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Letter to the Editor

Mounier-Kuhn Syndrome

Mounier-Kuhn Sendromu

Coşkun Doğan, Zeynep Çetinkaya

İstanbul Medeniyet University Faculty of Medicine, Department of Pulmonology, İstanbul, Türkiye

Keywords: Anatomy, chest diseases, Mounier-Kuhn syndrome

Dear Editor,

In the case report titled "Cases of Multiple Tracheobronchial Diverticulosis Characterized by Recurrent Pneumonia Episodes," published in the Medical Journal of Bakırköy, volume 20, issue 4, December 2024 (1) case 2 demonstrates tracheobronchomegaly with tracheal diverticula and cylindrical bronchiectasis of the right upper lobe, suggesting that this case should be considered in the differential diagnosis of Mounier-Kuhn syndrome (MKS).

We believe that evaluating the case from this perspective, providing radiological measurements of the trachea and main bronchi, and emphasizing the need to consider MKS in the differential diagnosis if the measurements fall within the range consistent with MKS as discussed below would enhance the educational value of the case.

A review of the literature on MKS reveals that, although its exact cause remains unknown, it is a rare congenital lung anomaly characterized by tracheobronchomegaly—an abnormal dilation of the trachea and main bronchi—resulting from a defect in the development of connective tissue and smooth muscle in the tracheobronchial system.

Although acquired forms of MKS have been described and attributed to factors such as barotrauma associated with intensive oxygen therapy in the neonatal period and prolonged exposure of the bronchial membrane to highly irritating substances, the presence of reported cases among siblings and cousins and its association with conditions such as Ehlers-Danlos syndrome, Marfan syndrome, and cutis laxa in children suggest that MKS may have an autosomal recessive inheritance pattern.

Although tracheal widening on a chest X-ray is important for the radiological diagnosis of MKS, the most sensitive imaging modality currently accepted is thoracic computed tomography (CT). MKS should be considered if a chest X-ray shows a tracheal diameter ≥30 mm, a right bronchial diameter ≥24 mm, and a left bronchial diameter ≥23 mm.

Transverse tracheal diameter exceeding 21 mm and anteroposterior tracheal diameter exceeding 23 mm in female patients, whereas in male patients, transverse tracheal diameter of ≥25 mm and anteroposterior tracheal diameter of ≥27 mm are considered diagnostic findings in thoracic CT for MKS. Additionally, in male patients, right and left main bronchus diameters of 21.1 mm and 18.4 mm, respectively, and in female patients, right and left main bronchus diameters of 19.8 mm and 17.4 mm, respectively, are also diagnostic of MKS.

Furthermore, tracheal diverticula, bronchiectasis, tracheobronchomalacia, and emphysema on thoracic CT scans are considered supportive radiological findings for the diagnosis. MKS is primarily diagnosed through radiological and bronchoscopic methods. Treatment of the syndrome focuses on preventing and managing bronchopulmonary infections, when present, and on supportive therapies, such as respiratory physiotherapy (2-5).

FOOTNOTES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Kaya H, Argun Barış S, Başyiğit İ, Boyacı H. Cases of multiple tracheobronchial diverticulosis characterized by recurrent pneumonia episodes. Med J Bakirkoy. 2024;20:354-6.
2. Rjimati M, Serraj M, Elbiaze M, Benjelloun MC, Amara B. Mounier-Kuhn syndrome (tracheobronchomegaly): radiological diagnosis. Radiol Case Rep. 2021;16:2546-50.
3. Kaya AG, Çiledağ A, Atasoy Ç, Karnak D. Flexible bronchoscopy and mechanical ventilation in managing Mounier-Kuhn syndrome: a case report. Sao Paulo Med J. 2018;136:266-9.
4. Fernández-Trujillo L, Sangiovanni S, Morales EI, Sua LF, García CA. Thoracic computed tomography scan and bronchoscopy appearance of Mounier-Kuhn syndrome: a case report. J Investig Med High Impact Case Rep. 2020;8:2324709620947892.
5. Suliman AM, Alamin MA, Hamza MM. Tracheobronchomegaly (Mounier-Kuhn syndrome) and bronchiectasis as rare manifestations of homocystinuria. Respir Med Case Rep. 2023;42:101808.

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Review

Effects of Rehabilitation Approaches on Children with Hemophilia: Systematic Review

Hemofili Hastası Çocuklarda Rehabilitasyon Yaklaşımlarının Etkileri: Sistematik Bir Derleme

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ABSTRACT

Hemophilia presents with symptoms such as pain, limited joint range of motion, and reduced functionality and diminished quality of life. The World Federation of Hemophilia recommends core treatment programs, including preventive, curative, rehabilitative, and palliative care, to improve quality of life. The aim of this study is to examine the effectiveness of physiotherapy approaches in children with hemophilia. In this systematic review, studies published in English were identified through searches of the Cochrane Central Register of Controlled Trials, MEDLINE, and physiotherapy evidence databases (PEDro). The quality of the included studies was assessed using the PEDro scale. Of 60 screened articles, nine randomized controlled trials met the inclusion criteria. According to PEDro scores, four studies were of good quality, whereas five were of low quality. A total of 295 participants aged 8-16 years were included: 175 had moderate hemophilia and 120 had mild-to-moderate hemophilia. The primary outcome measures were pain, functional capacity, and muscle strength; secondary outcomes included joint range of motion, swelling, and balance and gait parameters. Evidence suggested that, in addition to conventional physiotherapy, laser therapy and therapeutic resistive exercise significantly reduced pain and improved range of motion, muscle strength, and functional capacity. This review supports the integration of these modalities into physiotherapy programs for children with hemophilia.

Keywords: Haemophilia, physiotherapy, exercise, pediatric hemophilia, laser therapy

ÖZ

Hemofili ağrı, eklem hareket açıklığında kısıtlılık, azalmış fonksiyonellik ve yaşam kalitesi gibi semptomlarla kendini gösteren bir hastalıktır. Dünya Hemofili Federasyonu, yaşam kalitesini artırmak amacıyla önleyici, tedavi edici, rehabilite edici ve palyatif bakımı içeren temel tedavi programlarını önermektedir. Bu çalışmanın amacı, çocuklarda hemofiliye yönelik fizyoterapi yaklaşımlarının etkinliğini incelemektir. Bu sistematik derlemede, İngilizce yayımlanmış çalışmalar Cochrane Kontrollü Çalışmalar Merkezi Kayıtları, MEDLINE ve fizyoterapi kanıt veri tabanında (PEDro) taranmıştır. Dahil edilen çalışmaların kalitesi PEDro ölçeği kullanılarak değerlendirilmiştir. Tarama sonucunda 60 makale arasından, kriterleri karşılayan 9 randomize kontrollü çalışma derlemeye dahil edilmiştir. PEDro puanlamasına göre bu çalışmalardan 4'ü iyi, 5'i düşük kalitededir. Derlemeye 8 ile 16 yaş arasında toplam 295 katılımcı dahil edilmiştir; bunların 175'i orta düzeyde hemofiliye, 120'si ise hafif ile orta düzeyde hemofiliye sahiptir. Birincil sonuç ölçütleri; ağrı, fonksiyonel kapasite ve kas kuvveti olarak belirlenmiştir; ikincil ölçütler ise eklem hareket açıklığı, ödem ve denge/yürüme parametrelerini içermektedir. Bulgular, konvansiyonel fizyoterapiye ek olarak uygulanan lazer tedavisi ve dirençli egzersizlerin ağrı, hareket açıklığı, kas kuvveti ve fonksiyonel kapasite üzerinde anlamlı iyileşmeler sağladığını göstermektedir. Bu derleme, bu modalitelerin hemofili tanılı çocuklar için fizyoterapi programlarına entegre edilmesini desteklemektedir.

Anahtar Kelimeler: Hemofili, fizyoterapi, egzersiz, pediatrik hemofili, lazer tedavisi

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INTRODUCTION

Hemophilia is an X-linked recessive disorder caused by deficiencies in factor VIII (hemophilia A) or factor IX (hemophilia B), with hemophilia A being four times more common. It primarily affects males due to the inheritance of the X chromosome from the mother, occurring in 1 in 10,000 births overall and 1 in 5,000 male births (1-4).

During early childhood, the presence of frequent bruising, spontaneous bleeding in areas such as joints, muscles, and soft tissues, as well as excessive bleeding following trauma or surgery, may raise suspicion of hemophilia (4). The primary clinical manifestation of hemophilia is prolonged bleeding, which can occur in various parts of the body. Although the disease typically presents in early childhood and persists throughout life, bleeding in severe cases may not become apparent until the child begins physical activities such as walking or running. In mild cases, significant bleeding may not occur until a triggering event, such as trauma or surgery, has occurred (2,4).

The World Federation of Hemophilia (WFH) recommends core treatment programs, including preventive, curative, rehabilitative, and palliative care, to improve patients' quality of life (5). Although evidence-based studies are needed in the treatment of hemophilia, most current research is of low methodological quality. Therefore, it is important to conduct studies that focus on disease-specific needs and that align with models based on the World Health Organization's International Classification of Functioning, Disability and Health (ICF) (5).

Joint problems in patients with hemophilia begin in infancy and commonly affect the ankle, knee, and elbow joints. Symptoms include recurrent hemarthroses, flexion deformities, chronic synovitis, epiphyseal hypertrophy, cartilage damage, and hemophilic arthropathy (6). Hemarthroses lead to a cycle of bleeding and synovitis, causing joint hypertrophy and increased injury risk. Initially, pain may be manageable, but it can progress to irreversible flexion deformities and asymmetric epiphyseal hypertrophy, resulting in valgus deformities and hemophilic arthropathy (6-8). The WFH recommends primary prophylaxis as the best approach, though it can be challenging for children and highlights the need for personalized treatment. Hydrotherapy reduces bleeding frequency, pain, and joint instability. Ultrasound and pulsed shortwave electrotherapy can be beneficial, but may affect the epiphyseal growth plate, prompting debate over their use (9-14). Although a limited number of research articles examine the effectiveness of various intervention strategies, no systematic review has investigated physiotherapy and rehabilitation interventions in the pediatric hemophilia population. Considering that hemophilia is a lifelong condition, it is recommended that interventions begin as early as possible after diagnosis to help children adapt to the treatment process and integrate it into their daily lives as they grow (9-13). The literature lacks studies focusing particularly on the pediatric population due to ongoing debates regarding the benefits and risks of physiotherapy in practice. Therefore, the aim of this systematic review is to examine the effects of physiotherapy approaches in children with hemophilia.

METHODS

Search Strategy

This systematic review was conducted according to the Cochrane Collaboration standard guide (15) and prepared following the PRISMA Statement (16) for randomized studies. The Cochrane Central Register of Controlled Trials, MEDLINE, and physiotherapy evidence databases (PEDro) databases were used. All studies published up to June 2023 were reviewed. Initially, the authors (Beyza Tanrıöğen and Nilgün Yıldız) independently screened all titles, abstracts, and full-text articles for eligibility. Disagreements regarding inclusion were resolved through consensus meetings or by consulting another co-author, Rüstem Mustafaoğlu.

Eligibility Criteria

We included only randomized controlled trials (RCTs) involving pediatric patients with hemophilia that assessed physiotherapy, rehabilitation, or exercise interventions. Studies covering all types and severities of hemophilia (mild, moderate, and severe) were included. Excluded were non-English articles, book chapters, reviews, meta-analyses, non-randomized studies, and studies without physiotherapy or rehabilitation interventions.

Outcome Measures

The included studies were reviewed and classified according to the ICF model for hemophilia (17). The primary outcomes of the study were determined to be pain, functional capacity, and muscle strength. The secondary outcome measures were range of motion (ROM), swelling, and balance and gait parameters.

Data Extraction

In the present review, relevant data from included studies have been extracted by two authors (Beyza Tanrıöğen and Nilgün Yıldız) (Table 1).

Table 1. Summary of the included studies

Author, country, year	Age	N (IG/CG)	Type/ severity	Intervention	Control	Intensity/ duration/session	Outcomes measures	Results
Eid et al. (26), Egypt, 2013	10-14	30 (15-15)	A/moderate	Bicycle ergometer+resistance exercises	Gentle stretching Static muscle contraction aerobic exercise	Bicycle ergometer for 20 min, resistance exercise for 20 min: sand bags 2-6 kg, 3x10, 3 times/week for 3 months	Muscle strength, 6-MWT	Strength improved only in the study group (flexors: t=13.89, p=0.0001; extensors: t=16.26, p=0.0001). Between-group comparisons favored the study group (extensors: t=2.77, p=0.01; flexors: t=2.41, p=0.02). Functional capacity improved more in the study group (t=2.55, p=0.01)
El-Shamy and Abdelaal (25), Egypt, 2016	9-13	30 (15-15)	A	Active HILT+traditional physical therapy	Placebo HILT+traditional physical therapy	Total energy of 1500 J through 3 phases/3 sessions/ week 12 weeks 8 min	Pain-VAS, 6-MWT, gait assesment	Both of the groups had significant difference on pain and function after the intervention (p=0.001). Significant difference between the laser group has reported compared to placebo group.on VAS scores, and functional capacity (p=0.001 and p<0.003, respectively). Gait parameters also improved (p=0.001) in both groups, intervention group showed significantly superior effect (p=0.001)
El-Shamy (23), Egypt, 2017	9-13	30 (15-15)	A/mild to moderate	WBV+conventional physical therapy	Conventional physical therapy	30-40 Hz, 2-4 mm of peak-to-peak vertical plate displacement for 15 minutes/day, 3 days/week, 12 weeks	Quadriceps strength, 6-MWT	Significant difference between the mean values of quadriceps peak torque was observed in study group compared to CG (p<0.001, Cohen's d=6.66) and 6-MWT (p=0.006, Cohen's d=1.08) at baseline and after treatment
Azab et al. (22), Egypt, 2020	10-13	45 (15-15-15)	A/moderate	KT+exercise placebo taping+exercise	Exercise	KT group: 10 cm Kinesio tape vertically from sacrum to T12 vertebra, on both sides of the spine Placebo group: Same as the KT group, applied with 0% tension CG: Exercise was performed 3 times/ week for 30 min. for 12 weeks	Pain-NRS, 6-MWT	On KT group, pain decreased significantly (p=0.001, Cohen's d=1.61) compared to CG, but there was no significant difference compared to placebo group (p=0.19, Cohen's d=0.87). When it is compared to CG ,there was a significant difference in functional capacity in the KT group (p=0.039), but no significant difference was observed between KT and placebo group (p=0.58)
Eid and Aly (20), Egypt, 2015	9-13	30 (15-15)	A/moderate	Traditional physical therapy+LLLT traditional physical therapy+PEMF		Gallium-aluminum-arsenate laser 3 times a week, ASA magnetic field device Frequency: 15 Hz Intensity: 20 gauss Time: 20 min	Pain-VAS, ROM, circumference measurement, 6-MWT	In the 6th week, a significant improvement was observed on pain (p=0.02, MD=-0.67), knee flexion (p=0.001, MD=5.87), knee extention (p=0.02, MD=5.87), swelling (p=0.02, MD=-0.68) and function (p=0.03, MD=26.33)in the laser group compared to the PEMF. After 12 weeks, there was a significant improvement in pain (p=0.001, MD=-1.27), knee flexion (p=0.02, MD=4.67) and knee extention (p=0.001, MD=5.27) in the laser group compared to the PEMF group, while no significant improvement was observed in knee circumference measurements and 6-MWT parameters

Table 1. Continued

Author, country, year	Age	N (IG/CG)	Type/ severity	Intervention	Control	Intensity/ duration/session	Outcomes measures	Results
Elnaggar (21), Egypt, 2019	8-16	40 (20-20)	A/moderate	Active pulsed Nd: YAG laser+exercise	Placebo laser+exercise	Exercise 3 times a week, not exceeding 30 minutes, for 1 month Laser was applied 3 times a week for about 8 minutes for 1 month	Pain-NRS, postural stability-NeuroCom-balance system, weight bearing pattern-Tekscan HR Mat™, barefoot pressure mapping system	Active pulse laser group was compared to the placebo group; pain (p=0.004, η^2=0.26), directional control (p=0.02, η^2=0.16), endpoint excursion (p=0.003, η^2=0.29), center of gravity movement (p=0.003, η^2=0.30) velocity parameters improved more. There was no statistically significant difference between the maximum excursion parameter active laser and placebo groups (p=0.15)
Mohamed and Sherief (24), Egypt, 2014	10-14	30 (15-15)	Mild-moderate	Bicycle ergometer (group A)/treadmill training (group B)	Gentle stretching, isometric muscle contraction, balance and gait training, treadmill training	1 hour/session-3 times/week, for 3 months Group A: 20 minutes of bicycle ergometer Group B: 20 minutes of treadmill training	Balance and gait parameters-Biodex Gait Trainer 2TM	Significant positive differences on balance were obtained in both groups treadmill training (p=0.001, p=0.001, p=0.001) was more beneficial than bycle ergometer (p=0.01, p=0.01, p=0.01) on overall stability, antero-porterior and medio-lateral stability respectively. Gait parameters improved in both groups (p=0.01) but treadmill group showed significantly superior results
Abd-Elmonem et al. (27), Egypt, 2014	8-12	30 (15-15)	Mild-moderate	Treadmill training group: 20 minutes of training additionaly in control group	Therapeutic, ultrasonic modalities (1 MHZ/1.5 W/cm^2 /10 minutes), strengthening and stretching exercises	1 hour/session-5 times/week, for 3 months Treadmill training group: 20 minutes	Muscle strength-biodex isokinetic dynamometer	Both control and intervention groups achieved significant results on knee flexion and extention (p=0.001) muscle strength at different angles, treadmill training group showed superiority significantly (p=0.001)
Zaky and Hassan (28), Egypt, 2013	8-12	30 (15-15)	Moderate	Additional partial weight bearing program	Therapeutic exercise	3 sets/10 repetitons, 3 sessions/week, for 6 weeks	6-MWT, quadriceps muscle strength-Lafayette manual muscle test system	Both groups showed sigificant improvements after the treatment on muscle strength and function (p=0.001). In the comparison between the groups, no significant difference was found in functional walking (p=0.948), but significant differences were obtained between the two groups in the evaluation of muscle strength (p=0.025)

6-MWT: 6-minutes walk test, BMD: Bone mineral density, HILT: High intensity laser therapy, VAS: Visual analogue scale, CG: Control group, KT: Kinesio tape, NRS: Numerical rating scale, LLLT: Low level laser therapy, PEMF: Pulsed electromagnetic field, ROM: Range of motion, WBV: Whole body vibration, ESR: Erythrocyte sedimentation rate, Nd: YAG: Neodymium: yttrium-aluminium-garnet, η^2: Partial eta squared, MD: Mean difference, NRS: Numeric rating scale

Quality Assessment of the Studies

The PEDro scale assesses study quality in physiotherapy and rehabilitation using 11 yes/no items, with a maximum score of 10 points. Scores of 9-10 indicate excellent quality; scores of 6-8 indicate good quality; scores of 4-5 indicate sufficient quality; and scores below 4 indicate low quality (18,19).

RESULTS

Of 60 initially screened papers, 10 duplicates were removed, leaving 50 records, of which 9 studies were deemed eligible and included (Figure 1).

A total of 9 studies were included in the systematic review (Table 1), comprising 295 participants aged between 8 and 16 years. Among them, 205 had hemophilia A and 90 had unspecified hemophilia types. The severity of hemophilia was classified as moderate in 175 participants and as mild-to-moderate in 120 participants.

Study Quality

All included studies were RCTs with defined exclusion criteria. Allocation concealment was reported in 33% of the studies, subject blinding in 11%, evaluator blinding in 33%, and therapist blinding was not reported in any study. Key outcome data were obtained from more than 85% of participants in 33% of the studies. Intention-to-treat analysis was not conducted in any of the studies. However, statistical comparisons and variability measures for key outcomes were provided (Table 2).

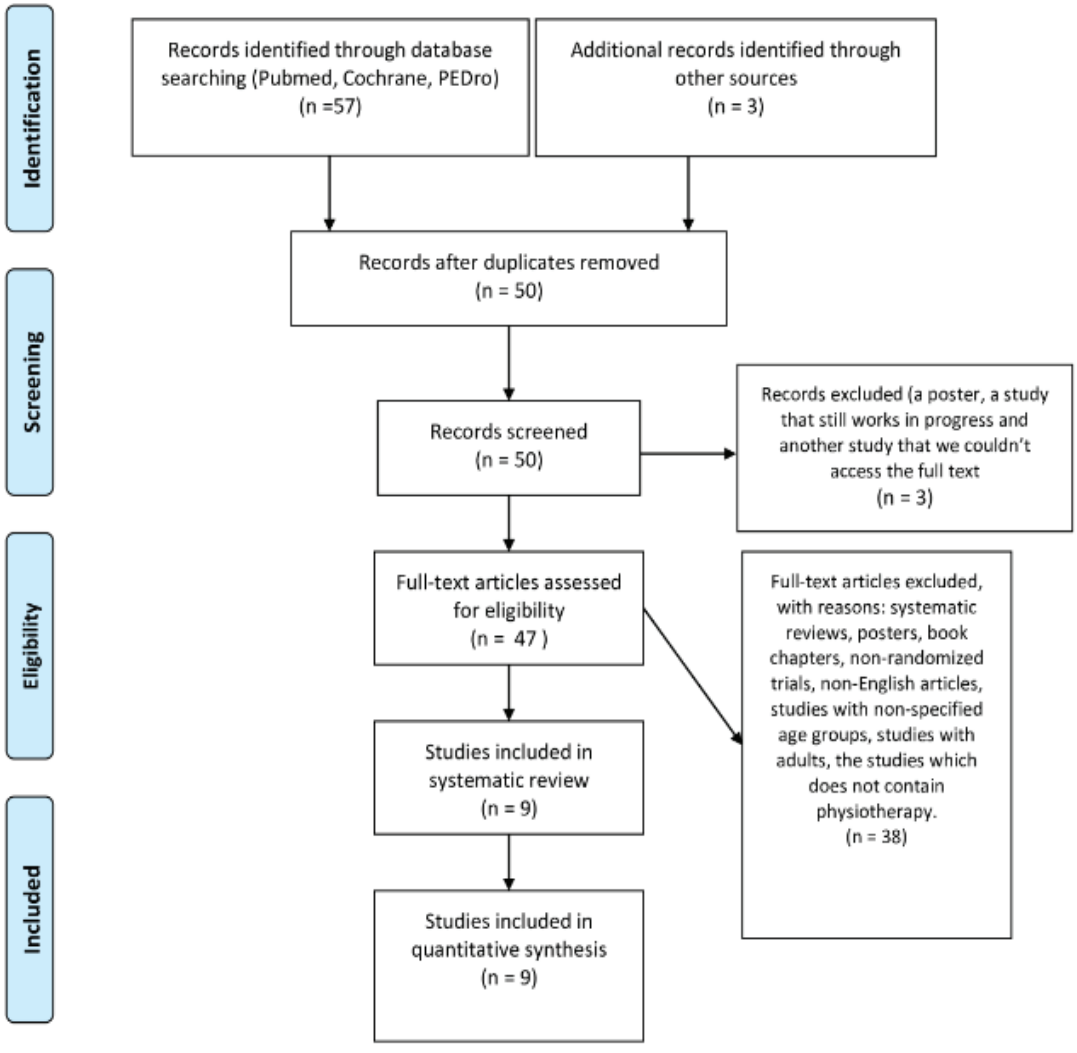

Figure 1. PRISMA flow diagram to demonstrate the process of research and study selection through the review
PRISMA: Preferred reporting items for systematic reviews and meta-analyses, PEDro: Physiotherapy evidence database

Table 2. PEDro scale using to determine the quality of the included studies

Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	PEDro score
Eid and Aly (20)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
Elnaggar et al. (21)	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6
Azab et al. (22)	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6
El-Shamy (23)	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	6
Mohamed et al. (24)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
El-Shamy and Abdelaal (25)	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5
Eid et al. (26)	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Abd-Elmonem et al. (27)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
Zaky and Hassan (28)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4

According to assessment of PEDro: Physiotherapy evidence databese (the symbols mean), Q: Question, Y: Yes, N: No

Outcome Measures

Four of the nine studies evaluated pain with the visual analog scale (VAS) and numerical rating scale (20-22, 25). Four studies evaluated muscle strength using an isokinetic dynamometer and a Lafayette Manual Muscle Tester (23,26-28).

Six studies evaluated functional capacity using the 6-minutes walk test (6-MWT) (20,22-24,26,28). In two studies, gait parameters were evaluated using the GAITRiteVR system and the Biodex Gait Trainer 2™ (23,25). In one study, ROM was evaluated with a universal goniometer (20). In one study, swelling was assessed with circumference measurements (20).

Evidence of Primary Outcomes

Pain

In the Azab et al. (22) study, researchers applied Kinesio taping (KT) to the patients for 12 weeks. The KT group showed a significant decrease in low back pain compared to the control group ($p<0.01$; Cohen's $d=1.61$). In another study, low-level laser therapy (LLLT) applied for 6 weeks [$p=0.02$; mean difference (MD)=-0.67] and 12 weeks ($p=0.001$; MD=-1.27) showed a significant improvement compared with pulsed electromagnetic field (PEMF) therapy (20). In Elnaggar's (21) study, the neodymium: yttrium-aluminum-garnet (Nd: YAG) laser treatment group experienced greater pain relief than the placebo group ($p=0.004$; $\eta^2=0.26$). Similarly, El-Shamy and Abdelaal (25) reported significant improvements in knee pain, as measured by VAS scores, in the active high-intensity laser therapy (HILT) group than the placebo HILT group ($p=0.001$). Overall, the evidence suggests that laser therapies effectively relieve pain in children with hemophilia, but it remains unclear which type of laser is most effective. KT also demonstrated positive results, although the evidence is currently limited to a single study.

Muscle Strength

When added to routine physical therapy, additional resistance exercises using sandbags and a bicycle ergometer resulted in significant improvements in knee flexor and extensor muscle strength (3 sessions/week for 12 weeks; flexors: $t=13.89$, $p=0.0001$; extensors: $t=16.26$, $p=0.0001$) (26). El-Shamy (23) found that adding whole-body vibration (WBV) to conservative treatment improved peak quadriceps muscle torque after 12 weeks ($p<0.001$; Cohen's $d=6.66$). Another study showed significant gains in quadriceps and hamstring strength after 12 weeks of additional treadmill training, delivered as five sessions per week ($p=0.001$ for both groups and for the between-group comparison) (27). A further study found that partial weight-bearing exercises led to greater improvements in muscle strength compared with static exercises ($p=0.025$), although no difference was observed in walking function ($p=0.948$) (28). Overall, resistance exercises, treadmill walking, WBV, and laser therapy were shown to enhance traditional treatments and to improve lower limb muscle strength.

Functional Capacity

The 6-MWT was the most commonly used outcome measure for assessing functional capacity. In the study by Eid et al. (26), both groups improved following resistance and aerobic training, although the between-group difference was only modest ($t=2.55$, $p=0.01$, favoring the intervention). Similarly, partial weight-bearing exercises led to significant improvements in both groups; however, the difference between them was not significant ($p=0.948$) (28). El-Shamy (23) found a significantly greater improvement in 6-MWT when WBV training was added to physiotherapy compared with physiotherapy alone ($p=0.006$, Cohen's $d=1.08$). In Azab et al.'s (22) study, functional capacity improved significantly in the KT group compared with the control group ($p=0.039$), but not when compared with placebo taping ($p=0.58$).

Laser-based therapies also showed benefits. HILT was significantly superior to placebo in children with hemophilic arthropathy (p=0.001) (25). LLLT showed greater improvement than PEMF at week 6 (p=0.03; MD=26.33), though this was not sustained at week 12 (p>0.05) (20). Overall, both exercise-based and laser interventions improved 6-MWT performance, though the most effective exercise modality remains unclear.

Evidence of Secondary Outcomes

Range of Motion

ROM was evaluated in only one study. Eid and Aly (20) found significant improvements in the LLLT group compared with the PEMF group at 6 weeks (flexion: p=0.001; extension: p=0.02; MD=5.87) and at 12 weeks (flexion: p=0.02, MD=4.67; extension: p=0.001, MD=5.27), with the 12-week program providing the most benefit. LLLT, applied in addition to conventional physiotherapy, effectively improved knee ROM in children with hemophilia.

Swelling

The same study reported a significant reduction in knee circumference in the LLLT group compared with PEMF at both 6 and 12 weeks (MD=-0.68; p=0.02), with no significant difference between the two time points (20). This indicates that laser therapy effectively reduced swelling in the short term.

Balance and Gait Parameters

El-Shamy and Abdelaal (25) assessed gait and balance outcomes and reported improvements in stride length, step length, speed, and cadence after 3 months of HILT (p=0.001). Mohamed and Sherief (24) found that both treadmill and bicycle training enhanced balance, with treadmill training being significantly superior (p=0.001). HILT enhances gait parameters, whereas treadmill training is superior among aerobic modalities because of its gait-specific nature.

DISCUSSION

This systematic review highlights that physiotherapy interventions, including resistance exercises and laser application, are effective for reducing pain intensity and improving muscle strength and functional capacity in children with hemophilia. While KT, WBV, and aerobic exercises also showed positive effects, the number of supporting studies remains limited. Future high-quality studies on these and other treatment methods are needed to provide more comprehensive evidence and enhance the understanding of physiotherapy's effectiveness in pediatric hemophilia.

In a randomized study by Castro-Sánchez et al. (29) investigating pain, KT application to the paraspinal muscles produced a significant reduction in pain compared with the placebo group (n=60, 4 weeks). Consistent with our study, Azab et al. (22) reported a significant reduction in pain in the KT group compared with the control group, whereas the placebo group showed no significant change. These findings support the pain-relieving effect of KT application in patients with hemophilia and low back pain and its addition to the treatment program. Demartis et al. (30) evaluated the effectiveness of HILT in hemophilic individuals with chronic arthropathy and found that HILT produced an analgesic effect shortly after application. This study supported El-Shamy and Abdelaal's (25) findings on HILT for pain, one of the studies we included. Nd: YAG laser therapy applied to the ankle 3 days a week for 4 weeks and LLLT and HILT applied to the knee joint 3 days a week for 12 weeks significantly relieved pain. Additionally, children in the LLLT and HILT groups covered greater distances in the 6-MWT, thereby improving physical fitness. However, it remains unclear whether these interventions are effective in other joints commonly affected by hemophilia (e.g., elbow, knee, and ankle hemarthroses).

All studies included in this review reported significant improvements at the end of the treatment. In these studies, both the intervention and control groups received a conventional physiotherapy program consisting of exercises such as ROM, stretching, strengthening, and progressive exercises tailored to the condition of the child with hemophilia. When additional methods—such as laser therapy, WBV therapy, and KT—were combined with exercise, more notable outcomes were observed. However, studies comparing these approaches to an untreated control group are needed to determine their true effectiveness.

Children with hemophilia experience greater reductions in muscle strength related to physical activity than their healthy peers do. This decreased level of physical activity can affect muscle function (31). Therefore, numerous studies have examined the effects of interventions on muscle strength. In the study by Hilberg et al. (32) involving individuals with hemophilia, a significant increase in isometric muscle strength, measured before and after treatment, was noted in participants who underwent low-resistance strength training. Eid et al. (26) demonstrated that progressive resistance training significantly improved muscle strength in children with hemophilia, supporting its inclusion in treatment programs. Similarly, El-Shamy (23) showed that WBV training can effectively enhance muscle strength when used alongside exercise. Most studies lasted 12 weeks, with one 6-week program, reporting mixed results for stretching

and isometric strengthening. Adding resistance exercises, treadmill walking, WBV, and laser therapy improves treatment effectiveness, but the optimal approach remains unclear due to limited research. Exercise programs should be implemented with caution, despite the absence of reported adverse effects.

Azab et al. (22) found a significant improvement in functional capacity in the KT group compared with the control group, whereas no difference was observed in the placebo group. This may be due to increased proprioceptive input enhancing movement awareness. The effect of laser therapy on functional capacity was evaluated in two studies, KT in one study, WBV in one study, and exercise in two studies. These results suggest that such interventions can be included in rehabilitation programs for children with hemophilia due to their positive effects on functional capacity.

LLLT is a therapeutic modality that reduces pain in patients with musculoskeletal disorders (33). In addition, it reduces swelling and contributes to the healing of soft tissue injuries by affecting the inflammatory process (34). These properties of LLLT have made it a preferred treatment approach for children with hemophilia. An increase in ROM was observed in the studies by Alves et al. (35) and Eid and Aly (20). In the study by Alves et al. (35), this improvement was attributed to the pain-reducing and anti-inflammatory effects of LLLT. Similarly, Eid et al. (26) reported significant increases in knee flexion and extension ROM following LLLT application. These findings suggest that LLLT may be a useful addition to rehabilitation programs for children with hemophilia to support improvements in ROM.

A notable finding in the study by Eid and Aly (20) was a reduction in swelling following application of both LLLT and PEMF. The decrease in swelling observed with these modalities may have contributed to improved physical function in children with hemophilia. These results suggest that LLLT and PEMF can be considered supportive options in rehabilitation programs to help manage swelling and enhance functional outcomes. However, findings from the current study suggest that LLLT offers faster and more effective outcomes compared to PEMF. Furthermore, its cost-effectiveness supports the preference for LLLT as a practical and accessible treatment option.

Improvements in balance and gait parameters have been reported through various interventions in children with hemophilia. Elnaggar (21) reported that pulsed Nd: YAG laser therapy significantly enhanced weight-bearing measures—such as forefoot contact area, hindfoot contact area, and total foot contact area—likely by reducing pain and restoring normal posture. This therapy also improved postural stability, including directional control and center-of-gravity velocity, indicating its potential to enhance balance. Additionally, gait training, included in conventional physical therapy, led to significant improvements in walking parameters (23). These findings support using pulsed Nd: YAG laser therapy and gait training to improve balance and gait in this population.

Overall, the evidence suggests that combining conventional physiotherapy with adjunctive modalities such as laser therapy, KT, WBV, and targeted exercise programs can effectively reduce pain and improve muscle strength, functional capacity, ROM, swelling, balance, and gait in children with hemophilia; however, further high-quality studies are needed to confirm these benefits and optimize intervention protocols.

Previous studies have not reported any adverse effects related to physiotherapy interventions; however, careful attention to exercise intensity remains essential. Although this does not mean that exercises can be performed without caution, under the supervision of a physiotherapist, exercise programs can be safely implemented for patients with hemophilia without causing bleeding or other adverse outcomes.

Study Limitations

This systematic review has several limitations that should be considered when interpreting the findings. Firstly, all included studies were conducted in Egypt, which may limit the generalizability of the results to broader populations and different healthcare settings.

Secondly, the studies included relatively small sample sizes. Although methodological quality was assessed using the PEDro scale, no studies were excluded based on quality due to the limited number of available trials. The heterogeneity in treatment approaches and the absence of standardized physiotherapy protocols and outcome measures also limited the ability to synthesize findings across studies effectively. Additionally, the lack of standardized guidelines for physiotherapy in pediatric hemophilia may have contributed to the variability observed in intervention strategies and measurement tools. Notably, none of the included studies addressed upper extremity hemophilic arthropathy, despite its recognized clinical importance.

Furthermore, the current evidence base does not include studies evaluating innovative rehabilitation modalities such as virtual reality, telerehabilitation, or aquatic therapy, which are gaining prominence in pediatric physiotherapy.

Future research should prioritize the design and implementation of high-quality, multicenter RCT involving

diverse populations, with adequate sample sizes and standardized outcome measures. Investigations should also consider both established and emerging rehabilitation approaches to enhance the evidence base for physiotherapy management in pediatric hemophilia.

CONCLUSION

The systematic review included various interventions such as cycling ergometry, resistance strengthening, treadmill training, WBV, KT, laser application, balance and gait training, and partial weight-bearing exercises. It recommends incorporating laser therapy and therapeutic resistance exercises to conventional physiotherapy to improve pain, ROM, muscle strength, and functional capacity in children with hemophilia. Although the optimal intervention period could not be determined due to the limited number of studies, it was observed that the greater positive effects were observed at 12 weeks compared to 6 weeks. Nevertheless, additional high-quality RCT are required to establish definitive evidence.

FOOTNOTES

Authorship Contributions

Concept: B.T., N.Y., R.M., Design: B.T., N.Y., R.M., Data Collection or Processing: B.T., R.M., Analysis or Interpretation: R.M., Literature Search: B.T., N.Y., R.M., Writing: B.T., N.Y., R.M.

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REFERENCES

1. Mehta P, Reddivari AKR. Hemophilia. 2021 Dec 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551607/
2. Strike K, Mulder K, Michael R. Exercise for haemophilia. Cochrane Database Syst Rev. 2016;12:CD011180.
3. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al.; Treatment Guidelines Working Group on Behalf of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. Haemophilia. 2013;19:e1-47.
4. Berntorp E, Shapiro AD. Modern haemophilia care. Lancet. 2012;379:1447-56.
5. Srivastava A, Bragley L, Ozelo MC. Principles of care. Haemophilia. 2020;26(Suppl 6):9-18.
6. Rodriguez-Merchan EC. Prevention of the musculoskeletal complications of hemophilia. Adv Prev Med. 2012;2012:201271.
7. Rodriguez-Merchan EC. Aspects of current management: orthopaedic surgery in haemophilia. Haemophilia. 2012;18:8-16.
8. Rodríguez-Merchán EC. Effects of hemophilia on articulations of children and adults. Clin Orthop Relat Res. 1996;7-13.
9. Beeton K, Padkin J. Physiotherapy in the management of hemophilia. In: Lee CA, Berntorp E, Hoots WK, editors. Textbook of hemophilia. 2nd ed. Wiley-Blackwell; 2010. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/9781444318555.ch31
10. Hilliard P, Funk S, Zourikian N, Bergstrom BM, Bradley CS, McLimont M, et al. Hemophilia joint health score reliability study. Haemophilia. 2006;12:518-25.
11. Ljung RC. Aspects of haemophilia prophylaxis in Sweden. Haemophilia. 2002;8(Suppl 2):34-7.
12. Petrini P. Identifying and overcoming barriers to prophylaxis in the management of haemophilia. Haemophilia. 2007;13(Suppl 2):16-22.
13. Biss TT, Chan AK, Blanchette VS, Iwenofu LN, McLimont M, Carcao MD; Association of Hemophilia Clinic Directors of Canada (AHCDC); Canadian Association of Nurses in Hemophilia Care (CANHC). The use of prophylaxis in 2663 children and adults with haemophilia: results of the 2006 Canadian national haemophilia prophylaxis survey. Haemophilia. 2008;14:923-30.
14. Tiktinsky R, Barmatz C. Hydrotherapy and its use in haemophilia. In: Buzzard B, Beeton K, editors. Physiotherapy management of haemophilia. Oxford: Blackwell Science; 2000. Available from: https://library.knu.edu.af/opac/temp/15452.pdf
15. Cumpston M, Thomas J, Higgins JPT, Chandler J, Cumpston M, Li T, et al.; editors. Cochrane handbook for systematic reviews of interventions. Hoboken (NJ): The Cochrane Collaboration; 2019. Available from: https://www.cochrane.org/handbooks-and-manuals/handbook
16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8:336-41. Erratum in: Int J Surg. 2010;8:658.
17. De la Corte-Rodriguez H, Rodriguez-Merchan EC. The ICF (International Classification of Functioning, Disability and Health) developed by the WHO for measuring function in hemophilia. Expert Rev Hematol. 2016;9:661-8.
18. Celik D, Karaborklu Argut S, Coban O, Eren I. The clinical efficacy of kinesio taping in shoulder disorders: a systematic review and meta analysis. Clin Rehabil. 2020;34:723-40.
19. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83:713-21.
20. Eid MA, Aly SM. LASER versus electromagnetic field in treatment of hemarthrosis in children with hemophilia. Lasers Med Sci. 2015;30:2179-87.
21. Elnaggar RK. Pulsed Nd:YAG laser: effects on pain, postural stability, and weight-bearing pattern in children with hemophilic ankle arthropathy. Lasers Med Sci. 2020;35:1075-83.
22. Azab AR, Elnaggar RK, Diab RH, Moawd SA. Therapeutic value of kinesio taping in reducing lower back pain and improving back muscle endurance in adolescents with hemophilia. J Musculoskelet Neuronal Interact. 2020;20:256-64.
23. El-Shamy S. Effect of whole body vibration training on quadriceps strength, bone mineral density, and functional capacity in children with hemophilia: a randomized clinical trial. J Musculoskelet Neuronal Interact. 2017;17:19-26.
24. Mohamed RA, Sherief AE. Bicycle ergometer versus treadmill on balance and gait parameters in children with hemophilia. Egyptian Journal of Medical Human Genetics. 2015;16:181-7.
25. El-Shamy SM, Abdelaal AAM. Efficacy of pulsed high-intensity laser therapy on pain, functional capacity, and gait in children with haemophilic arthropathy. Disabil Rehabil. 2018;40:462-8.

26. Eid M, Ibrahim M, Aly S. Effect of resistance and aerobic exercises on bone mineral density, muscle strength and functional ability in children with hemophilia. Egypt J Med Hum Genet. 2014;15:139-47.
27. Abd-Elmonem AM, Abd-Esattar Abonour A, Kamal ER. Effect of treadmill training on quadriceps and hamstring muscles strength in children with knee heamarthrosis. Int J Physiother Res. 2014;2: 591-8.
28. Zaky LA, Hassan WF. Effect of partial weight bearing program on functional ability and quadriceps muscle performance in hemophilic knee arthritis. Egyptian Journal of Medical Human Genetics. 2013;14:413-8.
29. Castro-Sánchez AM, Lara-Palomo IC, Matarán-Peñarrocha GA, Fernández-Sánchez M, Sánchez-Labraca N, Arroyo-Morales M. Kinesio taping reduces disability and pain slightly in chronic non-specific low back pain: a randomised trial. J Physiother. 2012;58:89-95. Erratum in: J Physiother. 2012;58:143.
30. Demartis F, De Cristofaro R, Fasulo MR, Boccalandro E, Cobianco A, Santagostino E. Analgesic effects of high intensity laser therapy (HILT) for chronic hemophilic artrhopathy: a pilot study on safety, tolerability and clinical outcomes. Energy Health. 2013;11:4-8.
31. Falk B, Portal S, Tiktinsky R, Weinstein Y, Constantini N, Martinowitz U. Anaerobic power and muscle strength in young hemophilia patients. Med Sci Sports Exerc. 2000;32:52-7.
32. Hilberg T, Herbsleb M, Puta C, Gabriel HH, Schramm W. Physical training increases isometric muscular strength and proprioceptive performance in haemophilic subjects. Haemophilia. 2003;9:86-93.
33. Clijsen R, Brunner A, Barbero M, Clarys P, Taeymans J. Effects of low-level laser therapy on pain in patients with musculoskeletal disorders: a systematic review and meta-analysis. Eur J Phys Rehabil Med. 2017;53:603-10.
34. Cotler HB, Chow RT, Hamblin MR, Carroll J. The use of low level laser therapy (LLLT) for musculoskeletal pain. MOJ Orthop Rheumatol. 2015;2:00068.
35. Alves AC, Vieira R, Leal-Junior E, dos Santos S, Ligeiro AP, Albertini R, et al. Effect of low-level laser therapy on the expression of inflammatory mediators and on neutrophils and macrophages in acute joint inflammation. Arthritis Res Ther. 2013;15:R116.

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Research

Hospitalization Durations, Frequencies and Causes for Patients with Congestive Heart Failure

Konjestif Kalp Yetersizlikli Hastaların Hastanede Yatış Süreleri, Yatış Sıklıkları ve Nedenleri

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ABSTRACT

Objective: Heart failure (HF) is a major contributor to global cardiovascular mortality and morbidity. Despite advances in treatment, mortality from HF continues to increase.

Methods: This study examined 57 male and 47 female patients (total n=104) who were treated for congestive HF (CHF) at our hospital between 01.01.2010 and 31.12.2012. We investigated parameters affecting the number and duration of hospitalizations among patients with HF during the previous year.

Results: The mean age was 75.62±10.53 years (range, 52-102 years). Eighty six (82%) cases were older than 65 years, and 45 (42.3%) had been hospitalized more than once for CHF in the previous year. Hospitalization rates were low: 2 times for 28 (26.9%) cases, three times for 6 (5.1%) cases, four times for 7 (6.7%) cases, five times for 2 (1.9%) cases, and finally six times for 1 (1%) case. The mean interval between the hospitalizations for 44 patients hospitalized more than once was 77.1±79.878 days, ranging between 5 and 360 days. Eleven (10.6%) cases were alcohol consumers and 21 (20%) were smokers. According to functional capacity (FC) by New York Heart Association (NYHA), 4 (3.8%) cases were classified as class I, 48 (46.2%) cases were classified as class II, 26 (25%) cases were classified as class III, and 26 (25%) cases were classified as class IV. A significant difference was found between FC and the total hospitalization period, and between FC and the hospitalization rate ($p<0.001$, for both). A significant association was found between alcohol use and hospitalization rate ($p=0.006$) and between alcohol use and total hospitalization period ($p=0.001$).

Conclusion: The incidence of HF is increasing in patients older than 65 years. The frequency and duration of hospitalization among patients do not differ between female and male patient groups. The frequency and duration of patient hospitalization increase as the NYHA functional class advances.

Keywords: Functional capacities, heart failure, morbidity of heart failure

ÖZ

Amaç: Kalp yetmezliği (KY), dünya genelinde kardiyovasküler mortalite ve morbiditeye neden olan önemli bir klinik tablodur. Tedavideki başarılara rağmen, KY nedeniyle ölümler sürekli artmaktadır.

Gereç ve Yöntem: Bu çalışma, hastanemizde 01.01.2010 ile 31.12.2012 tarihleri arasında konjestif KY (KKY) tedavisi gören 57 erkek ve 47 kadın hasta olmak üzere toplam 104 hastayı incelemiştir. Son bir yıl içinde KY olan hastaların hastaneye yatış sayısını ve sürelerini etkileyen parametreler araştırılmıştır.

Bulgular: Ortalama yaş 75,62±10,53 olup, 52 ile 102 arasında değişmektedir. Seksen altı (%82) olgu 65 yaşın üzerindedir ve 45 (%42,3) olgu geçen yıl KKY nedeniyle birden fazla hastaneye yatıştırılmıştır. Hastaneye yatış oranları düşüktür: 2 kez 28 (%26,9) olgu, 3 kez 6 (%5,1) olgu, 4 kez 7 (%6,7) olgu, 5 kez 2 (%1,9) olgu ve son olarak 6 kez 1 (%1) olgu hastaneye yatmıştır. Birden fazla hastaneye yatış gerçekleştiren 44 hasta için ortalama yatışlar arasındaki süre 77,1±79,878 gün olup, 5 ile 360 gün arasında değişmektedir. On bir (%10,6) olgu alkol tüketicisi ve 21 (%20) olgu sigara

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ÖZ

içicisidir. New York Kalp Derneği'ne (NYHA) göre fonksiyonel kapasite (FK) sınıflandırmasına göre, 4 (%3,8) olgu sınıf I, 48 (%46,2) olgu sınıf II, 26 (%25) olgu sınıf III ve 26 (%25) olgu sınıf IV olarak sınıflandırılmıştır. FK ile toplam hastanede kalma süresi ve FK ile hastaneye yatış oranı arasında anlamlı bir farklılık bulunmuştur (her ikisi için; p<0,001). Alkol kullanımı ile hastaneye yatış oranı ve alkol kullanımı ile toplam hastanede kalma süresi arasında da anlamlı bir farklılık bulunmuştur (p=0,006; p=0,001).

Sonuç: Altmış beş yaşın üzerindeki hastalarda KY insidansı artmaktadır. Hastaların yatış sıklığı veya süresi, kadın ve erkek hasta grupları arasında farklılık göstermemektedir. NYHA fonksiyonel sınıfı ilerledikçe hastaların yatış sıklığı ve süresi artmaktadır. Bizim yatış süresi ve sıklığına etkisiz bulduğumuz diğer parametreler için çok sayıda hastanın yer aldığı başka çalışamalarla araştırılması gerektiği kanısındayız.

Anahtar Kelimeler: Fonksiyonel kapasite, kalp yetmezliği, kalp yetmezliği morbiditesi

INTRODUCTION

Heart failure (HF) is a syndrome in which the heart cannot pump sufficient blood to the periphery to meet the body's changing oxygen and metabolic needs. Congestive HF (CHF) is characterized by fluid retention, including edema, in chronic HF.

The incidence of HF is increasing among populations with longer life expectancies. This makes HF a widespread and growing public health problem. HF is progressive. Unless the underlying problem is eliminated, the prognosis is always poor, with an impaired quality of life and high morbidity and mortality rates. Approximately half of patients diagnosed with HF die within five years, and more than 60% of patients with advanced HF die within one year (1). HF constitutes a substantial burden on both patients and society. No intervention has been found to stop the disease effectively. This result clearly shows that patients at high risk of HF should be treated before CHF becomes apparent.

A good understanding of the etiology and pathophysiology of CHF, recognition of the factors that cause and accelerate its onset and affect its course, and complete identification of the hemodynamic and structural disorders that cause myocardial failure are needed to help early diagnosis and effective treatment of CHF. It reduces morbidity and treatment costs and prolongs life expectancy. In this study, we examined the duration and frequency of hospitalization and the reasons for these hospitalizations among patients with CHF.

METHODS

In this study, the medical records of 104 patients hospitalized with a diagnosis of CHF in the Internal Medicine Clinic of the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital between 01.01.2010 and 31.12.2012 were analyzed. Patients presenting with clinical symptoms of CHF and inpatients diagnosed with CHF were included in the study.

Age, gender, home caregiver status, occupational status, number of hospitalizations for HF in the last year, duration of hospitalization, smoking, alcohol use, medications, comorbidities, ejection fraction (EF), HF class, and etiology of HF were analyzed.

The patients' functional capacity (FC) was classified according to the New York Heart Association (NYHA) classification. Echocardiograms were performed with our hospital's echocardiography device (Vivid 3, 2007, USA) using a 2.5-MHz probe.

The patients' EFs were categorized as follows: ≥50% (normal), 30-49% (moderately reduced), and ≤30% (severely reduced). Parameters affecting the number and duration of hospitalizations for HF during the previous year were investigated. As our study is a retrospective file review, patient consent is not applicable.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 16.0). Data were analyzed using paired-sample tests, independent-sample tests, and analysis of variance (ANOVA).

Findings

The mean age of the patients was 75.62±10.353 years, with a range of 52-102 years. Eighty-six (82.7%) of our patients were older than 65 years. For 18 patients under 65 years of age, the mean number of hospitalizations was 1.83±0.316, and the mean duration of hospitalization was 16.28±4.151 days. For 86 patients aged 65 years or older, the mean number of hospitalizations was 1.69±0.111, and the mean duration of hospitalization was 18.16±1.951 days. 59 (56.7%) of our patients were not working; 45 (43.3%) were retired. Of our patients, 48 (46.2%) were illiterate; 41 (39.4%) were primary school graduates; 11 (10.6%) were middle school graduates; 3 (2.9%) were high school graduates; and 1 (1.0%) was a university graduate. Among male patients, 11 (24%) were illiterate, 15 (26%) were primary school graduates, 7 (15%) were middle school graduates, 2 (4%)

were high school graduates, and 1 (2%) was a university graduate. Among female patients, 37 (65%) were illiterate, 26 (55%) were primary school graduates, 4 (7%) were middle school graduates, and 1 (2%) was a high school graduate. There were no female university graduates. Home care was provided by 67 relatives (64.4%), 27 caregivers (26.0%), and 10 patients themselves (9.6%). Sixty patients (57.7%) were hospitalized once last year. Forty-four patients (42.3%) were hospitalized for CHF more than once last year. Of these patients, 28 (26.9%) were hospitalized twice, 6 (5.8%) three times, 7 (6.7%) four times, 2 (1.9%) five times, and 1 (1.0%) six times. Among the 44 patients hospitalized more than once, the interval between the most recent and the preceding hospitalization ranged from 5 to 360 days, with a mean of 77.10±79.87 days (Table 1). Alcohol use was present in 11 (10.6%) of the patients. Smoking was present in 21 patients (20.2%). Comorbidities were also analyzed, with hypertension (HT) being the most common. Comorbidities and their rates are shown in (Table 2).

According to the etiology of HF, 50 (48.1%) patients had ischemic heart disease, 43 (41.3%) had HT, 5 (4.8%) had rheumatic heart valve disease (RHVD), 2 (1.9%) had cardiomyopathy, and 4 (3.8%) had other causes. According to NYHA, the patients' FC was classified as class I in 4 (3.8%) patients, class II in 48 (46.2%) patients, class III in 26 (25.0%) patients, and class IV in 26 (25.0%) patients. There were significant differences between the FC and the number of hospitalizations, and between the FC and the total length of hospitalization (p<0.001; for both) (Table 3). EF was severely reduced in 21 (20.2%) patients, moderately reduced in 48 (46.2%), and normal in 35 (33.7%) patients. According to analysis of variance (ANOVA), there were no significant associations between patients' EF and the number of hospitalizations, nor between patients' EF and the total length of hospitalization (p=0.333 and p=0.933). Eighty-four (80.0%) patients were admitted to the hospital with dyspnea, 13 (12.5%) with nausea and vomiting, 8 (7.7%) with altered mental status, 7 (6.7%) with chest pain, 4 (3.8%) with atrial fibrillation (AF) with rapid ventricular response, 2 (1.7%) with decompensated chronic renal failure (CRF), and 1 (1.0%) with chronic obstructive pulmonary disease (COPD) exacerbation. There was no significant association between age and readmission (p=0.62) or between age and total hospitalization days (p=0.68). There were no significant differences between genders in readmission (p=0.91) or total hospitalization days (p=0.50).

The relationship between educational status and rehospitalization was analyzed using ANOVA and the t-test; no significant association was found.

The relationship between who cared for patients at home and readmission was analyzed using ANOVA and t-tests, and no significant relationship was found.

There were no significant correlations between smoking and either the number of readmissions (p=0.37) or the total length of stay (p=0.56). However, a significant association was observed between alcohol use and both the number of readmissions and total hospitalization days. There were significant differences among alcohol use, number of hospitalizations, and total hospitalization duration (p=0.006; p=0.001).

Patients using the diuretic furosemide were hospitalized more frequently. There was a significant association

Table 1. The interval between the last and previous hospitalization

	Patients	Minimum	Maximum	Mean
The interval	44	5 days	360 days	77.10±79.87 days

Table 2. Comorbidities and their rates

Concomitant disease	Number of patients	Rate (%)
HT	79	76
DM	34	32.7
CRF	21	20.2
Prev. CVE	11	10.6
Kr. AF	15	14.4
COPD	22	21.2
Hyperthyroidism	4	3.8
Cardiac cirrhosis	2	1.9
Alzheimer	2	1.9
RCV	5	4.8
Entb-extb.	2	1.9
DCV	7	6.7
MVR	1	1
HL	82	78.8
Pace-macer	3	2.9
Parkinson's	3	2.9

HT: Hypertension, DM: Diabetes mellitus, CRF: Chronic renal failure, Prev. CVE: Previous cerebrovascular event, Kr. AF: Chronic atrial fibrillation, COPD: Chronic obstructive pulmonary disease, RCV: Rheumatic valvular disease, Entb-extb: Entubation-extubation, DCV: Degenerative valvular heart disease, MVR: Mitral valve replacement, HL: Hyperlipidemia

Table 3. According to NYHA, the patients' FC

FC (clas)	Patients'	Rate (%)
I	4	3.8
II	48	46.2
III	26	25.0
IV	26	25.0
Total	104	100

NYHA: New York Heart Association, FC: Functional capacity

between diuretic use (furosemide) and rehospitalization (p=0.024). There was no significant difference in the total length of hospitalization (p=0.183).

Calcium channel antagonists were used by 19 (18.3%), beta-blockers by 54 (51.9%), acetylsalicylic acid by 71 (68.3%), aldosterone antagonists by 44 (42.3%), digoxin by 21 (20.2%), angiotensin-converting enzyme inhibitors (ACE-I) by 27 (26.0%); and angiotensin II receptor blockers (ARB) by 8 (7.7%). Diuretic use was significantly associated with rehospitalization (p=0.024). There was no significant difference between the total length of hospitalization (p=0.183). There was a significant association between use of aldosterone antagonists and the number of hospitalizations (p=0.048), but no significant association with total length of stay (p=0.186). There was no significant association between beta-blocker use and readmission (p=0.053), nor between beta-blocker use and total length of hospitalization (p=0.775). There was no significant difference in readmission between patients who used digoxin and those who did not (p=0.643), nor in total length of stay (p=0.950). There was no significant association between ACE-I use and rehospitalization (p=0.648), and no significant difference in total hospitalization duration (p=0.216). There was no significant difference between ARB use and rehospitalization (p=0.208), and no significant difference in total length of stay (p=0.130). There were no significant differences in diabetes mellitus (DM), HT, COPD, previous cerebrovascular event (CVE), chronic AF, and readmission, and total hospitalization duration (p=0.087, p=0.717, p=0.187, p=0.017, p=0.204, p=0.104, p=0.959, p=0.968, p=0.222, p=0.714; respectively). There was no significant difference in rehospitalization by CRF comorbidity (p=0.170), but there was a significant difference in total hospitalization days (p=0.003).

DISCUSSION

HF is among the most important causes of death in our country and worldwide (2,3). Among patients older than 65 years, the most common cause of hospitalization is acute HF (4). Approximately 50% of patients hospitalized for HF are readmitted with the same diagnosis within the first year after discharge (5). The one-year mortality rate among these patients is higher than that among outpatients. HF is also an economically significant public health problem due to recurrent hospitalizations (6,7).

Despite its high prevalence, poor prognosis, and substantial economic burden, epidemiologic studies of patients hospitalized for HF have only recently been conducted (7-9). The HF prevalence and predictors in Türkiye (HAPPY) study, conducted by the Turkish Society of Cardiology, showed that the prevalence of systolic HF in Türkiye was 0.8% and that 1.7% of patients had asymptomatic left ventricular systolic dysfunction. Furthermore, results from HAPPY indicated that the prevalence of diastolic dysfunction among our country's population aged 35 years and older was approximately 9%. In addition, data from the same study indicate that, with rates of HT (49%), diabetes (11%), obesity (27%), and coronary artery disease (4%), the population over 35 years of age in our country has a high burden of risk factors for the development of HF (10).

In our study, 86 patients (82.7%) were older than 65 years of age, and 18 were younger than 65 years of age. Large-scale studies found that patients over 65 predominated. In a study by Timms et al. (11) readmission rates were relatively high among older people, especially those over 65.

There were no significant differences in the number of hospitalizations or in the duration of hospitalization between patients above and below 65 years of age (p=0.62 and p=0.68). We attributed this result to the high mean age of our patients, the large number of patients over 65 years of age, and the small number of patients under 65 years of age. It has been reported that at least 80% of hospitalizations for CHF occur in patients over 65 years of age (12). Among our patients, 82.7% were older than 65 years.

Babayan et al. (13) found that gender was not a differential factor for morbidity in HF. In our study, 57 (54.8%) patients were female and 47 (45.2%) were male. There was no significant difference between both sexes regarding readmission or total hospitalization days (p=0.91; p=0.50).

None of the patients in our study were actively working: 59 (56.7%) were unemployed and 45 (43.3%) were retired. This suggests that the high average age of the patients also played a role.

No significant correlation was found between educational status and rehospitalization or total length of hospitalization. The rates were lower than those reported in the HAPPY study (10). There was no association between the provider of home care and readmission or total length of stay.

Studies have shown that depending on the course of the disease and age, 20% to 55% of individuals with HF are re-hospitalized after discharge, often within the first 3-6 months (13-15).

In 44 patients with multiple hospitalizations, the interval between the last and previous hospitalization ranged from 5 to 360 days, with a mean of 77.10±79.87 days. This was

consistent with previous studies (11-15). In our study, 42.3% of our patients were hospitalized more than once and were re-hospitalized shortly after discharge. We hypothesize that this may be explained by their educational level and socioeconomic status.

There was a significant difference between alcohol use and the number of hospitalizations (p=0.006) and total days (p=0.001). Patients who used alcohol were hospitalized significantly more often and had a significantly longer total length of hospitalization than patients who did not use alcohol. Alcohol use is one of the causes of decompensation in chronic compensated HF (16,17). In the chronic HF survey conducted by Yılmaz et al. (18) the rate of alcohol use was 33.2%. The rate in our study was 10.6%, which is well below this.

There was no significant difference in readmission associated with DM comorbidity (p=0.087), and no significant difference in total length of stay (p=0.717). The Framingham Heart Study reported that the risk of developing HF among individuals with diabetes was increased twofold in men and fivefold in women (19).

There was no significant association between CRF comorbidity and rehospitalization (p=0.170), but there was a significant difference in total hospitalization days (p=0.003). Patients with CRF were hospitalized significantly longer than others.

The second prospective randomized study of ibopamine on mortality and efficacy showed that in patients with advanced HF, impaired renal function was a stronger predictor of mortality than left ventricular dysfunction or poor HF status (20).

The mean body mass index of the subjects in the study was 27.85±6.19, and this finding was similar to that reported for the Turkish version of the Chronic Heart Failure Questionnaire (18).

Our study found no association between obesity and the frequency of hospitalization or total hospitalization days (p>0.05). Nevertheless, we found that 61.5% of patients were overweight.

The etiology of HF was as follows: ischemic heart disease in 50 (48.1%) patients, HT in 43 (41.3%) patients, RHVD in 5 (4.8%) patients, cardiomyopathy in 2 (1.9%) patients, and other causes in 4 (3.8%) patients. Two separate studies found ischemic causes to be the primary etiology of HF (21,22).

They found multiple risk factors for CHF among hypertensive patients in a 20-year follow-up of participants in the Framingham Heart Study. A previous myocardial infarction was present in 34% of hypertensive women and in 52% of men with CHF. Thus, HT was associated with a five-to-six fold increased risk of CHF (23).

According to NYHA, class I was detected in 4 (3.8%) patients, class II in 48 (46.2%) patients, class III in 26 (25.0%) patients, and class IV FC in 26 (25.0%) patients. These data indicate that 52 patients (50%) were in the advanced stages (class III and class IV). A significant correlation was found between patients' FC and both total hospitalization duration and readmission (p<0.001, for both).

FC is graded according to the NYHA system, and the patient's perception generally carries greater weight in the evaluation. Although NYHA is a subjective measure, it is a crucial, established predictor of mortality and morbidity. In general, mortality doubles with each class, resulting in an eightfold higher mortality in class IV compared with class I. According to data from extensive studies such as SUPPORT, FRAMINGHAM, and IMPROVEMENT, many clinicians use the following practical mortality estimates: 5% for NYHA class I, 10% for class II, 15-20% for class III, and 40% for class IV. These values show significant changes under the treatments we use today, which substantially increase life expectancy. It has been shown that, with optimal treatment, these values can be reduced to 12% in class III, class IV patients (24). The study found no significant difference between EF and readmission (p=0.333), or between EF and total length of hospitalization (p=0.933).

In the study, most patients (80%) were admitted to the hospital for dyspnea. Studies conducted with patients with chronic HF found that patients were admitted to the hospital mostly due to increased complaints of dyspnea and fatigue (25).

In our study, 76 patients (73.1%) used the diuretic furosemide. A significant difference in the day of rehospitalization was observed with respect to diuretic use (p=0.024), whereas no significant difference was observed for total days (p=0.183). Diuretics relieve signs and symptoms of pulmonary and systemic venous congestion in patients with HF (26).

In patients with NYHA class II, class III CHF, the maximal response to diuretics is one-third to one-quarter of that in individuals without CHF, and the response decreases further as CHF progresses (27).

The result we reached in our study may be explained by the fact that a significant proportion of the patients were class II, class III, class IV, according to NYHA, and this group used diuretics more frequently because their symptoms were more severe and more difficult to control with diuretics.

In our study, 19 patients (18.3%) used calcium channel blockers. No significant difference was found between calcium channel blocker use and readmission or total hospitalization days (p=0.083 and p=0.068, respectively). Calcium-channel blockers are generally not recommended in HF with systolic dysfunction. Diltiazem and verapamil type calcium antagonists are not recommended in HF with systolic dysfunction, and combining them with beta-blockers is contraindicated (28). Our study found that the use of calcium channel antagonists did not affect either the number or the duration of hospitalizations.

In our study, 44 patients (42%) used aldosterone antagonists. A significant association was observed between aldosterone use and the number of hospitalizations (p=0.048), but not with total hospitalization days (p=0.186).

A single large randomized controlled trial of the aldosterone antagonist spironolactone in patients with severe HF (Randomized Aldactone Evaluation Study) was conducted (29). A 30% relative risk reduction (RRR) in deaths was observed at a median of 2 years following initiation of spironolactone treatment. A 35% RRR in hospitalizations for worsening HF was achieved. In our study, the significantly higher number of hospitalizations in the aldosterone-user group compared with the non-user group may be because aldosterone was used primarily in patients with a high functional class.

In our study, 22 patients (20.2%) used digoxin. There was no significant association between digoxin use and rehospitalization (p=0.643), nor was there a significant difference in total length of stay (p=0.950). In the Digitalis Investigation Group trial, NYHA class II, class IV patients with left ventricular EF ≤45% were randomized to placebo or digoxin (0.25 mg once daily) in addition to diuretic and ACE-I treatment (30).

In our study, 54 patients (51.9%) were using beta-blockers. There was no significant difference between beta-blocker use and readmission (p=0.053), nor between beta-blocker use and total length of stay (p=0.775). Beta-blocker therapy improves ventricular function and the patient's general health status, reduces hospitalizations for worsening HF, and positively affects survival. In three pivotal trials (Cardiac Insufficiency Bisoprolol Study II, Carvedilol Prospective Randomized Cumulative Survival, and Metoprolol Extended-release International Trial in HF), nearly 9,000 patients with mild to severe symptomatic HF were randomized to receive placebo or a beta-blocker (bisoprolol, carvedilol, or metoprolol succinate controlled release). In these three trials, beta-blocker treatment was associated with reduced mortality (RRR of approximately 34% in all trials) and reduced hospitalizations for worsening HF (RRR of 28-36%) within approximately one year of treatment (31).

In our study, 27 patients (26.0%) were on ACE-I. There were no significant differences between ACE-I use and readmission, nor between ACE-I use and total length of stay (p=0.648 and p=0.216). In two major randomized controlled trials (consensus and SOLVD treatment), approximately 2,800 patients with mild to severe symptomatic HF were randomized to receive either placebo or enalapril (32,33). In each of these studies, ACE-I therapy was shown to reduce mortality. The SOLVD treatment trial also showed a 26% RRR in hospitalizations for worsening HF.

In our study, 8 (7.7%) patients used ARBs. There was no significant difference between ARB use and readmission (p=0.208), nor between ARB use and total length of stay (p=0.130). In the two leading randomized, placebo-controlled trials (Val-HeFT and CHARM-added), ARB treatment reduced the risk of hospitalization for worsening HF (24% of patients in Val-HeFT and 17% in CHARM-added), but did not reduce all-cause hospitalizations (34,35).

Study Limitations

This study has several limitations that should be acknowledged. First, it is a single-center, retrospective analysis with a relatively small sample size (n=104), which may restrict the external validity and generalizability of the findings. Second, the study population predominantly consisted of elderly patients, thereby limiting the applicability of the results to younger individuals with heart failure. Third, the data were collected between 2010 and 2012, and thus may not fully reflect current standards of care or contemporary guideline-directed medical therapy. Finally, medication use and comorbid conditions were not randomized or prospectively controlled, so the influence of residual confounding on the observed associations cannot be excluded.

CONCLUSION

The prevalence of HF increases among patients older than 65 years. The average age of hospitalized patients with HF is high. There is no correlation between duration and frequency of hospitalization and the following variables: patient age over 65 years, gender, care methods, smoking status, history of previous CVE, concomitant COPD, AF, DM, EF, or levels of beta-blockers, ACE, calcium channel blockers, digoxin, and ARB. 42.3% of patients were readmitted to the hospital approximately 2.5 months after discharge. Among patients hospitalized for HF, the number of overweight and obese patients and their education levels were low. Alcohol

use, higher FC class (NYHA), diuretic use (furosemide), and spironolactone use are associated with increased frequency and prolonged duration of hospitalization. Accompanying CRF does not increase the frequency of hospitalization or prolong its duration.

The most common presenting symptom in patients with HF is dyspnea. In patients presenting with dyspnea, HF should be carefully considered in the differential diagnosis.

According to our findings, it is crucial to control HT, reduce alcohol consumption, improve monitoring and treatment, decrease the FC, and lower the incidence of chronic renal insufficiency. This is important for reducing the frequency and duration of hospital admissions for renal disease in our country. We propose that additional parameters that we found to be ineffective for the duration and frequency of hospitalization in our study should be investigated in other studies involving a larger patient population.

FOOTNOTES

Authorship Contributions

Concept: Ş.A.H., Design: Ş.A.H., Data Collection or Processing: E.B., Analysis or Interpretation: E.B, Literature Search: E.B., Writing: E.B.

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REFERENCES

1. EICHNA LW. The George E. Brown memorial lecture: circulatory congestion and heart failure. Circulation. 1960;22:864-86.
2. Türkiye İstatistik Kurumu. Ölum istatistikleri 2008. Ankara (Turkey): Türkiye İstatistik Kurumu Matbaası. 2009:25.
3. Felker GM, Adams KF Jr, Konstam MA, O'Connor CM, Gheorghiade M. The problem of decompensated heart failure: nomenclature, classification, and risk stratification. Am Heart J. 2003;145(2 Suppl):S18-25.
4. Fonarow GC. Epidemiology and risk stratification in acute heart failure. Am Heart J. 2008;155:200-7.
5. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al.; ESC committee for practice guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European society of intensive care medicine (ESICM). Eur J Heart Fail. 2008;10:933-89. Erratum in: Eur J Heart Fail. 2009;11:110. Erratum in: Eur J Heart Fail. 2010;12:416.
6. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, et al.; Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation. 2007;116:1482-7.
7. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al.; ADHERE scientific advisory committee and investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the acute decompensated heart failure national registry (ADHERE). Am Heart J. 2005;149:209-16.
8. Gheorghiade M, Ambrosy A. Heart failure in 2010: one step forward, two steps back. Nat Rev Cardiol. 2011;8:72-3.
9. Rudiger A, Harjola VP, Müller A, Mattila E, Säila P, Nieminen M, et al. Acute heart failure: clinical presentation, one-year mortality and prognostic factors. Eur J Heart Fail. 2005;7:662-70.
10. Değertekin M, Erol C, Ergene O, Tokgözoğlu L, Aksoy M, Erol MK, et al. Türkiye'deki kalp yetersizliği prevalansı ve öngördürücüleri: HAPPY çalışması [Heart failure prevalence and predictors in Türkiye: HAPPY study]. Turk Kardiyol Dern Ars. 2012;40:298-308.
11. Timms J, Parker VG, Fallat EH, Johnson WH. Documentation of characteristics of early hospital readmission of elderly patients. A challenge for inservice educators. J Nurses Staff Dev. 2002;18:136-43.
12. Uysal H. Konjestif kalp yetersizlikli hastalarda erken dönemde hastaneye tekrar yatış belirleyicileri. Kalp Yetersizliği Elektronik Haber Bülteni. 2009;1. Erişim adresi: http://www.tkd.org.tr/cg/007/kybulteni/?makale=67
13. Babayan ZV, McNamara RL, Nagajothi N, Kasper EK, Armenian HK, Powe NR, et al. Predictors of cause-specific hospital readmission in patients with heart failure. Clin Cardiol. 2003;26:411-8.
14. Gonseth J, Guallar-Castillón P, Banegas JR, Rodríguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. Eur Heart J. 2004;25:1570-95.
15. Proctor EK, Morrow-Howell N, Li H, Dore P. Adequacy of home care and hospital readmission for elderly congestive heart failure patients. Health Soc Work. 2000;25:87-96. Erratum in: Health Soc Work. 2000;25:168.
16. Topol EJ, editor. Textbook of cardiovascular medicine. Philadelphia: Lippincott Williams & Wilkins; 1998. Section VI: Heart Failure and Transplantation. p. 2179-327.
17. Topol EJ, editor. Manual of cardiovascular medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2004. Heart Failure and Transplantation. p. 101-75.
18. Yılmaz E, Eser E, Gürgün C, Kültürsay H. Kronik kalp yetersizliği anketi'nin (KKYA) Türkçe sürümünün geçerlilik ve güvenilirliği [Reliability and validity of the Turkish version of the chronic heart failure questionnaire]. Anadolu Kardiyol Derg. 2010;10:526-38.
19. Johnstonemd MT, Kinzfogl GP. Diabetes mellitus and heart disease. In: Diabetes and Cardiovascular Disease. Contemporary Cardiology series. Springer; p. 579-628.
20. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000;102:203-10.
21. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med. 2001;161:996-1002.
22. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342:1077-84.
23. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996;275:1557-62.

24. Levy WC, Linker DT. Prediction of mortality in patients with heart failure and systolic dysfunction. Curr Cardiol Rep. 2008;10:198-205.
25. Parshall MB, Welsh JD, Brockopp DY, Heiser RM, Schooler MP, Cassidy KB. Dyspnea duration, distress, and intensity in emergency department visits for heart failure. Heart Lung. 2001;30:47-56.
26. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. Int J Cardiol. 2002;82:149-58.
27. Brater DC, Chennavasin P, Seiwell R. Furosemide in patients with heart failure: shift in dose-response curves. Clin Pharmacol Ther. 1980;28:182-6.
28. Elliott WJ, Ram CV. Calcium channel blockers. J Clin Hypertens (Greenwich). 2011;13:687-9.
29. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N Engl J Med. 1999;341:709-17.
30. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336:525-33.
31. Domanski MJ, Krause-Steinrauf H, Massie BM, Deedwania P, Follmann D, Kovar D, et al.; BEST investigators. A comparative analysis of the results from 4 trials of beta-blocker therapy for heart failure: BEST, CIBIS-II, MERIT-HF, and COPERNICUS. J Card Fail. 2003;9:354-63.
32. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316:1429-35.
33. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325:293-302.
34. Cohn JN, Tognoni G. Valsartan heart failure trial investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667-75.
35. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al.; CHARM investigators and committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-alternative trial. Lancet. 2003;362:772-6.

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Research

How Effective are Culture Results in Pediatric Sepsis Survival? A Single-Center Experience

Pediatrik Sepsiste Kültür Sonuçları Sağkalıma Ne Kadar Etkilidir? Tek Merkez Deneyimi

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ABSTRACT

Objective: Sepsis is a clinical syndrome with many faces. For successful treatment of pediatric sepsis, clinicians need a comprehensive understanding of the disease's risk factors, diagnostic procedures, and therapeutic approaches. Our study compared clinical features, laboratory data, and prognostic variables between culture-positive and culture-negative sepsis cases in children admitted to a tertiary pediatric intensive care unit (PICU).

Methods: A total of 57 pediatric patients aged 1-month to 18 years who presented to University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital with suspected or confirmed sepsis between February 2022 and January 2023 were assessed. The study included those who fulfilled the diagnostic criteria for sepsis or septic shock. Demographic data, clinical variables, and outcome measures were analyzed.

Results: Among sepsis cases, 20 (35%) had a positive blood culture, whereas 37 (64.9%) had a negative blood culture. A significantly greater proportion of cases with positive blood cultures required mechanical ventilation (p=0.034) and had longer PICU stays (p=0.004). There were no statistically significant differences between the two groups in treatment modalities, such as therapeutic plasma exchange, renal replacement therapy, and use of inotropic agents. Mortality rates were higher in the culture-positive group, but the difference was not statistically significant (p=0.509).

Conclusion: Although microbiological culture is critical for sepsis diagnosis, culture-negative children may have poor outcomes. Identification of risk factors for mortality and morbidity helps determine which cases should be followed more closely, based on the severity of the disease process, and which require the most appropriate treatment.

Keywords: Culture, infection, organ dysfunction, pediatric, sepsis

ÖZ

Amaç: Sepsis, birçok klinik yüzü olan bir sendromdur. Pediatrik sepsiste başarılı bir tedavi süreci için klinisyenlerin hastalığın risk etmenlerini, tanı sürecini ve tedavi yaklaşımlarını kapsamlı biçimde bilmeleri gerekmektedir. Çalışmamızda, üçüncü basamak pediatrik yoğun bakım ünitesinde (PYBÜ) kültür-pozitif ve -negatif sepsis hastalarının klinik özellikleri, laboratuvar verileri ve prognostik değişkenleri karşılaştırılmıştır.

Gereç ve Yöntem: Şubat 2022 ile Ocak 2023 tarihleri arasında Sağlık Bilimleri Üniversitesi, Sancaktepe Şehit Prof. Dr. İlhan Varank Eğitim ve Araştırma Hastanesi'ne şüpheli ya da kesin sepsis tanısı ile başvuran, 1 ay ile 18 yaş arasındaki toplam 57 pediatrik olgu değerlendirildi. Çalışmaya, sepsis veya septik şok tanı kriterlerini karşılayanlar dahil edildi. Demografik veriler, klinik değişkenler ve sonuç verileri analiz edildi.

Bulgular: Sepsis hastalarının 20'sinde (%35) pozitif kan kültürü varken 37'sinde (%64,9) negatif kan kültürü vardı. Kan kültürü pozitif olan hastalar önemli ölçüde daha fazla mekanik ventilasyona ihtiyaç duydu ve PYBÜ'de daha uzun süre kaldılar (p=0,034; p=0,004). İki grup arasında terapötik plazma değişimi, renal replasman tedavisi ve inotropik ajan kullanımı açısından istatistiksel olarak anlamlı bir fark yoktu. Kültür-pozitif grupta mortalite oranları daha yüksekti ancak istatistiksel olarak anlamlı değildi (p=0,509).

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ÖZ

Sonuç: Kültür sonucunun sepsis tanısında kritik bir yeri olsa da, negatif kültürü olan sepsis hastaları da zayıf tedavi başarısı gösterebilirler. Mortalite ve morbiditeyi etkileyen risk faktörlerinin tanımlaması, hangi hasta grubunun daha kötü seyredeceğini belirleyerek, uygun tedavi yöntemi seçilmesine yardımcı olacaktır.

Anahtar Kelimeler: Kültür, enfeksiyon, organ disfonksiyonu, pediatrik, sepsis

INTRODUCTION

Sepsis is an infection characterized by immune dysregulation and microcirculatory disorders resulting in life-threatening organ dysfunction. Severe sepsis accounts for more than 8% of all admissions to the pediatric intensive care unit (PICU) (1). It remains a leading cause of morbidity and mortality in children, with an annual mortality rate ranging from 4% to 50%, depending on disease severity, risk factors, and geographic location (2). To achieve the best outcomes, clinicians must be familiar with the risk factors, diagnosis, and treatment of sepsis in children (1).

Over the past two decades, guidelines for the management of sepsis and septic shock have been established and revised. In 2016, the Surviving Sepsis Campaign modified current definitions and protocols for adult patients (3). Despite the enormous burden that sepsis imposes on pediatric healthcare, current definitions of pediatric sepsis and organ dysfunction are based on the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) (4). These definitions are important for clinicians in recognizing and treating critical cases; however, clinical concern for sepsis should not be limited to physiological or laboratory abnormalities. Sepsis in children is difficult to identify and is associated with a high prevalence of febrile infections, challenges in differential diagnosis, stronger physiological compensatory mechanisms than in adults. These shortcomings have been highlighted more frequently since the definitions were developed in 2005 (1,5).

Blood culture is essential for the identification and for guiding further treatment in children with sepsis. However, blood cultures in suspected cases are frequently negative, and pathogen identification remains difficult. Culture-negative sepsis (CNS) refers to sepsis that has not been microbiologically confirmed. Limited data exist on CNS in pediatric cases, whereas it has been identified in 28-49% of severe sepsis cases in adults (6). The relationship between pathogen culture results and clinical outcomes in children is rarely investigated and remains highly controversial. All this conflicting information highlights the need for further studies.

Our study aimed to compare the clinical and demographic characteristics, laboratory parameters, and prognostic factors between CNS and culture-positive sepsis (CPS) cases among children hospitalized in a tertiary PICU.

METHODS

Study Population

This retrospective study was conducted between February 2022 and January 2023 in the PICU of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, affiliated with University of Health Sciences Türkiye. The PICU, which serves children aged 1-month to 18 years, is equipped with 12 beds, 12 ventilators, 5 Prismaflex™ hemofiltration machines (Baxter, USA), and 9 isolation rooms. During the study period, a total of 456 pediatric cases were admitted to the unit. Of these, 57 cases meeting the diagnostic criteria for sepsis or septic shock were included in the study.

We enrolled cases of sepsis defined either by the IPSCC or by the 2020 guidelines for children, or diagnosed by the treating clinician (2,4).

Cases who did not meet these criteria, who were treated with antibiotics before hospitalization, or who died within 24 hours were excluded from the study. Cases with false-positive culture results, primarily due to contamination, were excluded. Some organisms, such as coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp. (other than *Bacillus anthracis*), *Propionibacterium acnes, Micrococcus* spp., viridans group *Streptococci, Enterococci,* and *Clostridium perfringens* were considered contaminants in cases that did not meet the criteria for sepsis (7).

To detect pathogens, blood cultures were obtained from two sites at admission, and other biological samples were collected for culture according to the suspected infection site, including sputum, pleural effusion, ascites, urine, stool, pus. The volume of blood collected was determined based on case weight (6).

Ethics committee approval was received from the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval no: 2023/29, date: 17.02.2023). This study was planned in accordance with the principles of the Declaration of Helsinki. As the study was retrospective and personal data were anonymized, informed consent was not required.

Patient Characteristics

Data were collected using a detailed form recording the case's age, gender, comorbidities, length of stay in the PICU, duration of invasive mechanical ventilation (IMV), requirement for extracorporeal treatment, treatment with inotropic agents, laboratory parameters, treatment outcomes, and mortality. Blood samples for all cases were collected at approximately the same time after onset, and the worst value within the first 24 hours after admission was recorded. Complete blood count, serum albumin, lactate dehydrogenase, procalcitonin, C-reactive protein, and blood gas analysis on admission were retrospectively obtained from our electronic health information system. To calculate the Pediatric Risk of Mortality III (PRISM III) score, data on 16 variables—temperature; systolic blood pressure; heart rate; partial pressure of arterial oxygen; partial pressure of arterial carbon dioxide; Glasgow Coma Scale score; pupillary reaction; prothrombin time and activated partial thromboplastin time; serum creatinine; serum urea nitrogen; serum potassium; blood glucose; serum bicarbonate; white blood cell count; and platelet count—were recorded within 24 hours of PICU admission (8).

Statistical Analysis

SPSS version 20.0 for Windows was used to perform statistical analyses. Descriptive statistics included counts, frequencies (%), ratios, medians, and standard deviations. The distributions of the variables were assessed using the Kolmogorov-Smirnov test. During the analysis of quantitative data, t-tests and Mann-Whitney U tests were used. The chi-square test was used to compare categorical variables, and the Fisher's exact test was used when chi-square test assumptions were not met.

RESULTS

During the study period, 57 of 456 cases were admitted to the PICU with a diagnosis of sepsis. The sex distribution was approximately equal. The cases' median ages were 41 (3-98) months and 21 (1-194) months in the blood culture-positive and blood culture-negative groups, respectively. There were no statistically significant differences in age, gender, or PRISM III score. Of the total cases, 20 (35%) had positive bacterial blood cultures, whereas 37 (64.9%) had negative bacterial blood cultures (Table 1). The pathogens isolated from positive cultures are shown in Table 2. The most frequent bacterium was *Pseudomonas aeruginosa* (24.3%).

Significantly more cases with positive blood cultures required mechanical ventilation and had longer PICU stays (p=0.034; p=0.004). There were no statistically significant differences between the two groups in treatment modalities, including therapeutic plasma exchange (TPE), continuous renal replacement therapy (CRRT), and inotropic agents. Mortality rates were higher in the CPS group, but the difference was not statistically significant (p=0.509) (Table 1).

Table 1. Demographics, clinical characteristics of children with septis according to the culture results.

		Sepsis		p
		Culture-positive sepsis (n=20)	**Culture-negative sepsis (n=37)**	
Gender, (%)	Male	10 (50%)	22 (59.5%)	0.492
	Female	10 (50%)	15 (40.5%)	
Age (month), mean (range)		41 (3-98)	21 (1-194)	0.219
PRISM III score		12.0 (0.0-30.0)	10.0 (0.0-40.0)	0.255
Mortality, (%)		6 (30.0)	7 (18.9)	0.509
Length of stay (day)		14.5 (4-90)	6.0 (2-59)	**0.017**
Length of stay >7 days, (%)		16 (80.0)	22 (59.5)	**0.004**
Requirement of IMV, (%)		16 (80.0)	19 (51.4)	**0.034**
Duration of IMV, days		8.0 (1-90)	7.0 (2-49)	0.683
Requirement of TPE, (%)		10 (50%)	11 (29.9%)	0.448
Requirement of CRRT, (%)		7 (35%)	16 (43.2%)	0.545
Requirement of inotropic agents, (%)		15 (75%)	18 (48.6)	0.054
Pathogens	Gram-positive bacteria	2 (10.0%)		-
	Gram-negative bacteria	12 (60.0%)		
	Fungus	2 (10.0%)		
	Multipl pathogens	4 (20.0%)		

Bold values indicate statistically significant results (p<0.05)
CRRT: Continuous renal replacement therapy, IMV: Invasive mechanical ventilation, PRISM III: Pediatric Risk of Mortality III, TPE: Therapeutic plasma exchange

Univariate analyses were performed on cases of sepsis. Statistically significant associations were observed between prolonged length of stay, requirement for IMV, inotropic agent use, CRRT, TPE, and mortality. In addition, the analysis showed that levels of leukocytes, lymphocytes, and albumin, as well as the lactate/albumin ratio, were significantly associated with mortality in septic cases (Tables 3 and 4).

DISCUSSION

In the diagnosis and treatment of sepsis, standard practice is to identify pathogens by culture. However, culture positivity in children is uncommon, and the impact of positive versus negative culture results on the prognosis of children with sepsis remains unclear. In our study, only 35% of children admitted to the PICU with a diagnosis of sepsis had a positive blood culture on admission. Although this rate is similar to the 30% positive culture rate of Hazwani et al. (6), it is lower than that reported in most other studies (9).

An important question is why the microorganisms can be identified in some cases of sepsis but not in others. Possible explanations for CNS exist. First, according to the Surviving Sepsis Campaign Guidelines, broad-spectrum antibiotics should be administered as soon as possible to improve outcomes in children (2). In recent years, broad-spectrum antibiotics have been administered early in suspected cases as a result of increased diagnostic vigilance. In our study, we addressed the first factor by excluding all patients who had received antibiotics before hospitalization. This methodological choice strengthens the validity of our findings regarding the CNS.

Another possibility is an the increasing prevalence of non-bacterial sepsis, such as viral or fungal sepsis, which is difficult to detect using conventional methods. Hazwani et al. (6) reported that the incidence of CNS was higher than that of CPS in the presence of respiratory tract infections. This finding supports the possibility of viral sepsis in some cases within the CNS group and may partially explain the lower rate of culture positivity. However, we did not

Table 2. Frequency of pathogens for the positive cultures

	Frequency (%)	Blood	Tracheal aspirate	Urine	Cerebrospinal fluid
Gram-positive, n (%)	6 (16.2%)				
Enterococcus species	3 (8.1%)	2	1	-	-
Methicillin-resistant *Staphylococcus aureus*	2 (5.4%)	-	2	-	-
Streptococcus pyogenes	1 (2.7%)	-	-	-	1
Gram-negative, n (%)	23 (62.1%)				
Pseudomonas aeruginosa	9 (24.3%)	4	5	-	-
Escherichia coli	4 (10.8%)	1	1	2	-
Klebsiella species	3 (8.1%)	3	-	-	-
Acinetobacter baumannii	3 (8.1%)	1	2	-	-
Stenotrophomonas maltophilia	3 (8.1%)	-	3	-	-
Neisseria meningitidis	1 (2.7%)	1	-	-	-
Fungus, n (%)	8 (21.6%)				
Candida species	8 (21.6%)	4	4	-	-

Table 3. Treatment modalities according to sepsis outcomes

	Outcome		p
	Mortality (%), (n=13)	Survival (%), (n=44)	
Length of stay >7 days	7 (22.6)	24 (77.4)	0.965
Requirement of IMV	13 (37.1)	22 (62.9)	**<0.001**
Requirement of CRRT	11 (47.8)	12 (52.2)	**<0.001**
Requirement of TPE	8 (38.1)	13 (61.9)	**0.036**
Requirement of inotropic agents	13 (39.4)	20 (60.6)	**<0.001**

Bold values indicate statistically significant results (p<0.05)
CRRT: Continuous renal replacement therapy, IMV: Invasive mechanical ventilation, TPE: Therapeutic plasma exchange

Table 4. Relationship between laboratory parameters and outcomes of sepsis patients

	Outcome		p
	Mortality (%), (n=13)	**Survival (%), (n=44)**	
Leukocyte	7850 (100-28050)	12565 (50-86300)	**0.036**
Neutrophil	4720 (70-24100)	8070 (0-76700)	0.073
Lymphocyte	860 (0-6180)	2165 (0-9720)	**0.010**
Platelet	111000 (55000-446000)	224500 (8000-680000)	0.227
RDW	15 (13-19.4)	14.3 (11.9-22.0)	0.151
CRP	62.59 (6.27-313.6)	62.41 (0.60-349.10)	0.581
Procalcitonin	7.16 (0.37-334.24)	18.44 (0.07-593.50)	0.732
Lactate	2.17 (1.3-10.0)	1.84 (0.8-16.6)	0.135
LDH	365 (206-3340)	384 (173-5316)	0.879
Albumin	2.74 (2.03-3.62)	3.31 (1.68-5.00)	**0.012**
Lactate/albumin ratio	0.77 (0.36-3.03)	0.54 (0.18-4.44)	**0.035**
Neutrophil/lymphocyte ratio	5.09 (1.60-28.02)	4.01 (0.32-102.13)	0.566
CRP/albumin ratio	23.79 (2.43-109.65)	18.58 (0.18-114.46)	0.458
PCT/albumin ratio	2.50 (0.14-92.33)	4.91 (0.01-201.18)	0.924
LDH/albumin ratio	139.50 (72.03-1403-36)	146.86 (53.35-2150.0)	0.621

Bold values indicate statistically significant results ($p<0.05$)
CRP: C-reactive protein, LDH: Lactate dehydrogenase, PCT: Procalcitonin, RDW: Red cell distribution width

routinely perform viral respiratory panels for all cases, which is a limitation of the study. Some CNS cases may have represented viral sepsis, particularly in the presence of upper or lower respiratory tract involvement. Future studies should include molecular viral diagnostics to clarify this issue.

Sepsis is a highly heterogeneous clinical syndrome with complex and variable manifestations. Non-infectious conditions, such as hematologic diseases or chronic inflammatory disorders, may clinically mimic sepsis and contribute to lower culture positivity rates. In the study by Huang et al. (9), no significant difference was found between the CNS and CPS groups in terms of overall comorbidities. However, in our study we did not perform a subgroup analysis comparing the CNS and CPS groups regarding chronic inflammatory conditions or immunodeficiencies. This limitation suggests that non-bacterial causes or sterile inflammatory processes may be more prevalent among culture-negative cases and highlights an important gap in understanding the clinical similarities and differences between the two groups.

In our study, CNS and CPS cases showed similar IMV duration, use of inotropic agents, need for TPE, and need for renal replacement therapy. The CPS group, on the other hand, had longer hospital stays and required mechanical ventilation more often than the CNS group. One possible explanation for this result is that children with culture-positive results typically require prolonged antibiotic therapy, particularly in cases of bacteremia and meningitis, and are more likely to develop extrapulmonary pediatric respiratory distress syndrome. Huang et al. (9) showed that children with CPS had a significantly longer length of stay than in our study. However, unlike in our study, the requirement for IMV was similar. Cases with CNS were not significantly different from cases with CPS in terms of inotropes, length of PICU stay, or hospital stay, according to Hazwani et al. (6). It is possible that variations in case demographics, organ dysfunctions, and bacterial resistance to antibiotics all play a role in these dissimilarities.

Several studies have examined the impact of microbiological culture results on the prognosis of patients with sepsis over the past decade. In meta-analyses of adult populations, no statistically significant correlation was found between culture results and mortality (10,11). Our findings revealed comparable mortality rates for the CNS and CPS groups, in accordance with the literature. However, Hazwani et al. (6) demonstrated that among pediatric cases, the CPS group had a higher mortality rate than the CNS group. Changes in diagnostic criteria and in the definition of sepsis over time may explain the differences in these results. Moreover, excluding cases with non-bacterial infections from the studies may contribute to these differences.

With advances in pediatric critical care, it is increasingly crucial to understand which aspects are most relevant to mortality in children with sepsis, as this will aid in risk classification and the better allocation of healthcare

resources. Numerous clinical and laboratory parameters were investigated for their prognostic value in studies (12-14).

The survivor group required statistically significantly fewer interventions, including mechanical ventilation, inotropic agents, TPE, and renal replacement support. Cases with high leukocyte counts and high lactate/albumin ratios, as well as low lymphocyte counts and low albumin levels upon admission, were statistically associated with poor prognosis. In our opinion, cases with the aforementioned risk factors can be monitored and treated more aggressively.

Study Limitations

The main limitations of this study were the small number of cases compared with sepsis studies in adults and the inclusion of patients from only one tertiary center. The inclusion of multiple centers could provide additional information and identify other prognostic factors in sepsis among children. Second, low culture positivity and the lack of standardized timing for culture collection may have affected the results of pathogen identification.

CONCLUSION

In conclusion, sepsis is a clinical syndrome with multiple manifestations. Although culture is important for diagnosis, it should not be forgotten that the prognosis may be poor in culture-negative cases. Identification of risk factors for mortality and morbidity helps determine which cases should be followed more closely according to the severity of the process and the most appropriate treatment.

ETHICS

Ethics Committee Approval: Ethics committee approval was received from the Scientific Research Ethics Committee of University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval no: 2023/29, date: 17.02.2023).

Informed Consent: As the study was retrospective and personal data were anonymized, informed consent was not required.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: K.B.G., C.D., Concept: K.B.G., Design: E.G.Ş., C.D., Data Collection or Processing: Y.Y.C., Analysis or Interpretation: A.S., Literature Search: E.G.Ş., F.V., Writing: E.G.Ş., C.D., F.V.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Miranda M, Nadel S. Pediatric sepsis: a summary of current definitions and management recommendations. Curr Pediatr Rep. 2023;11:29-39.
2. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med. 2020;21:e52-106.
3. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304-77.
4. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6:2-8.
5. Schlapbach LJ, Kissoon N. Defining pediatric sepsis. JAMA Pediatr. 2018;172:312-4.
6. Hazwani TR, Kazzaz YM, Alsugheir S, Aldelaijan S, Alsugheir F, Alali H, et al. Association between culture-negative versus culture-positive sepsis and outcomes of patients admitted to the pediatric intensive care unit. Cureus. 2020;12:e9981.
7. Hall KK, Lyman JA. Updated review of blood culture contamination. Clin Microbiol Rev. 2006;19:788-802.
8. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated pediatric risk of mortality score. Crit Care Med. 1996;24:743-52.
9. Huang H, Chen J, Dang H, Liu C, Fu YQ. Comparing outcomes between culture-positive and culture-negative septic shock in a PICU: a retrospective cohort study. Front Pediatr. 2022;10:1001565.
10. Kim JS, Kim YJ, Kim WY. Characteristics and clinical outcomes of culture-negative and culture-positive septic shock: a single-center retrospective cohort study. Crit Care. 2021;25:11.
11. Afzal MS, Nandan Chennuri R, Naveed H, Raveena Bai B, Hanif R, Shahzad Z, et al. Comparison of clinical outcomes between culture-positive and culture-negative sepsis and septic shock patients: a meta-analysis. Cureus. 2023;15:e35416.
12. Wang Y, Zhang H, Tang X, Li X. [A retrospective study on risk factors for prognosis of children with sepsis]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020;32:707-10. Chinese.
13. Tonial CT, Costa CAD, Andrades GRH, Crestani F, Bruno F, Piva JP, et al. Performance of prognostic markers in pediatric sepsis. J Pediatr (Rio J). 2021;97:287-94.
14. Vila Pérez D, Jordan I, Esteban E, García-Soler P, Murga V, Bonil V, et al. Prognostic factors in pediatric sepsis study, from the Spanish Society of Pediatric Intensive Care. Pediatr Infect Dis J. 2014;33:152-7.

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Research

Clinical Significance of Carotid Artery Intima-Media Thickness in Childhood Obesity

Obezite Hastalığı ile Takipli Olan Hastalardaki İnternal Karotis Arterin İntima Kalınlığının Takip Açısından Önemi

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ABSTRACT

Objective: This study aimed to investigate the correlation between carotid artery intima-media thickness (c-IMT) and increased body mass index (BMI), particularly in the context of childhood obesity. Furthermore, the study emphasizes the potential utility of c-IMT as a parameter for follow-up and monitoring during diagnosis and management.

Methods: This case-control study was conducted at the pediatric endocrinology unit and the well child polyclinic between January and August 2017. A total of 96 children aged 6 to 18 years were included. Anthropometric measurements, including height, weight, and waist circumference, were recorded, and BMI Z-scores were calculated accordingly. Biochemical tests included fasting blood glucose, insulin, total cholesterol, triglycerides, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. c-IMT was measured using B-mode ultrasonography with a 7.5 MHz linear probe, targeting both the common and internal carotid arteries. Morphological features of the artery, including luminal echogenicity and intima-media surfaces, were also evaluated.

Results: c-IMT values were significantly higher in obese children compared with the control group. There were no significant differences between the study groups in mean age or gender. When the two groups were compared, there was a significant increase in c-IMT levels among those with high ALT levels compared with those with normal ALT levels. A correlation between high AST levels and c-IMT was observed only in the obese patient group. A threshold of 0.8 mm was set as the upper limit for normal c-IMT values. No patient had a c-IMT measurement above 0.8 mm.

Conclusion: This study demonstrates that increased c-IMT in obese children may serve as an early indicator of endothelial dysfunction and preclinical atherosclerosis. Measuring c-IMT could be a non-invasive and practical method for risk stratification and early cardiovascular monitoring in pediatric obesity. Further longitudinal studies are warranted to establish its predictive value.

Keywords: Carotid intima-media thickness, childhood obesity, atherosclerosis, cardiovascular risk

ÖZ

Amaç: Bu çalışmanın amacı, çocukluk çağı obezitesinde karotis arter intima-media kalınlığı (k-IMK) ile artmış vücut kitle indeksi (VKİ) arasındaki ilişkiyi değerlendirmektir. Ayrıca, k-IMK'nin tanı ve tedavi sürecinde izlem parametresi olarak kullanılabilirliğine dikkat çekilmesi hedeflenmiştir.

Gereç ve Yöntem: Bu olgu-kontrol çalışması, Ocak-Ağustos 2017 tarihleri arasında çocuk endokrinoloji ünitesi ve çocuk sağlığı izlem polikliniğinde yürütülmüştür. Yaşları 6 ile 18 arasında değişen toplam 96 çocuk çalışmaya dahil edilmiştir. Boy, kilo ve bel çevresi ölçümleri alınarak VKİ Z-skorları hesaplanmıştır. Katılımcılardan 8-10 saatlik açlık sonrası alınan örneklerle açlık kan şekeri, insülin, total kolesterol, trigliserit, aspartat aminotransferaz (AST) ve alanin aminotransferaz (ALT) düzeyleri değerlendirilmiştir. k-IMK, B-mod ultrasonografi ve 7.5 MHz lineer prob kullanılarak, hem ortak hem

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ÖZ

de internal karotis arter seviyelerinde ölçülmüş; arter morfolojisi, lümen ekojenitesi ve intima-media yüzey özellikleri ayrıntılı olarak incelenmiştir.

Bulgular: k-IMT değerleri obez çocuklarda kontrol grubuna kıyasla anlamlı derecede yüksekti. Çalışma gruplarının yaş ortalamaları ve cinsiyetleri arasında anlamlı bir fark yoktu. Her iki grupta kendi içlerinde değerlendirildiğinde ALT düzeyi yüksek olanlarda, ALT düzeyi normal olanlara kıyasla k-IMT düzeylerinde anlamlı bir artış vardı. Sadece obez hasta grubunda, yüksek AST düzeyleri ile k-IMT arasında bir korelasyon vardı. Normal k-IMT değerleri için üst sınır olarak 0,8 mm'lik bir eşik belirlenmiştir. Hiçbir hastada k-IMT ölçümü 0,8 mm'nin üzerinde değildi.

Sonuç: Bu çalışma, çocukluk çağı obezitesinde k-IMK ölçümünün endotelyal disfonksiyon ve preklinik aterosklerozun erken göstergesi olabileceğini ortaya koymaktadır. k-IMK, obez çocuklarda kardiyovasküler riskin non-invaziv ve pratik bir değerlendirme yöntemi olarak kullanılabilir. Bulgular doğrultusunda, bu ölçümün uzun dönem sonuçlarını değerlendirmek amacıyla ileriye dönük, daha geniş örneklemli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Karotis intima-media kalınlığı, çocukluk obezitesi, ateroskleroz, kardiyovasküler risk

INTRODUCTION

Obesity, defined as excessive accumulation of adipose tissue, has become an increasingly prevalent global health concern, particularly among children. Rapid urbanization, sedentary lifestyles, and increased consumption of energy-dense foods have led to a sharp rise in childhood obesity rates (1). In addition to physical health problems, obese children often face social and psychological issues such as stigma, isolation, and depression. They are also at higher risk of developing asthma, obstructive sleep apnea, orthopedic disorders, gastrointestinal disturbances, and cardiovascular and metabolic diseases, including hypertension, dyslipidemia, and insulin resistance (2).

Childhood obesity is a well-established risk factor for vascular changes and the development of atherosclerosis. These changes are primarily mediated by chronic low-grade inflammation, which adversely affects endothelial function and smooth muscle activity (3). Evidence shows that children aged 9 to 12 years may exhibit early signs of vascular impairment, including increased arterial stiffness and increased intima-media thickness (IMT). Among the various diagnostic tools available, carotid artery IMT (c-IMT) measurement by B-mode ultrasonography has emerged as a reliable and non-invasive method for detecting subclinical atherosclerosis (4).

Body mass index (BMI) Z-scores are widely used to categorize obesity severity in children. A Z-score between +2.00 and +2.49 indicates moderate obesity, while a Z-score of +2.50 or higher indicates severe obesity (5). Although childhood obesity is often influenced by multifactorial environmental conditions, genetic predisposition plays a substantial role, with heritability estimates ranging from 25% to 80% (6). Positive family history, limited physical activity, and excessive screen time are well-documented contributors (7).

Despite its growing prevalence, childhood obesity remains an underrecognized problem, especially in terms of its long-term impact (8). It is associated with numerous complications, including insulin resistance, type 2 diabetes, precocious puberty, menstrual irregularities, infertility, polycystic ovary syndrome, hepatic steatosis, gallstones, orthopedic disorders, and various psychosocial issues (9). Cardiovascular complications such as coronary artery disease, cerebrovascular events, and hypertension are among the most severe and life-threatening consequences (10).

c-IMT measurement is supported by nearly two decades of research as a surrogate marker for atherosclerosis (11). It consists of a hypoechoic layer between two echogenic lines, representing the intima and media layers (12). The thickness reflects early vascular changes and correlates well with histological findings (13). Furthermore, c-IMT measurements are reproducible and suitable for longitudinal monitoring, making them ideal candidates for early cardiovascular risk stratification in children (14).

METHODS

Study Design and Setting

This research was designed as an epidemiological case-control study. It was conducted at the pediatric endocrinology unit and the well child polyclinic of the children's hospital between January and August 2017. The study protocol was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2018-12-13, date: 25.06.2018). Informed consent for participation and publication was obtained from the parents or legal guardians of all participants.

Statistical Analysis

Statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences) for Windows version 21.0 software package. Continuous variables were expressed as mean±standard deviation (SD) or median (minimum-maximum), while categorical variables were presented as numbers and percentages. Comparisons between two groups were performed using the Mann-Whitney U test for

continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

Study Population

A total of 96 children (aged 6-18 years) who presented to the outpatient clinics were included. Participants were divided into two groups based on BMI Z-scores calculated using the World Health Organization (WHO) growth reference data for ages 5-19 years: patient group (BMI Z-score ≥+2 SD) and control group (BMI Z-score <+2 SD).

Anthropometric measurements (height, weight, and waist circumference) were performed using standardized techniques. BMI was calculated as weight (kg)/height^2 (m^2). Z-scores were determined according to age and sex-specific reference values.

Laboratory Evaluation

Following an 8-10-hour fast, venous blood samples were collected. If fasting criteria were not met, the participant was asked to return the following day. The following biochemical parameters were measured using standard laboratory techniques: fasting blood glucose (FBG), insulin, total cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), c-IMT measurement.

Bilateral carotid artery evaluations were performed using B-mode ultrasonography with a 7.5 MHz linear-array transducer. Measurements were obtained from the common carotid artery and internal carotid artery on both the right and left sides. The arteries were assessed for morphological characteristics, including the echogenicity of the arterial lumen and the clarity and thickness of the intimal and medial layers. All measurements were performed by the same radiologist, who was blinded to the participants' clinical status to avoid observer bias.

RESULTS

A total of 96 children aged between 6 and 18 years were included in the study. Of the participants, 53 (55.2%) were girls and 43 (44.8%) were boys. The mean age was 11.8 years (range: 6-17 years). Anthropometric measurements, including weight, height, and BMI Z-scores, were calculated according to WHO age and sex-specific reference data. According to BMI Z-scores, 52 children were classified as obese (BMI SD score ≥+2), and 44 children were classified as controls (BMI SD score <+2). No significant differences were found between the study groups in mean age and gender. Routine biochemical evaluations revealed elevated ALT and AST values in both groups. However, elevated ALT values were associated with a simultaneous increase in c-IMT in both groups. Interestingly, an increase in AST values was associated with an increase in c-IMT values only in the obese group, whereas no such association was observed in the control group. Mean FBG, insulin, total cholesterol, and triglyceride levels were also higher in the obese group. c-IMT values were significantly greater in the obese group than in the control group ($p<0.05$).

Based on the distribution of values, the upper limit of normal c-IMT was determined to be 0.8 mm. Measurements below this threshold were considered non-pathologic.

DISCUSSION

This study demonstrated that c-IMT values were significantly higher in obese children compared with their non-obese peers (15). These findings are consistent with previous literature suggesting that obesity during childhood contributes to early vascular changes and the initiation of subclinical atherosclerosis.

Obesity, characterized by excessive adipose tissue accumulation, has been recognized as a chronic metabolic disorder with increasing global prevalence, especially among children and adolescents (16). The associated complications extend beyond physical appearance to include a wide range of metabolic, cardiovascular, and psychosocial outcomes. The accelerated onset of conditions typically associated with adulthood, such as type 2 diabetes, hypertension, dyslipidemia, and hepatic steatosis, highlights the critical need for early detection strategies in this population (17).

Studies have shown that early atherosclerotic changes, including endothelial dysfunction and intimal thickening, can occur even in asymptomatic obese children. These vascular alterations are thought to result from a chronic inflammatory state driven by excess adiposity and metabolic dysregulation (18). Notably, some evidence indicates that these changes may be partially reversible with early lifestyle interventions such as diet modification and physical activity, further emphasizing the importance of early risk assessment (19).

c-IMT measurement, a non-invasive and highly reproducible method, offers a valuable diagnostic window into early vascular health. It correlates strongly with histopathological findings and is increasingly recognized as a surrogate marker for cardiovascular disease risk in both adults and children. In this study, a c-IMT value of 0.8 mm was identified as the upper limit of normal. While this threshold may vary slightly between studies, it provides a practical reference point for identifying children at potential risk (20).

Importantly, the concurrent elevation of AST and c-IMT levels in the obese group suggests an association between

hepatic inflammation and vascular remodeling, which may represent a systemic response to obesity-related metabolic stress. Previous research has similarly linked elevated transaminases with both hepatic steatosis and endothelial dysfunction (20).

The findings of our study support the growing body of evidence that c-IMT measurement should be integrated into the cardiovascular risk assessment of obese pediatric patients (21). It may serve not only as a diagnostic tool but also as a target for monitoring treatment efficacy in clinical practice.

CONCLUSION

In this study, we found that c-IMT was significantly increased in obese children compared to non-obese controls, supporting its role as an early marker of subclinical atherosclerosis. Additionally, concurrent elevations of AST and ALT in these patients may indicate hepatic involvement as part of a systemic inflammatory process associated with obesity.

Our findings underscore the clinical relevance of c-IMT measurement in pediatric populations, especially for those with elevated BMI. c-IMT assessment, a non-invasive, reliable, and cost-effective method can be incorporated into routine clinical evaluation to stratify cardiovascular risk and guide early interventions in obese children.

Furthermore, in cases where transaminase levels, particularly ALT and AST, are elevated, c-IMT may serve as a complementary tool to abdominal ultrasonography for detecting early vascular changes. The identification of a 0.8 mm threshold as a practical upper limit for normal c-IMT values provides clinicians with a reference point for interpreting results.

c-IMT measurement should be considered during cardiovascular screening of children with obesity, particularly those with elevated liver enzymes.

Early detection of vascular changes via c-IMT can inform timely lifestyle or pharmacologic interventions to prevent long-term complications.

Further longitudinal and multicenter studies with larger sample sizes are necessary to validate the use of c-IMT as a standard screening modality and to establish age- and sex-specific normative values.

ETHICS

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2018-12-13, date: 25.06.2018).

Informed Consent: Informed consent for participation and publication was obtained from the parents or legal guardians of all participants.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: B.A., S.S.H., Concept: B.A., F.P., E.D.P.Ç., E.Ş., Design: M.E.M., E.Ş., Data Collection or Processing: M.E.M., F.P., Analysis or Interpretation: B.M., E.Ş., Literature Search: B.M., Writing: M.E.M.

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REFERENCES

1. Özilbey P, Ergör G. Determining the prevalence of obesity in primary school students and eating habits in İzmir. Tur J Public Health. 2015;13:30-9.
2. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. N Engl J Med. 2015;373:1307-17.
3. World Health Organization. Consideration of the evidence on childhood obesity for the Commission on Ending Childhood Obesity: report of the ad-hoc working group on science and evidence [Internet]. Geneva: WHO; 2016. Available from: https://iris.who.int/handle/10665/206549
4. Meyer AA, Kundt G, Steiner M, Schuff-Werner P, Kienast W. Impaired flow-mediated vasodilation, carotid artery intima-media thickening, and elevated endothelial plasma markers in obese children: the impact of cardiovascular risk factors. Pediatrics. 2006;117:1560-7.
5. Bots ML, Grobbee DE. Intima media thickness as a surrogate marker for generalised atherosclerosis. Cardiovasc Drugs Ther. 2002;16:341-51.
6. Mendes E, Mendeş B, Karacabey K. Obesity and exercise during adolescence. International Journal of Human Sciences [Internet]. 2011;8:963-77. Turkish.
7. Barsh GS, Farooqi IS, O'Rahilly S. Genetics of body-weight regulation. Nature. 2000;404:644-51.
8. Poskitt E, Edmunds L. Management of childhood obesity. Cambridge: Cambridge University Press; 2008. Available from: https://www.cambridge.org/core/books/management-of-childhood-obesity/A88F1A12056A64D292AD2CC2F9E76222.
9. Dündar Y, Evliyaoğlu O, Hatun Ş. Short stature and obesity in school children: a neglected problem. Turkiye Klinikleri J Pediatr. 2000;9:19-22.
10. Klish WJ, Kirkland J, Motil K. Comorbidities and complications of obesity in children and adolescents [Internet]. Waltham (MA): UpToDate; 2015 [cited 2026 May 18]. Available from: https://www.uptodate.com/contents/comorbidities-and-complications-of-obesity-in-children-and-adolescents
11. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature. 2006;444:875-80.
12. Bots ML, Sutton-Tyrrell K. Lessons from the past and promises for the future for carotid intima-media thickness. J Am Coll Cardiol. 2012;60:1599-604.

13. Tamura H, Suzue T, Jitsunari F, Hirao T. Evaluation of carotid arterial intima-media thickness (IMT) and its relation to clinical parameters in Japanese children. Acta Med Okayama. 2011;65:21-5.
14. Koçyiğit A, Doğan M, Yilmaz İ, Çağlar M, Hatipoğlu C, Koçyiğit F, et al. Relation of age and sex with carotid intima media thickness in healthy children. Turk J Med Sci. 2014;44:422-6.
15. Şimşek F, Ulukol B, Berberoğlu M, Başkan Gülnar S, Adıyaman P, Öcal G. Obesity prevalence in a primary school and a high school in Ankara. Ankara Üniversitesi Tıp Fakültesi Mecmuası. 2005;58:163-6. Turkish.
16. Gürel FS, İnan G. Childhood obesity-diagnostic methods, prevalence and etiology. Meandros Med Dent J. 2001;2:39-46.
17. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard growth study of 1922 to 1935. N Engl J Med. 1992;327:1350-5.
18. Zanchetti A, Crepaldi G, Bond MG, Gallus GV, Veglia F, Ventura A, et al. Systolic and pulse blood pressures (but not diastolic blood pressure and serum cholesterol) are associated with alterations in carotid intima-media thickness in the moderately hypercholesterolaemic hypertensive patients of the plaque hypertension lipid lowering Italian study. PHYLLIS study group. J Hypertens. 2001;19:79-88.
19. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa heart study. N Engl J Med. 1998;338:1650-6.
20. Koklu E, Kurtoglu S, Akcakus M, Koklu S, Buyukkayhan D, Gumus H, et al. Increased aortic intima-media thickness is related to lipid profile in newborns with intrauterine growth restriction. Horm Res. 2006;65:269-75.
21. Hatun Ş, Çizmecioğlu F. Obesity and insulin resistance syndrome in children (metabolic syndrome). Turk Klin J Pediatr Sci. 2006;2:40-6.

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Research

Differentiating Progressive Supranuclear Palsy from Idiopathic Normal Pressure Hydrocephalus: A Comparative Study of MR Parkinsonism Indices and Midbrain Qualitative Features

Progresif Supranükleer Palsi ile İdiyopatik Normal Basınçlı Hidrosefalinin Ayırt Edilmesi: MR Parkinsonizm İndeksleri ve Mezensefalon Niteliksel Özelliklerinin Karşılaştırmalı Çalışması

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ABSTRACT

Objective: Progressive supranuclear palsy (PSP) with ventricular dilatation and idiopathic normal pressure hydrocephalus (iNPH) may present with overlapping symptoms, particularly when gait disturbance predominates. This study compared midbrain qualitative signs and quantitative metrics to identify the most accurate marker for differentiating PSP from iNPH.

Methods: We retrospectively enrolled 32 patients with PSP, 33 with shunt-predictive iNPH, and 35 age-matched healthy controls, all of whom fulfilled established clinical criteria. High-resolution isotropic magnetization prepared rapid acquisition gradient echo (1.0 mm voxel size) was used to evaluate the hummingbird sign (HBS), morning glory sign, midbrain-to-pons area ratio (M/P), Magnetic Resonance Parkinsonism Index (MRPI), and its updated version, MRPI 2.0. Binary logistic regression analysis was performed to assess the predictive value of midbrain metrics and qualitative features.

Results: All imaging markers differed significantly among PSP, iNPH, and control subjects ($p<0.01$). The M/P ratio, MRPI, and MRPI 2.0 effectively distinguished all group pairs, with the M/P ratio demonstrating fair accuracy [area under the curve (AUC)=0.81; accuracy 74%]. Both MRPI versions achieved acceptable performance (AUC<0.78). The HBS demonstrated good discriminatory performance in differentiating PSP from iNPH (AUC=0.82; accuracy 81%) and emerged as the sole independent predictor in logistic regression [AUC=0.87; odds ratio (OR): 32; $p<0.01$]. The MRPI 2.0 outperformed all qualitative features (AUC=0.94; OR: 18; $p<0.01$) in distinguishing iNPH from healthy individuals.

Conclusion: Quantitative metrics for Parkinsonism showed stepwise differences across PSP, iNPH, and control groups. The HBS outperformed all quantitative measures in distinguishing PSP from iNPH when a predefined point-based system was applied.

Keywords: Hummingbird sign, progressive supranuclear palsy, idiopathic normal pressure hydrocephalus, Magnetic Resonance Parkinsonism Index, midbrain atrophy

ÖZ

Amaç: Ventriküler genişleme ile seyreden progresif supranüklear paralizi (PSP) ve idiyopatik normal basınçlı hidrosefali (iNPH), özellikle yürüme bozukluğunun belirgin olduğu klinik olarak örtüşen bulgulardır. Bu çalışma, PSP ile iNPH'yi ayırt etmede en doğru belirteci belirlemek için orta beyin ilişkili niteliksel bulgular ve niceliksel ölçümleri karşılaştırmıştır.

Gereç ve Yöntem: Tanımlanmış kriterleri karşılayan 32 PSP hastası, şant yanıtı öngörülebilen 33 iNPH hastası ve 35 yaş uyumlu sağlıklı kontrol grubu bu retrospektif çalışmaya dahil edildi. Yüksek çözünürlüklü izotropik *magnetization prepared rapid acquisition gradient echo* (1.0 mm voksel boyutu) kullanılarak hummingbird işareti (HBS), *morning glory* işareti, orta beyin-pons oranı (M/P), Manyetik Rezonans Parkinsonizm İndeksi (MRPI) ve güncellenmiş MRPI 2.0 değerlendirildi. Orta beyin ölçümlerinin ve niteliksel bulguların öngörü değerini belirlemek amacıyla lojistik regresyon analizi yapıldı.

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ÖZ

Bulgular: Tüm görüntüleme belirteçleri PSP, iNPH ve kontrol grupları arasında anlamlı farklılık gösterdi (p<0,01). M/P oranı orta derece [eğri altındaki alan (AUC)=0,81; doğruluk %74], MRPI ölçümleri ise kabul edilebilir performans gösterdi (AUC<0,78). HBS, PSP'yi iNPH'den ayırmada en iyi performansı gösterdi (AUC=0,82; doğruluk %81) ve regresyon analizinde tek bağımsız belirteç olarak öne çıktı [AUC=0,87; olasılık oranı (OR): 32; p<0,01]. MRPI 2.0 ise sağlıklı bireylerle karşılaştırıldığında iNPH lehine tüm niteliksel belirteçlerden üstün bulundu (AUC=0,94; OR: 18; p<0,01).

Sonuç: Parkinsonizmle ilişkili niceliksel ölçümler PSP, iNPH ve kontrol grupları arasında kademeli farklılık gösterdi. Literatürde tanımlanmış puanlama sistemi uygulandığında tek başına hummingbird işareti olası PSP'ni, iNPH'den ayırmada niceliksel ölçümlerden daha başarılıdır.

Anahtar Kelimeler: Hummingbird işareti, progresif supranükleer palsi, idiyopatik normal basınçlı hidrosefali, Manyetik Rezonans Parkinsonizm İndeksi, orta beyin atrofisi

INTRODUCTION

Progressive supranuclear palsy (PSP) is a primary tauopathy characterized by abnormal tau deposition leading to progressive neurodegeneration (1). Clinically, PSP presents with postural instability, gait disturbance, cognitive impairment, urinary symptoms, and frontal executive dysfunction; vertical supranuclear gaze palsy is a hallmark feature (2). However, early gaze palsy may be subtle, resulting in low sensitivity of the National Institute of Neurological Disorders and Stroke-Society for PSP (NINDS-SPSP) diagnostic criteria despite high specificity (3). This diagnostic challenge is particularly evident in Parkinsonism-predominant PSP from other parkinsonian disorders (4). Consequently, magnetic resonance imaging (MRI) plays an important role in early diagnosis, with qualitative imaging signs, such as the hummingbird sign (HBS) and the morning glory sign (MGS), proposed as suggestive markers of the PSP spectrum (5).

Idiopathic normal pressure hydrocephalus (iNPH), which has an estimated annual incidence of 5.5 per 100,000 and is considerably more common than PSP, is thought to result from impaired cerebrospinal fluid (CSF) absorption and altered brain compliance (6,7). Clinically, iNPH is characterized by gait instability, urinary incontinence, and frontal executive dysfunction (8). MRI features such as disproportionately enlarged subarachnoid space hydrocephalus (DESH), narrowed callosal angle, ventricular enlargement, and periventricular hyperintensities support the diagnosis (9). iNPH may be misdiagnosed as PSP due to overlapping clinical features, particularly parkinsonism and gait disturbance. Early differentiation often requires prolonged clinical surveillance or invasive CSF testing, and coexistence of PSP pathology and iNPH-related CSF disturbance has been reported (10). An accurate distinction is essential because treatment strategies differ substantially between the two conditions (11,12).

MRI assessment of PSP traditionally relies on qualitative midbrain atrophy features, including mesencephalic beaking and loss of lateral tegmental convexity (13). However, these signs may be subtle or absent in early or Parkinsonism-predominant cases, limiting the sensitivity of qualitative assessments. Consequently, several midbrain morphometric indices were proposed, including the MR Parkinsonism Index (MRPI), the midbrain-to-pons area ratio (M/P), and the more recent MRPI 2.0. Although initial reports suggested improved performance of MRPI 2.0 in distinguishing PSP from idiopathic Parkinsonism, subsequent studies have questioned its superiority in differentiating Parkinsonism-predominant PSP from other Parkinsonian disorders (14,15). Notably, the application of quantitative midbrain indices, including MRPI 2.0, for differentiating PSP from iNPH has received relatively limited attention in the literature. Therefore, the objective of this study was to investigate the diagnostic value of midbrain morphometric indices, including MRPI 2.0, when combined with classical qualitative MRI features, in differentiating the PSP spectrum from iNPH.

METHODS

Study Group Selection

This retrospective study was carried out at a single center between January 2018 and December 2024. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Non-Interventional Clinical Research Ethics Committee of Koç University under reference (approval no: 2025.318.IRB2.145, date: 11.07.2025). Patient data were reviewed using the institution's digital medical record system. Inclusion criteria for the PSP group were the fulfillment of the clinical diagnostic criteria for probable PSP spectrum, according to the neuropathologic guidelines of the NINDS-SPSP, and the availability of isotropic T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) imaging at diagnosis (3). All clinical diagnoses of PSP were confirmed by a neurologist specializing in movement disorders (Eser Buluş). Initially, 41 patients with probable PSP were identified; however, only 32 (14 females, 18 males) had corresponding MRI available at the time of diagnosis and were included in the study. Similarly, 46 patients presenting with the full

clinical triad suggestive of iNPH—gait disturbance, urinary incontinence, and cognitive impairment—were identified in the digital medical records. However, 13 of these did not demonstrate the supportive imaging features required for a diagnosis of shunt-predictive probable iNPH, as outlined in the criteria endorsed by the Japanese Society of Normal Pressure Hydrocephalus (16). Those imaging requisites include disproportionately enlarged subarachnoid spaces, an Evans index >0.3, and a steeply narrowed callosal angle [non-compartmental analysis (NCA) <90°]. The remaining 33 patients (14 females, 19 males) fulfilled the complete clinical triad and all required imaging features for shunt-predictive probable iNPH. Among these, 15 patients underwent ventriculoperitoneal shunt surgery. All included iNPH patients had pre-intervention MRI available, including isotropic T1-weighted MPRAGE sequences. Exclusion criteria for both groups included the absence of MRI at the time of diagnosis, the presence of space-occupying lesions or large areas of encephalomalacia, indicative of prior major trauma, large-vessel occlusion, or hemorrhage. However, no participants from either group met these exclusion criteria. For the control group, 35 age-matched healthy subjects (15 females, 20 males) were selected from individuals who attended the neurology outpatient clinics during the same period and presented with symptoms indicative of a non-neurodegenerative condition, including tension-type headache and migraine-type headache, or who attended for routine check-up. Control subjects were included only if their brain MRI examinations were normal, with no evidence of localized or diffuse abnormalities. Figure 1 illustrates the participant selection process with a flow diagram.

The Magnetic Resonance Parkinsonism Indices

All planimetric measurements were ultimately performed using isotropic T1-weighted MPRAGE images acquired in the sagittal orientation, with an isotropic voxel size of 1.0 mm, bandwidth of 180 Hz/pixel, repetition time/echo time of 2400/3.7 ms, field of view of 250×250×160 mm, matrix size of 205×256×256, and a flip angle of 8°. The isotropic MPRAGE datasets were subsequently reformatted into coronal-oblique, sagittal, and axial planes to enable measurement of midbrain area (M), pons area (P), lengths of the superior cerebellar peduncle (SCP) and middle cerebellar peduncle (MCP), third ventricular width (V3), and the left-to-right width of the frontal horns of the lateral ventricles (FH). The MRPI was calculated using the formula: MRPI=(P/M)×(MCP/SCP). The MRPI 2.0 was derived by incorporating ventricular dimensions into that formula: MRPI 2.0=MRPI×(V3/FH). All measurements were performed manually by a fellowship-trained neuroradiologist with 7 years of experience in the field. Figure 2 illustrates the planimetric measurements used to calculate MRPI and MRPI 2.0 in patients with PSP, patients with iNPH, and control subjects. The M/P, a conventionally recommended metric for differentiating PSP from other atypical Parkinsonian syndromes, was also calculated (17). All planimetric measurements were repeated after 4 weeks to assess the intra-rater agreement.

Qualitative Parameters

The HBS was independently evaluated by two experienced neuroradiologists, Yunus Emre Şentürk (6 years of neuroimaging experience) and Ahmet Peker (5 years of neuroimaging experience), according to the ordinal scoring system described by Kim et al. (18). This system evaluates four features: the shape of the third ventricle, the contour of the beak, the configuration of the midbrain, and the overall sagittal appearance of the midbrain-to-pons interface. Each feature was scored on a scale from 0 to 2. A total composite score >5 was considered indicative of a positive HBS, as this threshold yielded the best performance compared with other thresholds when accounting for the Kim et al. (18) series. Similarly, the MGS was independently evaluated by two raters (Yunus Emre Şentürk and Ahmet Peker) on axially reformatted MR images, in accordance with the method outlined by Adachi et al. (19). An imaginary horizontal line was drawn posterior to the cerebral aqueduct. A second line was then extended from the lateral margin of the cerebral peduncle to the point where the first line intersected the tegmentum. The MGS was considered positive when the lateral tegmental border of the midbrain was located medial to this second line. The HBS and MGS statuses of all cases were re-evaluated by the central rater after a minimum interval of four weeks to assess intra-rater agreement.

Statistical Analysis

All statistical analyses were performed using SPSS version 28 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of all continuous variables. Parameters following a normal distribution, such as the M/P, MRPI, and MRPI 2.0, were compared across groups using one-way analysis of variance, with post-hoc pairwise comparisons using Tukey's honestly significant difference test. The Cohen's kappa analysis was performed for all patients with PSP spectrum and iNPH to assess the inter- and intrarater reliability of HBS and MGS between the outcomes of the central (Yunus Emre Şentürk) and the co-rater (Ahmet Peker). Intrarater reliability was assessed using a two-way mixed-effects intraclass correlation coefficient for absolute agreement. Variables that demonstrated significant differences were subsequently included in a backward stepwise logistic regression (BSLR) model to evaluate the discriminatory power of individual planimetric

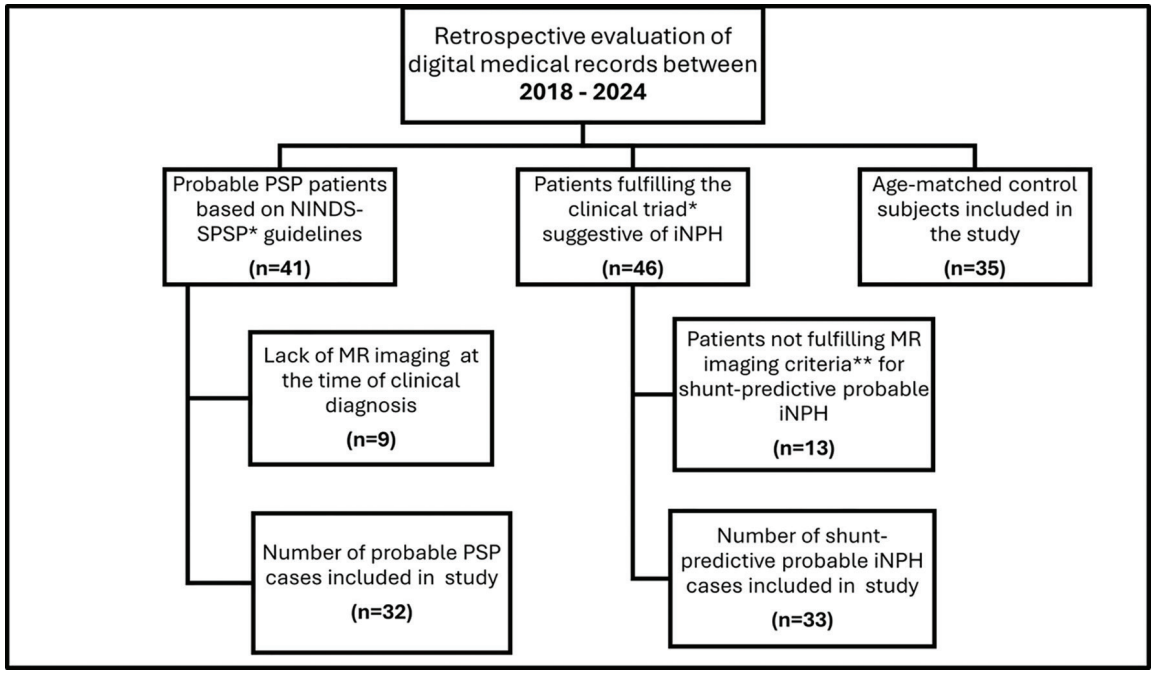

Figure 1. Flow chart of the study group selection process

*: NINDS-SPSP guidelines for the probable PSP diagnosis (see the reference number 3), **: Guidelines for management of idiopathic normal pressure hydrocephalus (third edition): endorsed by the Japanese Society of Normal Pressure Hydrocephalus (see the reference number 16)

NINDS-SPSS: National Institute of Neurological Disorders and Stroke-Society for progressive supranuclear palsy, PSP: Progressive supranuclear palsy, iNPH: Idiopathic normal pressure hydrocephalus, MR: Magnetic resonance

features for differentiating PSP from iNPH, and iNPH from control subjects. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographics

Baseline characteristics and symptoms on admission are presented in Table 1. Each group's mean age resembled that of the others, while the patients with PSP had a wider age range, with a mean age of 73±10 years. The gender distribution was similar across groups, as shown in Table 1.

The Quantitative Parkinsonism Features

The Evans index exceeded 0.3 in all iNPH patients and in 48% of those with PSP. The M/P ratio, MRPI, and MRPI 2.0 differed among groups based on analysis of variance statistics ($p<0.001$, for each analysis). Table 2 summarizes the distribution of means for each midbrain metric parameter. Post-hoc pairwise comparisons revealed notable mean differences in all three midbrain metrics between PSP and iNPH, and between iNPH and control subjects ($p<0.001$). Figure 3 presents box plots of the distribution of each midbrain metric across groups. These findings indicate a clear stepwise separation of the three groups, with iNPH values consistently falling between those of PSP and control subjects. All quantitative parkinsonism parameters demonstrated excellent intra-rater reliability, with kappa (κ) values of 0.94 for the M/P ratio, 0.92 for MRPI, and 0.91 for MRPI 2.0 (all $p<0.001$).

The Qualitative Assessment of the Midbrain

The presence of the HBS in each group was evaluated using the visual scoring system proposed by Kim et al. (18), in which a composite score of ≥5, agreed upon by both raters, was considered HBS-positive. HBS was identified in 29 patients with PSP (90.6%) and 9 patients with iNPH (27.3%); none of the control subjects exhibited this sign ($p<0.001$). In contrast, the MGS was less frequently observed, with 15 PSP patients (47.0%) and 4 iNPH patients (12.1%) classified as MGS-positive ($p=0.003$). None of the control subjects had a positive MGS.

The central rater identified HBS positivity in 39 (60%) cases, while the co-rater identified 36 (55%) cases. Interrater reliability for HBS was almost perfect ($\kappa=0.85$; $p<0.001$), with almost perfect intrarater agreement ($\kappa=0.89$; $p<0.001$). For the MGS, the central rater and co-raters identified 19 (29%) and 16 (24%) positive cases, respectively. Interrater agreement was substantial ($\kappa=0.77$; $p<0.001$), and intrarater agreement was almost perfect ($\kappa=0.85$; $p<0.001$).

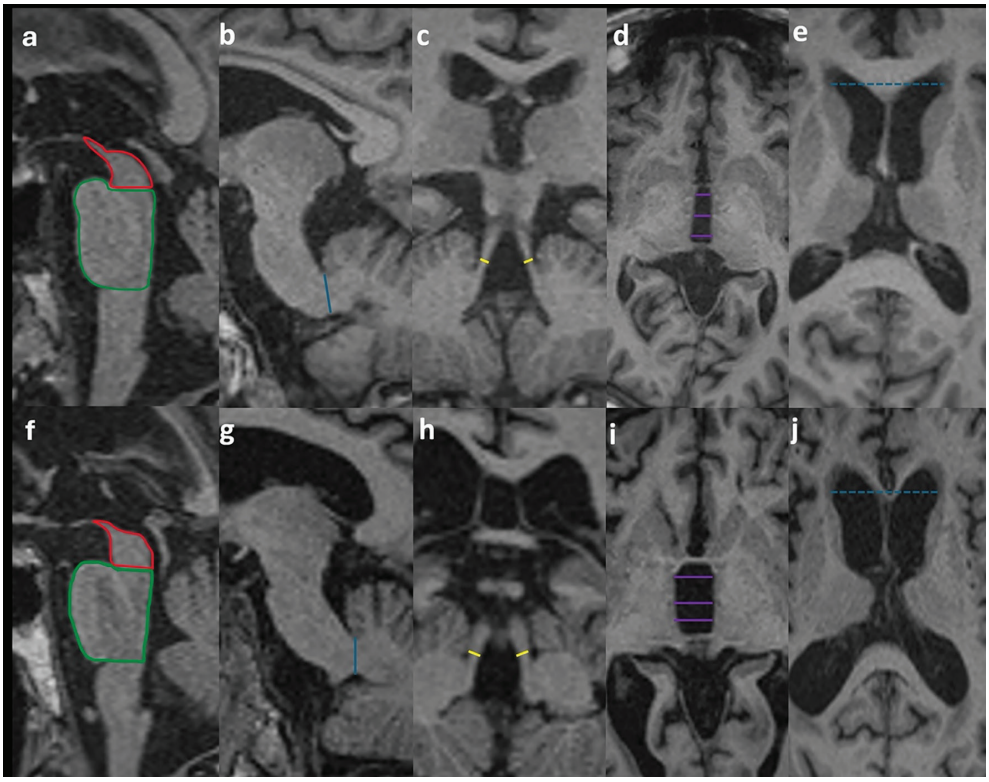

Figure 2. Representative isotropic T1-weighted MPRAGE series from a 65-year-old male with definite progressive supranuclear palsy (PSP) **(a-e)** and a 72-year-old male with definite idiopathic normal pressure hydrocephalus (iNPH) **(f-j)**. In the patient with PSP, the midbrain-to-pons area ratio (M/P) was 0.16; **a)**, the middle cerebellar peduncle (MCP) thickness was 9.4 mm; **b)**, the mean superior cerebellar peduncle (SCP) thickness was 2.5 mm; **c)**, the mean third ventricle width was 9 mm; **d)**, and the lateral ventricular bifrontal (FH) width was 33.0 mm; **e)**. the calculated MRPI [(P/M)×(MCP/SCP)] was 24.0, and MRPI 2.0 (MRPI×third ventricle size/FH) was 6.5. In the iNPH patient, the M/P ratio was 0.19; **f)**, the MCP thickness was 10 mm; **g)**, the mean SCP thickness was 3.2 mm; **h)**, the mean third ventricle width was 10 mm; **i)**, and the FH width was 56 mm; **j)**. the calculated MRPI was 16.1, and the MRPI 2.0 was 3.1. Both patients underwent standardized MRI measurement protocols to assess the diagnostic performance of midbrain metrics

MPRAGE: Magnetization-prepared rapid acquisition gradient echo, MRI: Magnetic resonance imaging, MRPI: Magnetic resonance parkinsonism index

Performances of Qualitative and Quantitative Parameters

The receiver operating characteristic analysis for both quantitative parameters is summarized in Table 3 and Figure 3. The M/P demonstrated good discriminatory performance between the PSP and iNPH groups, with an area under the curve (AUC) of 0.81 and an accuracy of 0.74. Although slightly lower than the M/P, MRPI and MRPI 2.0 also demonstrated fairly good performance, with AUCs of 0.77 and 0.74, and accuracies of 0.77 and 0.72, respectively. Overall, the midbrain morphometrics demonstrated superior performance in differentiating iNPH from control subjects. Among these, the MRPI and MRPI 2.0 demonstrated excellent discriminatory power, with AUCs of 0.93 and 0.92 and accuracies of 0.88 and 0.87, respectively. The M/P also performed well, though slightly below the threshold for excellence, achieving an AUC of 0.90 and an accuracy of 0.82. In the qualitative assessment of midbrain shape, the HBS demonstrated good diagnostic utility for distinguishing PSP from iNPH (AUC HBS: 0.82; AUC MGS: 0.67). In addition, HBS and MGS demonstrated poor efficacy in distinguishing iNPH from control subjects (AUC HBS: 0.62; AUC MGS: 0.55).

Logistic Regression Analysis

To evaluate the combined predictive value of quantitative midbrain metrics and qualitative imaging signs in distinguishing iNPH from PSP, a BSLR was performed. Collinearity was identified among the morphometric parameters because MRPI values are derived from the M/P. MRPI 2.0 was therefore retained due to its inclusion of ventricular dimensions. The final model combining MRPI 2.0, HBS, and MGS showed strong performance (Nagelkerke R^2=0.41; AUC=0.87; accuracy=81%). HBS was the strongest independent predictor of PSP [odds ratio (OR): 32; p<0.001), followed by MGS (OR: 9; p=0.021). The MRPI 2.0 was not an independent predictor (p=0.97).

A second BSLR model differentiating iNPH from controls similarly excluded the M/P and MRPI due to collinearity.

Table 1. Demographics and clinical characteristics

Study groups	PSP, n=32	iNPH, n=33	Control subjects, n=35
Age, year, (mean±SD)	73±10	75±6	74±5
Gender (female/male),	14/18	14/19	15/20
Lower extremity dyscoordination, n (%)	24, (75)	26, (79)	0
Cognitive impairment, n (%)	25, (78)	26, (79)	0
Urinary incontinence, n (%)	4, (13)	12, (36)	0
Gaze palsy, n (%)	10, (31)	1, (3)	0

iNPH: Idiopathic normal pressure hydrocephalus, SD: Standard deviation, PSP: Progressive supranuclear palsy

Table 2. Midbrain metric means and standard deviations across study groups*

Group	M/P ratio (mean±SD)	MRPI (mean±SD)	MRPI 2.0 (mean±SD)
Control subjects, n=35	0.286±0.041	10.71±1.69	2.18±0.68
iNPH, n=33	0.220±0.032	15.67±3.36	4.10±1.32
PSP, n=32	0.180±0.032	21.60±7.70	6.02±2.47

*: Statistically significant differences were observed across all groups for each midbrain metric, as determined by analysis of variance with F-statistics ($p<0.001$ for all comparisons), iNPH: Idiopathic normal pressure hydrocephalus, M/P: Midbrain-to-pons area ratio, MRPI: Magnetic Resonance Parkinsonism Index, PSP: Progressive supranuclear palsy, SD: Standard deviation

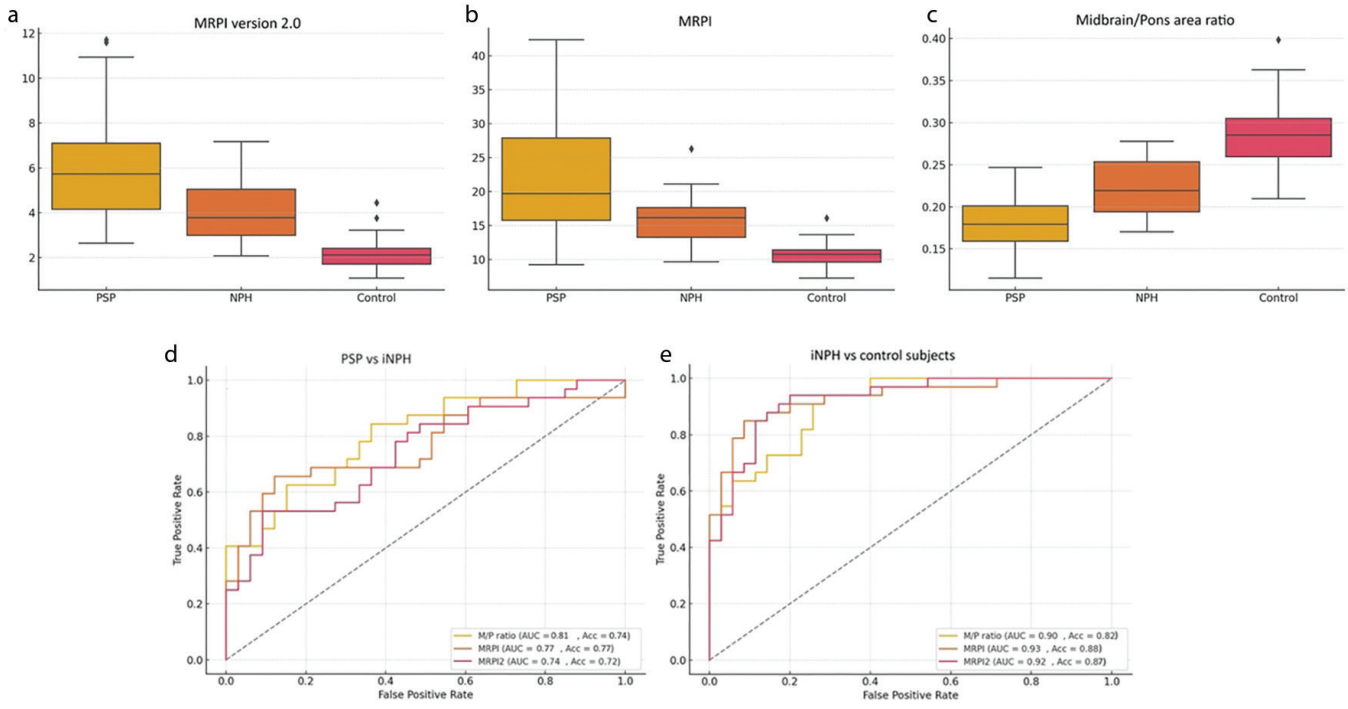

Figure 3. Box plot illustration of the Parkinsonism indices in progressive supranuclear palsy (PSP), idiopathic normal pressure hydrocephalus (iNPH), and age-matched control subjects. The indices include the midbrain-to-pons area ratio (M/P); **a)** Magnetic Resonance Parkinsonism Index (MRPI); **b)** and MRPI 2.0; **c)** One-way ANOVA analysis demonstrated significant differences among the three groups for each parameter ($p<0.01$). Subsequent Tukey HSD post-hoc analysis confirmed significant pairwise differences between the PSP, iNPH, and control groups for the M/P, MRPI, and MRPI 2.0 indices ($p<0.01$ for each pairwise comparison). **d)** ROC curve for differentiating PSP from iNPH. The M/P ratio shows good discriminatory performance and outperforms both MRPI and MRPI 2.0. **e)** ROC curve for differentiating iNPH from control subjects. All quantitative midbrain metrics demonstrate excellent discriminative performance favoring iNPH

ANOVA: Analysis of variance, HSD: Honestly significant difference, ROC: Receiver operating characteristic

Table 3. Performance of midbrain-based imaging metrics in the discrimination of PSP, iNPH, and control groups

Parameters	Group-wise comparison	AUC	Accuracy	Sensitivity, (%)	Specificity, (%)	Best cut-off
M/P ratio	PSP vs. iNPH	0.81	0.74	84	64	0.20
	PSP vs. control	0.98	0.96	94	97	0.22
	iNPH vs. control	0.90	0.82	94	71	0.27
MRPI	PSP vs. iNPH	0.77	0.77	66	88	18.9
	PSP vs. control	0.94	0.96	94	97	13.9
	iNPH vs. control	0.93	0.88	85	91	12.7
MRPI 2.0	PSP vs. iNPH	0.74	0.72	53	91	5.7
	PSP vs. control	0.98	0.93	97	89	2.8
	iNPH vs. control	0.93	0.87	94	80	2.5

iNPH: Idiopathic normal pressure hydrocephalus, M/P: Midbrain-to-pons area ratio, MRPI: Magnetic resonance parkinsonism index, PSP: Progressive supranuclear palsy, AUC: Area under the curve

MRPI 2.0 emerged as the only significant predictor (OR: 18.4), favoring an iNPH diagnosis over controls (Nagelkerke R^2=0.52; AUC=0.93; accuracy=87%).

DISCUSSION

The current study demonstrates that midbrain morphometric measurements are useful for differentiating the PSP spectrum from iNPH. Among quantitative indices, the M/P showed the highest overall accuracy in favoring PSP, whereas both MRPI and MRPI 2.0 demonstrated favorable but limited performance. Specifically, an M/P <0.2 yielded high sensitivity (84%) but poor specificity, whereas MRPI and MRPI 2.0 exhibited nearly 90% specificity at the expense of low sensitivity. These complementary performance patterns suggest that combining quantitative parameters may be more informative than relying on a single metric.

Among the qualitative parameters, only the HBS achieved good performance. When all quantitative and qualitative factors were combined, diagnostic performance improved, and the HBS emerged as a hallmark predictor distinguishing the PSP spectrum from iNPH. A challenge in interpreting HBS is the lack of a universally accepted verification method for equivocal cases. In this study, the systematic approach of Kim et al. (18) was applied, resulting in three clinically overt PSP cases being classified as HBS-negative. This stricter definition, favoring definite midbrain atrophy, likely contributed to the enhanced diagnostic performance of HBS in the combined regression model. Consistent with prior work by Kim et al. (18), who reported AUC values of 0.72-0.76 for HBS in PSP versus idiopathic parkinsonism, our cohort demonstrated an even higher AUC of 0.82 for distinguishing PSP from iNPH. Therefore, the diagnostic performance of HBS appears superior to the midbrain metric markers when either an informative scoring system is used or a scoring system is applied systematically.

Among quantitative parameters, the simpler M/P slightly outperformed the more complex MRPI and MRPI 2.0, despite MRPI 2.0 incorporating ventricular measurements to enhance discrimination. In our cohort, MRPI 2.0 showed poor sensitivity, which was likely influenced by ventricular enlargement observed in 48% of PSP cases, in which the Evans index exceeded 0.3. This ventriculomegaly may reduce the discriminatory advantage of the ventricular component of MRPI 2.0. Consistent with our results, Constantinides et al. (20) reported that the M/P outperformed MRPI, with both parameters showing comparable moderate-to-good diagnostic performance. As in their study, the combined use of M/P and MRPI failed to produce high specificity (>80%), likely due to collinearity between variables. Another series also questioned the performance of the MRPI, reporting a cutoff >13 with high specificity (84%) but low sensitivity (29%) (10). In contrast, our higher cut-off of 18.9 improved sensitivity but remained insufficient for standalone clinical decision-making compared to previous reports. A small study of 19 PSP and 17 iNPH cases reported considerable overlap between PSP and iNPH using MRPI 2.0 without providing diagnostic performance measurements (21). In contrast, the clearer stepwise differences observed across all quantitative metrics among the PSP, iNPH, and control groups are likely attributable to the larger sample size of our study.

Although MRPI 2.0 was designed to improve differentiation by incorporating ventricular dimensions, our findings indicate performance comparable to the original MRPI in distinguishing PSP from iNPH. Ventricular enlargement resembling iNPH has been reported in up to 38.2% of PSP cases, particularly in the Parkinsonism-predominant subtype. iNPH has been identified as one of the most frequent mimics of PSP (22,23). This overlap likely limits the added value of MRPI 2.0 in this context. Nonetheless, MRPI 2.0

has demonstrated excellent performance in distinguishing PSP from Parkinson's disease in larger series (24). MRPI 2.0 values were significantly higher in iNPH patients than in controls and outperformed HBS in distinguishing the two groups in our cohort. While classical markers such as NCA, DESH, and periventricular hyperintensities remain sufficient for diagnosing probable iNPH, MRPI 2.0 also achieved a sensitivity of 94% and specificity of 80% at a cutoff of 2.5, suggesting its potential utility as a supportive imaging marker in diagnosing probable iNPH.

Study Limitations

Our cohort has several limitations. First, the study design was retrospective and performed at a single center. Second, although all cases met established diagnostic criteria, complete exclusion of overlapping PSP and iNPH pathology is not possible because shunt-responsive PSP has been reported in the current literature (25). Third, the low sample size limited the performance of multivariable regression models; however, overfitting was minimized by restricting the number of variables included. Finally, PSP subtypes were not analyzed separately, although prior studies indicate no significant differences in MRPI among those PSP subtypes (15).

CONCLUSION

Quantitative midbrain indices, including MRPI 2.0 and previous morphometric parameters, showed a stepwise distribution among PSP, iNPH, and healthy control subjects. MRPI 2.0 did not outperform the original MRPI, and the simpler M/P ratio showed slightly better discriminatory power for distinguishing PSP from iNPH. Of all imaging features, the HBS remained the most reliable marker and an independent predictor of PSP versus iNPH.

ETHICS

Ethical Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Non-Interventional Clinical Research Ethics Committee of Koç University under reference (approval no: 2025.318.IRB2.145, date: 11.07.2025).

Informed Consent: Retrospective study.

Acknowledgment

The results of the current study were presented during a scientific session at the 48th European Society of Neuroradiology Annual Congress in September 2025.

FOOTNOTES

Author Contributions

Surgical and Medical Practices: E.B., Concept: Y.E.Ş., A.P., S.Y., Design: Y.E.Ş., Data Collection or Processing: Y.E.Ş., E.M.C., Analysis or Interpretation: Y.E.Ş., E.M.C., S.K., E.B., Literature Search: Y.E.Ş., A.P., M.B., Writing: Y.E.Ş., S.Y.

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REFERENCES

1. Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology. 1994;44:2015-9.
2. Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol. 2009;8:270-9.
3. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology. 1996;47:1-9.
4. Shin HW, Hong SW, Youn YC. Clinical aspects of the differential diagnosis of Parkinson's disease and parkinsonism. J Clin Neurol. 2022;18:259-70.
5. Kato N, Arai K, Hattori T. Study of the rostral midbrain atrophy in progressive supranuclear palsy. J Neurol Sci. 2003;210:57-60.
6. Lemcke J, Stengel D, Stockhammer F, Güthoff C, Rohde V, Meier U. Nationwide incidence of normal pressure hydrocephalus (NPH) assessed by insurance claim data in Germany. Open Neurol J. 2016;10:15-24.
7. Ishida T, Murayama T, Kobayashi S. Current research of idiopathic normal pressure hydrocephalus: pathogenesis, diagnosis and treatment. World J Clin Cases. 2023;11:3706-13.
8. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery. 2005;57(3 Suppl):S4-16; discussion ii-v.
9. Hashimoto M, Ishikawa M, Mori E, Kuwana N; Study of INPH on neurological improvement (SINPHONI). Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res. 2010;7:18.
10. Georgiopoulos C, Papadimitriou S, Nyholm D, Kilander L, Löwenmark M, Fällmar D, et al. Quantitative brain stem assessment in discriminating neurodegenerative disorders from normal pressure hydrocephalus. J Neuroimaging. 2024;34:612-8.
11. Clerici I, Ferrazzoli D, Maestri R, Bossio F, Zivi I, Canesi M, et al. Rehabilitation in progressive supranuclear palsy: effectiveness of two multidisciplinary treatments. PLoS One. 2017;12:e0170927.
12. Nikaido Y, Urakami H, Okada Y, Akisue T, Kawami Y, Ishida N, et al. Rehabilitation effects in idiopathic normal pressure hydrocephalus: a randomized controlled trial. J Neurol. 2023;270:357-68.

13. Mueller C, Hussl A, Krismer F, Heim B, Mahlknecht P, Nocker M, et al. The diagnostic accuracy of the hummingbird and morning glory sign in patients with neurodegenerative parkinsonism. Parkinsonism Relat Disord. 2018;54:90-4.
14. Quattrone A, Morelli M, Nigro S, Quattrone A, Vescio B, Arabia G, et al. A new MR imaging index for differentiation of progressive supranuclear palsy-parkinsonism from Parkinson's disease. Parkinsonism Relat Disord. 2018;54:3-8.
15. Madetko N, Alster P, Kutyłowski M, Migda B, Nieciecki M, Koziorowski D, et al. Is MRPI 2.0 more useful than MRPI and M/P ratio in differential diagnosis of PSP-P with other atypical parkinsonisms? J Clin Med. 2022;11:2701.
16. Nakajima M, Yamada S, Miyajima M, Ishii K, Kuriyama N, Kazui H, et al.; The research committee of idiopathic normal pressure hydrocephalus. Guidelines for management of idiopathic normal pressure hydrocephalus (third edition): endorsed by the Japanese society of normal pressure hydrocephalus. Neurol Med Chir (Tokyo). 2021;61:63-97.
17. Massey LA, Jäger HR, Paviour DC, O'Sullivan SS, Ling H, Williams DR, et al. The midbrain to pons ratio: a simple and specific MRI sign of progressive supranuclear palsy. Neurology. 2013;80:1856-61.
18. Kim YE, Kang SY, Ma HI, Ju YS, Kim YJ. A visual rating scale for the hummingbird sign with adjustable diagnostic validity. J Parkinsons Dis. 2015;5:605-12.
19. Adachi M, Kawanami T, Ohshima H, Sugai Y, Hosoya T. Morning glory sign: a particular MR finding in progressive supranuclear palsy. Magn Reson Med Sci. 2004;3:125-32.
20. Constantinides VC, Paraskevas GP, Velonakis G, Toulas P, Stefanis L, Kapaki E. Midbrain morphology in idiopathic normal pressure hydrocephalus: a progressive supranuclear palsy mimic. Acta Neurol Scand. 2020;141:328-34.
21. Önder H, Kocer B, Turan A, Kertmen H, Comoglu S. The overlap in neuroimaging findings between idiopathic normal pressure hydrocephalus and progressive supranuclear palsy. Ann Indian Acad Neurol. 2022;25:1087-91.
22. Fu MH, Huang CC, Wu KLH, Chen YF, Kung YC, Lee CC, et al. Higher prevalence of idiopathic normal pressure hydrocephalus-like MRI features in progressive supranuclear palsy: an imaging reminder of atypical parkinsonism. Brain Behav. 2023;13:e2884.
23. Onder H, Kocer B, Comoglu S. Idiopathic normal pressure hydrocephalus-like MRI features in patients with progressive supranuclear palsy: a comparative case-control study. Neurol Res. 2022;44:807-13.
24. Quattrone A, Sarica A, La Torre D, Morelli M, Mechelli A, Arcuri PP, et al. Progressive supranuclear palsy with marked ventricular dilatation mimicking normal pressure hydrocephalus. Neurol Sci. 2022;43:1783-90.
25. Schott JM, Williams DR, Butterworth RJ, Janssen JC, Larner AJ, Holton JL, et al. Shunt responsive progressive supranuclear palsy? Mov Disord. 2007;22:902-3.

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Research

Psychiatric Disorders in Fabry Disease: Investigating the Relationship Between Psychiatric Symptoms, Target Organ Involvement, and Lyso-Gb3 Levels

Fabry Hastalığında Psikiyatrik Bozukluklar: Psikiyatrik Semptomlar, Hedef Organ Tutulumu ve Lyso-Gb3 Düzeyleri Arasındaki İlişkinin Belirlenmesi

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ABSTRACT

Objective: This study aims to evaluate the psychological issues experienced by individuals diagnosed with Fabry disease (FD) and examine whether these issues are associated with serum globotriaosylsphingosine (Lyso-Gb3) levels and target organ involvement.

Methods: This study included 51 individuals: 22 FD patients (FD group) and 29 healthy controls (control group). The FD group comprised 18 adults and four pediatric patients, and both groups were matched for age and gender. The Symptom Checklist-90 (SCL-90) was administered to participants aged 15 years and older, while the Conners' Parent Rating Scale-Revised Long Form (CPRS-R/L) was used for pediatric patients. The FD group was also assessed for organ involvement and plasma Lyso-Gb3 levels.

Results: Somatization was the most prevalent psychiatric symptom among adult FD patients (32%). Compared with the healthy control group, adult FD patients exhibited higher scores across multiple SCL-90 subscales, including somatization, depression, anxiety, interpersonal sensitivity, and anger-hostility. However, a statistically significant difference was only observed in the somatization subscale (p=0.042). All SCL-90 subscale scores were significantly correlated with involvement of the central nervous system (CNS) and the cardiovascular system (CVS). No significant correlation was found between SCL-90 subscale scores and Lyso-Gb3 levels (p>0.05). Among pediatric patients, CPRS-R/L scores were higher in the FD group than in controls, with a significant difference observed only in the oppositional subscale (p=0.04).

Conclusion: Patients with FD exhibit a higher prevalence of psychiatric disorders than age- and sex-matched healthy controls. CNS and CVS involvement appears to be a significant risk factor for psychiatric comorbidities. No significant association was identified between serum Lyso-Gb3 concentrations and the presence of psychiatric disorders.

Keywords: Fabry disease, psychiatric disorders, enzyme replacement therapy, Lyso-Gb3

ÖZ

Amaç: Bu çalışmanın amacı, Fabry hastalığı (FH) tanısı almış bireylerde görülen psikolojik sorunları değerlendirmek ve bu sorunların serum globotriaozilsfingozin (Lyso-Gb3) düzeyleri ile hedef organ tutulumu arasındaki olası ilişkisini incelemektir.

Gereç ve Yöntem: Çalışmaya toplam 51 birey dahil edilmiştir: 22 FH (FH grubu) ve 29 sağlıklı kontrol (kontrol grubu). FH grubunda 18 erişkin ve 4 pediatrik hasta yer almış olup her iki grup yaş ve cinsiyet açısından eşleştirilmiştir. On beş yaş ve üzerindeki katılımcılara Belirti Tarama Listesi-90 (SCL-90) uygulanmış, pediatrik hastalarda ise Conners Ebeveyn Derecelendirme Ölçeği-Gözden Geçirilmiş Uzun Form (CPRS-R/L) kullanılmıştır. FH grubunda ayrıca organ tutulumu ve plazma Lyso-Gb3 düzeyleri değerlendirilmiştir.

Bulgular: Erişkin FH hastalarında en yaygın psikiyatrik belirti somatizasyon olup olguların %32'sinde saptanmıştır. Sağlıklı kontrol grubuna kıyasla erişkin FH hastalarında somatizasyon, depresyon, anksiyete, kişilerarası duyarlılık ve öfke-düşmanlık alt ölçeklerinde daha yüksek skorlar gözlenmiştir. Bununla birlikte istatistiksel olarak anlamlı fark yalnızca somatizasyon alt ölçeğinde saptanmıştır (p=0,042). Tüm SCL-90 alt ölçek

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ÖZ

skorları, merkezi sinir sistemi (MSS) ve kardiyovasküler sistem (KVS) tutulumları ile anlamlı düzeyde ilişkili bulunmuştur. Buna karşın, SCL-90 alt ölçek skorları ile Lyso-Gb3 düzeyleri arasında anlamlı bir korelasyon gözlenmemiştir (p>0,05). Pediatrik hastalarda ise CPRS-R/L skorları FH grubunda kontrol grubuna göre daha yüksek olmakla birlikte, istatistiksel olarak anlamlı fark yalnızca karşı gelme alt ölçeğinde saptanmıştır (p=0,04).

Sonuç: Fabry hastalığı olan bireylerde, yaş ve cinsiyet açısından eşleştirilmiş sağlıklı kontrollere kıyasla psikiyatrik bozuklukların görülme sıklığı daha yüksektir. MSS ve KVS tutulumu, psikiyatrik komorbiditeler açısından önemli risk faktörleri olarak görünmektedir. Lyso-Gb3 düzeyi ile psikiyatrik bozukluklar arasında bir korelasyon saptanmamıştır.

Anahtar Kelimeler: Fabry hastalığı, psikiyatrik bozukluklar, enzim replasman tedavisi, Lyso-Gb3

INTRODUCTION

Fabry disease (FD, OMIM#301500) is an X-linked glycosphingolipidosis caused by a deficiency of the lysosomal alpha-galactosidase A, leading to systemic accumulation of globotriaosylceramide (Gb3) and its derivatives (1). The progressive buildup of these substances in the parenchyma and endothelium triggers inflammatory processes, oxidative stress, and microvascular stenosis, ultimately causing target organ damage (2). FD manifests across a broad spectrum of clinical phenotypes, affecting the skin, eyes, gastrointestinal tract, heart, kidneys, the central nervous system (CNS), and the peripheral nervous system (PNS) (3). While accumulation begins early in life, clinical symptoms of organ involvement typically become apparent within the first decade. Consequently, FD patients span a wide age range, encompassing both pediatric and adult populations.

Previous studies suggest that individuals with FD exhibit a higher prevalence of psychiatric disorders, such as depression and anxiety, compared to the general population (4,5). Regular psychological assessments are crucial for early detection and intervention, which can significantly improve quality of life. However, the underlying causes of these psychiatric symptoms remain unclear. It is uncertain whether they stem solely from the stress of a chronic illness or from a complex interplay of factors (6). The scarcity of empirical research complicates efforts to elucidate the relationship between FD and psychiatric symptoms, thereby hindering the development of targeted interventions.

Globotriaosylsphingosine (Lyso-Gb3), a key biomarker for FD diagnosis and monitoring, has been linked to high-risk complications (7,8). However, no studies have explored the association between neuropsychiatric symptoms and Lyso-Gb3 levels. One major challenge in obtaining conclusive evidence is the difficulty of measuring Lyso-Gb3 in brain tissue. Additionally, while enzyme replacement therapy (ERT) has demonstrated positive effects on various organ systems, its impact on mental health remains inconclusive.

This study aims to assess the psychological well-being of FD patients, investigate the prevalence of psychiatric disorders in those undergoing ERT, and examine potential associations between these disorders, blood Lyso-Gb3 levels, and organ involvement.

METHODS

This cross-sectional descriptive study was conducted between April and June 2024 at the Pediatric Metabolism Outpatient Clinic of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital. The control group comprised individuals without chronic illnesses who sought medical care in general internal medicine and pediatric clinics. Informed consent was obtained from all participants prior to enrollment.

Participants

The study included 22 patients with FB diagnosed using enzymatic and genetic criteria; all were under regular clinical follow-up and were receiving ERT. Patients not meeting these criteria were excluded. The control group consisted of age- and gender-matched individuals with no history of chronic physical or severe psychiatric disorders, including schizophrenia, intellectual disability, autism spectrum disorder, or bipolar affective disorder. Involvement of the CNS and CVS was evaluated by brain MRI and echocardiography, respectively.

Assessment Tools

1. Lyso-Gb3 Measurement

Plasma Lyso-Gb3 levels were quantified from dried blood samples using liquid chromatography-mass spectrometry, with lyso-ceramide trihexoside (Matreya, Catalog No. 1520) as the reference standard. Organ involvement was recorded without specifying severity. Plasma Lyso-Gb3 levels were measured for each patient at six-month intervals.

2. Sociodemographic and Clinical Data

A structured data collection form was used to obtain demographic information (age, gender) and clinical parameters, including Lyso-Gb3 levels, duration of ERT, and organ involvement.

3. Psychiatric Assessment Tools

• **Symptom Checklist-90-R (SCL-90-R):** A validated self-report questionnaire measuring psychological distress across ten subscales (9). The Turkish adaptation was conducted by Dağ (10). Scores range from 0 to 4, with higher scores indicating greater psychological distress. Scores above 1 suggest clinically significant symptoms.

• **Conners' Parent Rating Scale-Revised Long Form (CPRS-R/L):** A parent-reported measure of children's psychological symptoms, including defiance, inattention, hyperactivity, anxiety, and social difficulties. The Turkish adaptation was validated by Kaner et al. (11). Higher scores indicate greater symptom severity.

Statistical Analysis

Statistical analyses were performed using the SPSS, version 22.0 (IBM Inc., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages, while numerical variables were presented as means and standard deviation. The normality of the distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. For comparisons between two independent groups, the Student's t-test was applied to normally distributed numerical variables, whereas the Mann-Whitney U test was used for non-normally distributed data. The chi-square test was used to compare categorical data. The Spearman's correlation analysis was conducted to evaluate the relationships between variables. Statistical significance was defined as a p-value of less than 0.05.

Ethical Considerations

This study was conducted in accordance with the ethical guidelines outlined in the World Medical Association's Declaration of Helsinki (2000). Ethical approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2022.07.05, date: 04.04.2022).

RESULTS

Adult Population

The median age of adult patients (n=18) included in the study was 44.5 years (range: 20-65 years). Of the total sample, nine individuals (50%) were female. Eight participants (44.4%) were diagnosed with symptomatic organ involvement, while the remaining participants were identified through family screening. Notably, all patients diagnosed through screening exhibited involvement of at least one organ. The mean duration of ERT was 5.8 years (range: 0.6-12 years). Among the 18 adult patients, the most commonly affected organ was the eye (n=15), followed by the kidney (n=14), the skin (n=13), the heart (n=9), the PNS (n=9), and the CNS (n=4) (Figure 1).

The most prevalent psychiatric condition among adult Fabry patients was somatization (32%), followed by depression (27.8%). Anxiety, interpersonal sensitivity, hostility, and other psychiatric symptoms each had a prevalence of 22.2%. The prevalence of obsessive-compulsive symptoms and

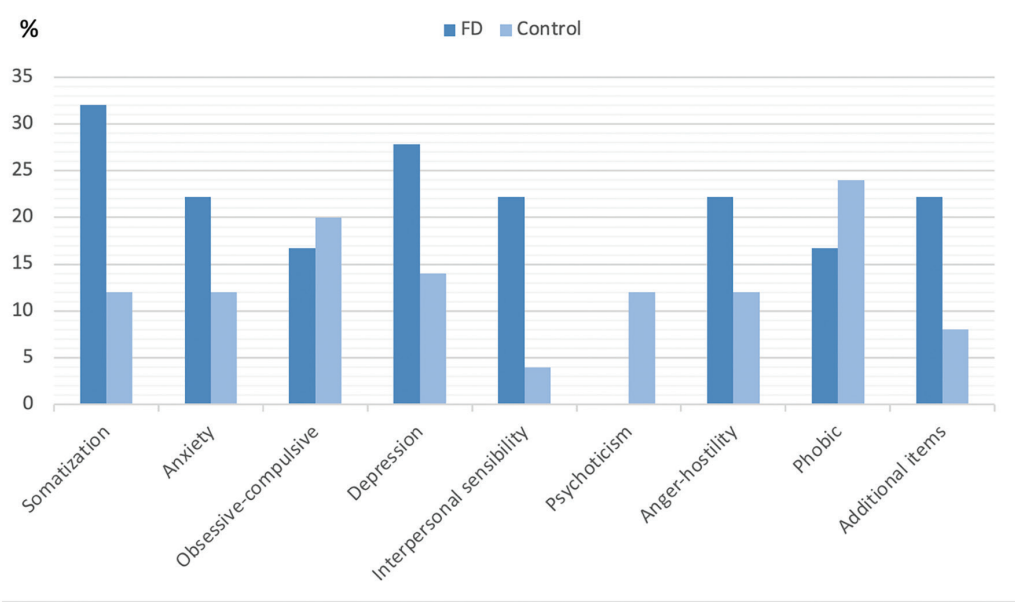

Figure 1. Comparison of the distribution of the SCL-90 subscale scores of FD patients and control group
SCL-90: Symptom Checklist-90, FD: Fabry disease

phobic symptoms was identical, with 16.7% of patients exhibiting both symptoms (Figure 2). Compared with the control group, a statistically significant difference was observed only on the somatization subscale ($p<0.05$); no significant differences were detected on the remaining subscales (Table 1). Although the differences did not reach statistical significance, the experimental group exhibited higher incidences of depression, anxiety, interpersonal sensitivity, and hostility than the control group (Figure 2). No statistically significant gender differences were observed across psychiatric subscales or overall symptoms.

No significant correlations were identified between Lyso-Gb3 levels and SCL-90 subscales (Table 2). However, CNS involvement demonstrated a significant association with all subscales except paranoia (Table 3). Additionally, cardiovascular system (CVS) involvement was significantly associated with all subscales except obsessive-compulsive symptoms, paranoia, and additional psychiatric symptoms (Table 3). A moderate correlation was observed between PNS involvement and the psychoticism and hostility subscales (Table 3).

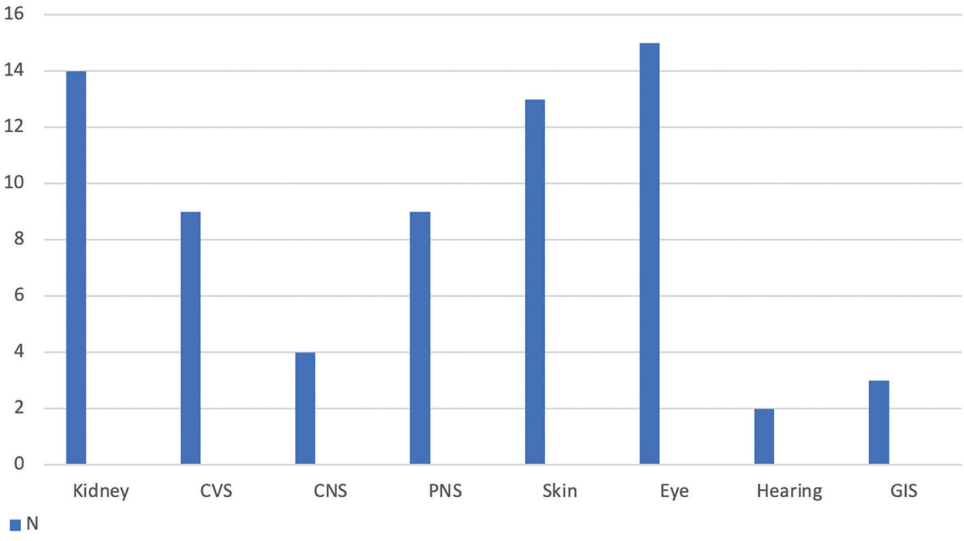

Figure 2. Target organ involvements of Fabry patients
CSN: Central nervous system, CVS: Cardiovascular system, GIS: Gastrointestinal system, PNS: Periferic nervous system

Table 1. Comparison of SCL-90 and Conners' subscales of Fabry patients and control group

Adults	**Fabry patients, n=18**	**Control group, n=25**	**p**
Somatization	0.88±0.76	0.71±0.59	0.042
Anxiety	0.50±0.40	0.68±0.53	0.366
Obsessive-compulsive disorder	0.80±0.60	0.81±0.59	0.834
Depression	0.72±0.62	0.84±0.67	0.529
Interpersonal sensibility	0.53±0.51	0.45±0.48	0.527
Psychoticism	0.21±0.28	0.48±0.57	0.300
Paranoid	0.42±0.43	0.44±0.48	0.940
Anger-hostility	0.59±0.80	0.69±0.63	0.274
Phobic	0.35±0.40	0.34±0.41	1.000
Additional items	0.74±0.51	0.64±0.52	
Pediatric	**Fabry patients, n=4**	**Control group, n=4**	
Oppositional	2.5±1.29	0.8±0.57	0.04
Cognitive problem	3±2.16	2±1.89	0.30
Hyperactivity	1.5±1.29	1.6±1.41	0.55
Anxious-shy	3.5±3.41	2±1.25	0.31

Table 1. Continued

Pediatric	Fabry patients, n=4	Control group, n=4	p
Perfectionism	5.5±3.69	2.8±0.95	0.14
Social problem	1.25±1.89	0.8±0.57	0.75
Psychosomatic	1.5±1.73	0.8±1	0.28
ADH index	1.5±1.73	0.4±0.5	0.15
Global index-restlessness-impulsivity	1±1.41	0.8±1	0.51
Global index-emotional lability	0.75±0.95	0±0	0.13
Conners total	2.25±1.89	0.8±1	0.10
DSM-IV inattention	1.75±0.95	1.6±1.41	0.29
DSM-IV hyperactivity	1.5±0.57	1.2±0.95	0.22
DSM-IV total	3.75±0.95	3.6±2.21	0.30

p<0.05 statistically significant. Significant p-values are shown in bold
ADH: Attention deficit hyperactivity, DSM: Diagnostic and Statistical Manual of Mental Disorders, SCL-90: Symptom Checklist-90

Table 2. Correlation status between SCL-90 subscales and Lyso-Gb3 levels of Fabry patients

SCL-90	r	p
Somatization	-0.096	0.704
Anxiety	-0.137	0.589
Obsessive-compulsive disorder	-0.008	0.974
Depression	-0.158	0.530
Interpersonal sensibility	0.050	0.843
Psychoticism	-0.088	0.729
Paranoid	0.229	0.361
Anger-hostility	0.093	0.713
Phobic	0.149	0.555
Additional items	-0.122	0.630

p<0.05 statistically significant. Significant p-values are shown in bold
SCL-90: Symptom Checklist-90, Lyso-Gb3: Globotriaosylsphingosine

Pediatric Population

The study included four pediatric patients, one of whom was male. The median age was 9.5 years (range: 6-16 years). All pediatric patients were diagnosed through family screening. The mean scores on the Conners' subscale in the pediatric Fabry patient group were higher than those in the control group. However, a statistically significant difference was observed only on the oppositional subscale (p=0.04) (Table 1).

DISCUSSION

Due to the absence of routine psychiatric evaluations in outpatient clinics, individuals with FD often remain undiagnosed and untreated for mental health conditions. Although prior research has investigated psychiatric disorders in FD, most studies have focused on depression and anxiety (4,5). The present study aimed to examine a broader spectrum of psychiatric disorders in Fabry patients, making it among the first to do so. Moreover, the study's findings on the correlation between psychiatric disorders and CNS and CVS involvement contribute valuable insights to the existing literature.

Although statistical significance was not reached for anxiety, depression, interpersonal sensitivity, and hostility, adult Fabry patients exhibit higher rates of these symptoms than the control group; a significant difference was observed only in the somatization subscale. Somatization is commonly associated with chronic physical illnesses and can serve as a manifestation of depression across different age groups (12). Patients experiencing cardiac discomfort or palpitations in the absence of underlying cardiac pathology may develop heightened anxiety due to the hereditary nature of FD and its potentially life-threatening implications.

Depression and anxiety are more prevalent among individuals with functional somatic symptoms than in the general population (13). If left untreated, depression can adversely affect both the prognosis of the somatic illness and the overall quality of life. The prevalence of depression in adult FD has been reported to range from 15% to 62%, whereas 10-25% of the general population experience at least one major depressive episode during their lifetime (14-17). The prevalence of depression in this study was 27.8%, slightly higher than general population norms, but lower than in previous studies of FD. Variability in findings across studies may be attributed to differences in assessment tools, the administration of ERT, and adherence to treatment (18,19). Given that patients in this study had undergone long-term ERT with high adherence, the observed lower prevalence aligns with findings suggesting that ERT may alleviate depressive symptoms, particularly in pediatric patients.

Table 3. Correlation between system involvements and SCL-90 subscales

	PNS		Eye		Skin	
	r	p	r	p	r	p
Somatization	0.383	0.116	0.368	0.133	0.393	0.107
Anxiety	0.316	0.202	0.308	0.214	0.256	0.305
Obsessive-compulsive disorder	0.287	0.248	0.026	0.919	0.171	0.497
Depression	0.187	0.458	0.345	0.160	0.217	0.387
Interpersonel sensibility	0.178	0.481	0.210	0.404	0.411	0.091
Psychoticism	0.530	**0.024**	0.237	0.344	0.389	0.110
Paranoid	-0.064	0.801	-0.027	0.914	0.276	0.267
Anger-hostility	0.544	**0.020**	0.211	0.400	0.364	0.138
Phobic	0.208	0.407	0.242	0.334	0.289	0.245
Additional items	-0.140	0.578	0.149	0.556	0.169	0.503

p<0.05 statistically significant. Significant p-values are shown in bold
CSN: Central nervous system, CVS: Cardiovascular system, GIS: Gastrointestinal system, PNS: Periferic nervous system, SCL-90: Symptom Checklist-90

Table 3. Continued

	CNS		CVS		Kidney		GIS	
	r	p	r	p	r	p	r	p
Somatization	0.628	**0.005**	0.722	**0.001**	0.428	0.076	0.441	0.067
Anxiety	0.725	**0.001**	0.689	**0.002**	0.414	0.088	0.577	**0.012**
Obsessive-compulsive disorder	0.553	**0.017**	0.306	0.216	0.207	0.409	0.103	0.685
Depression	0.811	**<0.001**	0.568	**0.014**	0.380	0.120	0.539	**0.021**
Interpersonel sensibility	0.715	**0.001**	0.542	**0.020**	0.092	0.717	0.419	0.083
Psychoticism	0.713	**0.001**	0.571	**0.013**	0.365	0.137	0.419	0.083
Paranoid	0.214	0.393	0.024	0.925	0.480	**0.044**	0.149	0.556
Anger-hostility	0.592	**0.010**	0.615	**0.007**	0.320	0.196	0.454	0.058
Phobic	0.812	**<0.001**	0.625	**0.006**	0.287	0.249	0.596	**0.009**
Additional items	0.774	**<0.001**	0.267	0.283	0.027	0.914	0.575	**0.013**

p<0.05 statistically significant. Significant p-values are shown in bold
CSN: Central nervous system, CVS: Cardiovascular system, GIS: Gastrointestinal system, PNS: Periferic nervous system, SCL-90: Symptom Checklist-90

The etiology of depression in FD remains debated. Some researchers propose that chronic pain, particularly acroparesthesia, plays a role, while others suggest that microvascular dysfunction affecting cerebral blood flow contributes to psychiatric symptoms (14,19-21). In the present study, a statistically significant correlation was found between depression and both CNS and CVS involvement. Fear of mortality associated with FD-related complications may further contribute to depressive symptoms, even among patients receiving ERT.

Previous research has demonstrated that FD frequently results in milder symptoms that manifest later in females. However, some studies suggest a higher prevalence of mental disorders, particularly depression, among female patients with FD (4,22). This phenomenon may be attributed to the generally higher prevalence of depression among females rather than to the disorder itself (23,24). Contrary to the prevailing notion, recent findings indicate a higher prevalence of this phenomenon among males (25). In our study, we did not observe significant gender-related differences in psychiatric symptoms. As noted by Ali et al. (6) in a meta-analysis on this subject, establishing a definitive gender-related association appears challenging.

Anxiety is a frequently reported psychiatric symptom in FD, with prevalence rates ranging from 20% to 37% (17,25). In this study, the prevalence of anxiety was 22.2%, mirroring trends observed for depression. A significant association was found between anxiety symptoms and involvement of the CNS and CVS, similar to findings for depression.

Psychoticism has been reported in FD patients, albeit infrequently (26). The increasing number of case reports suggests a need for further large-scale studies to assess its true prevalence.

Chronic illnesses characterized by persistent pain and high morbidity and mortality risks may contribute to elevated interpersonal sensitivity and hostility scores. Despite the limited pediatric sample size, the study found a significantly higher prevalence of oppositional defiant disorder in pediatric patients than in controls.

Higher attention deficit hyperactivity (ADH) index scores were observed in pediatric FD patients. Given the well-documented interrelation between psychiatric disorders and ADH, ADH is also frequently associated with anxiety and depression (27). Future research should incorporate additional psychological assessments to investigate ADHD in pediatric patients with FD.

No correlation was found between Lyso-Gb3 levels and psychiatric symptoms, suggesting that psychiatric manifestations in FD may not be solely attributable to biological factors.

Study Limitations

This study has several limitations. The lack of pre-ERT assessments prevents baseline comparisons. Additionally, the rarity of FD limits the sample size, potentially affecting correlation analyses.

CONCLUSION

A strong correlation was observed between CNS involvement and various psychiatric disorders in adult FD patients. Additionally, the association between CVS involvement and psychiatric symptoms suggests that severe organ complications contribute to psychological distress. Given the chronic, multisystemic nature of FD, patients with neurological involvement may be at higher risk for mental health conditions. Regular psychiatric assessments and timely interventions are essential to mitigate the psychological burden associated with CNS and CVS involvement.

Since no significant association was found between Lyso-Gb3 levels and psychiatric manifestations, its use as a biomarker for follow-up in this context is not recommended.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2022.07.05, date: 04.04.2022).

Informed Consent: Informed consent was obtained from all participants prior to enrollment.

FOOTNOTES

Authorship Contributions

Concept: M.E., S.Y., H.P., Design: M.E., S.Y., H.P., Data Collection or Processing: M.E., A.Ç., Analysis or Interpretation: M.E., S.Y., H.P., Literature Search: M.E., S.Y., A.Ç., Writing: M.E., S.Y., H.P., A.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Desnick RJ, Brady R, Barranger J, Collins AJ, Germain DP, Goldman M, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med. 2003;138:338-46.
2. Biancini GB, Vanzin CS, Rodrigues DB, Deon M, Ribas GS, Barschak AG, et al. Globotriaosylceramide is correlated with oxidative stress and inflammation in Fabry patients treated with enzyme replacement therapy. Biochim Biophys Acta. 2012;1822:226-32.
3. Schiffmann R, Warnock DG, Banikazemi M, Bultas J, Linthorst GE, Packman S, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant. 2009;24:2102-11.
4. Bolsover FE, Murphy E, Cipolotti L, Werring DJ, Lachmann RH. Cognitive dysfunction and depression in Fabry disease: a systematic review. J Inherit Metab Dis. 2014;37:177-87.
5. Tuttolomondo A, Pecoraro R, Simonetta I, Miceli S, Arnao V, Licata G, et al. Neurological complications of Anderson-Fabry disease. Curr Pharm Des. 2013;19:6014-30.
6. Ali N, Gillespie S, Laney D. Treatment of depression in adults with Fabry disease. JIMD Rep. 2018;38:13-21.
7. Nowak A, Mechtler T, Kasper DC, Desnick RJ. Correlation of Lyso-Gb3 levels in dried blood spots and sera from patients with classic and later-onset Fabry disease. Mol Genet Metab. 2017;121:320-4.
8. Nowak A, Mechtler TP, Hornemann T, Gawinecka J, Theswet E, Hilz MJ, et al. Genotype, phenotype and disease severity reflected by serum LysoGb3 levels in patients with Fabry disease. Mol Genet Metab. 2018;123:148-53.
9. Bech P, Bille J, Møller SB, Hellström LC, Østergaard SD. Psychometric validation of the Hopkins Symptom Checklist (SCL-90) subscales for depression, anxiety, and interpersonal sensitivity. J Affect Disord. 2014;160:98-103.
10. Dağ İ. Belirti Tarama Listesi (SCL-90-R)'nin üniversite öğrencileri için güvenirliği ve geçerliği. Turk Psikiyatri Derg. 1991;2:5-12. Available from: https://psycnet.apa.org/record/1997-86097-001
11. Kaner S, Buyukozturk S, Iseri E, Ak A, Ozaydın L. Adaptation study of Revised Conners' Parent Rating Scale-Long Form to Turkish population. 16th National Congress of Child and Adolescent Mental Health and Diseases; 2006; Antalya, Turkey.
12. Kallivayalil RA, Punnoose VP. Understanding and managing somatoform disorders: making sense of non-sense. Indian J Psychiatry. 2010;52(Suppl 1):S240-5.
13. Egede LE. Diabetes, major depression, and functional disability among U.S. adults. Diabetes Care. 2004;27:421-8.
14. Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med. 2007;9:34-45.

15. Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl RV, De Graaf R, Vollebergh W, et al. The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) surveys. Int J Methods Psychiatr Res. 2003;12:3-21. Erratum in: Int J Methods Psychiatr Res. 2003;12:165.
16. Laney DA, Gruskin DJ, Fernhoff PM, Cubells JF, Ousley OY, Hipp H, et al. Social-adaptive and psychological functioning of patients affected by Fabry disease. J Inherit Metab Dis. 2010;33(Suppl 3):S73-81.
17. Grewal RP. Psychiatric disorders in patients with Fabry's disease. Int J Psychiatry Med. 1993;23:307-12.
18. Sadek J, Shellhaas R, Camfield CS, Camfield PR, Burley J. Psychiatric findings in four female carriers of Fabry disease. Psychiatr Genet. 2004;14:199-201.
19. Bugescu N, Naylor PE, Hudson K, Aoki CD, Cordova MJ, Packman W. The psychosocial impact of Fabry disease on pediatric patients. J Pediatr Genet. 2016;5:141-9.
20. Körver S, Geurtsen GJ, Hollak CEM, van Schaik IN, Longo MGF, Lima MR, et al. Depressive symptoms in Fabry disease: the importance of coping, subjective health perception and pain. Orphanet J Rare Dis. 2020;15:28.
21. Löhle M, Hughes D, Milligan A, Richfield L, Reichmann H, Mehta A, et al. Clinical prodromes of neurodegeneration in Anderson-Fabry disease. Neurology. 2015;84:1454-64.
22. Sigmundsdottir L, Tchan MC, Knopman AA, Menzies GC, Batchelor J, Sillence DO. Cognitive and psychological functioning in Fabry disease. Arch Clin Neuropsychol. 2014;29:642-50.
23. Schermuly I, Müller MJ, Müller KM, Albrecht J, Keller I, Yakushev I, et al. Neuropsychiatric symptoms and brain structural alterations in Fabry disease. Eur J Neurol. 2011;18:347-53.
24. Whybra C, Kampmann C, Willers I, Davies J, Winchester B, Kriegsmann J, et al. Anderson-Fabry disease: clinical manifestations of disease in female heterozygotes. J Inherit Metab Dis. 2001;24:715-24.
25. Sigmundsdottir L, Tchan MC, Knopman AA, Menzies GC, Batchelor J, Sillence DO. Cognitive and psychological functioning in Fabry disease. Arch Clin Neuropsychol. 2014;29:642-50.
26. Liston EH, Levine MD, Philippart M. Psychosis in Fabry disease and treatment with phenoxybenzamine. Arch Gen Psychiatry. 1973;29:402-3.
27. Chronis-Tuscano A, Molina BS, Pelham WE, Applegate B, Dahlke A, Overmyer M, et al. Very early predictors of adolescent depression and suicide attempts in children with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2010;67:1044-51.

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Research

Evaluation of Demographic and Clinical Characteristics of Suicidal Drug Ingestion in Children and Adolescents: A Single-Center Retrospective Study

Çocuk ve Ergenlerde İntihar Amaçlı İlaç Alımının Demografik ve Klinik Özelliklerinin Değerlendirilmesi: Tek Merkezli Retrospektif Bir Çalışma

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ABSTRACT

Objective: Adolescence represents a high-risk period for self-harm behaviors. This study aimed to evaluate the demographic and clinical characteristics of patients aged 9-18 years who presented to the pediatric emergency department with suicidal drug ingestion, and to identify age-specific risk factors.

Methods: This retrospective cohort study included 67 patients admitted to a tertiary pediatric emergency department between January 2023 and December 2024. Patients were stratified into early adolescence (9-14 years) and mid-to-late adolescence (15-18 years) groups. Clinical outcomes and demographic data were analyzed.

Results: The cohort was 83.6% female with a mean age of 13.93±1.4 years. Multi-drug ingestion was identified in 56.7% of patients. While the gender distribution was similar across groups, the 15-18-year age group exhibited significantly higher rates of multidrug ingestion (78.6% vs. 41.0%; p=0.003), recurrent suicide attempts (53.6% vs. 23.1%; p=0.010), and symptomatic presentation (64.3% vs. 35.9%; p=0.022). Furthermore, multidrug ingestion significantly increased the risk of intoxication in the 9-14 age group (p=0.012).

Conclusion: Clinical complexity increases with age, characterized by higher rates of multidrug use and recurrence among older adolescents. Consequently, prevention strategies should prioritize safe medication storage and age-specific psychosocial interventions involving both families and schools.

Keywords: Child, adolescent, suicide, intoxication, multi-drug ingestion

ÖZ

Amaç: Ergenlik, kendine zarar verme davranışları açısından yüksek riskli bir dönemdir. Bu çalışma ile, intihar amaçlı ilaç alımı nedeniyle çocuk acil servisine başvuran 9-18 yaş arası hastaların demografik ve klinik özelliklerinin değerlendirilmesi ve yaşa özgü risk faktörlerinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Bu retrospektif kohort çalışmasına, Ocak 2023 ile Aralık 2024 tarihleri arasında üçüncü basamak bir çocuk acil servisine kabul edilen 67 hasta dahil edildi. Hastalar erken (9-14 yaş) ve orta-geç (15-18 yaş) ergenlik gruplarına ayrıldı. Klinik sonuçlar ve demografik veriler analiz edildi.

Bulgular: Çalışma grubunun %83,6'sının kız olduğu ve yaş ortalamasının 13,93±1,4 yıl olduğu saptandı. Hastaların %56,7'sinde çoklu ilaç alımı tespit edildi. Cinsiyet dağılımı gruplar arasında benzer olmakla birlikte; 15-18 yaş grubunda çoklu ilaç alımı (%78,6'ya karşı %41,0; p=0,003), tekrarlayan intihar girişimleri (%53,6'ya karşı %23,1; p=0,010) ve semptomatik başvuru (%64,3'e karşı %35,9; p=0,022) oranlarının anlamlı derecede daha yüksek olduğu gözlendi. Ayrıca, çoklu ilaç alımının 9-14 yaş grubunda intoksikasyon riskini anlamlı ölçüde artırdığı belirlendi (p=0,012).

Sonuç: Klinik tablonun karmaşıklığının yaşla birlikte arttığı, bu durumun özellikle büyük yaş grubundaki ergenlerde daha yüksek çoklu ilaç kullanımı ve tekrarlama oranları ile karakterize olduğu sonucuna varıldı. Önleme stratejilerinin, ilaçların güvenli saklanmasına ve aile ile okulları kapsayan yaşa özgü psikososyal müdahalelere odaklanması gerektiği vurgulandı.

Anahtar Kelimeler: Çocuk, ergen, intihar, intoksikasyon, çoklu ilaç alımı

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INTRODUCTION

Adolescence is a developmental phase characterized by an increased risk of self-harm and suicide attempts (1). Intentional self-poisoning by drug ingestion remains one of the most frequent methods of attempted suicide among adolescents (2-5). According to World Health Organization data, approximately 800,000 people die by suicide every year; young people aged 15-29 account for more than one-third of these deaths (1).

Recent epidemiological data indicate a shift in the patterns of suicidal behavior. While early adolescence is often characterized by impulsive actions, older adolescents tend to exhibit more planned behaviors involving more lethal methods and multi-drug regimens. In developing countries such as Türkiye, rapid socio-cultural changes, increasing academic pressure, and changing family dynamics may further exacerbate these risks, creating unique stress factors for adolescents (6). Furthermore, recurrence rates in developing countries have been reported to be significantly higher than in Western countries, potentially due to disparities in post-discharge psychosocial support.

Consistent with these data, we aimed to evaluate the demographic and clinical characteristics of patients aged 9-18 years who had attempted suicide and contribute to the literature by identifying age-specific risk factors.

METHODS

This retrospective cohort study was conducted at the pediatric emergency clinic of the hospital and covered admissions between January 1, 2023, and December 31, 2024. This retrospective study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-Interventional Clinical Research Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki (approval no: 2025-13-01, date: 23.07.2025). Due to its retrospective nature, informed consent was waived.

The study included patients aged 9-18 years who were admitted for intentional drug ingestion with suicidal intent and were observed during follow-up. Data regarding age, gender, amounts of drug, drug diversity (single vs. multiple drugs), time to presentation, clinical findings, and number of previous suicide attempts were evaluated retrospectively from patient files. Patients were divided into two age groups to assess developmental differences: 9-14 years (early adolescence) and 15-18 years (mid-to-late adolescence).

Intoxication risk was classified based on the development of moderate-to-severe clinical toxicity. To ensure objective classification, moderate-to-severe toxicity was defined as clinical criteria corresponding to a Poison Severity Score of grade 2 (moderate) or higher. This included persistent neurological symptoms (e.g., Glasgow Coma Scale <15, seizures, agitation), cardiovascular instability (e.g., hypotension, arrhythmia requiring treatment), or metabolic derangements requiring invasive interventions.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0. The normality of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean±standard deviation or median based on distribution. Categorical variables were summarized as frequencies (n) and percentages (%). Comparisons were performed using the Student's t-test, Mann-Whitney U test, and Pearson's chi-square test. When the expected count in any cell was less than 5, Fisher's Exact test was employed. To evaluate the impact of multi-drug ingestion on clinical severity, risk ratios (RRs) with 95% confidence intervals (CI) were calculated. A p-value of <0.05 was considered statistically significant.

RESULTS

The study population consisted of 67 patients, with a female predominance (83.6%; n=56) and a mean age of 13.92±1.39 years. Based on developmental stages, 58.2% (n=39) were in the early adolescence group (9-14 years), while 41.8% (n=28) were in the mid-to-late adolescence group (15-18 years).

Multi-drug ingestion was detected in 56.7% (n=38) of patients. Among cases of multi-drug ingestion, combinations of non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol, and of antidepressants and antipsychotics were frequently observed. Regarding time to presentation, 50.7% (n=34) presented more than 2 hours after ingestion. Symptomatic presentation was observed in 47.7% (n=32) of the patients. The spectrum of symptoms included gastrointestinal symptoms (n=25: nausea, vomiting, and abdominal pain) and neurological symptoms (n=12: somnolence, dizziness, and extrapyramidal symptoms). Cardiovascular symptoms, such as tachycardia, were also noted in a smaller subset of patients. The clinical course was generally favorable, with only one patient (1.49%) requiring intensive care unit (ICU) admission.

When demographic and clinical characteristics were compared across age groups (Table 1), markers of clinical complexity increased significantly with age. The 15-18-year age group exhibited a significantly higher rate of multi-drug ingestion (78.6%) than the 9-14-year age group (41.0%)

(p=0.003). Similarly, the history of recurrent suicide attempts (≥2) was significantly more frequent in the older group (53.6% vs. 23.1%; p=0.010). Symptomatic presentation was also significantly higher in the 15-18 age group (64.3% vs. 35.9%; p=0.022).

The distribution of ingested pharmacological agents varied by age (Table 2). Antidepressants were the most frequently ingested agents in the 15-18 age group (60.7%), a rate significantly higher than that in the 9-14 age group (30.8%) (p=0.018). No significant age-related differences were observed in the ingestion rates of antipsychotics, paracetamol, NSAIDs, or cold medications.

Risk analysis revealed that multidrug ingestion significantly predicted clinical severity (Table 3). Patients who ingested multiple drugs had a 1.74-fold higher risk of developing moderate-to-severe clinical toxicity compared with those who ingested a single drug [RR=1.74; 95% CI: (1.15-2.63); p=0.018]. Notably, subgroup analysis indicated that multidrug ingestion significantly increased the risk of intoxication in the 9-14-year age group (p=0.012). Conversely, the time to presentation (0-2 hours vs. >2 hours) was not identified as a statistically significant risk factor for the development of moderate-to-severe toxicity (RR=1.02; p=0.91).

Table 1. Clinical and demographic characteristics by age group

Variable	Early adolescence (9-14 years) (n=39)	Mid-to-late adolescence (15-18 years) (n=28)	p
Gender, n (%)			
Female	32 (82.1%)	24 (85.7%)	0.62
Male	7 (17.9%)	4 (14.3%)	
Time to presentation, n (%)			
0-2 hours	19 (48.7%)	13 (46.4%)	1.00
>2 hours	20 (51.3%)	15 (53.6%)	
Multi-drug ingestion, n (%)	16 (41.0%)	22 (78.6%)	**0.003***
Recurrent attempts (≥2), n (%)	9 (23.1%)	15 (53.6%)	**0.010***
Symptomatic presentation, n (%)	14 (35.9%)	18 (64.3%)	**0.022***

Data are presented as n (%)
*: Indicates statistical significance (p<0.05)

Table 2. Distribution of ingested drug groups by age

Drug Class	Early adolescence (n=39)	Mid-to-late adolescence (n=28)	p
Antidepressants	12 (30.8%)	17 (60.7%)	**0.018***
Antipsychotics	13 (33.3%)	13 (46.4%)	0.29
Paracetamol	9 (23.1%)	9 (32.1%)	0.43
NSAIDs	7 (17.9%)	8 (28.6%)	0.31
Cold medications	8 (20.5%)	6 (21.4%)	0.92
Others	6 (15.4%)	5 (17.9%)	0.78

Data are presented as n (%)
*: Indicates statistical significance (p<0.05), NSAID: Non-steroidal anti-inflammatory drug

Table 3. Assessment of intoxication risk ratios (n=67)

Risk factor	Moderate/severe toxicity (+)	Total (n)	Risk rate (%)	Risk ratio (RR)	p
Drug intake					**0.018***
Single drug	11	29	37.9%	1.00 (Ref)	
Multi-drug	25	38	65.8%	1.74 (1.15-2.63)	
Time to presentation					0.91
0-2 hours	17	32	53.1%	1.00 (Ref)	
>2 hours	19	35	54.3%	1.02	

*: Indicates statistical significance (p<0.05), CI: Confidence interval, Ref: Reference category

DISCUSSION

Adolescence is a developmental phase associated with a high risk of self-harm and suicide attempts. Suicide attempts are a significant public health problem both globally and in our country (1). Drug ingestion is one of the methods most frequently encountered in adolescent suicide attempts (2-5). In our study, by evaluating the demographic and clinical characteristics of children and adolescents aged 9-18 years presenting to the pediatric emergency department for suicidal drug ingestion, we determined that suicidal behaviors were more common in females and that the clinical presentation became more severe with increasing age.

Studies conducted in Türkiye report that the proportion of female cases ranges from 66.7% to 86.7%, while global studies show that suicide attempts are 3 to 9 times more common in girls (7-10). The higher incidence of suicide attempts among girls has been associated with a greater prevalence of mood disorders and increased sensitivity to psychosocial stressors (11,12). Our finding of a female prevalence of 83.6% aligns with national and international data.

When evaluated by age group, recurrent suicide attempts, multidrug ingestion, and the presence of associated symptoms were significantly more frequent in the 15-18 age group. While suicide attempts are frequent among younger adolescents due to insufficient developmental maturity, older adolescents prefer more planned suicidal behaviors and more toxic drugs (13).

Our study highlights a critical "cocktail effect" in older adolescents. The high rate of multidrug ingestion (78.6%) in the 15-18-year age group creates unpredictable toxicologic synergies. Our results showed that combinations, such as analgesics/NSAIDs and psychotropics, were frequently co-ingested. Unlike accidental poisonings, these mixtures complicate the clinical picture. This finding supports a more vigilant approach in the emergency department, in which history-taking must aggressively screen for co-ingestants.

A striking finding in our study is the recurrence rate of 53.6% in the 15-18-year age group. This rate is considerably higher than that reported in some Western studies (e.g., United States cohorts) (5,9). This disparity suggests a gap in post-discharge management in our setting. While medical stabilization is highly effective (as evidenced by low mortality and ICU admissions in our study), the lack of standardized safety planning and immediate psychosocial follow-up may contribute to high relapse rates. Interventions, such as creating a written safety plan before discharge, may help mitigate this risk (14,15).

The significantly higher use of antidepressants in the older age group (60.7%) likely reflects both a higher prevalence of diagnosed psychiatric conditions and greater access to prescribed medications among this demographic. This presents a therapeutic paradox in which the treatment modality becomes the instrument of the suicide attempt.

Study Limitations

This study has several limitations. First, its single-center, retrospective design may limit the generalizability of the findings. Second, the sample size (n=67), while sufficient for descriptive analysis, may be insufficient to detect rare clinical outcomes or small effect sizes, increasing the risk of type II error. Third, the reliance on patient files means that data regarding specific intent might be subject to documentation bias. Additionally, long-term psychiatric outcomes beyond the emergency department admission were not evaluated.

CONCLUSION

Our study reveals that suicidal drug ingestion among adolescents continues to be an important public health problem, and clinical characteristics vary with age. The increase in multidrug ingestion and recurrent suicide attempts during late adolescence indicates that this group should be managed as high-risk. In preventing suicide attempts among adolescents, early psychiatric evaluation, family- and school-based preventive approaches, and regulations regarding the safe storage of drugs are of critical importance. Furthermore, bridging the gap between acute medical care and long-term psychosocial support is essential to break the cycle of recurrence.

ETHICS

Ethics Committee Approval: This retrospective study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-Interventional Clinical Research Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki (approval no: 2025-13-01, date: 23.07.2025).

Informed Consent: Due to its retrospective nature, informed consent was waived.

FOOTNOTES

Authorship Contributions

Concept: E.E.S., Design: E.E.S., Data Collection or Processing: G.A., Analysis or Interpretation: E.E.S., Literature Search: E.E.S., G.A., Writing: E.E.S., G.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. World Health Organization. LIVE LIFE: an implementation guide for suicide prevention in countries. Geneva: WHO; 2021. Available from: https://www.mhinnovation.net/sites/default/files/content/document/LIVE%20LIFE_an%20implementation%20Guide%20for%20Suicide%20Prevention%20in%20Countries.pdf
2. Kurt F, Akbaba B, Yakut HI, Mısırlıoğlu ED. Ergen yaş grubunda ilaç alımı ile özkıyım girişiminin demografik ve klinik özelliklerinin değerlendirilmesi. J Pediatr Emerg Intensive Care Med. 2020;7:101-7.
3. Wang W, Cao Y, Chen F, Qiu J, Zhang X, Huang Z, et al. Clinical profiles and demographics of suicide attempts in early-to-mid adolescents in emergency departments: a retrospective study. Am J Emerg Med. 2026;101:54-60.
4. Weigel B, Adams A, Wahrenbrock T, Wahl M. Adolescent acetaminophen and ibuprofen self-poisoning, 2017-2022. Pediatr Emerg Care. 2024;40:776-80.
5. Gonzalez-Urdiales P, Kuppermann N, Dalziel SR, Prego J, Benito J, Mintegi S. Pediatric intentional self-poisoning evaluated in the emergency department: an international study. Pediatr Emerg Care. 2021;37:e1631-6.
6. Yavuz BE, Turan S, Mutlu C, Çamlı ŞE. A comparison of the social cognition and neurocognitive characteristics of adolescents with suicide behavior, adolescent with depression and healthy controls. Suicide Life Threat Behav. 2024;54:785-97.
7. Miranda-Mendizabal A, Castellví P, Parés-Badell O, Alayo I, Almenara J, Alonso I, et al. Gender differences in suicidal behavior in adolescents and young adults: systematic review and meta-analysis of longitudinal studies. Int J Public Health. 2019;64:265-83.
8. Castaldo L, Serra G, Piga S, Reale A, Vicari S. Suicidal behaviour and non-suicidal self-injury in children and adolescents seen at an Italian paediatric emergency department. Ann Ist Super Sanita. 2020;56:303-14.
9. Ostanin J, Miranda H, Shugar S, Abdo D, Mejia MC, Hennekens CH, et al. Suicidal behaviors among United States adolescents: increasing clinical and public health challenges. Children (Basel). 2025;12:57.
10. Kırcı G, Öztürk D, Bölükbaşı H, Özer E. Çocuk acil servisine 2016-2021 yılları arasında başvuran intoksikasyon olgularının değerlendirilmesi. Adli Tıp Bülteni. 2023;28:66-73.
11. Arat C, Türkmenoğlu Y, Akşahin BG, Yılmaz B, Sarıtaş Ü, Hamilçıkan B, et al. Çocuk acil servisimize zehirlenme ile başvuran özkıyım olgularının değerlendirilmesi. Van Med J. 2016;23:7-12.
12. Akman Ö. İlaç alımı ile özkıyım girişiminde bulunan ergen yaş grubunun değerlendirilmesi. Türk Çocuk Hastalıkları Dergisi. 2019;13:7-12.
13. Hawton K, Townsend E, Deeks J, Appleby L, Gunnell D, Bennewith O, et al. Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. BMJ. 2001;322:1203-7.
14. Albaum C, Irwin SH, Muha J, Schumacher A, Clarissa S, Finkelstein Y, et al. Safety planning interventions for suicide prevention in children and adolescents: a systematic review and meta-analysis. JAMA Pediatr. 2025;179:886-95.
15. Chiew AL, Gluud C, Brok J, Buckley NA. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database Syst Rev. 2018;2:CD003328.

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Research

Diagnostic and Prognostic Value of Anti-Phospholipase A2 Receptor Antibodies in Patients with Membranous Nephropathy

Membranöz Nefropatili Hastalarda Anti-Fosfolipaz A2 Reseptör Antikorlarının Tanısal ve Prognostik Değeri

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ABSTRACT

Objective: This study aimed to evaluate the diagnostic and prognostic significance of anti-phospholipase A2 receptor (PLA2R) in primary membranous nephropathy (PMN) patients and determine the most appropriate cut-off value.

Methods: Between June 2022 and June 2023, 74 patients who were followed up with PMN, secondary MN, non-MN nephrotic syndrome and 15 healthy volunteers were included. Anti-PLA2R antibody levels were evaluated by enzyme-linked immunosorbent assay (ELISA) (EUROIMMUN, Lübeck, Germany). Receiver operating characteristic (ROC) curve analysis was performed.

Results: The ELISA kit showed sensitivity of 30% and specificity of 100% when the cut-off value of 20 relative units (RU)/mL was used. According to the ROC curve analysis, the cut-off value was found to be 1.19 RU/mL. When using this value, sensitivity was 66.6% and specifity was 72.7%. However when cut-off value was used 2 RU/mL, sensitivity and specifity was 46.6% and 100%, respectively. Only part of PMN patients were antibody positive; all other groups were negative. All PMN patients were antibody positive at diagnosis; and as for patients with active disease 25% were positive and 25% were borderline. Whereas for patients with complete and partial remission and 18.8% of these were antibody positive. Anti-PLA2R positive patients had higher mean proteinuria and lower mean albumin. Anti-PLA2R positive PMN patients had lower mean hemoglobin and hematocrit values.

Conclusion: Anti-PLA2R may be helpful in diagnosis in PMN patients when secondary causes are well excluded at the time of diagnosis and also be helpful in predicting progression during follow-up.

Keywords: Antibody, enzyme-linked immunosorbent assay, phospholipase A2 receptor, primary membranous nephropathy, proteinuria

ÖZ

Amaç: Bu çalışmada, primer membranöz nefropatili (PMN) hastalarda anti-fosfolipaz A2 reseptörünün (PLA2R) tanısal ve prognostik öneminin değerlendirilmesi ve en uygun eşik değerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Haziran 2022 ile Haziran 2023 tarihleri arasında, PMN, sekonder MN, MN dışı nefrotik sendrom tanısı ile takip edilen 74 hasta ile 15 sağlıklı gönüllü çalışmaya dahil edildi. Anti-PLA2R antikor düzeyleri enzim bağlantılı immünosorbent test (ELISA) yöntemiyle (EUROIMMUN, Lübeck, Almanya) değerlendirildi. Alıcı çalışma özelliği (ROC) eğrisi analizi yapıldı.

Bulgular: ELISA kiti, 20 göreceli/bağıl birimler (RU)/mL eşik değeri kullanıldığında %30 duyarlılık ve %100 özgüllük göstermiştir. ROC eğrisi analizine göre, eşik değeri 1,19 RU/mL olarak bulunmuştur. Bu değer kullanıldığında duyarlılık %66,6 ve özgüllük %72,7 olmuştur. Ancak eşik değeri 2 RU/mL kullanıldığında duyarlılık ve özgüllük sırasıyla %46,6 ve %100 olmuştur. PMN hastalarının sadece bir kısmı antikor pozitifti; diğer

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ÖZ

tüm gruplar negatifti. Tüm PMN hastaları tanı anında antikor pozitifti; aktif hastalığı olan hastaların %25'i pozitif, %25'i ise sınırda idi. Tam ve kısmi remisyonda olan hastaların ise %18,8'i antikor pozitifti. Anti-PLA2R pozitif hastaların ortalama proteinüri değerleri daha yüksek, ortalama albümin değerleri ise daha düşüktü. Anti-PLA2R pozitif PMN hastalarının ortalama hemoglobin ve hematokrit değerleri daha düşüktü.

Sonuç: Anti-PLA2R, tanı anında sekonder nedenler iyi bir şekilde dışlandığında PMN hastalarında tanıya yardımcı olabilir ve ayrıca takip sürecinde progresyonu tahmin etmede de faydalı olabilir.

Anahtar Kelimeler: Antikor, enzim bağlantılı immünosorbent test, fosfolipaz A2 reseptör, primer membranöz nefropati, proteinüri

INTRODUCTION

Membranous nephropathy (MN) is defined histopathologically by immune complex deposition along the outer basement membrane and by thickening of the glomerular capillary walls. As an autoimmune glomerular disease, MN may arise at any age, yet remains the most frequent cause of nephrotic syndrome among adults. Primary MN (PMN) is predominantly idiopathic. If it is due to a known etiological cause, it is called secondary MN (SMN) (1).

The association of phospholipase A2 receptor (PLA2R) with MN was first reported in 2009. PLA2R currently represents the most commonly recognized autoantigen in MN (1-4). This molecule is a 185-kDa glycoprotein of the mannose receptor family, and the antibodies against it are mainly immunoglobulin G4 (IgG4) (5,6).

PLA2R-associated MN accounts for approximately 80% of PMN cases. PMN constitutes 70-75% of MN diagnoses identified on biopsy; thus, PLA2R-associated MN represents 55% of all MN cases overall (7).

Studies show that anti-PLA2R may be an important biomarker for diagnosing PMN, assessing treatment response, and predicting prognosis. In this way, serologic tests hold potential as a non-invasive alternative to biopsy, which is currently considered the gold standard in diagnosing MN (1,5-7).

Immunofluorescence (IFT) and enzyme-linked immunosorbent assay (ELISA) tests have been used to measure anti-PLA2R antibodies. IFT has high sensitivity and specificity. However, the results of IFT are not quantitative. For that reason, the ELISA tests are mainly used for determining quantitative antibody titres (1,2). The ELISA test is more convenient because more samples can be run at a time and it provides objective and quantitative results (8-10).

This study aimed to determine anti-PLA2R antibody levels and positivity rates using a commercial ELISA kit (EUROIMMUN, Lübeck, Germany) and to identify the most appropriate cut-off value for this kit. The relationship between this antibody and both disease activity and prognostic parameters of the disease was also evaluated.

METHODS

Ethics Committee Approval

Ethical approval for the study was granted by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval no: 2022/120, date: 30.06.2022). The authors declared that the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant included in this study.

Study Design

This cross-sectional investigation included 74 adult patients diagnosed and followed up at the Karadeniz Technical University Faculty of Medicine Nephrology Clinic between June 2022 and June 2023**,** and 15 healthy adult volunteers who served as the control group. The control group had neither kidney disease nor autoimmune disease. Among the 74 patients, 30 were diagnosed with PMN by biopsy after excluding secondary causes, 10 with SMN, and 34 with non-MN nephrotic syndrome. All PMN patients were examined to exclude secondary causes such as autoimmune diseases (antinuclear antibodies, anti-double stranded deoxynucleic acid, etc.), hepatitis (hepatitis B virus, hepatitis C virus), malignancy, and other diseases, in order to correctly diagnose PMN. Disease activity was classified as active disease, partial remission, or complete remission. Complete remission was defined as proteinuria <0.3 g/24 hours and normal serum albumin. Partial remission was defined as proteinuria <3.5 g/24 hours and a >50% reduction from baseline. Active disease was defined as the absence of the above conditions. PLA2R levels were evaluated according to disease activity. All kidney biopsies were evaluated in the same pathology laboratory. Patients' demographic information and laboratory results were obtained from the hospital information system (HIS). Serum specimens were collected from both the patient population and healthy control participants for analysis and were stored at -80 °C until the study day. Anti-PLA2R levels were quantified by ELISA.

Measurement of Anti-PLA2R

Serum samples were thawed at room temperature after being retrieved from the deep freezer. Anti-PLA2R antibody

concentrations were quantified using a commercial ELISA kit (EUROIMMUN, Lübeck, Germany) that employs purified human recombinant PLA2R antigen and a calibration curve prepared from five standards [2, 20, 100, 500, and 1500 relative units (RU)/mL]. Positivity for the antibody was evaluated based on the manufacturer's recommended cut-off values: values <14 RU/mL were interpreted as negative, values from ≥14 to <20 RU/mL as borderline, and those ≥20 RU/mL as positive.

To identify the optimal cut-off value, receiver operating characteristic (ROC) curve analysis was performed on ELISA results, using the pathological renal biopsy findings as the gold standard. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the anti-PLA2R IgG ELISA test were calculated at different cut-off values, including 40 RU/mL, 14 RU/mL, and 2 RU/mL (as used in other studies), as well as the cut-off values recommended by the manufacturer and derived from ROC curve analysis (11).

Biochemical Parameters

Clinical biochemistry test results indicating disease activity were collected from the HIS. Urine total protein, urine creatinine, urine albumin, glucose, creatinine, albumin, blood urea nitrogen, estimated glomerular filtration rate, low-density lipoprotein, high-density lipoprotein, alanine aminotransferase, cholesterol, triglycerides, total calcium, potassium, sodium, hemoglobin, and hematocrit values were analyzed. In this study, the lowest values that our devices (AU5800 and AU680, Beckman Coulter, Japan) could measure, 0.5 mg/dL for urine albumin and 1 mg/dL for urine total protein, were used. 24 hours urine samples were used to calculate proteinuria levels. Patients were divided into two groups according to proteinuria level: <3.5 g/day and >3.5 g/day.

Study Analysis

Statistical Analysis

All statistical analyses were conducted using SPSS software version 24.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequencies and percentages, whereas continuous variables are summarized using appropriate descriptive statistics, including mean, standard deviation (SD), median, and range. The distribution of numerical data was evaluated. For variables not conforming to a normal distribution, comparisons were performed with the Mann-Whitney U or Kruskal-Wallis tests, as appropriate. Associations between categorical variables were assessed using the Pearson chi-square test. Spearman's rank correlation analysis was applied to examine relationships between non-normally distributed continuous variables. The diagnostic performance of antibody levels measured by the ELISA kit in predicting PMN was evaluated using ROC curve analysis. A p-value below 0.05 was considered statistically significant.

RESULTS

This study included 89 individuals, 15 of whom were healthy volunteers. The mean age of the 74 patients was 44.1 years (SD: 12.7; range 21-65); 40 (54.1%) were male. Thirty patients (40.5%) had PMN, 10 (13.5%) had SMN, and 34 (45.9%) had non-MN nephrotic syndrome. Of the 10 SMN patients, five had hypertensive nephropathy, two had systemic lupus erythematosus, one had IgM nephropathy, one had anti-neutrophil cytoplasmic antibodies-associated glomerulonephritis, and one had infection-related glomerulonephritis. Of the 34 non-MN patients, 13 had IgA nephropathy, 11 had focal segmental glomerulosclerosis, 5 had membranoproliferative glomerulonephritis, 2 had minimal change disease, 1 had renal amyloidosis, and 1 had post-streptococcal glomerulonephritis. The mean age of PMN patients was 46.9 years (SD: 11.6; range 21-63); 18 (60%) were male. The mean age of SMN patients was 46.6 years (SD: 11.7; range 28-63); 3 (30%) were male. The mean age of non-MN nephrotic syndrome patients was 41.0 years (SD: 13.5; range 21-65); 19 (55.9%) were male.

Patient characteristics are presented in Table 1. Of the 30 PMN patients, 29 (96.7%) had received immunosuppressive therapy, while one (3.3%) had not. The numbers of patients receiving therapy, either alone or in combination, were as follows: 28 (93.3%) received steroids; 22 (73.3%) received cyclosporine A; two (6.7%) received tacrolimus; two (6.7%) received mycophenolate mofetil; one (3.3%) received azathioprine; and one (3.3%) received cyclophosphamide.

Anti-PLA2R antibody was positive in 9 of 30 PMN patients, whereas it was negative in all patients with SMN, in those with non-MN nephrotic syndrome, and in healthy volunteers. In one of the PMN patients, the anti-PLA2R antibody result was borderline. In this study, mean anti-PLA2R antibody levels were 31.8±55.3 RU/mL in patients with PMN, 1.1±0.09 RU/mL in patients with SMN, 1.1±0.1 RU/mL in patients with non-MN nephrotic syndrome, and 1.1±0.1 RU/mL in the healthy volunteers.

Among the 30 patients with PMN, four (13.3%) were enrolled at diagnosis, and all four had positive anti-PLA2R results (32.66, 119.2, 104.4, and 204 RU/mL, respectively).The remaining 26 patients (86.7%) were evaluated during follow-up. Of these, four had active disease; one was anti-PLA2R positive and another was borderline. Seventeen patients

Table 1. The features of the patients

	PMN (n=30) (mean±SD)	SMN (n=10) (mean±SD)	Non-MN (n=34) (mean±SD)	p
BUN (mg/dL)	21.8±10.2	21.8±13.5	18.1±10.2	0.11
Creatinine (mg/dL)	1.1±0.8	1.1±0.7	1.1±0.6	0.99
Urine total protein (mg/dL)	145.8±173.7	52±58.6	98.2±132.3	0.18
Albumin (g/L)	35.4±6.5	39.6±3.7	38.6±6.7	0.08
Hemoglobin (g/dL)	13.3±1.7	12.6±1.7	13.9±1.5	0.09
Hematocrit (%)	40.4±4.7	37.7±4.5	41.7±4.4	0.05
eGFR (mL/min/L)	82.4±36.2	79.9±35.2	85.7±34.8	0.79
Proteinuria (gr)	3±3.2	1.6±1.8	2.4±3.3	0.12

p<0.05 indicates statistical significance
BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, PMN: Primary membranous nephropathy, SD: Standard deviation, SMN: Secondary membranous nephropathy

were in partial remission, four of whom were anti-PLA2R positive. The remaining five patients were in complete remission, and all were anti-PLA2R negative (Figure 1).

The ELISA kit manufacturer's recommended cut-off value for anti-PLA2R antibody was 20 RU/mL. Using this cut-off value, sensitivity and specificity were 30% and 100%, respectively. ROC curve analysis (area under the curve=0.706 and p=0.003) determined a cut-off value of 1.19 RU/mL (Figure 2). The sensitivity, specificity, PPV, and NPV of the anti-PLA2R IgG ELISA test at different cut-off values are shown in Table 2.

The mean values of parameters related to glomerular disease activity were compared between patients who were anti-PLA2R IgG ELISA-positive and those who were anti-PLA2R IgG ELISA-negative. Anti-PLA2R antibody-positive patients had significantly higher mean proteinuria (p=0.015) and significantly lower mean albumin (p=0.010) levels than antibody-negative patients (Table 3).

Among those with positive anti-PLA2R IgG results, 44.4% had proteinuria levels <3.5 g/day and 55.6% had proteinuria levels >3.5 g/day. Among the patients with negative anti-PLA2R IgG results, 81.2% had proteinuria levels <3.5 g/day and 18.8% had proteinuria levels >3.5 g/day. Proteinuria levels differed significantly (p=0.027) between patients with positive and negative anti-PLA2R IgG ELISA results.

Differences in mean hemoglobin (p=0.030) and hematocrit (p=0.039) values between ELISA-confirmed anti-PLA2R IgG-positive and -negative individuals with PMN were statistically significant, whereas no significant differences were found in other parameters. The mean hemoglobin value of anti-PLA2R antibody positive patients was 12.3±1.3 and the mean hemoglobin value of negative patients was 13.9±1.7. The mean hematocrit value of anti-PLA2R antibody positive patients was 37.6±3.9, while the mean hematocrit value of negative patients was 41.7±4.7. The mean hemoglobin and

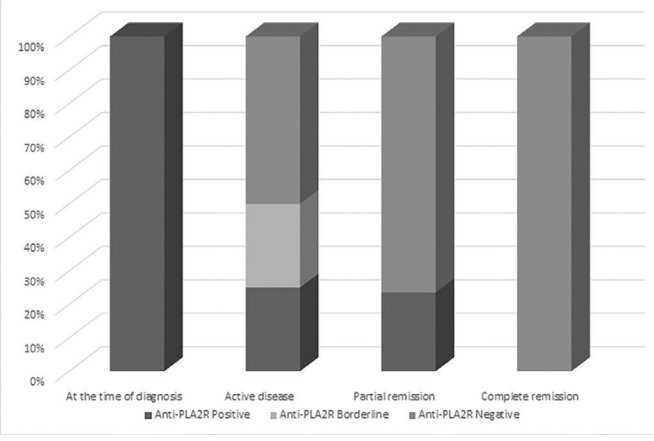

Figure 1. Anti-PLA2R positivity according to disease stages in 30 PMN patients
PMN: Primary membranous nephropathy, PLA2R: Phospholipase A2 receptor

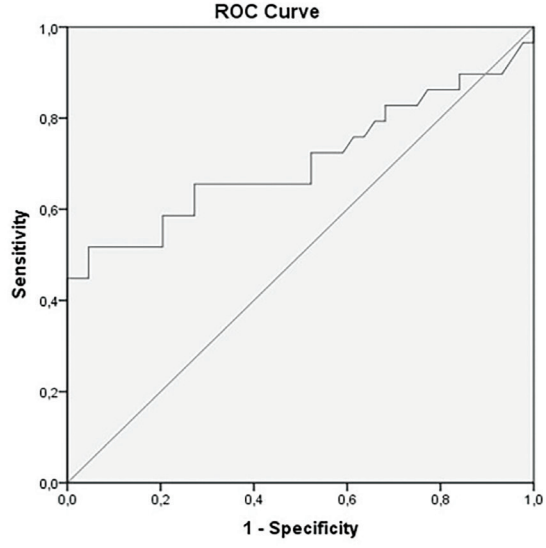

Figure 2. ROC curve analysis
ROC: Receiver operating characteristic

Table 2. Sensitivity, specificity, PPV and NPV of the test at different cut-off values

Cut-off value	Sensitivity	Specificity	PPV	NPV
40 RU/mL	20%	100%	100%	64.7%
20 RU/mL	30%	100%	100%	67.6%
14 RU/mL	33.3%	100%	100%	68.7%
2 RU/mL	46.6%	100%	100%	73.3%
1.19 RU/mL	66.6%	72.7%	62.5%	76.2%

NPV: Negative predictive value, PPV: Positive predictive value

hematocrit values of anti-PLA2R IgG-positive PMN patients were significantly lower than those of anti-PLA2R IgG-negative PMN patients (Table 4).

DISCUSSION

As a chronic immune-mediated glomerular disease, MN remains the predominant cause of nephrotic syndrome among adults. Accurate diagnosis of MN, effective treatment planning, and prognosis assessment are crucial. Anti-PLA2R antibodies are hypothesized to help differentiate primary

Table 3. Comparison of mean values of parameters associated with glomerular disease activity in patients with positive and negative anti-PLA2R IgG ELISA test

	Anti-PLA2R positive (mean±SD)	Anti-PLA2R negative (mean±SD)	p
BUN (mg/dL)	23.4±11.1	19.4±10.6	0.214
Creatinine (mg/dL)	1.1±0.6	1.1±0.7	0.913
eGFR (mL/min/L)	79.6±39.5	85±34.2	0.620
Albumin (mg/dL)	32.3±5.8	38.2±6.3	0.010
Proteinuria (gr)	3.6±2.1	2.4±3.2	0.015

p<0.05 indicates statistical significance
BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, PLA2R: Phospholipase A2 receptor, SD: Standard deviation, ELISA: Enzyme-linked immunosorbent assay, IgG: Immunoglobulin G

Table 4. Results of biochemical clinical parameters according to anti-PLA2R ELISA test in patients with PMN

	Anti-PLA2R positive (mean±SD)	Anti-PLA2R negative (mean±SD)	p
Urine total protein* (mg/dL)	171.9±147.9	129±188.9	0.140
Urine creatinine (mg/dL)	50.1±25.6	51.3±21.9	0.835
Urine albumin† (mg/dL)	125.4±119.7	95.7±156	0.127
Proteinuria (gr)	3.6±2.1	2.8±3.7	0.127
Glucose (mg/dL)	91.2±24.4	98.1±40.9	0.417
BUN (mg/dL)	23.4±11.1	20.4±9.8	0.472
Creatinine (mg/dL)	1.1±0.6	1.1±0.9	0.908
eGFR (mL/min/L)	79.6±39.5	86.4±34.2	0.594
Albumin (g/L)	32.3±5.8	37±6.6	0.069
LDL‡ (mg/dL)	115.4±40.1	147.8±62.1	0.153
HDL‡ (mg/dL)	68.3±41.1	64.2±16.5	0.532
Cholesterol‡ (mg/dL)	215.5±78.5	242.1±80.7	0.340
Triglyceride‡ (mg/dL)	159.3±55.5	150.2±79.8	0.417
Total calcium (mg/dL)	8.8±0.6	9.2±0.4	0.153
Potassium (mEq/L)	4.3±0.4	4.5±0.4	0.199
Sodium (mEq/L)	137.8±3.4	139±1.4	0.365
ALT (U/L)	23.2±16.3	19.6±8.3	0.799
Hemoglobin (g/dL)	12.3±1.3	13.9±1.7	0.030
Hematocrit (%)	37.6±3.9	41.7±4.7	0.039

p<0.05 indicates statistical significance
*Urine total protein of one patient was less than 1 in HIS, †: Urine albumin of five patients was less than 0.5 in HIS, ‡: LDL, HDL, cholesterol and triglyceride values of two patients could not be used in the study as it was not available
ALT: Alanine aminotransferase, BUN: blood urea nitrogen, eGFR: Estimated glomerular filtration rate, HDL: High density lipoprotein, LDL: Low density lipoprotein, PLA2R: Phospholipase A2 receptor, SD: Standard deviation, HIS: Hospital information system, ELISA: Enzyme-linked immunosorbent assay, PMN: Primary membranous nephropathy

MN from secondary forms of the disease. In addition to the diagnosis, these antibodies have been found to be useful in treatment decisions, assessment of clinical response, and prediction of prognosis (1,12,13).

Despite the cross-sectional design of the study, clinical characteristics were comparable across the PMN, SMN, and non-MN nephrotic syndrome groups, and there were no statistically significant differences ($p>0.05$) (Table 1). Using the manufacturer's recommended cut-off (20 RU/mL), anti-PLA2R positivity was detected only in PMN patients and not in other patient groups or healthy volunteers. These results indicate high specificity and high PPV. Accordingly, when secondary causes (e.g., autoimmune diseases, infections such as hepatitis, or malignancy) are carefully excluded, anti-PLA2R positivity may reduce the need for biopsy in MN patients in line with Kidney Disease: Improving Global Outcomes (KDIGO) 2021 (14). However, biopsy decisions should still be individualized. This may allow rapid diagnosis of MN and may reduce the risk of biopsy-related complications (4). These findings are consistent with Kim et al. (15), who reported negative anti-PLA2R results in SMN, non-MN nephrotic syndrome, and healthy controls.

The optimal cut-off value for the anti-PLA2R ELISA has not yet been standardized (4). In studies using the commercial ELISA kit (EUROIMMUN, Lübeck, Germany), anti-PLA2R positivity rates reported in PMN vary across populations. Differences across studies may reflect immunosuppressive therapy (IST) status, the presence of other target antibodies [e.g., thrombospondin type 1 domain-containing 7A (THSD7A)], *PLA2R* gene polymorphisms, and the interval between diagnosis and testing (11). Using the 20 RU/mL cut-off, positivity has been reported as 50% in Japanese patients, 62.2% in Chinese patients, 25% in Australian patients, and 48.5% in Greek patients (11,16). In our study, positivity at 20 RU/mL was 30% among PMN patients, closely similar to the rate reported in Australian patients.

Several factors may contribute to low or undetectable anti-PLA2R levels in patients with PMN. Anti-PLA2R may be negative when serum is collected during immunologic remission or while the patient is receiving IST. In addition, antibodies other than anti- PLA2R (e.g., THSD7A or other not-yet-identified antibodies) may contribute to the pathogenesis (8,17). In our study, anti-PLA2R was negative in some PMN patients; this may be explained by the factors mentioned above.

In our study, all four patients evaluated at the time of diagnosis, before initiation of IST, were anti-PLA2R positive, whereas anti-PLA2R was negative in all patients who were in complete remission and had normal proteinuria during follow-up (Figure 1). These findings support the view that anti-PLA2R may be a diagnostic and prognostic marker, particularly in patients who have not yet received treatment. KDIGO 2021 notes that anti-PLA2R levels >50 RU/mL may indicate high risk for progression and recommends monitoring antibody levels every 3-6 months. Decreasing antibody levels can predict clinical remission (14). In our study, the finding that all patients in complete remission were anti-PLA2R negative supports this. In addition, antibody seroconversion under IST may indicate a reduced risk of relapse. Therefore, anti-PLA2R monitoring may be a useful marker for predicting treatment response and determining the treatment plan.

Several studies have shown that the sensitivity, specificity, PPV, and NPV of ELISA assays vary according to the cut-off value used. Liu et al. (11), determined the cut-off value of 2.6 RU/mL by ROC analysis in Chinese patients and showed that increasing the cut-off increased specificity and PPV, whereas sensitivity and NPV decreased. Similarly, an Italian study reported sensitivity and specificity values of 61.1% and 99.7% at a cut-off of 20 RU/mL; lowering the cut-off to 14 RU/mL slightly increased sensitivity (63.5%) while maintaining high specificity. Alternatively, an ROC-derived cut-off of 2.7 RU/mL resulted in 83.3% sensitivity and 95.1% specificity (18). In our study, ROC analysis determined 1.19 RU/mL as the optimal cut-off (sensitivity 66.6%, specificity 72.7%, PPV 62.5%, NPV 76.2%). Applying a higher cut-off of 2 RU/mL reduced sensitivity to 46.6% but increased specificity to 100%. At a cut-off of 1.19 RU/mL, the risk of missed diagnoses decreases, and negative results more confidently rule out PMN; however, the increased risk of false- positive results may complicate diagnosis. At a cut-off of 2 RU/mL, diagnostic confidence increases, although some cases may be missed. In general, a higher cut-off may better reflect true clinical activity during follow-up. Nevertheless, the limited sample size restricts diagnostic reliability in our study. Larger studies are needed.

Anti-PLA2R antibody levels and proteinuria are widely used markers for prognostic assessment in MN (10). Previous studies have shown that anti-PLA2R antibodies are associated with disease activity and prognosis (19,20). Radice et al. (20) reported a linear association between anti-PLA2R positivity and higher proteinuria as well as lower serum albumin levels, and also demonstrated that anti-PLA2R antibody levels correlate with disease activity as assessed by proteinuria and other biomarkers. Consistent with these findings, anti-PLA2R-positive patients in our study had higher mean proteinuria ($p=0.015$) and lower mean serum albumin ($p=0.010$). Proteinuria >3.5 g/day is commonly

used to define nephrotic proteinuria and is routinely used to monitor MN activity (21-23). Our findings also showed a significant difference in proteinuria between anti-PLA2R-positive and anti-PLA2R-negative groups (p=0.027); anti-PLA2R positivity was more frequent among patients with nephrotic-range proteinuria. These results support the use of anti-PLA2R antibodies as a prognostic indicator with respect to proteinuria, a marker of disease activity. While Akiyama et al. (24) reported lower albumin in antibody-positive PMN patients, in our study, significantly lower hemoglobin and hematocrit values were also observed in anti-PLA2R-positive patients, whereas most other laboratory parameters did not differ significantly between groups.

The prognosis of PMN is heterogeneous: approximately one-third of patients achieve spontaneous remission, one-third have persistent proteinuria with stable renal function, and one-third progress to end-stage renal failure (21). Anemia is a serious complication in chronic renal failure and has been associated with high proteinuria (25,26). The combination of higher proteinuria and lower hemoglobin and hematocrit observed in anti-PLA2R-positive patients may be relevant to progression to chronic renal failure. Finally, detection of anti-PLA2R antibodies before the onset of proteinuria and before pathological diagnosis has been reported (27), further supporting their clinical importance and the need for additional studies.

Study Limitations

Our study had limitations. First, the number of patients was relatively low compared with those in other studies. Furthermore, because this was a cross-sectional study and because of financial difficulties, we were unable to follow up with patients; therefore, the relationship between remission/relapse rates and anti-PLA2R antibodies could not be determined.

CONCLUSION

In our study, a positive anti-PLA2R result using the manufacturer's recommended cut-off value may help to rule in PMN and reduce the need for biopsy, whereas a negative result may still require biopsy for confirmation. ROC curve analysis identified 1.19 RU/mL as the optimal cut-off; however, overall diagnostic performance in our dataset was better at 2 RU/mL. Anti-PLA2R positivity was associated with higher proteinuria and lower hemoglobin and hematocrit, suggesting that this antibody may have prognostic value and be linked to progression to chronic renal failure. Larger prospective studies are needed to clarify the clinical significance of anti-PLA2R antibody levels in MN.

ETHICS

Ethics Committee Approval: Ethical approval for the study was granted by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval no: 2022/120, date: 30.06.2022).

Informed Consent: Informed consent was obtained from each participant included in this study.

FOOTNOTES

This work was presented at the 7th National Congress of Clinical Microbiology, Muğla, Türkiye, in 2023.

This work is also included in Mustafa Erdem Sarp's thesis.

Authorship Contributions

Surgical and Medical Practices: M.E.S., R.K.K., Concept: M.E.S., I.B., G.B., N.K., R.K.K., E.Ö., F.A., Design: M.E.S., I.B., G.B., N.K., R.K.K., E.Ö., F.A., Data Collection or Processing: M.E.S., R.K.K., Analysis or Interpretation: M.E.S., I.B., G.B., Literature Search: M.E.S., I.B., G.B., N.K., R.K.K., E.Ö., F.A., Writing: M.E.S., I.B., G.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Ronco P, Beck L, Debiec H, Fervenza FC, Hou FF, Jha V, et al. Membranous nephropathy. Nat Rev Dis Primers. 2021;7:69.
2. Gu Y, Xu H, Tang D. Mechanisms of primary membranous nephropathy. Biomolecules. 2021;11:513.
3. Efe O, So PNH, Anandh U, Lerma EV, Wiegley N. An updated review of membranous nephropathy. Indian J Nephrol. 2024;34:105-18.
4. Ragy O, Abass W, Kanigicherla DAK, Shinkins B, Bestall J, King N, et al. PLA2R autoantibodies, a multifaceted biomarker in nephrotic syndrome and membranous nephropathy. Nephrol Dial Transplant. 2025;40:1458-69.
5. Keri KC, Blumenthal S, Kulkarni V, Beck L, Chongkrairatanakul T. Primary membranous nephropathy: comprehensive review and historical perspective. Postgrad Med J. 2019;95:23-31.
6. Akiyama S, Imai E, Maruyama S. Immunology of membranous nephropathy. F1000Res. 2019;8:F1000 Faculty Rev-734.
7. Hogan JJ, Zee J, Beck LH. Towards optimizing use of PLA2R antibody testing in membranous nephropathy. J Nephrol. 2021;34:557-9.
8. De Vriese AS, Glassock RJ, Nath KA, Sethi S, Fervenza FC. A proposal for a serology-based approach to membranous nephropathy. J Am Soc Nephrol. 2017;28:421-30.
9. Timmermans SA, Damoiseaux JG, Heerings-Rewinkel PT, Ayalon R, Beck LH Jr, Schlumberger W, et al.; Limburg Renal Registry. Evaluation of anti-PLA2R1 as measured by a novel ELISA in patients with idiopathic membranous nephropathy: a cohort study. Am J Clin Pathol. 2014;142:29-34.

10. De Vriese AS, Wetzels JFM. Membranous nephropathy: treatment and prognosis. UpToDate. Updated September 19, 2025. Available from: https://www.uptodate.com/contents/membranous-nephropathy-treatment-and-prognosis
11. Liu Y, Li X, Ma C, Wang P, Liu J, Su H, et al. Serum anti-PLA2R antibody as a diagnostic biomarker of idiopathic membranous nephropathy: the optimal cut-off value for Chinese patients. Clin Chim Acta. 2018;476:9-14.
12. Alsharhan L, Beck LH Jr. Membranous nephropathy: core curriculum 2021. Am J Kidney Dis. 2021;77:440-53.
13. Obrisca B, Ismail G, Jurubita R, Baston C, Andronesi A, Mircescu G. Antiphospholipase A2 receptor autoantibodies: a step forward in the management of primary membranous nephropathy. Biomed Res Int. 2015;2015:249740.
14. Kidney Disease: Improving Global Outcomes (KDIGO) glomerular diseases work group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100:S1-276.
15. Kim YG, Choi YW, Kim SY, Moon JY, Ihm CG, Lee TW, et al. Anti-phospholipase A2 receptor antibody as prognostic indicator in idiopathic membranous nephropathy. Am J Nephrol. 2015;42:250-7.
16. Provatopoulou S, Kalavrizioti D, Stangou M, Kouri MN, Kalliakmani P, Papasotiriou M, et al. Circulating anti-phospholipase A2 receptor antibodies as a diagnostic and prognostic marker in Greek patients with idiopathic membranous nephropathy - a retrospective cohort study. Rom J Intern Med. 2019;57:141-50.
17. Fervenza FC, Glassock RJ, Bleyer AJ. American Society of Nephrology Quiz and Questionnaire 2012: glomerulonephritis. Clin J Am Soc Nephrol. 2013;8:1460-5.
18. Porcelli B, Guarnieri A, Ferretti F, Garosi G, Terzuoli L, Cinci F, et al. Diagnostic accuracy of anti-phospholipase A2 receptor (PLA2R) antibodies in idiopathic membranous nephropathy: an Italian experience. J Nephrol. 2021;34:573-9.
19. Hoxha E, Thiele I, Zahner G, Panzer U, Harendza S, Stahl RA. Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. J Am Soc Nephrol. 2014;25:1357-66.
20. Radice A, Trezzi B, Maggiore U, Pregnolato F, Stellato T, Napodano P, et al. Clinical usefulness of autoantibodies to M-type phospholipase A2 receptor (PLA2R) for monitoring disease activity in idiopathic membranous nephropathy (IMN). Autoimmun Rev. 2016;15:146-54.
21. Hoxha E, Harendza S, Zahner G, Panzer U, Steinmetz O, Fechner K, et al. An immunofluorescence test for phospholipase-A_2-receptor antibodies and its clinical usefulness in patients with membranous glomerulonephritis. Nephrol Dial Transplant. 2011;26:2526-32.
22. Haider MZ, Aslam A. Proteinuria. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Updated 2023 Sep 4. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564390/
23. Claudio P. Primary membranous nephropathy: an endless story. J Nephrol. 2023;36:563-74.
24. Akiyama S, Akiyama M, Imai E, Ozaki T, Matsuo S, Maruyama S. Prevalence of anti-phospholipase A2 receptor antibodies in Japanese patients with membranous nephropathy. Clin Exp Nephrol. 2015;19:653-60.
25. Fishbane S, Spinowitz B. Update on anemia in ESRD and earlier stages of CKD: core curriculum 2018. Am J Kidney Dis. 2018;71:423-35.
26. Shiferaw WS, Akalu TY, Aynalem YA. Risk factors for anemia in patients with chronic renal failure: a systematic review and meta-analysis. Ethiop J Health Sci. 2020;30:829-42.
27. Burbelo PD, Joshi M, Chaturvedi A, Little DJ, Thurlow JS, Waldman M, et al. Detection of PLA2R autoantibodies before the diagnosis of membranous nephropathy. J Am Soc Nephrol. 2020;31:208-17.

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Research

Preoperative Radiographic Instability does not Always Require Syndesmotic Screw Fixation in Isolated Lateral Malleolus Fractures

Preoperatif Radyografik İnstabilite, İzole Lateral Malleol Kırıklarında Her Zaman Sindezmoz Vidası ile Tespiti Gerektirmez

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ABSTRACT

Objective: To compare pain, functional outcomes, and complication rates in patients with isolated lateral malleolus fractures who were considered to have syndesmotic instability on preoperative radiographic evaluation but were treated with or without syndesmotic screw fixation according to intraoperative assessment after fibular fixation.

Methods: This retrospective cohort study included 43 adult patients who underwent surgical treatment for isolated lateral malleolus fractures and had preoperative radiographic findings suggestive of syndesmotic instability. After open reduction and internal fixation of the fibula, syndesmotic stability was reassessed intraoperatively under fluoroscopy using the Cotton test, with additional external rotation stress testing when needed. Patients were divided into a stable group who did not require syndesmotic fixation (n=23) and an unstable group who underwent syndesmotic screw fixation (n=20). Pain was assessed using the visual analogue scale (VAS) at 1 year postoperatively, and functional outcome was assessed using the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score at 2 years postoperatively.

Results: The median age was 28 years [interquartile range (IQR), 22-45], and the median follow-up was 30 months (IQR, 26-44). Baseline demographic characteristics and follow-up duration were comparable between groups. Median VAS scores were 1 (IQR, 1-2) in the stable group and 1 (IQR, 1-2.75) in the unstable group (p=0.633). Median AOFAS scores were 91 (IQR, 88-93) and 90.5 (IQR, 82.25-93.50), respectively (p=0.750). Complication rates were 4.3% and 15.0%, respectively; the difference was not statistically significant (p=0.395).

Conclusion: Selective syndesmotic fixation based on intraoperative assessment after fibular fixation may be a reasonable strategy for radiographically unstable, isolated lateral malleolus fractures.

Keywords: Isolated lateral malleolus fracture, syndesmotic instability, syndesmotic screw fixation, Cotton test, intraoperative assessment, ankle fracture

ÖZ

Amaç: Bu çalışmada, preoperatif radyografik değerlendirmede sindezmotik instabil olduğu düşünülen izole lateral malleol kırıklı hastalarda, fibula tespiti sonrası yapılan intraoperatif değerlendirmeye göre sindezmoz vidası uygulanan ve uygulanmayan olguların ağrı, fonksiyonel sonuçlar ve komplikasyon oranları açısından karşılaştırılması amaçlandı.

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ÖZ

Gereç ve Yöntem: Bu retrospektif kohort çalışmasına, preoperatif radyografilerinde sindezmotik instabilite düşündüren bulgular saptanan ve izole lateral malleol kırığı nedeniyle cerrahi tedavi uygulanan 43 erişkin hasta dahil edildi. Fibulanın açık redüksiyon ve internal tespitinin ardından sindezmotik stabilite, floroskopi eşliğinde Cotton testi ile yeniden değerlendirildi; gerekli görülen olgularda ek olarak dış rotasyon stres testi uygulandı. Hastalar, intraoperatif değerlendirme sonucuna göre sindezmoz tespiti gerekmeyen stabil grup (n=23) ve sindezmoz vidası uygulanan instabil grup (n=20) olarak iki gruba ayrıldı. Ağrı düzeyi postoperatif 1. yılda görsel analog skala (VAS) ile, fonksiyonel sonuçlar ise postoperatif 2. yılda Amerikan Ortopedik Ayak ve Ayak Bileği Derneği Ayak Bileği (AOFAS) Arka Ayak Skoru ile değerlendirildi.

Bulgular: Ortanca yaş 28 [çeyrekler arası aralık (ÇAA), 22-45] yıl, ortanca takip süresi ise 30 (ÇAA, 26-44) ay idi. Gruplar arasında başlangıç demografik özellikleri ve takip süreleri açısından anlamlı fark saptanmadı. Ortanca VAS skoru stabil grupta 1 (ÇAA, 1-2), instabil grupta 1 (ÇAA, 1-2,75) idi (p=0,633). Ortanca AOFAS skoru sırasıyla 91 (ÇAA, 88-93) ve 90,5 (ÇAA, 82,25-93,50) olarak bulundu (p=0,750). Komplikasyon oranları sırasıyla %4,3 ve %15,0 olup, gruplar arasında istatistiksel olarak anlamlı fark yoktu (p=0,395).

Sonuç: Fibula tespiti sonrası yapılan intraoperatif değerlendirmeye dayalı seçici sindezmoz tespiti, radyografik olarak instabil görünen izole lateral malleol kırıklarında uygun bir tedavi stratejisi olabilir.

Anahtar Kelimeler: İzole lateral malleol kırığı, sindezmotik instabilite, sindezmoz vidası, Cotton testi, intraoperatif değerlendirme, ayak bileği kırığı

INTRODUCTION

Ankle fractures are among the most common injuries in orthopedic trauma practice, accounting for approximately 9-10% of all lower extremity fractures (1). Restoration of anatomical congruity and joint stability is essential for successful treatment, and the integrity of the distal tibiofibular syndesmosis plays a central role in ankle stability, load transmission, and long-term functional outcome. The distal tibiofibular syndesmosis is a complex ligamentous structure that stabilizes the distal tibia and fibula and comprises the anterior and posterior inferior tibiofibular ligaments, the interosseous ligament, and the interosseous membrane. These structures contribute differently but synergistically to syndesmotic stability. Previous studies have shown that the interosseous ligament contributes 22% to overall stability, the anterior inferior tibiofibular ligament contributes 35%, the superficial posterior inferior tibiofibular ligament contributes 9%, and the deep posterior inferior tibiofibular ligament contributes 33%. The anterior inferior tibiofibular ligament is the primary restraint to fibular external rotation, whereas the posterior inferior tibiofibular ligament primarily resists posterior translation (2,3).

Failure to recognize syndesmotic injury may result in chronic instability, persistent pain, functional impairment, and early degenerative change. Clinical and intraoperative stress tests, including the Cotton test, fibular translation test, squeeze test, and external rotation stress test, are commonly used to evaluate syndesmotic integrity by detecting abnormal motion or pain provocation relative to the contralateral side (4-6). Preoperative radiographic parameters, such as medial clear space (MCS) widening and decreased tibiofibular overlap (TFO), are widely used to identify syndesmotic instability. However, because these measurements are based on static imaging, they may not always reflect true mechanical stability. Previous studies have shown that some fractures meeting radiographic criteria for instability may appear stable during intraoperative assessment (7). This discrepancy continues to complicate indications for syndesmotic fixation. Unnecessary fixation may increase implant-related complications, reoperation rates, and cost, whereas failure to stabilize true instability may adversely affect long-term outcomes (8,9).

Although preoperative radiographic findings may suggest syndesmotic instability in isolated lateral malleolus fractures, it remains unclear whether all such patients require syndesmotic screw fixation after definitive fibular reduction and fixation. Because restoration of fibular length, alignment, and rotation may re-establish syndesmotic stability in a subset of cases, intraoperative dynamic assessment may provide additional guidance for surgical decision-making. Nevertheless, the adequacy of commonly used intraoperative stress tests, such as the Cotton test and external rotation stress test, remains controversial. The purpose of this study was to compare clinical outcomes in patients with isolated lateral malleolus fractures who were deemed radiographically unstable preoperatively and were treated, with or without syndesmotic screw fixation, based on intraoperative findings following fibular fixation. We hypothesized that omission of syndesmotic screw fixation in patients without residual instability on intraoperative assessment would not result in worse pain or functional outcomes compared with patients who underwent syndesmotic fixation.

METHODS

This retrospective cohort study evaluated patients who underwent surgical treatment for isolated lateral malleolus fractures at a single tertiary referral center. The study protocol was approved by the Acıbadem Mehmet Ali Aydınlar

University Medical Research Evaluation Board (approval no: 2026-03/27, date: 05.02.2026), and all procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki.

Patients who underwent operative treatment for an isolated lateral malleolus fracture were screened for eligibility. Patients aged 18 years or older were considered for inclusion. Only patients with preoperative radiographic findings suggestive of syndesmotic instability who underwent intraoperative syndesmotic assessment after fibular fixation were included in the study. Exclusion criteria were: open fractures; associated bimalleolar or trimalleolar fractures; pilon fractures; previous surgery on the ipsilateral ankle; syndesmotic fixation performed by methods other than screw fixation; and insufficient clinical follow-up. After applying the inclusion and exclusion criteria, 43 patients were included in the final analysis. Standard preoperative ankle radiographs, including anteroposterior, lateral, and mortise views, were reviewed for all patients. Syndesmotic instability was assessed using established radiographic parameters, specifically the MCS and the TFO. Radiographic measurements were performed independently by two experienced orthopaedic surgeons. In cases of disagreement, the final decision was reached by consensus. Only patients who were considered radiographically unstable based on these preoperative measurements constituted the study population. All patients underwent open reduction and internal fixation of the fibular fracture through a standard lateral approach. After restoration of fibular length, alignment, and rotation, fracture fixation was performed using plate-and-screw osteosynthesis according to standard operative principles. Because all included patients had preoperative radiographic findings suggestive of syndesmotic instability, syndesmotic stability was reassessed intraoperatively after definitive fibular fixation. Under fluoroscopic guidance, dynamic syndesmotic evaluation was performed using the Cotton test, and an additional external rotation stress assessment was performed at the operating surgeon's discretion when further confirmation was required. The purpose of this intraoperative reassessment was to determine whether instability persisted after anatomic reduction and stabilization of the fibula, as fixation alone may restore apparent syndesmotic stability in a subset of patients. Because restoration of fibular length and rotation may re-establish apparent syndesmotic stability in some fractures, intraoperative dynamic assessment was used to determine whether syndesmotic fixation remained necessary after definitive fibular fixation. If no pathologic widening or residual instability of the distal tibiofibular joint was observed during intraoperative testing, no additional syndesmotic fixation was performed. If persistent instability was demonstrated, syndesmotic fixation was performed using a trans-syndesmotic screw under fluoroscopic control. In patients treated with syndesmotic screw fixation, implant removal was routinely planned between postoperative weeks 8 and 12 according to institutional practice.

Patients were categorized based on the results of the intraoperative Cotton test performed after fibular fixation. Patients with no residual syndesmotic instability, and therefore no need for syndesmotic fixation, were assigned to the stable group (Cotton test-negative, n=23). Patients with persistent intraoperative instability requiring syndesmotic screw fixation were assigned to the unstable group (Cotton test-positive, n=20). This grouping strategy allowed the comparison of outcomes between patients who were considered unstable on preoperative radiographic assessment but who were managed differently based on intraoperative syndesmotic evaluation after fracture fixation.

Patients were followed weekly until the third postoperative week, then every 3 months during the first postoperative year, and annually thereafter. During follow-up, wound problems, infection, and other surgery-related adverse events were recorded. In the syndesmotic fixation group, implant-related complications, including loosening, pull-out, breakage, or migration of the syndesmotic screw, were also documented. Pain and functional outcomes were assessed using validated clinical measures. Pain severity was evaluated using the visual analogue scale (VAS) at 1 year postoperatively. Functional outcome was assessed using the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score at 2 years postoperatively. The primary outcomes of the study were to compare postoperative pain and functional outcomes between patients with preoperatively suspected syndesmotic instability who did or did not require syndesmotic screw fixation, based on intraoperative assessment after fibular fixation. Secondary outcomes included a comparison of complication rates between the two groups.

Statistical Analysis

Normality of continuous variables was assessed using both the Kolmogorov-Smirnov and Shapiro-Wilk tests. Because age, follow-up duration, postoperative first-year VAS scores, and postoperative second-year AOFAS scores were not normally distributed, continuous variables were presented as medians and interquartile ranges (IQRs). Categorical variables were expressed as numbers and percentages. Comparisons between the stable and unstable groups were performed using the Mann-Whitney U test for continuous

variables and the chi-square or Fisher's exact test, as appropriate, for categorical variables. All statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 30.0 (IBM Corp., Armonk, NY, USA). Given the retrospective design of the study, no a priori sample size calculation was performed. A post-hoc sensitivity (power) analysis based on the final sample size of 43 patients (23 in the stable group and 20 in the unstable group), assuming a two-sided alpha of 0.05 and a power of 80%, indicated that the study was powered to detect a large between-group effect size.

RESULTS

A total of 43 patients met the inclusion criteria and were included in the final analysis. Based on the intraoperative Cotton test performed after fibular fixation, 23 patients were assigned to the stable group (Cotton test-negative) and 20 patients to the unstable group (Cotton test-positive). The overall median age was 28 years (IQR, 22-45). The cohort consisted predominantly of male patients (33/43, 76.7%), and the right ankle was more frequently involved than the left (29/43, 67.4% vs. 14/43, 32.6%). Normality testing demonstrated that age, follow-up duration, postoperative first-year VAS and second-year AOFAS scores were not normally distributed, as shown by both Kolmogorov-Smirnov and Shapiro-Wilk analyses (all p<0.05) (Table 1). Accordingly, continuous variables were expressed as the median and IQR, and non-parametric methods were used for comparisons between groups.

There were no significant between-group differences in baseline demographic characteristics (Table 2). The median age was 31 years (IQR, 24-45) in the stable group and 26 years (IQR, 20.25-42.75) in the unstable group (p=0.150). Sex distribution was also comparable between groups (male: 69.6% vs. 85.0%; p=0.294), as was injury side (right-sided injuries: 73.9% vs. 60.0%; p=0.331). The median follow-up duration for the entire cohort was 30 months. Follow-up duration was similar between the two groups, with a

Table 1. Normality assessment of continuous study variables

	Kolmogorov-Smirnov*	df	Sig.	Shapiro-Wilk	df	Sig.
Age	0.180	43	0.001	0.874	43	<0.001
Follow-up	0.207	43	<0.001	0.874	43	<0.001
VAS 1st year	0.348	43	<0.001	0.793	43	<0.001
AOFAS 2nd year	0.178	43	0.001	0.900	43	0.001

Values are presented as test statistics for normality
*Lilliefors significance correction was applied for the Kolmogorov-Smirnov test
VAS: Visual analogue scale, AOFAS: American Orthopaedic Foot and Ankle Society, Sig.: Significance, df: Degrees of freedom

Table 2. Comparison of baseline characteristics, clinical outcomes, and complications between groups

	Stable group (Cotton-) (n=23)	Unstable group (Cotton+) (n=20)	p*
Age (year)	31 (24-45)	26 (20.25-42.75)	0.150
Gender, n (%)			
Male	16 (69.6)	17 (85)	0.294
Female	7 (30.4)	3 (15)	
Side, n (%)			
Right	17 (73.9)	12 (60)	0.331
Left	6 (26.1)	8 (40)	
Follow-up (months)	34 (26-44)	29.50 (26-42.5)	0.434
VAS (1 year)	1 (1-2)	1 (1-2.75)	0.633
AOFAS (2 years)	91 (88-93)	90.50 (82.25-93.50)	0.750
Complication, n (%)			
None	22 (95.7)	17 (85)	0.395
Revision	0 (0)	1 (5)	
Infection	1 (4.3)	2 (10)	

Continuous variables are presented as median (interquartile range), and categorical variables as number (%)
* p-values were calculated using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test, as appropriate, for categorical variables
VAS: Visual analogue scale, AOFAS: American Orthopaedic Foot and Ankle Society

median of 34 months (IQR, 26-44) in the stable group and 29.5 months (IQR, 26-42.5) in the unstable group (p=0.434). Clinical outcomes did not differ significantly between groups. At 1 year postoperatively, the median VAS pain score was 1 (IQR, 1-2) in the stable group and 1 (IQR, 1-2.75) in the unstable group (p=0.633). At 2 years postoperatively, the median AOFAS Ankle-Hindfoot Score was 91 (IQR, 88-93) in the stable group and 90.5 (IQR, 82.25-93.50) in the unstable group (p=0.750) (Table 2).

Complications were infrequent overall. No complications occurred in 39 patients (90.7%); 4 patients (9.3%) experienced at least one complication. One patient (2.3%) required revision surgery because of screw pull-out, and 3 patients (7.0%) developed infections. The overall complication rate was 4.3% (1/23) in the stable group and 15.0% (3/20) in the unstable group; however, this difference did not reach statistical significance (p=0.395) (Table 2). Overall, patients with preoperative radiographic findings suggestive of syndesmotic instability had comparable pain, functional outcomes, and complication rates, regardless of whether syndesmotic screw fixation was required on intraoperative assessment.

DISCUSSION

In this study, patients with isolated lateral malleolus fractures and preoperative radiographic parameters suggestive of syndesmotic instability had similar mid-term pain, functional outcomes, and complication profiles irrespective of whether syndesmotic screw fixation was added after an intraoperative assessment performed following fibular fixation. These results are clinically relevant because they challenge the assumption that radiographic instability detected preoperatively uniformly necessitates syndesmotic fixation. Instead, they support the notion that anatomic restoration of the fibula may, in some cases, sufficiently restore distal tibiofibular stability, making intraoperative dynamic evaluation a potentially useful determinant of the need for additional fixation. Given the persistent debate regarding the sensitivity and specificity of intraoperative stress tests, our findings do not imply that syndesmotic fixation can be safely omitted in all radiographically unstable fractures; rather, they suggest that selective fixation guided by post-fixation intraoperative assessment may achieve satisfactory outcomes without apparent short- to mid-term clinical disadvantage.

Preoperative radiographic parameters are widely used to assess syndesmotic instability in ankle fractures, with increased MCS and decreased TFO generally regarded as key indicators. However, because these measurements are derived from static imaging, they may not accurately reflect the functional severity of mechanical instability (10,11). This limitation has been consistently highlighted in the literature. Gardner et al. (12) reported that standard radiographic measurements lack sufficient sensitivity for evaluating reduction of the distal tibiofibular syndesmosis and suggested that advanced imaging modalities may provide greater diagnostic accuracy. Likewise, Nielson et al. (13) demonstrated that tibiofibular clear space and TFO on conventional radiographs were not significantly associated with magnetic resonance imaging-confirmed syndesmotic injury, further underscoring the diagnostic shortcomings of static radiographic assessment. Radiographic findings suggestive of instability also do not invariably correspond to intraoperative dynamic evaluation. Jenkinson et al. (14) demonstrated that discrepancies may exist between preoperative radiographic indicators and intraoperative stress testing in ankle fractures caused by external rotation mechanisms, emphasizing the importance of intraoperative assessment in guiding fixation decisions. Consistent with these observations, a subset of patients in the present study fulfilled preoperative radiographic criteria for syndesmotic instability but had negative intraoperative Cotton test findings; accordingly, syndesmotic screw fixation was not performed in these cases.

The anatomical and biomechanical characteristics of the distal tibiofibular syndesmosis further underscore the limitations of static radiographic evaluation. Rather than functioning as a rigid articulation, the syndesmotic complex is a dynamic structure that allows a small but physiologically important degree of motion necessary for normal ankle mechanics. Beumer et al. (9) demonstrated that measurable micromotion exists even in an intact syndesmosis, challenging the traditional view of the distal tibiofibular joint as a fixed construct. In agreement with this concept, Hu et al. (15), using three-dimensional kinematic analysis, showed that the fibula undergoes position- and load-dependent translation and rotation relative to the tibia under physiological conditions. These findings indicate that subtle syndesmotic motion may represent normal functional behavior rather than pathological instability. Taken together, these biomechanical insights suggest that static radiographic measurements may inadequately capture the dynamic stability of the syndesmosis. This may partly explain the discrepancy between preoperative radiographic indicators and intraoperative stress testing observed in both the literature and the present study. Reliance on static parameters alone may therefore overestimate instability and lead to unnecessary fixation.

In the present study, the absence of significant differences in pain scores and functional outcomes between the stable and unstable groups suggests that selective syndesmotic fixation, guided by intraoperative stability testing, may be a safe and reasonable strategy. Such an approach may offer important clinical advantages by reducing complications related to unnecessary implant placement. Syndesmotic screw fixation has been associated with a range of adverse events, including screw loosening, breakage, and mechanical irritation at the fixation site (16-21). Huang et al. (18) evaluated radiographic changes after syndesmotic screw removal and found that syndesmotic diastasis occurred predominantly before, rather than as a result of, screw removal; moreover, removal did not significantly alter TFO or clear space measurements. These findings question routine reliance on implant-based stabilization and further emphasize the dynamic nature of the syndesmotic complex. Collectively, the available evidence, together with the findings of the present study, supports a selective fixation strategy based on intraoperative functional assessment. Avoiding routine syndesmotic screw placement in patients without confirmed residual instability may help minimize implant-related morbidity without compromising clinical outcomes. Schepers et al. (22) reported that routine removal of syndesmotic screws was associated with clinically relevant complications, including wound infection, recurrent syndesmotic diastasis, and implant failure. They further noted that early screw removal increased the risk of recurrent diastasis, whereas prolonged retention increased the likelihood of screw breakage. These findings support a selective approach to both fixation and screw removal, with careful consideration of timing and indications. Similarly, Wójtowicz et al. (23) found no significant functional differences between patients with retained and removed syndesmotic screws in their study, but emphasized that removal should be reserved for clearly indicated cases because of procedure-related morbidity and the absence of consistent clinical benefit. This further reinforces the importance of avoiding routine hardware removal unless specific symptoms or indications are present. In addition, a recent systematic review evaluating fixation techniques for Weber B ankle fractures found that syndesmotic screws did not result in superior functional outcomes compared with cases managed without screw fixation, while remaining prone to complications such as loosening and breakage (24). This finding aligns with the present results, which show no statistically significant difference in complication rates between the stable and unstable groups, and further supports the view that the inherent disadvantages of screw fixation may outweigh its benefits in the absence of confirmed instability. Although the complication rate was numerically higher in the unstable group, the difference was not statistically significant, which further supports the potential value of avoiding unnecessary fixation.

To the best of our knowledge, studies specifically focusing on isolated lateral malleolus fractures that meet preoperative radiographic criteria for syndesmotic instability yet demonstrate intraoperative stability remain scarce. Most previous investigations have concentrated on radiographic assessment, fixation techniques, or screw removal outcomes, rather than directly correlating intraoperative stability testing with subsequent pain and functional outcomes in this distinct subgroup. The present study addresses this clinically relevant gap by evaluating outcomes according to intraoperative Cotton test findings and selective syndesmotic fixation. In doing so, it provides additional insight into the role of dynamic intraoperative assessment in surgical decision-making and contributes to the ongoing debate regarding potential overtreatment when fixation decisions rely solely on static radiographic parameters.

Study Limitations

Several limitations of this study should be considered. The retrospective design may introduce selection bias and preclude causal interpretation. The relatively small sample size may have limited the ability to detect subtle but clinically relevant between-group differences. Intraoperative syndesmotic instability was assessed using dynamic stress tests, mainly the Cotton test, with additional external rotation stress testing when required; however, the diagnostic performance of these methods may remain a matter of debate. Moreover, postoperative advanced imaging was not routinely performed; therefore, syndesmotic reduction was not evaluated with computed tomography. The single-center nature of the study may also restrict the generalizability of the findings. Nevertheless, this study has notable strengths. It examined a well-defined, clinically relevant subgroup of isolated lateral malleolus fractures with preoperative radiographic suspicion of syndesmotic instability and addressed a practical surgical question regarding the need for additional syndesmotic fixation after fibular stabilization. The direct comparison of selectively fixed and nonfixed patients provides clinically meaningful evidence that supports an intraoperatively guided treatment strategy in appropriately selected cases.

CONCLUSION

Among patients with isolated lateral malleolus fractures who were considered to have syndesmotic instability on

preoperative radiographic evaluation, a selective treatment strategy based on intraoperative assessment after fibular fixation resulted in similar levels of pain, functional outcomes, and complication rates irrespective of whether syndesmotic screw fixation was performed. Our findings indicate that routine syndesmotic fixation may not be necessary in all radiographically unstable cases, and they support the potential value of intraoperative dynamic evaluation in surgical decision-making. However, these results should be interpreted with caution, and prospective studies with larger cohorts are warranted to validate this approach.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (approval no: 2026-03/27, date: 05.02.2026).

Informed Consent: Retrospective study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: Y.İ., M.Y.A., D.A., T.K., Concept: Y.İ., M.Y.A., D.A., T.K., Design: Y.İ., M.Y.A., D.A., T.K., Data Collection or Processing: Y.İ., M.Y.A., D.A., T.K., Analysis or Interpretation: Y.İ., M.Y.A., D.A., T.K., Literature Search: Y.İ., M.Y.A., D.A., T.K., Writing: Y.İ., M.Y.A., D.A., T.K.

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REFERENCES

1. Cao MM, Zhang YW, Hu SY, Rui YF. A systematic review of ankle fracture-dislocations: recent update and future prospects. Front Surg. 2022;9:965814.
2. Van Heest TJ, Lafferty PM. Injuries to the ankle syndesmosis. J Bone Joint Surg Am. 2014;96:603-13.
3. Bejarano-Pineda L, Guss D, Waryasz G, DiGiovanni CW, Kwon JY. The syndesmosis, part I: anatomy, injury mechanism, classification, and diagnosis. Orthop Clin North Am. 2021;52:403-15.
4. Harper MC. An anatomic and radiographic investigation of the tibiofibular clear space. Foot Ankle. 1993;14:455-8.
5. Zalavras C, Thordarson D. Ankle syndesmotic injury. J Am Acad Orthop Surg. 2007;15:330-9.
6. Sman AD, Hiller CE, Refshauge KM. Diagnostic accuracy of clinical tests for diagnosis of ankle syndesmosis injury: a systematic review. Br J Sports Med. 2013;47:620-8.
7. Kaya E, Tasdemir Z, Erdogan O, Akbas F. Reliability of preoperative CT and intraoperative manual tests in syndesmosis injury. North Clin Istanb. 2024;11:52-9.
8. Vivtcharenko VY, Giarola I, Salgado F, Li S, Wajnsztejn A, Giordano V, et al. Comparison between cotton test and tap test for the assessment of coronal syndesmotic instability: a cadaveric study. Injury. 2021;52(Suppl 3):S84-8.
9. Beumer A, Valstar ER, Garling EH, Niesing R, Ranstam J, Löfvenberg R, et al. Kinematics of the distal tibiofibular syndesmosis: radiostereometry in 11 normal ankles. Acta Orthop Scand. 2003;74:337-43.
10. Sowman B, Radic R, Kuster M, Yates P, Breidiel B, Karamfilef S. Distal tibiofibular radiological overlap: does it always exist? Bone Joint Res. 2012;1:20-4.
11. Dikos GD, Heisler J, Choplin RH, Weber TG. Normal tibiofibular relationships at the syndesmosis on axial CT imaging. J Orthop Trauma. 2012;26:433-8.
12. Gardner MJ, Demetrakopoulos D, Briggs SM, Helfet DL, Lorich DG. Malreduction of the tibiofibular syndesmosis in ankle fractures. Foot Ankle Int. 2006;27:788-92.
13. Nielson JH, Gardner MJ, Peterson MG, Sallis JG, Potter HG, Helfet DL, et al. Radiographic measurements do not predict syndesmotic injury in ankle fractures: an MRI study. Clin Orthop Relat Res. 2005;216-21.
14. Jenkinson RJ, Sanders DW, Macleod MD, Domonkos A, Lydestadt J. Intraoperative diagnosis of syndesmosis injuries in external rotation ankle fractures. J Orthop Trauma. 2005;19:604-9.
15. Hu WK, Chen DW, Li B, Yang YF, Yu GR. Motion of the distal tibiofibular syndesmosis under different loading patterns: a biomechanical study. J Orthop Surg (Hong Kong). 2019;27:2309499019842879.
16. Vohra R, Singh A, Thorat B, Patel D. Instability of the distal tibiofibular syndesmosis. J Orthop Surg (Hong Kong). 2023;31:10225536231182349.
17. van den Bekerom MP, Hogervorst M, Bolhuis HW, van Dijk CN. Operative aspects of the syndesmotic screw: review of current concepts. Injury. 2008;39:491-8.
18. Huang CT, Huang PJ, Lu CC, Shih CL, Cheng YM, Chen SJ. Syndesmosis changes before and after syndesmotic screw removal: a retrospective radiographic study. Medicina (Kaunas). 2022;58:445.
19. Andersen MR, Frihagen F, Madsen JE, Figved W. High complication rate after syndesmotic screw removal. Injury. 2015;46:2283-7.
20. Song DJ, Lanzi JT, Groth AT, Drake M, Orchowski JR, Shaha SH, et al. The effect of syndesmosis screw removal on the reduction of the distal tibiofibular joint: a prospective radiographic study. Foot Ankle Int. 2014;35:543-8.
21. Kennedy MA, Sama AE, Sigman M. Tibiofibular syndesmosis and ossification. Case report: sequelae of ankle sprain in an adolescent football player. J Emerg Med. 2000;18:233-40.
22. Schepers T, Van Lieshout EM, de Vries MR, Van der Elst M. Complications of syndesmotic screw removal. Foot Ankle Int. 2011;32:1040-4.
23. Wójtowicz BG, Chawrylak K, Lesman J, Makowski H, Kuczyński K, Maciejowski M, et al. Routine removal of syndesmotic screws after tibiofibular syndesmosis fixation does not affect patient function and is associated with a higher risk of postoperative complications. J Clin Med. 2025;14:3276.
24. Lim B, Shaalan M, O'hEireamhoin S, Lyons F. Syndesmotic fixation in Weber B ankle fractures: a systematic review. PLoS One. 2024;19:e0304148.

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Research

Is Atopy Less Common in *Helicobacter pylori*-Positive Patients? A Retrospective Study

Helicobacter pylori-Pozitif Hastalarda Atopi Daha mı Az Görülüyor? Retrospektif Bir Çalışma

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ABSTRACT

Objective: *Helicobacter pylori* (*H. pylori*) has been implicated in modulating systemic immune responses and may potentially influence the onset of atopic disorders. Nevertheless, its specific relationship with systemic atopic markers remains unclear. We investigated the link between *H. pylori* infection and systemic indicators of atopy by analyzing serum immunoglobulin E (IgE) levels alongside peripheral inflammatory parameters.

Methods: In this retrospective analysis, data from 312 adult patients (246 females, 66 males) assessed for *H. pylori* infection between January 2023 and January 2025 were reviewed. Infection status was determined using stool antigen assays and/or histological examination of endoscopic biopsy specimens. Laboratory results included serum total IgE, eosinophil counts, complete blood count, C-reactive protein (CRP), and systemic inflammation markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio, systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation. Comparative statistical evaluations were performed between *H. pylori*-positive and -negative groups.

Results: Serum IgE concentrations were not significantly different between *H. pylori*-positive and -negative individuals (median: 42.5 IU/mL vs. 37.5 IU/mL; p=0.891). Similarly, eosinophil counts and the majority of inflammatory indices exhibited no substantial variation. Notably, neutrophil counts were slightly elevated in the *H. pylori*-positive cohort (median: 4.00 vs. 3.60 x10^3/μL; p=0.043). Other markers, such as NLR, PLR, SII, SIRI, and CRP, did not differ significantly.

Conclusion: *H. pylori* infection in adults was not associated with significant alterations in systemic atopic markers, including serum IgE and eosinophil counts, or with prominent changes in inflammatory indices. A mild rise in neutrophil levels may suggest a subtle systemic immune response rather than a marked inflammatory state.

Keywords: Atopy, eosinophil, *Helicobacter pylori*, IgE, monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation, systemic inflammation response index

ÖZ

Amaç: *Helicobacter pylori'nin (H. pylori)*, sistemik bağışıklık yanıtını ve atopik hastalıkların gelişimini etkileyebileceği öne sürülmüştür. Ancak, *H. pylori* enfeksiyonun sistemik atopi belirteçleri üzerindeki etkisi belirsizliğini korumaktadır. Bu çalışmada, *H. pylori* enfeksiyonu ile sistemik atopi aktivitesi arasındaki ilişki, serum immünoglobulin E (IgE) düzeyleri ve periferik enflamatuvar indeksler ölçülerek değerlendirilmiştir.

Gereç ve Yöntem: Bu geriye dönük çalışmada, Ocak 2023 ile Ocak 2025 tarihleri arasında *H. pylori* enfeksiyonu açısından dışkı antijen testi ve/veya endoskopik biyopsi ile değerlendirilmiş toplam 312 yetişkin bireyin (246 kadın, 66 erkek) kayıtları incelendi. Katılımcılara ait serum toplam IgE düzeyleri, eozinofil sayımları, tam kan sayımı bulguları, C-reaktif protein (CRP) düzeyleri ve sistemik enflamasyon göstergeleri nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR), monosit/lenfosit oranı, sistemik immün-enflamasyon indeksi (SII), sistemik enflamatuvar yanıt indeksi (SIRI) ve toplam sistemik enflamasyon indeksi, analiz kapsamına alındı. *H. pylori*-pozitif ve -negatif bireyler arasındaki farklar uygun istatistiksel yöntemlerle karşılaştırıldı.

Bulgular: Serum IgE düzeylerinde *H. pylori*-pozitif ve negatif bireyler arasında anlamlı bir farklılık saptanmadı (medyan: 42,5 IU/mL vs. 37,5 IU/mL; p=0,891). Eozinofil düzeyleri ve çoğu enflamasyon parametresi açısından da gruplar arasında belirgin bir fark görülmedi. Bununla birlikte, nötrofil sayılarında *H. pylori*-pozitif bireylerde hafif bir artış gözlendi (medyan: 4,00 vs. 3,60 x10^3/μL; p=0,043). NLR, PLR, SII, SIRI ve CRP gibi diğer enflamatuvar göstergeler istatistiksel fark göstermedi.

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ÖZ

Sonuç: *H. pylori* enfeksiyonu, erişkin bireylerde sistemik IgE aracılı atopik aktivite ya da belirgin enflamatuvar değişikliklerle ilişkili bulunmamıştır. Nötrofil sayısındaki mütevazı artış, sınırlı bir sistemik enflamatuvar etkiyi yansıtabilir.

Anahtar Kelimeler: Atopi, eozinofil, *Helicobacter pylori*, IgE, monosit/lenfosit oranı, nötrofil/lenfosit oranı, sistemik immün-enflamasyon indeksi, sistemik enflamasyon, sistemik enflamasyonun birleşik indeksi, sistemik enflamatuvar yanıt indeksi

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative, microaerophilic microorganism colonizing the gastric mucosa and represents one of the most widespread chronic infections worldwide (1). Its association with peptic ulcer, chronic gastritis, and cancer is well established and has been thoroughly investigated (1,2). In recent years, increasing attention has been directed toward the bacterium's role in modulating immune responses, with particular interest in its potential involvement in autoimmune and atopic disorders (3-5).

In many industrialized nations, a decline in *H. pylori* prevalence has paralleled an increase in atopic diseases (4,6). This trend aligns with the hygiene hypothesis and the "old friends" theory, both of which propose that limited microbial exposure during early development may impair immunological tolerance and promote allergic sensitization (4,6,7).

Large-scale epidemiological data demonstrated a negative relationship between *H. pylori* colonization and atopy (5,8,9). This protective effect appears to be more pronounced when colonization occurs in early childhood (8,9). Immunologically, this may be explained by enhanced regulatory T-cell (Treg) activity, downregulation of Th2-mediated pathways, and modulation of dendritic cell signaling-all contributing to a more balanced immune state (10,11).

Animal model experiments have provided further insight into these mechanisms. For instance, certain *H. pylori* virulence factors, such as VacA and neutrophil-activating protein, have been shown to reduce immunoglobulin E (IgE) production, inhibit eosinophilic infiltration, and ameliorate allergic airway inflammation in mice (3,11,12). These findings suggest that *H. pylori* may influence systemic immunity beyond the gastric environment, potentially via immunologic communication along the gut-lung and gut-skin axes (5).

However, despite these promising findings, the relation of *H. pylori* and atopy is not entirely consistent across studies. Divergent results may reflect differences in bacterial strain virulence (e.g., presence of CagA or VacA), genetics, environmental factors, and most importantly, the age at initial colonization (9,10,13). While certain studies have explored biomarkers such as total IgE and eosinophil count, few have simultaneously evaluated these markers in the context of confirmed *H. pylori* infection.

The present study aimed to evaluate if *H. pylori* infection affects systemic atopic activity by evaluating total serum IgE levels and peripheral inflammatory indices. Comparisons were made between *H. pylori* infected patients and non-infected ones, and to assess whether the bacterium might be associated with immunological patterns indicative of protection against atopy. We hypothesized that *H. pylori* infection may be associated with reduced systemic indicators of atopic reactivity—namely, lower serum IgE levels and decreased eosinophil counts—when compared to uninfected individuals.

METHODS

Ethical Statement

The study was approved by the Koşuyolu High Specialization Training and Research Hospital Clinical Research Ethics Committee (approval no: 2025-KAEK-43, date: 28.01.2025). The authors complied with the Declaration of Helsinki and relevant national guidelines. Due to the retrospective nature of the study, previously collected data were used, and obtaining informed consent from participants was not required.

Design

This research was conducted as a retrospective, observational study at a single medical center. Patient data were obtained from individuals evaluated in the internal medicine and gastroenterology outpatient clinics of the University of Health Sciences Türkiye, Fatih Sultan Mehmet Training and Research Hospital between January 2023 and January 2025. The primary objective was to determine the prevalence of atopy and to analyze immunological parameters among patients diagnosed with *H. pylori* infection.

The inclusion criteria encompassed patients aged 18 years and older with *H. pylori* infection, diagnosed by either stool antigen testing or histopathological examination of gastric biopsies obtained during endoscopy. In routine clinical practice, the diagnostic modality was selected according to the clinical indication. Stool antigen testing was generally used

as a non-invasive first-line test, whereas endoscopic biopsy was performed in patients undergoing upper gastrointestinal endoscopy for clinical reasons. Therefore, not all patients underwent both diagnostic procedures. Patients were considered *H. pylori*-positive if either stool antigen testing or histopathological examination demonstrated infection.

Exclusion criteria included any history of immunodeficiency, cancer, autoimmune disorders, or current use of corticosteroids or other immunosuppressive agents. The control group consisted of *H. pylori*-negative individuals matched by age and sex, all of whom had undergone the same diagnostic procedures during the same period.

Clinical and Laboratory Data

All clinical and laboratory information was retrospectively obtained from patients' hospital records.

The variables mentioned below were recorded:

- Demographic characteristics, including age and sex,
- *H. pylori* infection status (positive or negative), determined via stool antigen testing and/or endoscopic biopsy,
- Patient-reported atopic history was extracted from electronic medical records and clinical documentation (diagnoses such as allergic rhinitis, asthma, or dermatitis were identified based on physician notes and/or ICD codes when available),
- Total serum IgE concentrations,
- Absolute eosinophil counts along with their respective percentages,
- Complete blood count (CBC),
- Levels of C-reactive protein (CRP).

Based on the CBC data, the following systemic inflammatory indices were calculated:

- Neutrophil-to-lymphocyte ratio (NLR): Neutrophil count/lymphocyte count ratio,
- Platelet-to-lymphocyte ratio (PLR): Platelet count/lymphocyte count ratio,
- Monocyte-to-lymphocyte ratio (MLR): Monocyte count/lymphocyte count ratio,
- Systemic inflammation response index (SIRI): Calculated as (neutrophil count×monocyte count)/lymphocyte count,
- Systemic immune-inflammation index (SII): Calculated as (neutrophil count×platelet count)/lymphocyte count,
- Aggregate index of systemic inflammation (AISI): Defined as (neutrophil count×monocyte count×platelet count)/lymphocyte count.

All test results were obtained from the most recent available laboratory data within a three-months period before or after the *H. pylori* diagnostic assessment.

Statistical Analysis

IBM SPSS Statistics software (version 25.0) was used for the statistical analyses. The distribution patterns of continuous variables were evaluated with the Shapiro-Wilk test. Normally distributed data were given as mean±standard deviation, whereas non-normally distributed variables were given as medians and interquartile ranges (IQR).

To compare individuals with and without *H. pylori*, an Independent Samples t-test was used. In cases where the data did not meet normality assumptions, the Mann-Whitney U test was used. Categorical data were presented as counts and percentages, and differences between groups were assessed using the chi-square test or Fisher's exact test, depending on the expected cell frequencies.

To evaluate the relationships between total serum IgE levels and inflammatory indices, Pearson's or Spearman's correlation coefficients were used. In all tests, a p-value below 0.05 (two-tailed) was considered statistically significant.

RESULTS

A total of 312 patients were evaluated in the study: 246 women (78.8%) and 66 men (21.2%). The average age was not significantly different between patients with and without *H. pylori* infection (52.01±12.68 vs. 52.60±14.77 years, respectively; p=0.725) (Table 1).

In the combined analysis according to *H. pylori* status assessed by stool antigen and endoscopic biopsy, patients with stool antigen positivity were significantly younger than those who were negative (median age: 51.0 vs. 55.5 years; p=0.048), and hemoglobin levels were slightly lower in the stool antigen-positive group (p=0.037), while no other hematologic or biochemical parameters differed significantly. In contrast, based on endoscopic evaluation, biopsy-proven *H. pylori*-positive patients were significantly older than biopsy-negative individuals (median age: 58.0 vs. 52.0 years; p=0.037), and lymphocyte counts were higher in the biopsy-positive group (p=0.035), whereas the remaining parameters showed no significant differences (Table 2).

Serum total IgE levels were slightly higher in *H. pylori*-positive individuals, with a median of 42.5 IU/mL (IQR: 19-92.25), compared to a median of 37.5 IU/mL (IQR: 15-108) in the negative group; however, this difference was not statistically significant (p=0.891) (Figure 1). Similarly,

Table 1. General characteristics of the study population (n=312)

Variable	Value
Gender	
Female	246 (78.8%)
Male	66 (21.2%)
Atopy	
Negative	311 (99.7%)
Positive	1 (0.3%)
***H. pylori* in stool**	
Negative	128 (41.0%)
Positive	184 (59.0%)
Endoscopic *H. pylori*	
Negative	273 (87.5%)
Positive	39 (12.5%)
Age (years)	52.18±13.30
IgE (IU/mL)	93.49±187.97
Eosinophil count (x10^3/µL)	0.18±0.14
Lymphocyte count (x10^3/µL)	2.29±0.69
Monocyte count (x10^3/µL)	0.43±0.23
Neutrophil count (x10^3/µL)	4.17±1.63
Platelet (x10^3/µL)	269.41±72.23
CRP (mg/L)	3.49±7.40
Hemoglobin (g/dL)	13.26±1.53

H. pylori: *Helicobacter pylori*, IgE: Immunoglobulin E, CRP: C-reactive protein

no significant difference was noted in eosinophil counts between the two groups (p=0.348) (Table 3, Figure 2).

Regarding systemic inflammatory profiles, neutrophil counts were significantly elevated in the *H. pylori*-positive group [median: 4.00 (IQR: 3.27-5.00)] in comparison to the uninfected group [median: 3.60 (IQR: 3.00-4.50); p=0.043]. On the other hand, inflammatory markers—including NLR, PLR, MLR, SII, SIRI, and AISI—and CRP levels did not show statistically significant differences between the groups (all p-values >0.05). Levels of hemoglobin, lymphocytes, monocytes, and platelets were also similar between the two groups (Table 3). The modest increase in neutrophil counts among *H. pylori*-positive patients may reflect a low-grade systemic inflammatory response. Although not accompanied by elevations in CRP or other markers, this finding aligns with prior studies suggesting that *H. pylori* infection may sustain chronic, subclinical inflammation.

A full comparison encompassing both stool antigen and endoscopic findings for *H. pylori* is presented in Table 4.

In conclusion, while the majority of immunological and hematological parameters appeared comparable between the groups, a slight elevation in neutrophil counts was observed among *H. pylori*-positive individuals, potentially indicating a low-grade systemic inflammatory effect. Differences in age and lymphocyte levels were also noted in subgroup analyses stratified by diagnostic method (stool antigen versus biopsy); however, these variations did not reflect significant systemic immune alterations.

Table 2. Comparison of clinical and laboratory parameters according to *H. pylori* status (stool vs. endoscopic) (n=312)

Parameter	Stool *H. pylori* negative	Stool *H. pylori* positive	p-value	Endoscopic *H. pylori* negative	Endoscopic *H. pylori* positive	p-value
Age (years)	55.50 (46.00-63.75)	51.00 (42.25-60.00)	0.048*	52.00 (42.00-61.50)	58.00 (58.00-62.00)	0.037*
IgE (IU/mL)	37.50 (14.20-98.25)	43.00 (20.70-93.00)	0.521	41.00 (18.45-96.00)	42.00 (12.00-76.00)	0.591
Eosinophil count (x10^3/µL)	0.2 (0.1-0.2)	0.2 (0.1-0.2)	0.562	0.2 (0.1-0.2)	0.2 (0.1-0.2)	0.613
Lymphocyte count (x10^3/µL)	2.2 (1.8-2.7)	2.2 (1.8-2.7)	0.730	2.2 (1.8-2.61)	2.5 (1.9-3.0)	0.035*
Monocyte count (x10^3/µL)	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.464	0.4 (0.3-0.5)	0.4 (0.3-0.6)	0.174
Neutrophil count (x10^3/µL)	3.7 (3.02-4.6)	4.05 (3.2-4.9)	0.107	3.9 (3.1-4.8)	3.9 (3.3-5.1)	0.524
Platelet (x10^3/µL)	265.00 (223.00-302.00)	257.50 (214.25-312.00)	0.873	260 (217-308.5)	265 (223-289)	0.770
CRP (mg/L)	1.85 (0.82-3.16)	1.62 (0.87-3.64)	0.941	1.64 (0.84-3.42)	2.08 (0.95-3.69)	0.375
Hemoglobin (g/dL)	13.40 (12.52-14.40)	13.10 (12.10-14.00)	0.037*	13.2 (12.3-14.2)	13.6 (12.5-14.4)	0.198

*Statistically significant
H. pylori: *Helicobacter pylori*, IgE: Immunoglobulin E, CRP: C-reactive protein

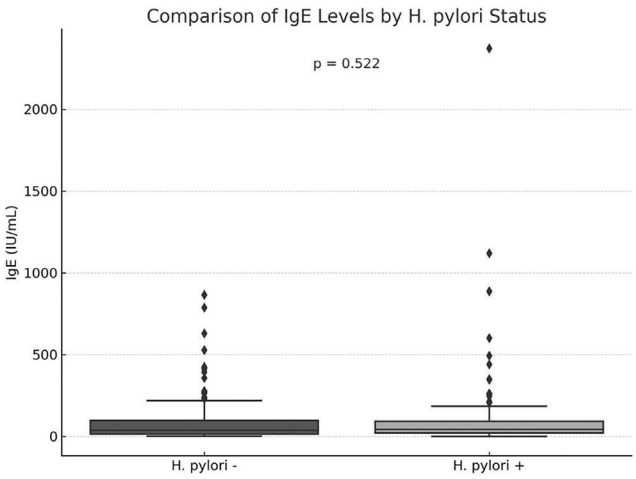

Figure 1. IgE levels by *H. pylori* status
IgE: Immunoglobulin E, *H. pylori*: *Helicobacter pylori*

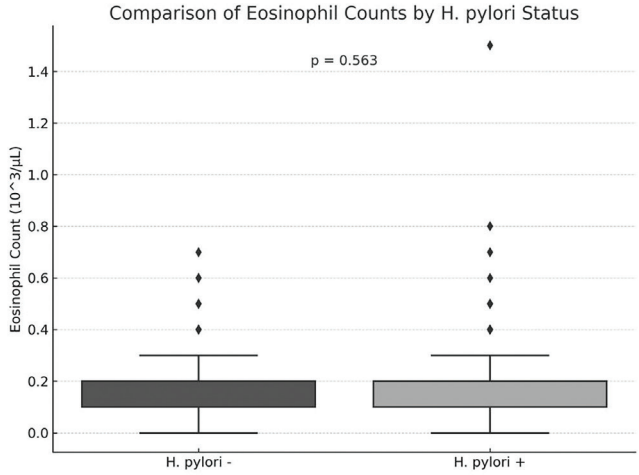

Figure 2. Eosinophil counts by *H. pylori* status
H. pylori: *Helicobacter pylori*

Table 3. Laboratory parameters by *H. pylori* status (n=312)

	***H. pylori* negative**	***H. pylori* positive**	**p-value**
Age (years)	52.60±14.77	52.01±12.68	0.725
IgE (IU/mL)	37.5 (15-108)	42.5 (19-92.25)	0.891
Eosinophil count (x10³/µL)	0.17 (0.10-0.20)	0.20 (0.10-0.20)	0.348
Lymphocyte count (x10³/µL)	2.24 (1.80-2.60)	2.20 (1.80-2.80)	0.337
Monocyte count (x10³/µL)	0.40 (0.30-0.50)	0.40 (0.30-0.50)	0.835
Neutrophil count (x10³/µL)	3.60 (3-4.50)	4 (3.27-5)	0.043
Platelet (x10³/µL)	265.5 (226.5-304.5)	261 (215-308.25)	0.805
CRP (mg/L)	1.79 (0.80-3.23)	1.69 (0.90-3.61)	0.672
Hemoglobin (g/dL)	13.48±1.37	13.17±1.59	0.112
NLR	1.79 (1.28-2.22)	1.78 (1.33-2.40)	0.456
PLR	117.08 (97.79-153.12)	116.95 (93.34-148.45)	0.550
MLR	0.18 (0.16-0.22)	0.17 (0.14-0.22)	0.417
SII	459.54 (327.13-571.73)	459 (329.45-632.56)	0.438
SIRI	0.66 (0.50-0.95)	0.71 (0.48-1.09)	0.402
AISI	177.60 (121.28-249.28)	179.75 (127.05-280.42)	0.429

H. pylori: *Helicobacter pylori*, IgE: Immunoglobulin E, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

DISCUSSION

In the present study, no statistically significant difference was found in total IgE between individuals having *H. pylori* infection or not having *H. pylori* infection. This suggests that colonization with *H. pylori* may not have a direct effect on IgE-mediated systemic allergic responses.

To evaluate the potential association between *H. pylori* and allergic predisposition, both humoral and cellular aspects of the immune response were taken into account. Total serum IgE, a well-established marker of atopic sensitization, reflects the activity of Th2-driven B cells and is typically elevated in allergic conditions such as asthma, allergic rhinitis, and atopic dermatitis.

In addition to serum IgE measurements, this study included several inflammation-based indices derived from standard hematologic tests: namely NLR, PLR, MLR, SII, SIRI, and AISI. These markers have garnered increasing attention as indicators of low-grade systemic inflammation. While not specific to allergic responses, they offer valuable insight

Table 4. Overall comparison of clinical and laboratory parameters according to combined *H. pylori* status (stool antigen and endoscopic diagnosis)

	H. pylori		
	Negative	**Positive**	**p-value**
Age (years)	52.60±14.77	52.01±12.68	0.725
IgE (IU/mL)	37.5 (15-108)	42.5 (19-92.25)	0.891
Eosinophil count (x10^3/µL)	0.17 (0.10-0.20)	0.20 (0.10-0.20)	0.348
Lymphocyte count (x10^3/µL)	2.24 (1.80-2.60)	2.20 (1.80-2.80)	0.337
Monocyte count (x10^3/µL)	0.40 (0.30-0.50)	0.40 (0.30-0.50)	0.835
Neutrophil count (x10^3/µL)	3.60 (3-4.50)	4 (3.27-5)	0.043*
Platelet (x10^3/µL)	265.5 (226.5-304.5)	261 (215-308.25)	0.805
CRP (mg/L)	1.79 (0.80-3.23)	1.69 (0.90-3.61)	0.672
Hemoglobin (g/dL)	13.48±1.37	13.17±1.59	0.112
NLR	1.79 (1.28-2.22)	1.78 (1.33-2.40)	0.456
PLR	117.08 (97.79-153.12)	116.95 (93.34-148.45)	0.550
MLR	0.18 (0.16-0.22)	0.17 (0.14-0.22)	0.417
SII	459.54 (327.13-571.73)	459 (329.45-632.56)	0.438
SIRI	0.66 (0.50-0.95)	0.71 (0.48-1.09)	0.402
AISI	177.60 (121.28-249.28)	179.75 (127.05-280.42)	0.429

*Statistically significant
H. pylori: *Helicobacter pylori*, IgE: Immunoglobulin E, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

into the overall inflammatory status in immune-mediated conditions, including both allergic and autoimmune disorders.

By simultaneously evaluating IgE levels and inflammation-related indices, the study sought to determine whether *H. pylori* exerts its effects on allergic responses via conventional IgE-mediated mechanisms, through alternative immune regulation, or potentially by engaging both pathways. This integrated strategy enabled a broader analysis of immune activity, encompassing both adaptive and innate components potentially influenced by *H. pylori* colonization.

Numerous prior studies, both epidemiological and experimental, have described an inverse correlation between *H. pylori* presence and allergic manifestations. Findings from large-scale population studies and meta-analyses indicate that being exposed to *H. pylori* in early years of life may be associated with reduced risk of atopic disorders such as asthma and allergic rhinitis (5,8,9). These protective effects have been attributed to the bacterium's capacity to enhance Treg cell responses, inhibit Th2-dominant immunity, and influence dendritic cell behavior (3,10,11). Experimental models further support this hypothesis: *H. pylori*-derived components such as VacA and neutrophil-activating protein have been shown to suppress IgE synthesis, reduce eosinophil-driven inflammation, and limit histamine release (3,11). In murine studies, *H. pylori* colonization has been linked to reduced allergic airway inflammation and fewer dermatitis-like skin lesions (12).

In contrast to earlier reports, our results indicate that *H. pylori* colonization in adults does not result in a detectable decrease in systemic IgE concentrations. This inconsistency may be attributed to factors such as host genetic variability, environmental influences, or strain-specific differences in *H. pylori* virulence. Although no IgE-lowering effect was observed, the possibility of broader immunoregulatory roles for *H. pylori*, independent of IgE-mediated mechanisms, cannot be excluded.

As a prevalent cause of chronic infections globally, *H. pylori* has a prolonged and complex interaction with the human immune system (14). The absence of significant differences in atopic parameters between infected and uninfected individuals in this study does not necessarily contradict prevailing theories that reduced microbial exposure—including the decline of *H. pylori*—may add to the rising incidence of atopy, particularly in developed countries (4). According to the hygiene hypothesis and the related "old friends" theory, insufficient microbial contact during early life may impair immune regulation by limiting Treg cell maturation and favoring a Th2-skewed immune profile (1,4).

Although the anti-inflammatory effects of *H. pylori* have traditionally been examined in the context of gastrointestinal disorders, more recent evidence points to its potential impact on distant mucosal immune responses via the gut-lung and gut-skin axes (5).

Inflammatory indices such as NLR, PLR, and SII are increasingly regarded as sensitive markers for detecting low-grade systemic inflammation. Their utility in identifying underlying immunologic activity in both allergic and autoimmune diseases is becoming more widely recognized (15,16). Nonetheless, in the present study, no statistically significant differences in these indices were observed between *H. pylori*-positive and -negative individuals.

Discrepancies in findings across the literature may be partially attributable to variations in *H. pylori* virulence determinants, particularly the presence of CagA and VacA (17). Certain studies have failed to confirm a protective effect, potentially due to differences in bacterial strain, the age at infection onset, host genetic background, or environmental exposures (9,10). Notably, *H. pylori* colonization occurring earlier in life appears to exert a more pronounced immunomodulatory influence compared to infections acquired later (8,9).

Study Limitations

First, this being a retrospective study, the analysis cannot establish causality between *H. pylori* infection and systemic markers of atopy. The findings are based solely on existing clinical and laboratory records, without prospective follow-up or in-depth clinical assessments of allergic diseases.

Another limitation relates to the diagnostic methods used to determine *H. pylori* infection. Because the study was retrospective and based on routine clinical records, the diagnostic modality was selected according to clinical indications rather than by a predefined research protocol. Non-invasive stool antigen testing was generally used as an initial diagnostic approach, whereas histopathological examination of gastric biopsies was performed in patients undergoing upper gastrointestinal endoscopy for clinical reasons. Consequently, not all patients underwent both diagnostic procedures. Although this reflects real-world clinical practice, the use of different diagnostic pathways may have introduced a degree of diagnostic heterogeneity between subgroups.

Third, atopy was evaluated indirectly using laboratory surrogates, primarily total serum IgE concentrations and eosinophil counts. While these biomarkers are informative, they do not capture the complete clinical spectrum of allergic conditions and may not accurately represent the severity or presence of atopy in every case.

The inflammatory indices assessed—such as NLR, PLR, and SII—are non-specific markers that may be affected by a wide range of confounding variables, including acute or chronic infections, comorbid conditions, and medication use. In our retrospective dataset, detailed information on potential confounders such as smoking status, body mass index, chronic diseases (e.g., diabetes, cardiovascular conditions), and use of antihistamines or immunomodulatory agents was not consistently available. As a result, these factors could not be fully accounted for in the analysis and may have introduced bias or masked subtle differences between the study groups.

Additionally, data on *H. pylori* virulence-related factors, including CagA and VacA status, timing of infection onset, and any history of eradication therapy, were unavailable. These variables likely play a crucial role in modulating immune responses and therefore represent key avenues for future research.

Moreover, due to the retrospective design, we lacked access to cytokine panel measurements [e.g., interleukin (IL)-4, IL-5, IL-10], which could have deepened our understanding of immune polarization (Th1/Th2 balance) in *H. pylori*-infected individuals.

No a priori sample size or power analysis was performed because of the retrospective design. While the sample size was adequate for preliminary group comparisons, it may not have been sufficient to detect smaller effect sizes.

Because the study was conducted in a single tertiary referral center, the results may not be broadly generalizable. Differences in population demographics, environmental exposures, and regional microbiological patterns could influence the associations observed and limit the extrapolation of these findings to wider settings.

CONCLUSION

These findings suggest that *H. pylori* colonization in adulthood does not appear to be associated with significant alterations in systemic atopic markers, including total IgE levels and eosinophil counts. In many industrialized nations, *H. pylori* prevalence has been progressively decreasing, largely as a result of widespread antibiotic use and enhanced hygiene standards. Although this study does not demonstrate a direct link between the bacterium's decline and the increasing incidence of allergic disorders, the findings are consistent with broader hypotheses suggesting that reduced microbial exposure—including the disappearance of *H. pylori*—may impair normal immune system development. These alterations in the microbial landscape underscore the importance of ongoing research

into how such ecological changes may influence immune regulation.

Prospective studies initiated in early life are warranted to clarify the potential protective role of early *H. pylori* colonization in atopy development.

ETHICS

Ethics Committee Approval: The study was approved by the Koşuyolu High Specialization Training and Research Hospital Clinical Research Ethics Committee (approval no: 2025-KAEK-43, date: 28.01.2025).

Informed Consent: Retrospective study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: M.E., İ.K., Concept: M.E., İ.K., Design: M.E., İ.K., Data Collection or Processing: M.E., Analysis or Interpretation: E.G.Ö., Literature Search: M.E., İ.K., Writing: İ.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Malfertheiner P, Camargo MC, El-Omar E, Liou JM, Peek R, Schulz C, et al. Helicobacter pylori infection. Nat Rev Dis Primers. 2023;9:19.
2. Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, et al. Global prevalence of Helicobacter pylori infection and incidence of gastric cancer between 1980 and 2022. Gastroenterology. 2024;166:605-19. Erratum in: Gastroenterology. 2025;168:850.
3. Zuo ZT, Ma Y, Sun Y, Bai CQ, Ling CH, Yuan FL. The protective effects of helicobacter pylori infection on allergic asthma. Int Arch Allergy Immunol. 2021;182:53-64.
4. Miftahussurur M, Nusi IA, Graham DY, Yamaoka Y. *Helicobacter*, hygiene, atopy, and asthma. Front Microbiol. 2017;8:1034.
5. Liu M, Wang Y, Du B. Update on the association between Helicobacter pylori infection and asthma in terms of microbiota and immunity. Allergy Asthma Clin Immunol. 2024;20:4.
6. Rook GA. Regulation of the immune system by biodiversity from the natural environment: an ecosystem service essential to health. Proc Natl Acad Sci U S A. 2013;110:18360-7.
7. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299:1259-60.
8. Lim JH, Kim N, Lim SH, Kwon JW, Shin CM, Chang YS, et al. Inverse relationship between Helicobacter pylori infection and asthma among adults younger than 40 years: a cross-sectional study. Medicine (Baltimore). 2016;95:e2609.
9. Ness-Jensen E, Langhammer A, Hveem K, Lu Y. *Helicobacter pylori* in relation to asthma and allergy modified by abdominal obesity: the HUNT study in Norway. World Allergy Organ J. 2019;12:100035.
10. Clyne M, Ó Cróinín T. Pathogenicity and virulence of *Helicobacter pylori*: a paradigm of chronic infection. Virulence. 2025;16:2438735.
11. Sehrawat A, Sinha S, Saxena A. Helicobacter pylori neutrophil-activating protein: a potential Treg modulator suppressing allergic asthma? Front Microbiol. 2015;6:493.
12. Wang S, Wang X, Liu J, Li Y, Sun M, Zhu G, et al. Helicobacter pylori infection attenuates 2,4-dinitrochlorobenzene-induced atopic dermatitis-like skin lesions in C57/BL6 mice. Allergy Asthma Clin Immunol. 2023;19:97.
13. Lionetti E, Leonardi S, Lanzafame A, Garozzo MT, Filippelli M, Tomarchio S, et al. Helicobacter pylori infection and atopic diseases: is there a relationship? A systematic review and meta-analysis. World J Gastroenterol. 2014;20:17635-47.
14. Chen Y, Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. J Infect Dis. 2008;198:553-60.
15. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88:218-30.
16. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20:6212-22.
17. Noverr MC, Huffnagle GB. The 'microflora hypothesis' of allergic diseases. Clin Exp Allergy. 2005;35:1511-20.

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Research

Cranial Magnetic Resonance Imaging Findings in Neonates with Mild Hypoxic-Ischemic Encephalopathy (Sarnat Stage I): A Retrospective Cohort Study

Hafif Hipoksik-İskemik Ensefalopati (Sarnat Evre I) olan Yenidoğanlarda Kraniyal Manyetik Rezonans Görüntüleme Bulguları: Retrospektif Kohort Çalışması

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ABSTRACT

Objective: Perinatal asphyxia is among the leading causes of morbidity in the newborn period and can give rise to hypoxic-ischemic encephalopathy (HIE). While therapeutic hypothermia is well established for moderate-to-severe HIE, the optimal management of infants with mild HIE—Sarnat stage I—remains controversial. What is becoming increasingly clear, however, is that a mild HIE may not always be a benign condition and that subtle brain injury may be present even with a mild clinical presentation. We aimed to evaluate cranial magnetic resonance imaging (MRI) findings in newborns with perinatal asphyxia classified as Sarnat stage I and to explore whether infants with normal versus abnormal imaging differ in their clinical presentation or laboratory markers.

Methods: We conducted a retrospective cohort study of newborns admitted to our neonatal intensive care unit with perinatal asphyxia who met the criteria for Sarnat stage I HIE. Demographic data, Apgar scores, umbilical cord blood gas values, maternal risk factors, and neuroimaging results were recorded. Cranial MRI scans were classified as normal or abnormal, and the two groups were compared.

Results: Sixty-six neonates were enrolled. MRI was normal in 54 (81.8%) patients and abnormal in 12 (18.2%) patients. Infants in the abnormal group tended to have lower Apgar scores and more pronounced metabolic acidosis, although neither difference reached statistical significance. The most common abnormal findings were hemorrhagic in nature-subdural, intraventricular, and parenchymal hemorrhages each accounted for a third of abnormal scans.

Conclusion: Nearly one-fifth of neonates with mild HIE demonstrated abnormal cranial MRI findings. Closer follow-up may be considered, since mild HIE may be associated with subclinical brain injury.

Keywords: Cranial MRI, hypoxic-ischemic encephalopathy, intracranial hemorrhage, perinatal asphyxia

ÖZ

Amaç: Perinatal asfiksi, yenidoğan döneminde morbiditenin önde gelen nedenlerinden biridir ve hipoksik-iskemik ensefalopatiye (HİE) yol açabilir. Orta ve ağır HİE için terapötik hipotermi iyi tanımlanmış bir tedavi yaklaşımıdır; ancak hafif HİE (Sarnat evre I) olan bebeklerin optimal yönetimi halen tartışmalıdır. Bununla birlikte giderek daha net anlaşılmaktadır ki hafif HİE her zaman benign bir durum değildir ve klinik olarak hafif seyretse bile altta yatan ince (subklinik) beyin hasarı bulunabilir. Bu çalışmada, perinatal asfiksiye bağlı Sarnat evre I HİE tanısı alan yenidoğanlarda kraniyal manyetik rezonans görüntüleme (MRG) bulgularını değerlendirmeyi ve MRG'si normal olanlar ile anormal olanlar arasında klinik ve laboratuvar özellikler açısından fark olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntem: Yenidoğan yoğun bakım ünitemize yatırılan, perinatal asfiksi öyküsü olan ve Sarnat evre I HİE kriterlerini karşılayan bebeklerin dahil edildiği retrospektif bir kohort çalışması yürütüldü. Demografik veriler, Apgar skorları, umbilikal kord kan gazı değerleri, maternal risk faktörleri ve nörogörüntüleme sonuçları kaydedildi. Kraniyal MRG bulguları normal ve anormal olarak sınıflandırıldı ve iki grup karşılaştırıldı.

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ÖZ

Bulgular: Toplam 66 yenidoğan çalışmaya dahil edildi. MRG bulguları 54 (%81,8) hastada normal, 12 (%18,2) hastada anormal olarak saptandı. Anormal MRG grubundaki bebeklerde daha düşük Apgar skorları ve daha belirgin metabolik asidoz eğilimi gözlenmekle birlikte, bu farklar istatistiksel olarak anlamlı değildi. En sık saptanan anormallikler hemorajik nitelikte olup; subdural, intraventriküler ve parankimal kanamalar anormal MRG bulgularının her biri yaklaşık üçte birini oluşturdu.

Sonuç: Hafif HİE tanısı alan yenidoğanların yaklaşık beşte birinde kraniyal MRG'de anormal bulgular saptanmıştır. Hafif HİE'nin subklinik beyin hasarı ile ilişkili olabileceği göz önünde bulundurularak bu hastaların daha yakın izlenmesi düşünülebilir.

Anahtar Kelimeler: Beyin MRG, hipoksik-iskemik ensefalopati, intrakraniyal kanama, perinatal asfiksi

INTRODUCTION

Perinatal asphyxia remains one of the emerging problems in the neonatal period-responsible for about a quarter of all neonatal deaths and disproportionately affecting low- and middle-income settings. It is characterized by a failure of gas exchange and a cascade of hypoxemia, hypercapnia, and metabolic acidosis that can ultimately injure multiple organ systems, including the brain. Despite advances in perinatal care over recent decades, asphyxia continues to drive a substantial share of neonatal mortality and long-term neurodevelopmental disability (1-3).

Hypoxic-ischemic encephalopathy (HIE) represents the neurological manifestation of perinatal asphyxia and is graded using the Sarnat staging system (4). For moderate-to-severe disease (Sarnat stage II-III), therapeutic hypothermia is the standard treatment for neonates (5). The management of mild hypoxic-ischemic encephalopathy remains controversial, as emerging data suggest that a subset of these infants may still develop neurodevelopmental impairment (6). Current guidelines do not recommend routine hypothermia for mild HIE due to insufficient evidence regarding long term benefit, although emerging data suggest that a subset of these infants may still be at risk for adverse neurodevelopmental outcomes (7,8).

Neuroimaging, particularly cranial magnetic resonance imaging (MRI), plays a critical role in the evaluation of hypoxic-ischemic brain injury. MRI is considered the most sensitive modality for detecting hypoxic-ischemic brain injury and identifying characteristic injury patterns associated with perinatal asphyxia, including white matter injury, basal ganglia-thalamic involvement, and hemorrhagic lesions (9-12). However, the prognostic value of MRI in infants with mild HIE remains less well defined, and normal early neuroimaging does not necessarily exclude later neurodevelopmental impairment (8).

The aim of this retrospective observational study was to evaluate cranial MRI findings in neonates with perinatal asphyxia classified as Sarnat stage I and to compare clinical and laboratory characteristics between infants with normal and abnormal MRI findings, particularly focusing on the presence of intracranial hemorrhage (ICH) on early MRI.

METHODS

Ethics Committee and Patient Consent

This single-center retrospective study was conducted in accordance with the Declaration of Helsinki. This study was approved by the University of Health Sciences Türkiye, Haseki Training and Research Hospital Non-Interventional Ethics Committee (approval no: 34-2026, date: 25.02.2026). Due to the retrospective design and the use of anonymized data, informed consent procedures were addressed in accordance with institutional policies and ICMJE requirements. The study was performed in accordance with the Declaration of Helsinki.

Study Design and Population

This cohort study was carried out in the Neonatal Intensive Care Unit of University of Health Sciences Türkiye, Haseki Training and Research Hospital. We reviewed the medical records of all newborns admitted between March 2022 and March 2026 who had a diagnosis of perinatal asphyxia.

Infants were eligible if they were born at or after 28 weeks of gestation and showed evidence of perinatal asphyxia, defined as an umbilical cord or first-hour arterial blood gas pH ≤7.10 and/or base excess ≤-12 mmol/L. In addition, they were required to be classified as Sarnat stage I (mild HIE) on clinical examination, to have a normal amplitude-integrated electroencephalography (aEEG) tracing, and to show no indication for therapeutic hypothermia under our unit's protocol.

We excluded infants with moderate or severe HIE (Sarnat stage II-III) requiring therapeutic hypothermia, major congenital anomalies or chromosomal abnormalities, inborn errors of metabolism, incomplete clinical or imaging records, and gestational age below 28 weeks.

From each medical record, we extracted demographic information (gestational age, birth weight, sex), perinatal details (mode of delivery, 1- and 5-minute Apgar scores, maternal risk factors including placental abruption, preeclampsia, gestational hypertension, and diabetes), laboratory values (umbilical cord pH, base excess, lactate, bicarbonate, and pCO_2), and neuroimaging results from cranial MRI and aEEG.

Cord Blood Gas Analysis

After the umbilical cord was clamped for the first time at 30-40 seconds of life, the newborn was transferred to the attending pediatrician or nurse. A second clamp was then placed roughly 4-5 cm from the umbilicus, and 1 mL of blood was drawn into Sarstedt Monovette lithium heparin tubes. Samples were analyzed without delay on Siemens Rapidlab 1265 analyzers.

Neuroimaging Evaluation

All MRI examinations were performed within the first 7 days of life using a 1.5-T Philips system. (Intera 1.5 T; Healthcare, Best, The Netherlands). Sagittal T1-weighted images (T_R=450-550 ms; T_E=15-30 ms; slice thickness=5 mm) and axial T2-weighted images (T_R=3,000-3,150 ms; T_E=150 ms; slice thickness=2-5 mm) were acquired.

Because of the study's retrospective design, MRI acquisition was not fully standardized across all patients. In particular, advanced sequences such as diffusion-weighted imaging (DWI)—which is highly sensitive for detecting acute hypoxic-ischemic injury—were not routinely performed on all infants. Similarly, susceptibility-weighted imaging (SWI) was obtained when clinically indicated rather than as part of a uniform imaging protocol.

This variability in imaging sequences may have limited detection of subtle ischemic lesions and should therefore be considered when interpreting the frequency and pattern of MRI abnormalities in this cohort.

The average imaging time was approximately 30 minutes. A neonatologist was present throughout the procedure and administered bolus midazolam sedation if needed.

Neonatal ICH was assessed on SWI and T1-weighted images. ICH was categorized into five subtypes: subdural, subarachnoid, germinal matrix, intraventricular, and parenchymal hemorrhage (11). MRI findings were reported by experienced radiologists. Because of the retrospective design, formal inter-rater reliability testing was not feasible-a limitation we acknowledge.

Amplitude-Integrated Electroencephalography

All enrolled neonates underwent continuous neurological monitoring with aEEG during the first 24 hours of life. Two-channel recordings were routinely obtained for any infant admitted with perinatal asphyxia or neurological concern—including a 5-minute Apgar score below 5, cord pH below 7.10, multiorgan failure, or clinical seizures—both to characterize the background pattern and to help detect subclinical seizure activity. A normal aEEG background was defined as a continuous or discontinuous normal-voltage pattern.

Statistical Analysis

All analyses were performed with IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Before selecting tests, we assessed the distribution of continuous variables using histogram inspection and the Shapiro-Wilk test. Variables with a normal distribution are reported as mean±standard deviation; those with a non-normal distribution are reported as median and interquartile range (IQR). Categorical data are presented as counts and percentages.

Group comparisons between infants with normal and abnormal MRI were performed using Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using either the chi-square test or Fisher's exact test, depending on expected cell counts.

We also performed a multivariable logistic regression analysis to identify independent predictors of abnormal MRI. With only 12 outcome events and seven predictor variables, the event-per-variable ratio was approximately 1.7-well short of the conventional threshold of 10. These results should therefore be taken as exploratory and interpreted with appropriate caution. All tests were two-tailed; a p-value below 0.05 was considered statistically significant.

RESULTS

General Characteristics of the Study Population

Sixty-six neonates with perinatal asphyxia who were classified as Sarnat stage I HIE were included in the analysis. Mean gestational age was 37.1±2.9 weeks (range: 30-41.6 weeks), and mean birth weight was 2844±801 g (range: 1100-4120 g). Most infants were male (63.6%; n=42). Delivery was by cesarean section in 59.1% (n=39) and by vaginal delivery in 40.9% (n=27). The median 1-minute Apgar score was 6 (IQR: 4-7), rising to 7.5 (IQR: 6-8) at five minutes.

Cord blood gas values reflected the expected degree of metabolic acidosis. Mean umbilical cord pH was 7.02±0.10, base excess -14.1±3.7 mmol/L, lactate 8.7±3.4 mmol/L, bicarbonate 14.0±3.2 mmol/L, and pCO_2 69.9±16.6 mmHg. The full clinical characteristics are presented in Table 1.

A maternal risk factor was identified in 45.5% of pregnancies. Placental abruption was the most common (18.2%), followed by gestational hypertension (7.6%) and preeclampsia (6.1%). In just over half of cases (54.5%), no maternal risk factor was documented.

Comparison Between Neonates with Normal and Abnormal MRI Findings

Cranial MRI was normal in 54 infants (81.8%) and abnormal in the remaining 12 (18.2%). Infants with abnormal MRI findings tended to be slightly younger (36.1±3.5 vs. 37.4±2.7 weeks; p=0.18) and lighter at birth (2630±890 vs. 2890±780 g; p=0.24), though neither difference was statistically significant. Males were somewhat more common in the abnormal MRI group (75.0% vs. 61.1%; p=0.36).

Apgar scores at both time points were lower in the abnormal MRI group. At one minute, the median was 5 (IQR: 3-6) compared with 6 (IQR: 4-7) in those with normal scans. At five minutes, median scores were 7 (IQR: 6-7) and 8 (IQR: 7-8), respectively (p=0.19 for both comparisons).

Biochemical markers also indicated the same trend. Mean cord pH was 6.96±0.11 in the abnormal MRI group versus 7.04±0.09 in those with normal scans (p=0.13). Base excess was more negative (-16.2±4.1 vs. -13.5±3.4 mmol/L; p=0.09), and lactate levels were higher (10.1±3.9 vs. 8.2±3.1 mmol/L; p=0.08). None of these differences achieved statistical significance (all p>0.05). The full comparative dataset is presented in Table 1.

In multivariable logistic regression analysis, none of the variables examined—gestational age, birth weight, sex, 5-minute Apgar score, cord pH, base excess, or lactate—showed a statistically significant association with abnormal MRI; however, given the limited number of events, these findings should be interpreted as exploratory rather than conclusive." Full results are shown in Table 2, and a forest plot of odds ratios and their 95% confidence intervals for each predictor is presented in the Figure 1.

Among the 12 infants with abnormal scans, subdural hemorrhage, intraventricular hemorrhage, and parenchymal hemorrhage each appeared in four cases (33.3% each). Subarachnoid hemorrhage and germinal matrix hemorrhage were not identified in any infant.

DISCUSSION

In this single-center, retrospective cohort of neonates with mild HIE, most infants had normal cranial MRI findings; yet nearly one in five infants showed structural abnormalities despite being classified as Sarnat stage I, lending further support to the view that mild HIE is not a uniformly benign diagnosis.

Recent studies in this area consistently show that infants with mild HIE can present with subtle white matter injury or hemorrhagic lesions on MRI even when their clinical picture

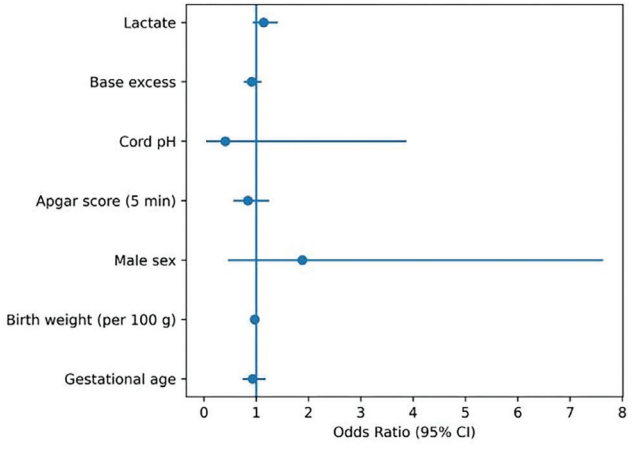

Figure 1. A forest plot showing odds ratios and 95% confidence intervals for each predictor

Table 1. Clinical and biochemical characteristics of the study population by MRI findings

Variable	All patients (n=66)	Normal MRI (n=54)	Abnormal MRI (n=12)	p-value
Gestational age (weeks), mean±SD	37.1±2.9	37.4±2.7	36.1±3.5	0.18
Birth weight (g), mean±SD	2844±801	2890±780	2630±890	0.24
Male sex, n (%)	42 (63.6)	33 (61.1)	9 (75.0)	0.36
Cesarean delivery, n (%)	39 (59.1)	31 (57.4)	8 (66.7)	0.55
Apgar score at 1 min, median (IQR)	6 (4-7)	6 (4-7)	5 (3-6)	0.21
Apgar score at 5 min, median (IQR)	7.5 (6-8)	8 (7-8)	7 (6-7)	0.19
Umbilical cord pH, mean±SD	7.02±0.10	7.04±0.09	6.96±0.11	0.13
Base excess (mmol/L), mean±SD	-14.1±3.7	-13.5±3.4	-16.2±4.1	0.09
Lactate (mmol/L), mean±SD	8.7±3.4	8.2±3.1	10.1±3.9	0.08
HCO_3 (mmol/L), mean±SD	14.0±3.2	14.3±3.1	13.2±3.4	0.27
pCO_2 (mmHg), mean±SD	69.9±16.6	68.8±15.9	74.6±18.8	0.29

Continuous variables are presented as mean±SD or median (interquartile range) depending on data distribution. Categorical variables are presented as number (percentage). Comparisons between the normal MRI and abnormal MRI groups were performed using Student's t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables
SD: Standard deviation, MRI: Magnetic resonance imaging

Table 2. Multivariable logistic regression analysis of factors associated with abnormal MRI findings

Variable	OR	95% CI	p-value
Gestational age (per week)	0.93	0.74-1.18	0.55
Birth weight (per 100 g)	0.97	0.89-1.06	0.49
Male sex	1.88	0.46-7.63	0.38
Apgar score (5 min)	0.84	0.56-1.25	0.38
Cord pH	0.41	0.04-3.87	0.43
Base excess (per mmol/L)	0.91	0.76-1.10	0.33
Lactate (per mmol/L)	1.14	0.93-1.41	0.21

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression analysis. Variables included in the model were selected based on clinical relevance and univariate associations

appears reassuring (6,7). Wu et al. (8) noted that while MRI carries strong prognostic weight in moderate-to-severe disease, its predictive accuracy is appreciably lower when encephalopathy is mild.

The findings of our study—lower Apgar scores, more pronounced metabolic acidosis, and higher lactate in infants with abnormal MRI—appear to be in line with prior reportssuggesting that biochemical markers may capture the severity of cerebral injury more accurately than clinical staging alone however, these observations should be interpreted cautiously given the limited sample size and lack of statistical significance (7,10). Glass et al. (7) and Chalak et al. (6) have both drawn attention to the limited ability of the Sarnat system to identify the highest-risk infants within the mild HIE group (13). Importantly, the biochemical trends we observed are biologically coherent: lower cord pH and more negative base excess in the abnormal MRI group fit well with what we know about the pathophysiology of hypoxic-ischemic brain injury and mirror findings from earlier series that relied primarily on biochemical severity rather than on clinical scoring to gauge cerebral injury risk.

Neuroprotective pharmacotherapy remains an open and active area of research. Magnesium sulfate has been proposed as a means of limiting excitotoxic neuronal damage through N-methyl-D-aspartate receptor blockade, while allopurinol may help curb oxidative stress during reperfusion (13-15). Both agents have shown encouraging signals in experimental and early clinical work (15,16), though our study was not designed to evaluate treatment effects.

Our abnormality rate of 18.2% is notably lower than the rates reported by other groups. Li et al. (17) found brain injury on early MRI in 61% of 142 mild HIE infants, with watershed injury (23%), deep gray nuclei involvement (20%), and punctate white matter lesions (18%) being the most frequent patterns. Glass et al. (7) similarly identified MRI abnormalities in around 54% of neonates with mild neonatal encephalopathy. Several factors likely explain the difference in our cohort: stricter application of Sarnat stage I criteria, variation in MRI scoring systems used across studies, and the limited routine use of DWI—the sequence most sensitive for acute ischemic injury in the neonatal brain—in our protocol. The use of a 1.5-T rather than a 3-T scanner may also have reduced our ability to detect subtle parenchymal changes. Going forward, incorporating DWI and a standardized scoring tool such as the Weeke score—which has been shown to detect abnormalities most frequently in mild HIE populations (18) would strengthen future investigations from our center.

Mild HIE is not a homogeneous condition. Wu et al. (8) have shown that MRI's prognostic accuracy drops considerably in the mild range, and Chalak et al. (6) demonstrated that neuroimaging abnormalities can occur in Sarnat stage I infants who appear neurologically intact on early examination—particularly when Apgar scores are low or biochemical evidence of hypoxia-ischemia is present (10). These observations are entirely consistent with what we found in our cohort.

Taken together, lower cord pH, more negative base excess, and elevated lactate—all of which we also observed as trends in our cohort—have been proposed as markers of heightened cerebral injury risk even when clinical staging points to mild disease (7,13). Wu et al. (8) pointed out that neuroimaging may capture injury severity that clinical scores simply miss, especially in early or attenuated presentations. The absence of statistical significance in our study should, therefore, be interpreted cautiously, as the study may have been underpowered to detect clinically meaningful associations; the absence more likely reflects the constraints of a small sample and the inherent variability of mild HIE populations.

The predominance of hemorrhagic findings in our cohort—subdural, intraventricular, and parenchymal hemorrhages—may be interpreted cautiously. Brouwer et al. (11)

described the full spectrum of ICH in term newborns and highlighted the roles of vascular fragility and reperfusion injury following hypoxia-ischemia. Hemorrhagic lesions can therefore coexist with and complicate the hypoxic-ischemic process, and recognizing them is directly relevant to neurodevelopmental surveillance. Their presence should prompt careful, long-term follow-up regardless of the infant's initial clinical grading.

Study Limitations

Several limitations of this study merit acknowledgment. The retrospective single-center design limits the generalizability of our findings. The relatively small overall sample and particularly the low number of infants with abnormal MRI (n=12) meant that the study was underpowered to detect statistically significant associations; the event-per-variable ratio in the logistic regression was roughly 1.7, far below the conventional threshold of 10, so those results should be viewed as hypothesis-generating rather than confirmatory. Formal inter-rater reliability testing for MRI interpretation was not performed. DWI was not routinely acquired in all patients, which likely led to some underestimation of ischemic injury. Because long-term neurodevelopmental follow-up data were unavailable, we cannot comment on outcomes. Taken together, these constraints mean that the lack of statistical significance is better understood as reflecting methodological limitations than as evidence that the observed clinical trends are unimportant—a question that prospective studies will need to address more rigorously.

CONCLUSION

Although the majority of neonates with mild HIE had normal cranial MRI findings, a clinically meaningful subset—nearly one in five—showed structural brain abnormalities. A reassuring clinical picture does not rule out underlying cerebral injury. Hemorrhagic lesions, in particular, may reflect vascular fragility or reperfusion injury occurring alongside the hypoxic-ischemic process. Our findings support a thorough multimodal assessment—clinical, biochemical, and neuroimaging—in every neonate with Sarnat stage I HIE. Prospective studies using standardized MRI protocols, validated scoring systems, and long-term neurodevelopmental follow-up are needed to improve risk stratification and guide management in this understudied population.

ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Haseki Training and Research Hospital Non-Interventional Ethics Committee (approval no: 34-2026, date: 25.02.2026).

Informed Consent: Retrospective study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: B.C., Concept: B.C., D.K., Design: B.C., H.G.Y., H.Ç., Data Collection or Processing: B.C., H.G.Y., D.K., H.Ç., D.B., N.G., Analysis or Interpretation: B.C., N.G., Literature Search: B.C., H.G.Y., D.K., D.B., Writing: B.C., H.G.Y., D.K., H.Ç., D.B., N.G.

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REFERENCES

1. Lawn JE, Cousens S, Zupan J; Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? Lancet. 2005;365:891-900.
2. Wu YW, Backstrand KH, Zhao S, Fullerton HJ, Johnston SC. Declining diagnosis of birth asphyxia in California: 1991-2000. Pediatrics. 2004;114:1584-90.
3. Aslam HM, Saleem S, Afzal R, Iqbal U, Saleem SM, Shaikh MW, et al. "Risk factors of birth asphyxia". Ital J Pediatr. 2014;40:94.
4. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976;33:696-705.
5. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al.; National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005;353:1574-84.
6. Chalak LF, Nguyen KA, Prempunpong C, Heyne R, Thayyil S, Shankaran S, et al. Prospective research in infants with mild encephalopathy identified in the first six hours of life: neurodevelopmental outcomes at 18-22 months. Pediatr Res. 2018;84:861-8.
7. Glass HC, Bonifacio SL, Sullivan J, Rogers E, Ferriero DM, Goldstein R, et al. Magnetic resonance imaging and ultrasound injury in preterm infants with seizures. J Child Neurol. 2009;24:1105-11.
8. Wu Y, Monsell S, Glass H, Wisnowski J, Mathur A, Mckinstry R, et al. How well does neonatal neuroimaging correlate with neurodevelopmental outcomes in infants with hypoxic-ischemic encephalopathy? Pediatr Res. 2023;94:1018-25.
9. Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. Lancet Neurol. 2010;9:39-45.

10. Prempunpong C, Chalak LF, Garfinkle J, Shah B, Kalra V, Rollins N, et al. Prospective research on infants with mild encephalopathy: the PRIME study. J Perinatol. 2018;38:80-5.
11. Brouwer AJ, Groenendaal F, Koopman C, Nievelstein RJ, Han SK, de Vries LS. Intracranial hemorrhage in full-term newborns: a hospital-based cohort study. Neuroradiology. 2010;52:567-76.
12. Barkovich AJ, Hajnal BL, Vigneron D, Sola A, Partridge JC, Allen F, et al. Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems. AJNR Am J Neuroradiol. 1998;19:143-9.
13. Nair J, Kumar VHS. Current and emerging therapies in the management of hypoxic ischemic encephalopathy in neonates. Children (Basel). 2018;5:99.
14. Ilves P, Kiisk M, Soopõld T, Talvik T. Serum total magnesium and ionized calcium concentrations in asphyxiated term newborn infants with hypoxic-ischaemic encephalopathy. Acta Paediatr. 2000;89:680-5.
15. Rodríguez-Fanjul J, Durán Fernández-Feijóo C, Lopez-Abad M, Lopez Ramos MG, Balada Caballé R, Alcántara-Horillo S, et al. Neuroprotection with hypothermia and allopurinol in an animal model of hypoxic-ischemic injury: is it a gender question? PLoS One. 2017;12:e0184643.
16. Kaandorp JJ, van Bel F, Veen S, Derks JB, Groenendaal F, Rijken M, et al. Long-term neuroprotective effects of allopurinol after moderate perinatal asphyxia: follow-up of two randomised controlled trials. Arch Dis Child Fetal Neonatal Ed. 2012;97:F162-6.
17. Li Y, Wisnowski JL, Chalak L, Mathur AM, McKinstry RC, Licona G, et al. Mild hypoxic-ischemic encephalopathy (HIE): timing and pattern of MRI brain injury. Pediatr Res. 2022;92:1731-6.
18. Machie M, Weeke L, de Vries LS, Rollins N, Brown L, Chalak L. MRI score ability to detect abnormalities in mild hypoxic-ıschemic encephalopathy. Pediatr Neurol. 2021;116:32-38.

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Hidradenoma papilliferum Presenting as a Painful Clitoral Mass: A Rare Case Report

Ağrılı Klitoral Kitle ile Prezente olan *Hidradenoma papilliferum*: Nadir Bir Olgu Sunumu

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ABSTRACT

Hidradenoma papilliferum (HP) is a rare, benign, slow-growing tumor of apocrine origin, primarily located in the anogenital region of adult women. We report a rare case of HP in a 52-year-old postmenopausal woman presenting with a painful, nodular lesion on the clitoral area. Histopathologic examination confirmed the diagnosis after surgical excision. The lesion showed positive expression for estrogen and progesterone receptors, and p63 in myoepithelial cells. Although HP is typically asymptomatic and commonly seen on labial structures, its occurrence in the clitoris with painful presentation is rare. Awareness of such atypical localizations is crucial for proper diagnosis and management.

Keywords: *Hidradenoma papilliferum*, apocrine tumor, clitoris, vulvar mass

ÖZ

Hidradenoma papilliferum (HP), genellikle erişkin kadınlarda anogenital bölgede görülen nadir, benign ve yavaş büyüyen apokrin kökenli bir tümördür. Bu çalışmada, klitoral bölgede ağrılı nodüler bir lezyon ile başvuran 52 yaşında postmenopozal bir kadının nadir bir HP olgusu sunulmuştur. Cerrahi eksizyon sonrası yapılan histopatolojik inceleme ile tanı doğrulanmıştır. Lezyonda myoepitelyal hücrelerde p63 ve lüminal hücrelerde östrojen ve progesteron reseptörlerinin pozitif ekspresyonu saptanmıştır. HP genellikle labial yapılarda ve asemptomatik olarak izlenirken, klitoris yerleşimi ve ağrılı klinik bulgularla seyretmesi oldukça nadirdir. Bu tür atipik lokalizasyonlara yönelik farkındalık, doğru tanı ve yönetim açısından önem taşımaktadır.

Anahtar Kelimeler: *Hidradenoma papilliferum*, apokrin tümör, klitoris, vulvar kitle

INTRODUCTION

Hidradenoma papilliferum (HP) is a rare tumor with apocrine features, typically arising in the vulvar region. According to clinical observations, these lesions grow slowly and are generally benign. Although initially described in the anogenital area, cases have also been reported in less typical locations such as the head, neck, breast, and even extremities (1-3). Recent studies have identified specialized glandular structures in the anogenital region that embryologically resemble mammary tissue. It is thought that these mammary-like glands may play a role in the development of lesions such as HP (4).

In clinical practice, HP lesions are usually 1-2 cm in size, well-circumscribed, and superficially nodular. Based on our observations, these lesions may appear skin-colored or reddish and are typically solitary. Although often asymptomatic, some patients may present with pain, itching, or bleeding (5,6). Accurate diagnosis, which is critical for distinguishing HP from other benign or malignant neoplasms, requires both clinical and pathological evaluation.

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CASE REPORT

A 52-year-old postmenopausal woman presented with a three-month history of a small, painful mass in the clitoral region. Clinical examination revealed a nodular, tender lesion localized to the clitoris. Despite the typical asymptomatic nature of HP lesions in the anogenital area, this case exhibited pronounced symptoms, including sharp pain and discomfort. Surgical excision was performed for both symptom relief and definitive diagnosis.

Histopathological evaluation of the excised papillary lesion revealed features consistent with HP. The papillary lesion was lined by a bilayered epithelium forming gland-like structures (Figure 1A, 1B; x40, x200). Myoepithelial cells in the basal layer showed positive expression for p63 (Figure 1C; x200), and positive staining was observed for estrogen and progesterone receptors in the luminal cells (Figure 1D, 1E; x200).

Although recurrence rates are low in such cases, the patient was placed under clinical follow-up. Written informed consent was obtained from the patient for publication of the case and accompanying images.

DISCUSSION

HP is a rare apocrine tumor, most commonly observed in females aged between 20 and 90 years. The youngest reported case in the literature involved a 16-year-old patient (5). While the majority of cases are asymptomatic, symptoms such as pain, bleeding, itching, and ulceration can occasionally occur (6). For instance, a case of HP located in the external auditory canal was reported to cause an unusual symptom hearing loss (7).

HP most frequently affects the labia minora and labia majora. According to published data, 50% of cases are located on the labia minora, 40% on the labia majora, 7% on the fourchette, and only 3% are localized to the clitoris (8). Approximately 60% of ectopic HP cases have been identified in the head and neck region (9). Lesion sizes generally range from 3 to 25 mm, presenting as solitary, bluish, or reddish nodules (10).

In the case presented in this study, HP was localized to the clitoris, representing a rare location. The lesion measured approximately 12 mm in diameter, had a smooth surface with no ulceration, appeared yellow, was painful, and

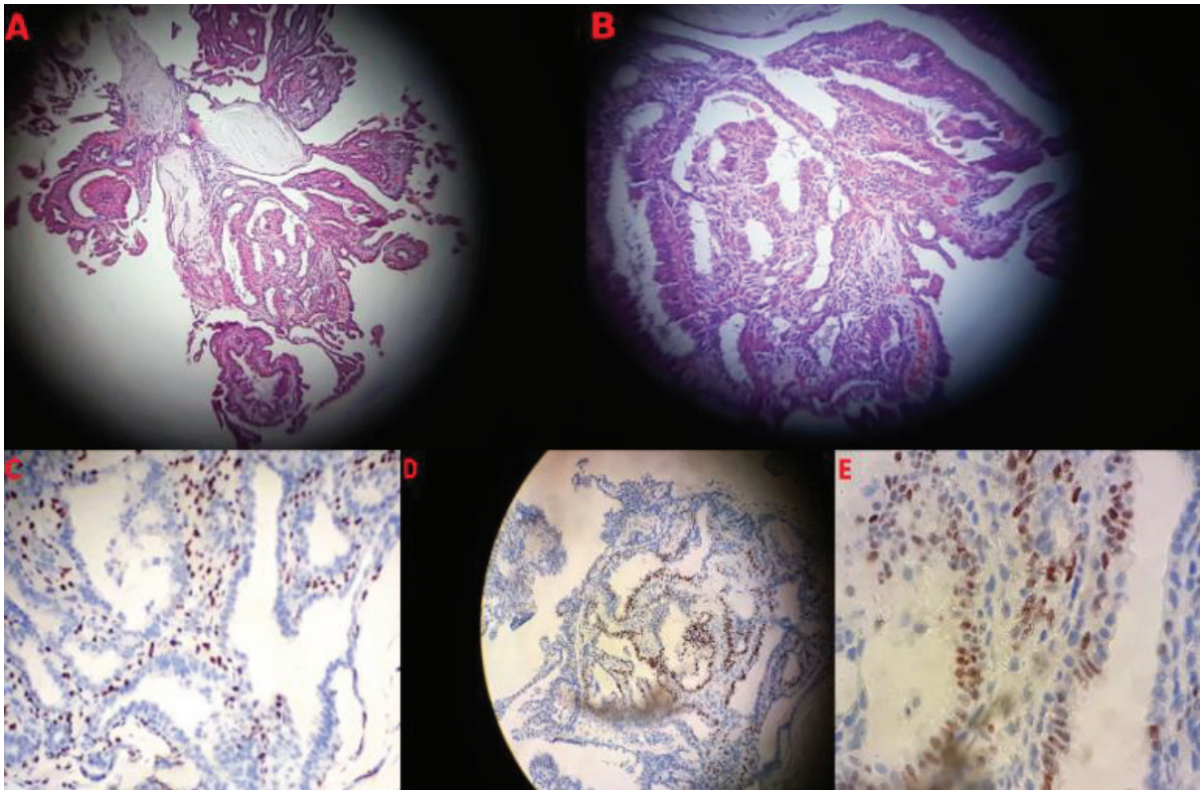

Figure 1. Histological and immunohistochemical features of hidradenoma papilliferum. **A)** The papillary lesion is lined by a bilayered epithelium resembling glandular structures (x40). **B)** The papillary lesion is lined by a bilayered epithelium resembling glandular structures (x200). **C)** Myoepithelial cells located at the basal layer exhibit positive expression for p63 (x200). **D)** Estrogen receptors show positive staining in the luminal epithelial cells (x200). **E)** Progesterone receptors show positive staining in the luminal epithelial cells (x200)

resembled a lipoma. Despite its benign appearance on clinical examination, histopathological evaluation confirmed the diagnosis of HP.

Current literature indicates that HP originates from mammary-like glands in the anogenital region (11). These glands, thought to arise from ectopic mammary tissue developed during embryogenesis, may provide the basis for HP development. They are considered normal anatomical components of the anogenital area. Due to histological similarities, such lesions can be mistaken for benign breast tumors (11).

Hormonal influences are also thought to contribute to the development of HP. Estrogen receptor expression is commonly observed in these tumors (12). An increase in tumor incidence has been reported following puberty, which corresponds with rising estrogen levels. However, in some cases, estrogen and progesterone receptors were negative, while prolactin receptors were positive. This suggests that other hormones may also play a role in the pathogenesis of HP (13).

Although the etiology of HP remains unclear, its higher prevalence among individuals of reproductive age and those who are sexually active has led to the hypothesis that sexually transmitted infections may play a role. While a few cases associated with HPV have been described, current findings are not sufficient to establish a direct causal relationship (14,15).

Study Limitations

This report describes a single case, which limits the generalizability of the findings. Immunohistochemical analysis was restricted to a few markers, and no molecular studies were performed to further explore possible etiological factors. Additionally, long-term follow-up data are currently lacking.

CONCLUSION

This case highlights the clinical and pathological variability encountered in the diagnosis and classification of lesions originating from anogenital mammary-like glands. The presence of the lesion in the clitoral region and its atypical clinical appearance distinguish it from similar cases in the literature. Surgical excision proved to be an effective method for both diagnosis and treatment. Further studies are warranted to investigate the molecular pathogenesis of such lesions in detail and to standardize diagnostic criteria, thereby improving clinicopathological comparisons.

ETHICS

Informed Consent: Written informed consent was obtained from the patient for publication of the case and accompanying images.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: M.K., Consept: M.K., Design: M.K., Data Collection or Processing: Z.K., Analysis or Interpretation: Z.K., Literature Search: Ş.G. Writing: Z.K.

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REFERENCES

1. van der Putte SC. Anogenital "sweat" glands. Histology and pathology of a gland that may mimic mammary glands. Am J Dermatopathol. 1991;13:557-67.
2. Tresserra F, Grases PJ, Izquierdo M, Cararach M, Fernandez-Cid A. Fibroadenoma phyllodes arising in vulvar supernumerary breast tissue: report of two cases. Int J Gynecol Pathol. 1998;17:171-3.
3. Kondo RN, Melhado IP, Moreira CR, Crespigio J. Ectopic hidradenoma papilliferum. An Bras Dermatol. 2018;93:474-5.
4. Rosmaninho AD, de Almeida MT, Costa V, Sanches MM, Lopes C, Selores Gomes Meirinhos MM. Ectopic hidradenoma papilliferum. Dermatol Res Pract. 2010;2010:709371.
5. Konstantinova AM, Michal M, Kacerovska D, Spagnolo DV, Stewart CJ, Kutzner H, et al. Hidradenoma papilliferum: a clinicopathologic study of 264 tumors from 261 patients, with emphasis on mammary-type alterations. Am J Dermatopathol. 2016;38:598-607.
6. Kurashige Y, Kishida K, Kurashige K, Minemura T, Nagatani T. Hidradenoma papilliferum of the vulva in association with an anogenital mammary-like gland. J Dermatol. 2014;41:411-3.
7. Shimon SV, Alenezi SM, Camela E, Maderal AD, Romanelli P. A rare case of ectopic hidradenoma papilliferum of the external auditory canal. Cureus. 2024;16:e61237.
8. Seo GJ, Seo JH, Cho KJ, Cho HS. Hidradenoma papilliferum of the anus: a report of 2 cases and review of the literature. Ann Coloproctol. 2019;35:361-3.
9. Minami S, Sadanobu N, Ito T, Natsuaki M, Yamanishi K. Non-anogenital (ectopic) hidradenoma papilliferum with sebaceous differentiation: a case report and review of reported cases. J Dermatol. 2006;33:256-9.
10. Bannatyne P, Elliott P, Russell P. Vulvar adenosquamous carcinoma arising in a hidradenoma papilliferum, with rapidly fatal outcome: case report. Gynecol Oncol. 1989;35:395-8.
11. Kazakov DV, Spagnolo DV, Kacerovska D, Michal M. Lesions of anogenital mammary-like glands: an update. Adv Anat Pathol. 2011;18:1-28.
12. Abudu EK, Umanah IN, Ekpo MD, Etuk EB, Onwuezobe IA, Obi-Ihesie A. A giant ectopic hidradenoma papilliferum in a Niger delta region of Nigeria. Rare Tumors. 2011;3:e50.
13. Elouarradi R, Hocar O. Hidradénome papillifère [Hidradenoma papilliferum]. Pan Afr Med J. 2014;17:274. French.
14. Veraldi S, Schianchi-Veraldi R, Marini D. Hidradenoma papilliferum of the vulva: report of a case characterized by unusual clinical behavior. J Dermatol Surg Oncol. 1990;16:674-6.
15. Kazakov DV, Mikyskova I, Kutzner H, Simpson RH, Hes O, Mukensnabl P, et al. Hidradenoma papilliferum with oxyphilic metaplasia: a clinicopathological study of 18 cases, including detection of human papillomavirus. Am J Dermatopathol. 2005;27:102-10.