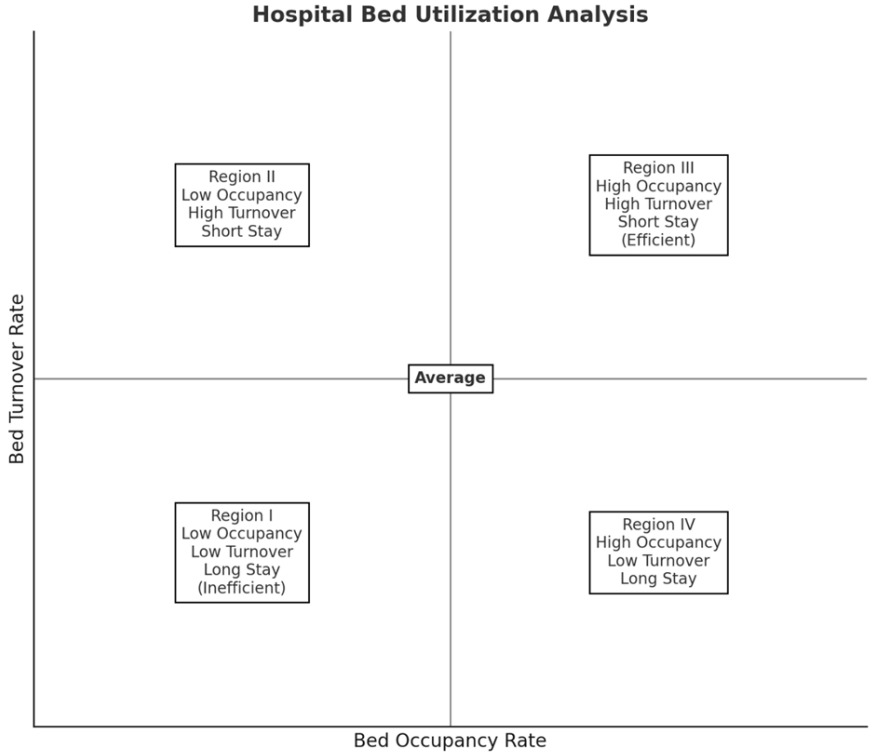

Figure 1. Pabon Lasso Modeli (Pabon Lasso, 1986).

2.1. According to the Pabon Lasso Model

Hospitals located in Region I are characterized by a low bed occupancy rate and a low bed turnover rate. Therefore, these hospitals are considered inefficient institutions (Mehrtak et al., 2014).

Region II is defined by a low occupancy rate but a high bed turnover rate. Typically, maternity hospitals and centers providing short-term treatment services are found in this region. These hospitals have unused bed capacity, while patient circulation is relatively high (Younsi, 2014).

Hospitals in Region III exhibit both high bed occupancy rates and high bed turnover rates. This indicates effective and efficient utilization of resources within these hospitals (Kalhor et al., 2016).

Region IV is characterized by a lower turnover rate and a high occupancy rate. Institutions in this region generally provide services to patients requiring long-term hospitalization and involve higher costs (Khalilabad et al., 2020).

The data used in this study were obtained from the 2023 Health Statistics Yearbook published by the Ministry of Health. The collected data were organized using Excel software, and the Pabon Lasso Graph was employed

during the analysis process. This method enabled a detailed annual evaluation of hospital bed utilization efficiency and revealed performance differences among institutions. Table 1 presents the values of bed occupancy rate, average length of stay, and bed turnover rate according to different hospital types. The relevant data were extracted from the 2023 Health Statistics Yearbook.

Table 1. Bed occupancy rate, average length of stay, and bed turnover rate by type of institution

Years	Bed Occupancy Rate			Average Length of Stay			Bed Turnover Rate		
	MoH	University	Private	MoH	University	Private	MoH	University	Private
2002	60.6	69.8	32	5.7	8.6	3.1	38.8	29.7	37.5
2003	61.4	72.9	33.1	5.6	8.5	3	39.7	31.5	40.8
2004	68.2	74.7	35.1	5.6	8.3	2.8	44.8	32.9	46.2
2005	65.2	79.2	42	5.2	8.2	2.7	45.8	35.3	57
2006	67.5	79.7	48	5.2	7.8	2.4	47.9	37.4	74.3
2007	64.8	76.5	46	4.7	6.9	1.8	50.7	40.8	93.4
2008	63.8	84.4	50.7	4.5	6.6	1.8	52.1	46.4	101.9
2009	65	80.7	50.3	4.6	6.1	2	51.4	48.6	92.1
2010	64.3	72.9	50.8	4.4	6.2	2	52.9	43.1	91.1
2011	66.4	73.6	53.6	4.3	5.8	2	55.9	46.2	95.6
2012	66.4	76.7	51.5	4.3	6.1	2.3	56.3	45.6	81.8
2013	69.3	74.1	50.5	4.4	6	2.2	57.9	45.2	83.2
2014	71.1	76.7	56.1	4.3	5.9	2.4	59.8	47.4	83.9
2015	71.7	75.5	59.6	4.3	5.6	2.5	60.5	49.3	86.6
2016	68.7	76	60.3	4.4	5.7	2.6	56.9	48.9	85.9
2017	69	73.4	61.4	4.5	5.6	2.7	56.2	48	83.8
2018	68	69.5	61.8	4.5	5.5	2.8	55	46.5	80.1
2019	67.3	69.8	60.7	4.6	5.3	3	54	48.3	78
2020	50	57.7	56.1	5.2	5.7	3	35.2	36.8	68.1
2021	52.8	63.6	58.1	5	5.4	3	38.7	43.3	70.9
2022	56.1	66.9	57.0	4.7	5.2	2.8	43.9	46.6	73.9
2023	58.8	65.0	50.9	4.7	5.2	2.8	45.9	45.3	67.4

Source: Ministry of Health, 2023 health statistics yearbook.

3. Results

In this study, the Pabon Lasso Graph was utilized to analyze hospital bed utilization efficiency. The Pabon Lasso method provides a comparative assessment of institutional performance by simultaneously visualizing three key indicators that evaluate efficiency in healthcare service delivery.

The indicators represented in the graph are as follows:

- Bed Occupancy Rate (BOR): Displayed on the horizontal axis (as a percentage), indicating the proportion of hospital bed usage.
- Bed Turnover Rate (BTR): Shown on the vertical axis, reflecting how many times a bed is used within a year.
- Average Length of Stay (ALOS): Represented by curves on the graph. ALOS indicates the average duration of hospitalization per patient and is calculated using the formula: ALOS = (365 × BOR) / BTR.

In the Pabon Lasso graph, the ALOS curves were determined based on the arithmetic mean of annual data for each hospital type during the period 2002–2023. Accordingly:

- The average ALOS was calculated as 4.8 days for Ministry of Health (MoH) hospitals,
- 6.4 days for university hospitals,
- And 2.5 days for private hospitals.

The graph was constructed using these reference ALOS values, with each hospital type represented by different colors and markers. Additionally, the years were indicated to emphasize temporal changes, and year labels were designed to match the corresponding institutional colors.

Figure 2 demonstrates the bed utilization efficiency of Ministry of Health, university, and private hospitals over the period 2002–2023 using the Pabon Lasso Graph. Institutions are plotted annually, allowing for a visual assessment of performance trends through the application of ALOS curves.

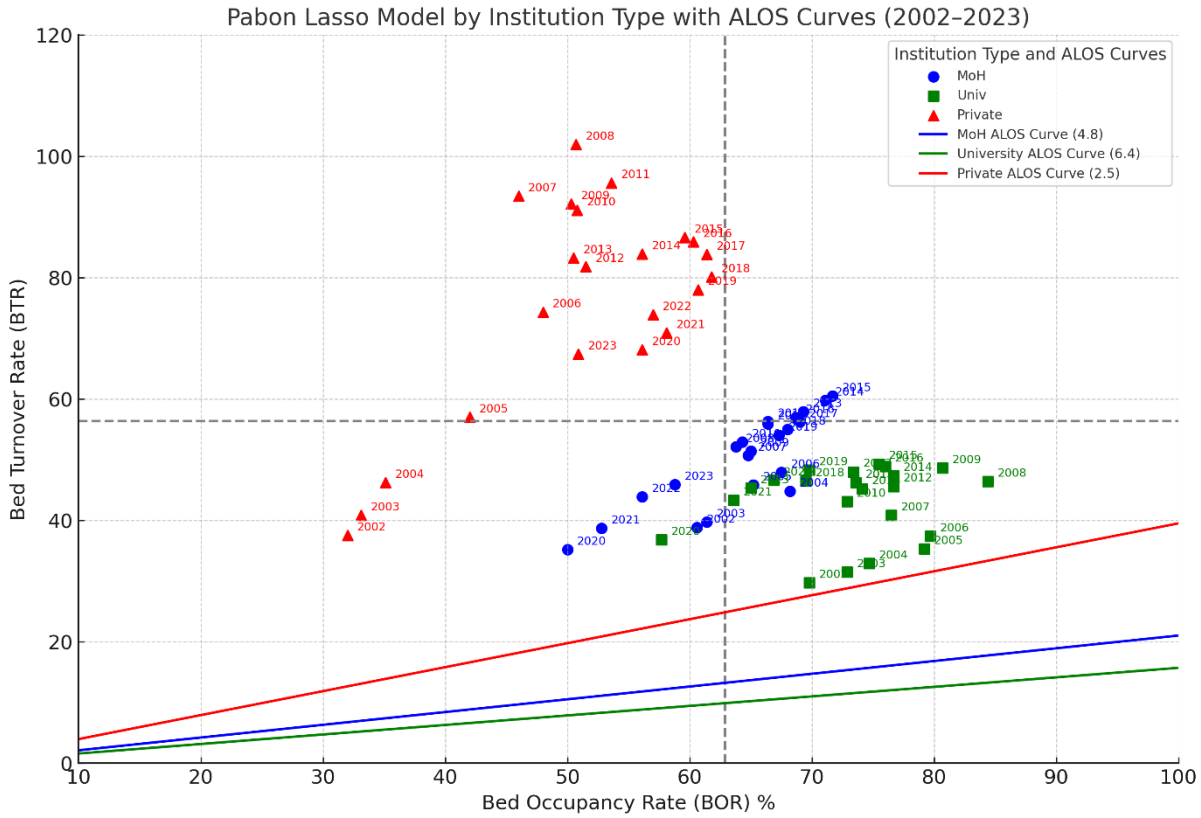

Figure 2. Pabon lasso graph for the period 2002–2023 by hospital type.

4. Discussion

Numerous indicators have been proposed in the literature to measure hospital performance. In this study, multiple indicators were utilized to evaluate the performance of different types of healthcare institutions (Ministry of Health, university, and private hospitals) in Türkiye. The Pabon Lasso Graph categorizes institutions into four primary performance regions based on the axes of Bed Occupancy Rate (BOR) and Bed Turnover Rate (BTR).

4.1. Ministry of Health (MoH) Hospitals According to the Pabon Lasso Model

For the evaluation of MoH hospitals' efficiency, performance indicators were divided into four distinct periods.

4.1.1. Period 1: Performance indicators for 2002–2003

During this period, MoH hospitals were positioned in Region I of the Pabon Lasso Graph, reflecting structural issues in healthcare service delivery. Low bed occupancy rates, low bed turnover rates, and prolonged average lengths of stay indicated inefficient use of resources within the healthcare system. Challenges in accessing healthcare services, infrastructural deficiencies, bureaucratic inefficiencies, and inequalities in service delivery were among the primary reasons for initiating the Health Transformation Program (HTP) (Republic of Türkiye Ministry of Health, 2003). The main objectives of HTP were to improve accessibility, enhance service efficiency, increase patient satisfaction, and ensure the effective use of healthcare resources. The positioning of MoH hospitals in Region I during 2002–2003 is considered a reflection of pre-HTP inefficiencies. Similarly, Yiğit and Kumru (2016) reported that hospitals in Türkiye were located in Region I in 2003, indicating low hospital efficiency during this period (Yiğit & Kumru, 2016).

4.1.2. Period 2: Performance indicators for 2004–2006

This period marks the initial phase following the implementation of HTP. An increase in bed occupancy rates was observed; however, bed turnover rates remained low. The presence of extended lengths of stay and the rising patient load due to increased demand led to higher capacity utilization, although overall efficiency had yet to be achieved.

4.1.3. Period 3: Performance indicators for 2007–2019

This period is characterized by high bed occupancy rates, high turnover rates, and shorter lengths of stay, reflecting the intended outcomes of the Health Transformation Program. For MoH hospitals, this was the most efficient period. Çalışkan (2016) found that 25% of hospitals were located in the efficient region when evaluating the performance of Public Hospital Unions. Similarly, Taşkaya (2020) reported that training and research hospitals in Türkiye were positioned in the efficient region in 2017, which aligns with the findings of this study (Çalışkan, 2016; Taşkaya, 2020).

4.1.4. Period 4: Performance indicators for 2020–2023

The effects of the COVID-19 pandemic, which began in

December 2019 and rapidly spread worldwide, were evident during this period. This era was characterized by the postponement of elective surgeries, limited outpatient services, and a focus on emergency and COVID-19 cases. Consequently, MoH hospitals were positioned in Region I, with notably low bed occupancy rates. The need for intensive care services and prolonged treatment durations for COVID-19 patients also led to a decline in bed turnover rates. A study evaluating the bed utilization performance of general hospitals reported similar findings, indicating that performance indicators in 2020 reached their lowest levels due to the impact of the pandemic (Işıkçelik & Ağırbaş, 2023).

4.2. University Hospitals According to the Pabon Lasso Model

For the evaluation of university hospitals' efficiency using the Pabon Lasso Model, performance indicators were categorized into three distinct periods.

4.2.1. Period 1: Performance indicators 2002–2019

Between 2002 and 2019, university hospitals were consistently positioned in Region IV. This positioning is characterized by high bed occupancy rates coupled with low bed turnover rates. Additionally, the prolonged average length of stay in university hospitals further supports this classification. The data indicate that these hospitals primarily managed complex cases requiring extended hospitalization, contributing to their sustained presence in Region IV.

4.2.2. Period 2: Performance indicators 2020–2021

During the COVID-19 pandemic, university hospitals shifted to Region I in 2020 and 2021. This shift is attributed to the postponement of non-emergency surgeries and the limitation of outpatient services, as hospitals focused predominantly on COVID-19 cases.

4.2.3. Period 3: Performance indicators 2022–2023

In the post-pandemic normalization period (2022–2023), university hospitals returned to Region IV. This repositioning can be explained by their continued focus on complex and long-term treatments, resulting in high bed occupancy rates and low turnover rates. The nature of university hospitals, which typically handle specialized and prolonged care cases, remains a key factor influencing this performance pattern.

4.3. Private Hospitals According to the Pabon Lasso Model

For the evaluation of private hospitals' efficiency using the Pabon Lasso Model, performance indicators were divided into two distinct periods.

4.3.1. Period 1: Performance indicators 2002–2004

Before and immediately after the implementation of the Health Transformation Program (HTP), access to private hospitals largely depended on individuals' ability to pay out-of-pocket. During this period, private hospitals primarily served high-income groups and had a limited patient base. The integration of the private sector into the healthcare system was still limited at this stage.

4.3.2. Period 2: Performance indicators 2005–2023

The HTP introduced structural changes that affected not only public hospitals but also private hospitals. In 2005, private hospitals were allowed to establish agreements with the Social Security Institution (SSI), significantly altering their role within the healthcare system. This enabled citizens to access contracted private hospitals at lower costs, in addition to public hospitals. The encouragement of private investments in the health sector led to a notable increase in the number of private hospitals. Through integration into the healthcare system, private hospitals transitioned from an inefficient position in Region I to Region II on the Pabon Lasso Graph. With SSI agreements and increased patient access, private hospitals improved their bed turnover rates, focused on short-term hospitalizations, and enhanced their commercial efficiency. This transformation positioned private hospitals as more active and dynamic players within Türkiye's healthcare system.

4.4. General Evaluation According to the Pabon Lasso Model

The analysis of performance indicators for different hospital types (Ministry of Health, university, and private hospitals) in Türkiye between 2002 and 2023 using the Pabon Lasso Model clearly reveals the structural transformations and policy impacts within the healthcare system. Throughout this period, the Health Transformation Program (HTP) and the COVID-19 pandemic emerged as the two primary factors influencing hospital efficiency.

MoH hospitals, which exhibited low bed occupancy and turnover rates prior to HTP, experienced increased capacity utilization following the program's implementation, achieving peak efficiency between 2007 and 2019 with high occupancy, high turnover rates, and shorter lengths of stay. However, during 2020–2023, the pandemic led to a decline in efficiency, resulting in a more restricted service delivery structure.

University hospitals, due to their complex case profiles and extended treatment durations, consistently demonstrated high occupancy rates and low turnover rates throughout the analysis period. Aside from the temporary decline in efficiency during the pandemic, no significant structural changes were observed in their performance. This stability aligns with their core mission focused on research, education, and advanced treatment within the healthcare system.

Regarding private hospitals, these institutions exhibited inefficiency before HTP due to limited access and low patient volumes. However, after 2005, with SSI agreements and incentives for private investment, they underwent rapid transformation. By focusing on short-term hospitalizations and accelerating patient turnover, private hospitals enhanced their commercial efficiency and moved into more efficient regions on the Pabon Lasso Graph.

In summary, healthcare policies implemented in Türkiye, along with global health crises, have led to varying performance shifts across hospital types. The Health Transformation Program significantly improved efficiency in MoH and private hospitals, while its impact on university hospitals remained limited due to their

structural characteristics. The pandemic, on the other hand, caused temporary efficiency losses across all hospital types. These findings highlight the healthcare system's resilience capacity and demonstrate how policy interventions yield differentiated effects depending on hospital type.

5. Conclusion

This study analyzed the efficiency levels of Ministry of Health, university, and private hospitals in Türkiye between 2002 and 2023 using the Pabon Lasso Model, highlighting the impact of health policies on hospital performance. The findings indicate that the Health Transformation Program (HTP) significantly improved efficiency, particularly in Ministry of Health and private hospitals. University hospitals, due to their structural characteristics, demonstrated a stable performance characterized by high bed occupancy rates and low turnover rates. The COVID-19 pandemic led to temporary efficiency losses across all hospital types, causing substantial changes in healthcare service delivery.

In conclusion, health policies and crisis periods in Türkiye's healthcare system have produced varying impacts depending on hospital type. This underscores the need for flexible and institution-specific strategies to ensure sustainable efficiency in healthcare services. Future studies are recommended to provide more comprehensive analyses by incorporating additional factors such as patient satisfaction, financial sustainability, and service quality.

6. Limitations

This study has several limitations. Firstly, the analysis relied solely on data from the 2023 Health Statistics Yearbook published by the Ministry of Health Republic of (Türkiye Ministry of Health, 2023). Additionally, only three indicators—Bed Occupancy Rate (BOR), Bed Turnover Rate (BTR), and Average Length of Stay (ALOS)—were considered, while other performance metrics such as cost, patient satisfaction, and service quality were not evaluated.

Moreover, the structural nature of the Pabon Lasso Model focuses exclusively on quantitative data, without accounting for qualitative factors such as service scope, patient profiles, and case complexity across hospital types. This limitation is particularly relevant for institutions like university hospitals that manage long-term and complex cases. Furthermore, extraordinary circumstances such as the COVID-19 pandemic during the analysis period may have caused deviations in certain years' data.

7. Recommendations

This study focused solely on the case of Türkiye, limiting the generalizability of the results to healthcare systems in other countries. Therefore, future research should address these limitations by utilizing more comprehensive data sources, incorporating additional performance indicators, and conducting international comparisons.

Author Contributions

The percentages of the author' contributions are presented below. The author reviewed and approved the final version of the manuscript.

	M.Y.Ö.
C	100
D	100
S	100
DCP	100
DAI	100
L	100
W	100
CR	100
SR	100
PM	100
FA	100

C= concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest

The author declares no conflict of interest related to this study.

Ethical Consideration

This study does not require ethics committee approval as it uses only publicly available data from the Ministry of Health's Health Statistics Yearbook (2023) and does not involve the collection of data from human participants.

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Review
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A SYSTEMATIC REVIEW OF NURSING INTERVENTION STUDIES FOR LYMPHEDEMA AFTER BREAST CANCER

Gizem ALKILINÇ[1]*, Merve AKINCI[2], Betülay KILIÇ[1]

[1]*University of Health Sciences, Gulhane Faculty of Nursing, Department of Nursing Sciences, Division of Internal Medicine Nursing, 06010, Ankara, Türkiye*
[2]*Kırıkkale University, Vocational School of Health Services, 71450, Kırıkkale, Türkiye*

Abstract: This systematic review aims to evaluate the effectiveness of nursing interventions in managing lymphedema after breast cancer treatment and their impact on clinical outcomes. Randomized controlled trials (RCTs) published between 2014 and 2024, examining nursing interventions for lymphedema after breast cancer treatment, were included. A search was conducted in PubMed, ScienceDirect, Scopus, Web of Science, Wiley, DergiPark, Turkish National Thesis Center, and Google Scholar using relevant keywords. A total of 402 studies were screened. Exclusion criteria included studies that did not involve nursing interventions (n=126), were non-interventional (n=7), were not RCTs (n=48), were unrelated to lymphedema (n=39) or breast cancer (n=32), were published outside the 2014–2024 period (n=27), were systematic reviews (n=67), research protocols (n=8), or conference abstracts/book chapters (n=9). Eighteen RCTs met the inclusion criteria. Nursing interventions were categorized into 11 types: educational programs (theory-based, web/mobile), exercise, complex decongestive therapy, bandaging, compression garments, kinesio therapy, simple lymphatic drainage, myofascial release, laser therapy, negative pressure massage, and intermittent pneumatic compression. Intervention groups showed improvements in quality of life, self-care, and upper extremity function, along with reduced arm volume and lymphedema-related symptoms. Overall, interventions yielded positive outcomes. Further research is needed to assess long-term effects.

Keywords: Nursing, Lymphedema, Breast cancer

***Corresponding author:** University of Health Sciences, Gulhane Faculty of Nursing, Department of Nursing Sciences, Division of Internal Medicine Nursing, 06010, Ankara, Türkiye
E mail: 220901013@ogrenci.sbu.edu.tr (G. ALKILINÇ)
Gizem ALKILINÇ https://orcid.org/0009-0002-5842-4044
Merve AKINCI https://orcid.org/0000-0003-3019-8444
Betülay KILIÇ https://orcid.org/0000-0002-4178-4003

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1. Introduction

Breast cancer is the most common type of cancer among women worldwide, with 2.3 million women diagnosed and 670.000 deaths reported globally in 2022 (WHO, 2022). One in five women undergoing breast cancer treatment develops lymphedema as a complication (Gillespie et al., 2018; DiSipio et al., 2013). Lymphedema occurs due to impaired lymphatic drainage, often resulting from axillary lymph node dissection, radiotherapy, fibrosis, or inflammation following breast cancer surgery. This impairment leads to the abnormal accumulation of protein-rich fluid in the interstitial space (Dönmez and Kapucu, 2017). The incidence of unilateral arm lymphedema after breast cancer treatment has been reported to range from 8.4% to 21.4% (DiSipio et al., 2013). Lymphedema symptoms vary depending on the severity of fluid retention and are characterized by swelling, a sensation of heaviness, tightness, pain, and functional impairment in the affected limb (Chowdhry et al., 2016; Armer et al., 2003). These symptoms hinder daily activities and negatively affect fine and gross motor skills. Consequently, individuals experience functional limitations in work, household chores, personal care, and social interactions (DiSipio et al., 2013). Lymphedema significantly impacts the quality of life, leading to physical and psychological challenges (Dönmez and Kapucu, 2017). Physically, patients may experience pain in the hand, arm, and shoulder, restricted joint mobility, and a sense of heaviness and fullness in the upper extremity. Psychologically, they may face body image disturbances, anxiety, anger, embarrassment, and social isolation (Fu et al., 2013).

Early preventive measures and appropriate interventions can significantly reduce the risk of lymphedema development or help maintain control over the condition (Temur and Kapucu, 2018). Nurses play a critical role in preventing, managing, and monitoring lymphedema by encouraging patients to take responsibility for their care (Dönmez and Özdemir, 2016). Recommended strategies for lymphedema prevention, symptom management, and treatment include assessing high-risk patients, developing educational programs that incorporate prevention strategies, increasing patient awareness of risk factors, and teaching self-care practices to promote active participation in the treatment process (Szuba et al., 2002; O'Toole et al., 2013; Temur and Kapucu, 2018). Additionally, lymphedema management includes various therapeutic approaches such as skin care, limb elevation,

massage, physical activity, manual lymphatic drainage, pneumatic pumps, laser therapy, compression garments, and both medical and surgical treatments (Dönmez and Özdemir, 2016).

Nurses play a key role in preventing and managing lymphedema (Gül and Erdim, 2009). By assessing factors such as patients' ideal weight, limb measurements, capacity to perform daily activities, surgical history, existing comorbidities, and history of radiotherapy, nurses can identify the risk of lymphedema development at an early stage (Akkaş Gürsoy et al., 2010). Additionally, nurses are responsible for determining the needs of lymphedema patients throughout the care process, from admission to discharge, and implementing appropriate nursing interventions. Supporting patients in maintaining self-care skills during treatment is crucial. Early detection of potential complications is critical in preventing lymphedema progression, and referring patients to specialists when necessary enhances treatment effectiveness (Lasinski, 2013). In this context, this study aims to evaluate the effectiveness of nursing-based interventions in lymphedema management after breast cancer to improve patient care and promote the widespread adoption of evidence-based practices in lymphedema management.

To achieve this objective, a systematic review was conducted of randomized controlled trials published between 2014 and 2024 that investigated the effectiveness of nursing interventions for lymphedema management after breast cancer. The study evaluates the impact of nursing interventions on patient outcomes. Additionally, the effectiveness of methods used in lymphedema treatment and the role of nurses in this process were identified to develop recommendations for clinical practice.

2. Review

2.1. Research Model

This is a systematic review. The PRISMA checklist was used for the systematic review (Page et al., 2021).

Research Questions

- What are the nursing interventions used in the management of lymphedema following breast cancer treatment?
- Is there an effect of nursing interventions on the management of lymphedema after breast cancer treatment?
- How do nursing interventions apply in randomized controlled trials conducted between 2014 and 2024, and impact patient outcomes in the management of lymphedema after breast cancer?

2.2. Literature Search Strategy

In the systematic review, publications evaluating the effectiveness of nursing interventions in managing breast cancer-related lymphedema were reviewed. Searches were conducted in PubMed, ScienceDirect, Scopus, Web of Science, and Wiley databases using the keywords "oncology," "breast cancer," "lymphedema," "nursing," and "randomized controlled trial." Additionally, searches were performed in DergiPark, Turkish National Thesis Center of the Council of Higher Education, and Google Scholar using the Turkish equivalents of these keywords: "oncology", "breast cancer," "lymphedema," "nursing," and "randomized controlled trial." Studies published between 2014 and 2024 that addressed breast cancer-related lymphedema were accessible in full text, and included nursing interventions were included in the systematic review. The search was conducted between July 15 and August 15, 2024.

2.3. Study Selection and Identification

In this systematic review, two independent researchers screened studies, and the results were compared to ensure consistency. As a result of the literature search, a total of 402 studies were evaluated. Studies were excluded if they did not include nursing interventions (n=126), were not intervention studies (n=7), were not randomized controlled trials (n=48), were unrelated to lymphedema (n=39), were not published between 2013 and 2024 (n=27), were not focused on breast cancer (n=32), were systematic reviews (n=67), were research protocols (n=8), or were conference abstracts or book chapters (n=9). Eighteen studies that met the inclusion criteria were analyzed (Figure 1).

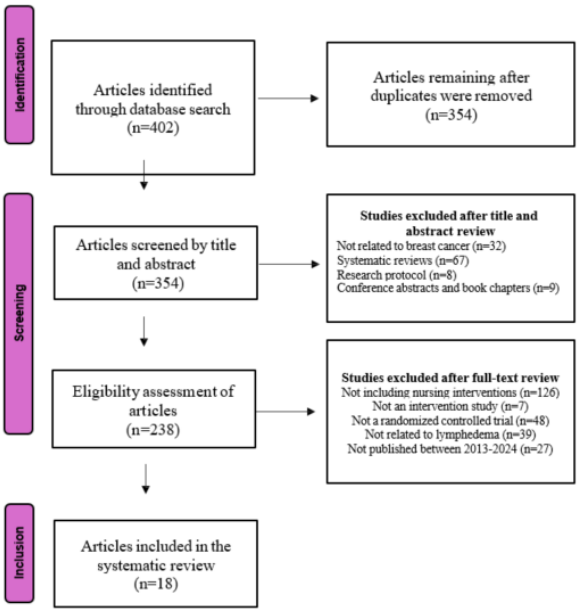

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram (Page et al., 2021).

2.4. Inclusion Criteria

The systematic review included studies published in English and Turkish literature, which are randomized controlled trials containing a nursing intervention for lymphedema following breast cancer, published between 2014 and 2024, and accessible in full text.

2.5. Exclusion Criteria

Studies focusing on cancers other than breast cancer, systematic reviews, research protocols, conference

abstracts, book chapters, and studies unrelated to lymphedema were excluded from the review.

2.6. Data Collection Tools and Processes

The researchers developed a data extraction tool to collect the research data. This tool allowed for examining data such as author information, publication year, sample size, study design, applied interventions, and control group characteristics of the studies included in the systematic review. The first researcher independently conducted the data collection process, which was verified by the second researcher for validation purposes.

In the data analysis process, a standardized data summary form was created and presented in table format (Table 1). The table was organized to include information such as the year, authors, study type, sample size, and key findings.

Table 1. Citation information for randomized controlled trials examining the effectiveness of nursing interventions in the management of lymphedema after breast cancer

Author	Year	Country	Sample	Control Group	Intervention Group	Findings
Şhi et al.	2023	China	108 patients (n=56 control, n=52 intervention)	Standard care	Lymphedema prevention program based on the information-attitude-practice theory	The intervention group showed less deterioration in grip strength, significant improvement in upper extremity dysfunction and quality of life; no statistically significant difference was found in lymphedema incidence.
Kim et al.	2023	South Korea	30 patients (n=15 control, n=15 intervention)	Placebo intervention	Myofascial release + Complex decongestive therapy	Myofascial release improved pain, shoulder range of motion, chest mobility, and shoulder function, and reduced arm volume.
Lin et al.	2022	China	200 patients (n=50 control, n=50 G1, n=50 G2, n=50 G3 intervention groups)	Joint range of motion exercises	G1: Range of motion exercises + Intensive Monitoring G2: Range of motion exercises + Aerobic Exercise + Intensive Monitoring G3: Range of motion exercises + Progressive Resistance Exercise + Intensive Monitoring	In group G3, the best improvement in quality of life and prevention of lymphedema development were observed; in group G2, the best early-stage results in pain control were achieved. Intensive monitoring was found to be effective in increasing exercise motivation.
Pajero et al.	2022	Spain	43 patients (n=21 control, n=22 intervention)	Kinesio taping Intervention was applied in the group receiving Complex Decongestive Therapy + Intermittent Pneumatic Compression.	In the kinesio taping group, participants received Complex Decongestive Therapy + Intermittent Pneumatic Compression.	Complex Decongestive Therapy and Intermittent Pneumatic Compression resulted in a greater reduction in arm volume and more improvement in shoulder range of motion compared to kinesio taping. In contrast, kinesio taping was found to be more effective in reducing pain and improving patient satisfaction.

Table 1. Citation information for randomized controlled trials examining the effectiveness of nursing interventions in the management of lymphedema after breast cancer (continuing)

Author	Year	Country	Sample	Control Group	Intervention Group	Findings
Deveci	2022	Türkiye	210 patients (n=35 control, n=37 intervention)	Both the intervention and control groups received online standard lymphedema education.	In addition, the intervention group was provided with the Mobile Lymphedema Self-Care Support Program (m-LODEP), which was installed on their phones, and its usage was demonstrated. Data were collected via phone before the intervention, at the first month, and at the third month.	In the experimental group, the Mobile Lymphedema Self-Care Support Program (m- LODEP) led to an increase in self-care scores, improvement in quality of life, reduction in symptoms, and a decrease in arm circumference. In the control group, symptoms decreased and arm measurements were reduced.
Bozdemir and Aygin	2021	Türkiye	60 patients (n=30 control, n=30 intervention)	Standard care	They received training based on the model of activities of daily living.	In the intervention group, significant improvement was observed in upper arm circumference, the Subjective Perception of Postoperative Functional Arm Disability (SPOFIA), and the Disabilities of the Arm, Shoulder, and Hand (DASH) scores compared to the control group.
Lampinen et al.	2021	USA	28 patients (n=13 control, n=15 intervention)	Manual lymphatic drainage	Negative Pressure Massage Therapy	Negative Pressure Massage Therapy has led to improvements in L-Dex (Lymphedema Index) scores and volume differences between extremities compared to manual lymphatic drainage.
Omidi et al.	2020	Iran	105 patients (randomized in 3 blocks with 35 patients in each group)	Standard care	The group-based education and social network-based education were administered.	Group-based and social network-based educations resulted in improvements in quality of life, but were not effective in reducing the fear of cancer recurrence.

Table 1. Citation information for randomized controlled trials examining the effectiveness of nursing interventions in the management of lymphedema after breast cancer (continuing)

Author	Year	Country	Sample	Control Group	Intervention Group	Findings
Cal	2020	Türkiye	72 patients (n=35 control, n=37 intervention)	Standard care	Nursing interventions based on the Health Belief Model	Nursing interventions based on the Health Belief Model resulted in positive changes in lymphedema prevention behaviors, improvement in upper extremity functions, reduction in side effects, increased quality of life, development in self-efficacy, and a decrease in the frequency of lymphedema.
Torres-Lacomba et al.	2020	Spain	150 patients (30 patients in each group, 5 groups)	All participants followed the same treatment process, with only different bandaging/taping methods applied.	Five groups: Multilayer bandaging, simplified multilayer bandaging, cohesive bandaging, adhesive bandaging, kinesio taping.	Simplified multilayer bandaging and cohesive bandaging showed the most effective results. Kinesio taping and adhesive bandaging were found to be less effective. A reduction in symptoms was observed in all groups after treatment; however, no significant difference was found between the groups. Kinesio taping was perceived as the most comfortable, while multilayer bandaging was considered the most uncomfortable.
Ridner et al.	2020	USA	160 patients (n=80 control, n=80 intervention)	Brochure (approximately 2 hours)	Web-based multimedia modules (12 modules, each 30 minutes).	The web-based multimedia modules group showed improvement in biobehavioral symptoms (e.g., mood). However, no significant differences were found between the groups in terms of symptom burden, psychological well-being, function, costs, and arm volume.
Kilmartin et al.	2019	USA	22 patients (n=11 control, n=11 intervention)	Complex Decongestive Therapy + Inactive Laser	Complex Decongestive Therapy + Active Low-Level Laser Therapy	In the intervention group, improvements were reported in symptoms and lymphedema symptom distress, while no significant difference was observed in arm volume.
Pajero et al.	2019	Spain	30 patients (n=15 control, n=15 intervention)	Compression garments (for 4 weeks)	Kinesio taping (for 4 weeks)	Kinesio taping reduced lymphedema volume more than compression garments, increased upper extremity range of motion, alleviated symptoms more effectively, and was perceived as more comfortable by the patients.
Temur and Kapucu.	2019	Türkiye	61 patients (n=31 control, n=30 intervention)	The group that did not receive education.	The group that received lymphedema management program education.	No lymphedema development was observed in the intervention group, while 61.2% of the control group developed lymphedema. The intervention group had a higher quality of life and significantly lower symptom scores compared to the control group.
Arinaga et al.	2019	Japan	43 patients (n=21 control, n=22 intervention)	The group receiving traditional treatment.	The group applying the holistic self-care program.	Significant improvements were observed in the intervention group in parameters such as edema, volume changes, transepidermal water loss, mental health, BCRL symptoms, exercise frequency, self-care duration, and satisfaction.

Table 1. Citation information for randomized controlled trials examining the effectiveness of nursing interventions in the management of lymphedema after breast cancer (continuing)

Author	Year	Country	Sample	Control Group	Intervention Group	Findings
Ammitzbøl et al.	2019	USA	130 patients (n=68 control, n=62 intervention)	The group receiving traditional treatment.	The group that received supervised group exercise three times a week for 20 weeks, followed by self-administered resistance exercise for the subsequent 30 weeks.	No significant difference was found in arm volume and lymphedema development in the intervention group, and the exercise program did not have any negative effects.
Arıkan Donmez	2016	Türkiye	52 patients (n=27 control, n=25 intervention)	The group receiving routine care procedures.	The group that performed light exercises, aerobic exercises, stretching exercises, and simple lymphatic drainage massage.	No lymphedema development was observed in the intervention group, while 59.3% of the control group developed lymphedema. At week 6, a significant increase in arm circumference was observed in the control group. In the intervention group, pain, limitations in activities of daily living, heaviness, tightness, and numbness sensation decreased.
Pekyavaş et al.	2014	Türkiye	45 patients (randomized into 3 groups)	Complex Decongestive Therapy	Group 1 : Bandaged Complex Decongestive Therapy, Group 2 : Complex Decongestive Therapy with Bandaging + Kinesio Taping, Group 3: Complex Decongestive Therapy with Kinesio Taping without Bandaging	Kinesio taping and complex decongestive therapy significantly reduced edema after treatment. The application of kinesio taping alone also resulted in a reduction in edema. Symptoms decreased in all groups, but complex decongestive therapy was effective in reducing arm volume only during the treatment period.

3. Results

In this systematic review, 18 randomized controlled trials published between 2014 and 2024 that met the inclusion criteria were analyzed, and the findings are summarized in Table 1. The studies' results showed that nursing interventions have significant effects on the management of lymphedema after breast cancer.

Among the interventions used in lymphedema management, methods such as exercise programs, education based on the information-attitude-practice theory, kinesiology therapy, manual lymphatic drainage, compression garments, and negative pressure massage were prominent. The findings indicate that these interventions improve patients' quality of life, enhance upper extremity functions, and reduce lymphedema-related symptoms (Shi et al., 2023; Lin et al., 2022).

It has been determined that exercise programs, particularly aerobic exercises and range-of-motion exercises, improve upper extremity functions and contribute to the prevention of lymphedema (Lin et al.,

2022; Çal, 2020; Arinaga et al., 2019; Arıkan Dönmez, 2016). Kinesiology therapy applications have been reported to be effective in reducing arm volume and alleviating symptoms, and they are also found to be more comfortable for patients (Pajero et al., 2019; Torres-Lacomba et al., 2020; Pekyavaş et al., 2014). Cognitive-behavioral educational interventions have improved patients' self-care behaviors but did not create a statistically significant difference in the development of lymphedema (Shi et al., 2023). Although web-based multimedia modules improved biopsychosocial symptoms, they did not significantly affect symptom burden, psychological well-being, function, costs, and arm volume (Ridner et al., 2020). Compression garments and bandages (Torres-Lacomba et al., 2020; Temur and Kapucu, 2019), as well as multilayer bandaging, are effective in the treatment of lymphedema, but they were less comfortable compared to kinesiology therapy.

The 18 randomized controlled trials included in this systematic review classified nursing interventions for lymphedema management into 11 categories. The interventions examined include theory-based lymphedema prevention programs, web-based and mobile education programs, exercise programs, intermittent pneumatic compression, negative pressure massage, bandaging and compression garments, simple lymphatic drainage, complex decongestive therapy, myofascial relaxation, laser therapy, and education.

Theory-based programs are grounded in approaches such as the Health Belief Model and activities of daily living. In contrast, web-based and mobile education programs contain multimedia modules and social network-based content. Exercise programs include resistance, aerobic, and stretching exercises; complex decongestive therapy, simple lymphatic drainage, intermittent pneumatic compression, compression garments, and negative pressure massage are considered interventions to improve the physical symptoms of lymphedema. Educational interventions include brochures, web-based programs, and education based on holistic self-care programs. The distribution of interventions by type is summarized in Table 2.

Table 2. Distribution of studies by type of intervention applied

Intervention Type	n	%
Theory-Based Lymphedema Prevention Programs	3	11.5
Web-Based and Mobile Education Programs	3	11.5
Exercise Programs	3	11.5
Intermittent Pneumatic Compression	1	3.8
Negative Pressure Massage	1	3.8
Bandaging, Compression Garments, and Kinesiology Therapy	4	15.4
Simple Lymphatic Drainage	2	7.7
Complex Decongestive Therapy	4	15.4
Myofascial Relaxation	1	3.8
Laser Therapy	1	3.8
Education	3	11.5
Total	26	100

n has been expanded.

4. Discussion

Lymphedema following breast cancer is a chronic complication that negatively impacts patients' physical functionality, quality of life, and psychosocial well-being. This condition, which is challenging to treat and manage, leads to limitations in daily activities, affecting individuals' independence and social life (Donahue et al., 2023). Effective lymphedema management requires a multidisciplinary approach, with nurses playing a critical role in this process (Fu et al., 2005). This systematic review aims to determine the effectiveness of nursing interventions in the management of lymphedema following breast cancer and to identify the most effective practices. The findings suggest that nursing interventions positively impact patients' physical and psychosocial health.

Exercise-based interventions are among the commonly used methods for preventing and treating lymphedema. Studies have shown that resistance and aerobic exercises, in particular, improve upper extremity functions, reduce symptoms such as pain and swelling, and enhance overall quality of life (Lin et al., 2022; Ammitzbøll et al., 2019). A study conducted by Arıkan Dönmez (2016) reported that light aerobic exercises and stretching movements help prevent the development of lymphedema and enable patients to perform daily living activities more comfortably.

Physiological mechanisms also support the effectiveness of exercise in lymphedema management. The literature indicates that aerobic exercises increase the release of β-endorphins from the pituitary gland, which produces analgesic and anti-inflammatory effects (Grossman and Sutton, 1985; Shrihari, 2019). Additionally, the increased activity of the muscle pump during exercise may accelerate lymphatic circulation and reduce edema (Nelson, 2016). Personalized exercise programs should be developed to ensure the effectiveness of exercise

interventions. Furthermore, exercise programs should be tailored to the patient's individual needs and, ideally, administered under the guidance of a lymphedema specialist with experience working with patients who have lymphedema or are at risk for its development (Arıkan Dönmez and Kapucu, 2017). Regular follow-up and motivation are also considered necessary to maintain the long-term effectiveness of the exercises.

In the studies examined in this review, it has been observed that kinesio tape applications are effective in reducing arm volume and alleviating symptoms and are perceived as a more comfortable intervention by patients (Pajero et al., 2019; Torres-Lacomba et al., 2020; Pekyavaş et al., 2014). Kinesio therapy has been reported to increase lymph flow by providing elastic support to the skin, which can help reduce edema (Vergili and Oktaş, 2015). However, compression garments and bandaging applications also play an important role in lymphedema management (Borman, 2016). A study by Lacomba et al. (2020) found that multilayer bandages were effective in treating lymphedema but were less preferred than Kinesio tape regarding patient comfort. Similarly, a study by Pekyavaş et al. (2014) found that kinesio tape effectively reduced lymphedema volume when combined with complex decongestive therapy. These findings emphasize the importance of nurses customizing treatment plans by considering each patient's characteristics and needs. The effectiveness of different physical interventions in lymphedema treatment may vary depending on factors such as the patient's clinical condition, lifestyle, and response to treatment. Therefore, nurses should develop personalized treatment approaches tailored to the patient's needs, ensuring that the treatment process is more effective and sustainable while addressing the patient's holistic nursing care needs. The findings of this study suggest that nurses should create individualized treatment plans for patients and that different physical interventions should be personalized according to patients' requirements.

In addition to physical interventions, patient education and psychosocial support programs play a crucial role in managing lymphedema. Education-based interventions help improve patients' self-care skills, preventing the progression of lymphedema and encouraging active participation in the treatment process (Shi et al., 2023; Temur and Kapucu, 2019). The studies reviewed in this article show that information-attitude-behavior-based education increases patients' awareness of lymphedema management; however, it does not have a direct effect on physical parameters (Shi et al., 2023). Moreover, it is noted that social support groups and web-based education positively affect psychosocial well-being but do not provide significant benefits regarding lymphedema volume or symptom control (Ridner et al., 2020; Omidi et al., 2020). In a study by Arinaga et al. (2019), significant improvements in parameters such as edema, volume changes, transepidermal water loss, mental health, self-care duration, and satisfaction were observed in patients who underwent a holistic self-care program. This finding demonstrates that a holistic approach contributes to physical recovery and improves individuals' emotional and psychological well-being. The results of these studies highlight the need for nurses to focus not only on physical treatment methods but also on interventions such as patient education and psychosocial support in addition to physical therapy techniques. Managing lymphedema requires patients to be conscious of their actions and actively engage in their health processes. Therefore, developing individualized education programs and providing psychosocial support to patients are of great importance.

5. Conclusion

This systematic review evaluated the effectiveness of nursing interventions in the management of lymphedema following breast cancer. The findings demonstrate that physical interventions, such as exercise programs, manual lymphatic drainage, kinesio tape applications, and compression therapy, effectively prevent lymphedema and reduce symptoms. In particular, cognitive-behavioral-based educational programs and web-based support systems have enhanced patients' self-care skills and awareness. However, they showed limited impact in managing physical symptoms. However, despite the lack of statistically significant differences between some interventions, individual intervention types have notably improved patients' comfort and satisfaction. Based on these findings, it is recommended that nursing interventions in lymphedema management be individualized, incorporating both physical and educational approaches to optimize patient outcomes. Future research should comprehensively evaluate the long-term effects of various nursing interventions in lymphedema care to identify the most effective strategies for improving physical and psychosocial outcomes. The resulting evidence will contribute to the development of evidence-based clinical guidelines, enabling the standardization of nursing practices, enhancing patients' quality of life, and reducing the burden on the healthcare system.

Author Contributions

The percentages of the authors' contributions are presented below. All authors reviewed and approved the final version of the manuscript.

	G.A.	B.K.	M.A.
C	30	40	30
D	30	40	30
S		100	
DCP	50		50
DAI	40	20	40
L	45	10	45
W	45	10	45
CR	10	80	10
SR	10	80	10

C= concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision.

Conflict of Interest

The authors declared that there is no conflict of interest.

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