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References should start on a separate page in the article file, not at the end of the article. Tables, table descriptions, images/figures and image/figure descriptions should also be added to the main article file on a separate page after the references. Table/Picture/figure descriptions should be immediately below the tables/ pictures/figures.

About article sections

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Research Paper:

- Mirza E, Oltulu R, Oltulu P, et al. Dry eye disease and ocular surface characteristics in patients with keratoconus. Saudi J Ophthalmol. 2022;36(1):117-21. doi: 10.4103/sjopt.sjopt_37_21.
- Vikse BE, Aasarød K, Bostad L, et al. Clinical prognostic factors in biopsy-proven benign nephrosclerosis. Nephrol Dial Transplant. 2003;18(3):517-23. doi: 10.1093/ndt/18.3.517.

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Single Author Books:
- Danovitch GM. Handbook of Kidney Transplantation. Boston: Little, Brown and Company (Inc.), 1996: 323-8.

Book Chapter:
- Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III,İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-50.
- Davison AM, Cameron JS, Grünfeld JP, et al. Oxford Textbook of Clinical Nephrology. In: Williams G, ed. Mesengiocapillary glomerulonephritis. New York: Oxford University Press, 1998: 591- 613.
- **Journal article published online ahead of print:**
- Doğan GM, Sığırcı A, Akyay A, et al. A Rare Malignancy in an Adolescent: Desmoplastic Small Round Cell Tumor. Turkiye Klinikleri J Case Rep. 10.5336/caserep.2020-77722. Published online: 31 December 2020.
- Cai L, Yeh BM, Westphalen AC, et al. Adult living donor liver imaging.DiagnIntervRadiol. 2016 Feb 24.doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Meeting Reports:
- Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report:
- Cusick M, Chew EY, Hoogwerf B, A et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis:
- Kaplan SI. Post-hospital home health care: elderly access and utilization (dissertation). St Louis (MO): Washington Univ; 1995.

Website and Social Media Channels: Author. Title. Website: URL. Date and year

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When sharing patient photos, ensure that the identity is not recognized one-to-one, and images sufficient to identify the disease should be shared. For sharing images that reveal the patient's identity, a consent form in which the patient authorizes the sharing of the image is necessary.

Table 1. Limitations according to article types

	limitation of article	abstract	references	Tables	Figures
Research Article	4000	300	50	6	6
Review	6000	300	85	6	10
Case Presentations	1500	200	15	3	5
Letters to the Editor	1000	(-)	8	(-)	(-)
Editorial	1000	(-)	20	3	3
Original Image Report	200	(-)	5	1	3

Article Types

Selcuk Medical Journal publishes the types of articles briefly described below:

Research Articles: This is the most important type of article that provides new results based on original research. The main text of original articles should be structured with the subheadings Introduction, Methods, Results, Discussion, Conclusion and References. Please refer to Table 1 for word count and specifications. Statistical analysis is often necessary to support leconclusions. Statistical analyses should be performed in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983:7;1489-93). Information on statistical analyses should be provided under a separate subheading in the Materials and Methods section and the statistical software used throughout the process should be indicated. Units should be prepared in accordance with the International System of Units (SI). Limitations, drawbacks and shortcomings of the article should be stated in the Discussion section before the conclusion paragraph.

Review Articles: Review articles should be articles that review a sufficient number of scientific articles, summarize the subject at the current level of knowledge and technology, evaluate and interpret the findings by comparing them. Techniques and applications in the latest scientific studies with all the developments in basic and applied sciences are evaluated. Reviews prepared by authors who have extensive knowledge of a particular field and have a scientific background with high citation potential will be accepted by our journal. Acceptance of manuscripts from these authors can also be by invitation. The main text should include Introduction, Clinical and Research Results and Conclusion. Please see Table 1 for word count and specifications.

Case Presentations: Educational case reports on rare cases or conditions that pose difficulties in diagnosis and treatment, offer new treatments or reveal information not included in the literature are accepted for publication in our journal. The case report should include the subheadings Introduction, Case Presentation and Discussion and Coclusion. Interesting and unusual pictures are an advantage in the evaluation process.

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If patient identity is disclosed in patient-identifying pictures, patient consent must be provided to share the picture. Please see Table 1 for word count and specifications.

Letter to the Editor: This type of article discusses important parts, overlooked aspects or missing parts of a previously published article. Articles on topics that may attract the attention of the journal, especially on topics that may attract the attention of readers, especially on educational topics, can be submitted in the form of Letters to the Editor. Readers can also submit their comments on published articles as a Letter to the Editor. Abstract, Keywords and Tables, Figures, Images and other media should not be included. The text should not include subheadings. Please see Table 1 for word count and specifications.

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Original Image Report: Interesting, descriptive or educational images (illustration or photography) from any field of medicine can be submitted for evaluation in this section, along with a few lines of explanatory text and references. Article length should not exceed 200 words. A summary, discussion, or conclusion is not required, but a brief title should be included. Please see Table 1 for word count and specifications.

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Research Article

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OPEN

RESEARCH ARTICLE

Efficacy of Endobiliary Radiofrequency Ablation in the Treatment of Benign Biliary Strictures

Benign Biliyer Darlıklarının Tedavisinde Endobiliyer Radyofrekans Ablasyon Yöntemi Etkinliği

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ABSTRACT

Objective: This study aimed to evaluate the efficacy of endobiliary radiofrequency ablation (RFA) in the percutaneous treatment of benign bilioenteric anastomotic strictures that are resistant to percutaneous balloon dilatation and long-term drainage.

Materials and Methods: The clinical data of 22 patients who underwent endobiliary RFA between September 2016 and June 2019 were included in the study. Indications comprised bilioenteric anastomotic strictures secondary to cholecystectomy (n = 8; 36.36%), the Whipple procedure (n = 6; 27.28%), Klatskin tumor (n = 6; 27.28%), and anastomotic strictures related to transplantation (n = 2; 9.09%). In these patients treated with endobiliary RFA, technical and clinical success rates, recurrence, and procedure-related morbidity and mortality rates were evaluated.

Results: Endobiliary RFA was performed in 19 patients with bilioenteric anastomotic strictures resistant to standard percutaneous treatment, in one patient with a bilioenteric anastomotic stricture accompanied by a significant stone burden in the bile ducts, and in two patients with post-transplant anastomotic strictures. Marked reductions in serum biomarkers were observed after the procedure. The mean duration of drainage catheter use prior to endobiliary RFA was 82 days (standard deviation: 39 days). During this period, seven patients (31.81%) developed symptoms of cholangitis due to catheter-related complications and were treated with catheter exchange and appropriate antibiotics. The mean symptom-free period after endobiliary RFA and catheter removal was 587 days. No major complications related to endobiliary RFA were observed. The technical success rate was 100%, and the primary clinical success rate was 95.4%.

Conclusion: Currently, there is no established standard definitive treatment for benign biliary strictures. Recurrence rates associated with all treatment modalities remain unacceptably high. In our study, endobiliary RFA yielded effective results in a selected group of patients who had been treated with percutaneous interventions but, despite the benign etiology, could not be freed from catheterization, which significantly impaired patient comfort.

Keywords: Benign biliary stricture, endobiliary radiofrequency ablation, percutaneous treatment

ÖZET

Amaç: Perkütan balon dilatasyonuna ve uzun süreli drenaja dirençli olan benign bilioenterik anastomoz darlıklarının perkütan tedavisinde endobiliyer radyofrekans ablasyon (RFA) etkinliğini değerlendirmek amaçlandı.

Gereç ve Yöntemler: Eylül 2016-haziran 2019 yılları arasında endobiliyer RFA uygulanmış 22 hasta bulguları çalışmaya dahil edildi. Endikasyon olarak kolesistektomi (n:8; % 36,36), Whipple prosedürü (n:6 ;%27,28), Klatskin tümörü (n:6 %27,28) nedeniyle bilioenterik anastomoz darlıkları ve nakile (n:2 % 9,09) bağlı anastomoz darlıkları vardı. Endobiliyer RFA uygulanan bu hastalarda teknik ve klinik başarı, nüks, prosedüre bağlı morbidite ve mortalite oranları incelendi.

Bulgular: Standart perkütan tedaviye dirençli 19 hasta, bilioenterik anastomoz darlığı ve safra yollarında belirgin taş yükü bulunan tek hasta ve karaciğer nakilli anastomoz darlığı bulunan 2 hastaya endobiliyer RFA uygulandı. Prosedür sonrası serum belirteçlerinde belirgin düşüşler gözlendi. Endobiliyer RFA öncesinde drenaj kateterlerinin ortalama kullanım süresi 82 gün (standart sapma 39 gün) oldu. Bu süreçte yedi hastada (% 31,81) kateter ilişkili komplikasyonlar nedeniyle kolanjit semptomları gelişti ve kateter değişimi ve uygun antibiyotikler ile tedavi edildi. Endobilier RFA ve kateter çıkarıldıktan sonraki ortalama semptomsuz geçen süremiz ortalama 587 gün oldu . Endobiliyer RFA ya bağlı majör komplikasyon izlenmedi. Teknik başarı oranımız % 100, primer klinik başarı oranımız % 95,4 idi.

Sonuç: Benign biliyer darlıklarının günümüzde standart kesinleşmiş tedavisi yoktur. Tüm modalitelerin nüks oranları halen kabul edilebilir düzeylerde değildir. Çalışmamızda perkutan girişimle tedavi edilmiş ancak benign bir neden olmasına rağmen hasta konforunu ciddi oranda bozan kateterizasyondan kurtulamayan seçilmiş hasta grubunda endobiliyer RFA sonuçlarının etkin olduğu bilgisi elde edildi.

Anahtar Kelimeler: Benign biliyer darlık, endobiliyer radyofrekans ablasyon, perkütan tedavi

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INTRODUCTION

Benign biliary stricture is a rare condition, with most cases resulting from surgical trauma during open or laparoscopic cholecystectomy. Biliary strictures may also develop during the healing process following hepatobiliary surgeries that involve the creation of a bilioenteric anastomosis, such as liver transplantation and the Whipple procedure, due to ischemia or inflammation (1). Patients may be asymptomatic or may present with jaundice, pain, pruritus, bile stones, cholangitis, sepsis, or biliary cirrhosis. Treatment options include endoscopic interventions, percutaneous interventions, and surgical reconstruction. Although the choice of optimal treatment depends on the operator, it remains controversial (2). No significant differences have been demonstrated in success rates among various techniques, including surgical treatment, percutaneous interventional treatment, multiple plastic stent placement, or covered metallic stents (3). Recurrence rates associated with these procedures are high, with an average of approximately 20% (2). Although endobiliary radiofrequency ablation (RFA) is primarily used in the treatment of malignant biliary obstruction, data on its use in the treatment of benign bilioenteric anastomotic strictures remain limited (3–5).

This study aimed to evaluate the safety and efficacy of endobiliary RFA in the treatment of benign bilioenteric anastomotic strictures that are resistant to percutaneous balloon dilatation and long-term drainage.

MATERIALS AND METHODS

This retrospective study was conducted in accordance with the ethical principles and was approved by the local ethics committee (No. 2306/2020). Prior to treatment, the benefits and potential complications of the procedure were explained to the patients, and written informed consent was obtained. Institutional data records between September 2016 and June 2019 were retrospectively reviewed. Data from 22 patients who underwent endobiliary RFA were obtained. Demographic characteristics of the patients were recorded. Exclusion criteria included the presence of malignant biliary strictures or response to standard percutaneous treatments. The study population comprised 19 patients who did not respond to balloon dilatation followed by long-term drainage with large-caliber catheters, one patient who developed cholestatic findings and large intrahepatic bile duct stones secondary to a bilioenteric anastomotic stricture, and two patients who developed anastomotic strictures after liver transplantation. Clinical data obtained from patient records and radiological data from the hospital imaging archive system were reviewed. Data regarding technical success, clinical success, recurrence, and procedure-related morbidity and mortality were collected. Technical success was defined as the spontaneous passage of bile into the intestines via the natural biliary pathway following removal of the existing catheter. Clinical success was defined as the absence of cholestatic findings and normalization of related laboratory parameters, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, and alkaline phosphatase.

Complete blood count, prothrombin time, partial thromboplastin time, international normalized ratio (INR), and platelet count were assessed. Patients with an INR < 1.5 and a platelet count > 100,000/mL were considered suitable for the procedure. All procedures were performed under moderate sedoanalgesia and local anesthesia. Sedoanalgesia was administered by an external anesthesia team using a combination of fentanyl (50–100 µg), midazolam (3–4 mg), ketamine (10–20 mg), and propofol (20–50 mg). For local anesthesia, 10 cc of prilocaine was used. After placement of a 0.035-inch guidewire (Radifocus® Guidewire M Stiff Type Guide Wire, Terumo) through the existing catheter with its tip positioned in the intestine, a 10F vascular sheath was introduced, and cholangiograms were obtained to localize the stricture. An 8F (2.6 mm), 90-cm bipolar RFA probe (Habib Percutaneous HBP, EMcision) was advanced over the guidewire and positioned centrally within the stricture. The distal end of the catheter contains two stainless steel electrodes spaced 8 mm apart, generating thermal energy over a 25-mm zone (Figure 2B). The RFA probe was connected to a generator (ERBE, VIO), and ablation was performed twice using a power output of 7 W for a total duration of 90 seconds (40 + 40 + 10 seconds), in accordance with the manufacturer's protocol. In patients with both right and left biliary drainage catheters, endobiliary RFA was performed separately for each side. Following endobiliary ablation, balloon dilatation was carried out using high-pressure balloon catheters with diameters of 8–10 mm (Mustang™ PTA Balloon Dilatation Catheter, Boston Scientific), after which a 14F internal–external biliary drainage catheter (Biliary Drainage Catheters, Bioteque Corporation) was placed (Figure 1a–d). A broad-spectrum antibiotic effective against biliary pathogens (cefixime 400 mg), initiated prior to treatment, was recommended to be continued for 15 days after the procedure. The first follow-up evaluation was performed 30 days later by injecting contrast material through the existing catheter. In patients with no residual stricture on cholangiography and normal passage of contrast into the intestine, a 5F safety catheter with its distal tip positioned in the bowel was placed. After two weeks, patients were re-evaluated using the same method, and in the absence of signs of cholangitis or cholestasis, the catheter was removed.

After completion of treatment, patients were followed at 3-month intervals during the first year and at 6-month intervals thereafter. Follow-up assessments included hepatobiliary ultrasonography and evaluation of laboratory parameters (AST, ALT, total bilirubin, GGT, and alkaline phosphatase).

Statistical Analysis

Statistical analyses were performed using IBM SPSS (Statistical Package for the Social Sciences) Statistics version 31. Descriptive statistics, including mean, standard deviation, median, quartiles, and minimum–maximum values, were used for numerical (quantitative) variables. Frequency tables with counts and percentages were used for categorical (qualitative) variables. To determine whether statistically significant differences existed between dependent numerical

variables measured at two different time points (pre- and post-treatment), difference values were first calculated. The normality of data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. For data that did not demonstrate a normal distribution, the Wilcoxon signed-rank test was used to evaluate differences between paired measurements. A confidence level of 95% was applied, and p values < 0.05 were considered statistically significant.

Sample Size and Power Analysis

Power analysis for the sample size of 22 patients was conducted using data from the direct bilirubin variable, which was considered the primary outcome parameter. With an effect size of 0.68, a margin of error of 0.05, and a confidence level of 95%, the minimum required statistical power of 80% to detect a difference of 2.48 units was achieved, indicating that the sample size was adequate for the study.

RESULTS

Endobiliary RFA was performed in 22 patients (mean age, 60.5 years; range, 31–80 years), of whom 81.81% (n = 18) were male and 18.18% (n = 4) were female, who presented to our unit between September 2016 and June 2019. Presenting symptoms among patients undergoing endobiliary RFA included jaundice (n = 12), right upper quadrant pain (n = 5), pruritus (n = 17), and cholangitis (n = 15), at varying frequencies. Indications for percutaneous endobiliary RFA are listed in Table 1. In 20 patients, the initial intervention was performed via a percutaneous approach due to a history of

Table 1. Indications for percutaneous endobiliary RF ablation

		Etiology		
Etiology	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
Cholecystectomy (iatrogenic)	8	36.36	8	36.36
Klatskin tm	5	22.73	13	59.09
Periampullary region tm	1	4.55	14	63.64
Pancreas tm	5	22.73	19	86.36
Hepatocellular carcinoma	1	4.55	20	90.91
Transplantation	2	9.09	22	100.00

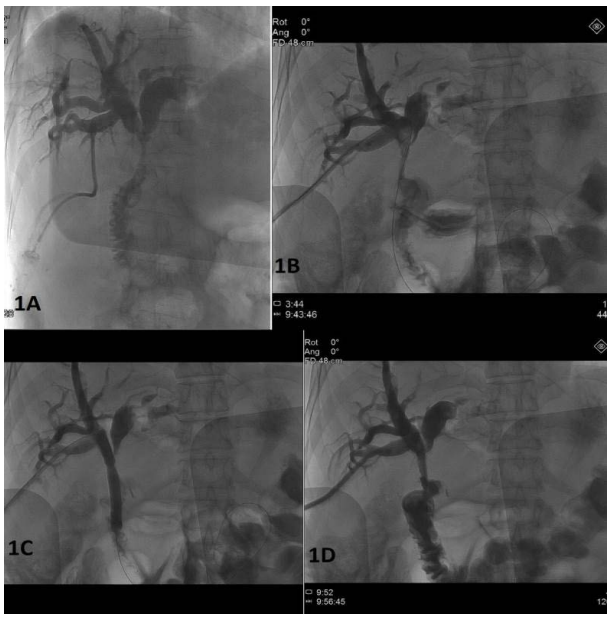

Figure 1.
- Standard percutaneous treatment approach in bilioenteric anastomotic stricture, long-term catheterization
- Endobiliary rf ablation application in stricture area
- Dilatation of stricture area through balloon catheters right after endobiliary rf ablation
- Insertion of a large diameter (10-14F) catheter after endobiliary RF ablation and balloon dilatation

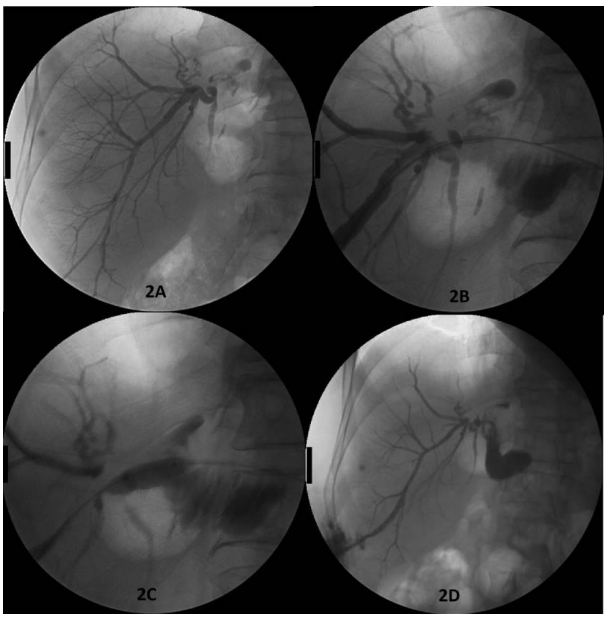

Figure 2.
- Bilioenteric anastomotic stricture in the transplanted liver in percutaneous transhepatic cholangiography
- Endobiliary rf ablation application in stricture area
- Dilatation of the stricture area with balloon catheters right after endobiliary rf ablation
- Insertion of a large diameter (10-14F) catheter after endobiliary RF ablation and balloon dilatation

prior surgical procedures. In the remaining two patients who had undergone liver transplantation, an endoscopic approach was initially attempted. Bilateral access and catheterization were performed in seven patients (31.82%) with bilioenteric anastomoses, and endobiliary RFA was applied from both sides. Right-sided access was used in 14 patients (63.64%), while left-sided access was used in one patient (4.55%).

In the two liver transplant recipients, percutaneous intervention was performed due to unsuccessful endoscopic treatment. To shorten the catheterization period in these immunosuppressed patients, endobiliary RFA and balloon dilatation were performed one month after establishing percutaneous biliary drainage, followed by catheter-based follow-up using a 14F catheter for one month. After this period, control cholangiograms were obtained, and catheterization was continued with a 5F catheter for an additional two weeks. In the absence of cholestasis or cholangitis, the safety catheter was removed (Figure 2a–d). In one patient with common bile duct injury following cholecystectomy who developed a stricture at the bilioenteric anastomosis, multiple large stones were present in the intrahepatic bile ducts. These large intrahepatic stones were visualized using cholangioscopy, fragmented using pneumatic and laser lithotripsy, and removed percutaneously. After percutaneous cholangioscopy and cholangiography, balloon dilatation of the stricture was performed, and a 14F catheter was placed. Despite the absence of cholestasis or cholangitis at the 1-month follow-up, endobiliary RFA was performed for the anastomotic stricture based on a multidisciplinary board decision due to the patient's predisposition to stone formation (Figure 3a–d).

Prior to endobiliary RFA, the mean duration of drainage catheter use was 82 days (standard deviation: 39 days). During this period, seven patients (33%) developed symptoms of cholangitis due to catheter-related complications and were treated with catheter exchange and appropriate antibiotic therapy. In all 19 patients who did not respond to biliary drainage with balloon dilatation and long-term large-caliber catheters, in one patient with a bilioenteric anastomosis in whom intrahepatic stones were fragmented and removed percutaneously, and in the two liver transplant recipients, catheter removal was successfully achieved after endobiliary RFA. The technical success rate was 100%. The primary clinical success rate was 95.94% (n = 21). The mean symptom-free period after endobiliary RFA and catheter removal was 587 days (range: 210–1170 days). In four patients (18.18%) who experienced recurrence of symptoms after the procedure, secondary clinical success was improved by repeat percutaneous intervention consisting of endobiliary RFA, balloon dilatation, and biliary drainage with a 14F catheter for one month (Tables 2 and 3).

Serum biochemical markers in patients who underwent percutaneous biliary intervention and endobiliary RFA demonstrated statistically significant reductions after treatment. Significant differences were observed between pre- and post-treatment values of AST, ALT, GGT, alkaline

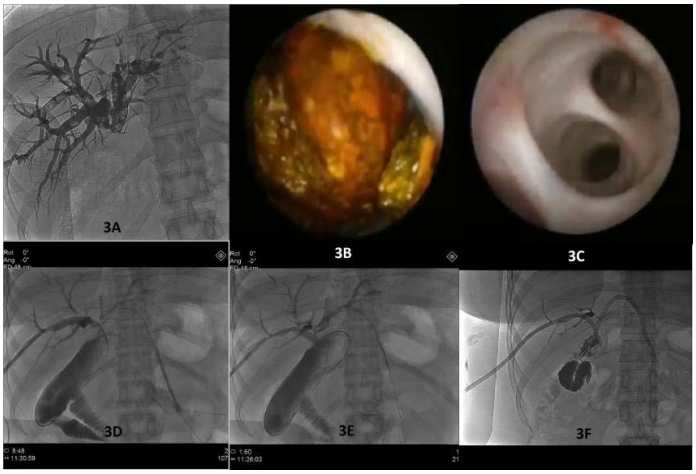

Figure 3.

- Stricture in percutaneous transhepatic cholangiography and many stones in intrahepatic bile ducts are observed in the patient with bilioenteric anastomotic stricture formation following choledochal injury in gall bladder operation.
- Stones are observed in bile ducts in the percutaneous cholangioscopy.
- Monitorization of bile ducts through cholangiography after the pneumatic and laser lithotripsy of biliary stones and their percutaneous removal
- Endobiliary rf ablation application in stricture area
- Dilatation of stricture area through balloon catheters right after endobiliary rf ablation
- Insertion of large diameter (10-14F) biliary catheters accessing through both lobes after endobiliary RF ablation and balloon dilatation

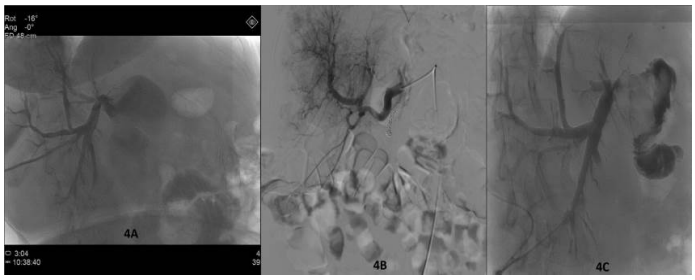

Figure 4.

- Biliary drainage catheter insertion following endobiliary RF ablation in the patient who had bilioenteric anastomosis due to Klatskin tumor.
- Bleeding from the mass in the jejunum, in the vicinity of anastomosis three months after endobiliary RF ablation
- Filling defect for the polypoid tumoral mass filling jejunal loop in percutaneous transhepaticcholangiography (arrow)

Table 2. Descriptive statistics for numerical variables

	The Smallest	The largest	Mean± Standard Deviation
Age	31	80	60,55±10,65
Time from initial biliary intervention to endobiliary radiofrequency ablation (months)	0	7	2,73±1,31
Time elapsed (months) for additional biliary intervention after endobiliary radiofrequency ablation	0	24	3,91±6,63
Duration of additional endobiliary radiofrequency ablation (months)	0	24	2,32±5,81
Symptom-free period following radiofrequency ablation (months)	7	39	19,59±9,88

Table 3. Frequency table for the categories of numerical variables

		Number	Percentage
Time from the first biliary intervention to endobiliary radiofrequency ablation (months)	0	1	4,5
	1	3	13,6
	2	1	4,5
	3	16	72,7
	7	1	4,5
Time elapsed (months) for additional biliary intervention after endobiliary radiofrequency ablation	0	15	68,2
	7	1	4,5
	8	1	4,5
	9	1	4,5
	11	1	4,5
	12	1	4,5
	15	1	4,5
	24	1	4,5
Duration of additional endobulbar radiofrequency ablation (months)	0	18	81,8
	7	1	4,5
	9	1	4,5
	11	1	4,5
	24	1	4,5
Symptom-free period following endoscopic radiofrequency ablation (months)	7	1	4,5
	8	1	4,5
	9	1	4,5
	11	1	4,5
	12	3	13,6
	14	1	4,5
	15	3	13,6
	16	1	4,5
	17	1	4,5
	18	1	4,5
	24	2	9,1
	30	1	4,5
	31	1	4,5
	32	1	4,5
	34	1	4,5
	36	1	4,5
	39	1	4,5
	Total	22	100,0

Table 4. Examination of whether there is a statistically significant difference between serum marker measurements before and after endobiliary radiofrequency ablation

	Mean± Standard Deviation	The Smallest	The Greatest	Median (Q2)	Q1-Q3	p-value
Pre-RF SGOT	560,13±1629,27	13	7729	84	43,25-279,25	
Post-RF SGOT	68,66±212,05	9,2	1017	23,1	15,55-31,52	<0,001
Pre-RF SGPT	89,73±80,64	12	400,2	78,15	38,75-119,2	
Post-RF SGPT	26,27±15,36	6,2	73	23,2	15,4-34,47	<0,001
Pre-RF GGT	376,55±306,54	99	1377	287,5	169,75-389,5	
Post-RF GGT	125,82±103,41	24	422	98,5	55,5-129,25	<0,001
Pre-RF alkaline phosphatase	411,18±214,37	118	983	379	254,25-528	
Post-RF alkaline phosphatase	188,73±92,85	73	422	178,5	112,25-231,25	<0,001
Pre-RF direct bilirubin	3,11±3,85	0,27	17,1	1,77	0,62-3,70	
Post-RF direct bilirubin	0,63±0,50	0,12	1,9	0,41	0,24-0,95	<0,001
Pre-RF total bilirubin	4,23±4,46	0,55	20,02	2,81	1,74-4,31	
Post-RF total bilirubin	1,03±0,76	0,18	2,81	0,82	0,50-1,27	<0,001

Q1: 1. Quarter, Q3: 3. Quarter

phosphatase, direct bilirubin, and total bilirubin ($p < 0.001$) (Table 4).

No complications, including bleeding, perforation, bile leakage, pancreatitis, or cholecystitis, were observed after endobiliary RFA. Three patients experienced transient postprocedural pain that responded to analgesic therapy. In one patient with a history of tumor surgery, signs of gastrointestinal bleeding developed three months after endobiliary RFA. Computed tomography angiography revealed a tumoral mass with active bleeding in the jejunum adjacent to the choledochojejunostomy. Hemostasis was achieved by endovascular coil embolization (Figure 4a, b). This patient died 12 months after endobiliary RFA due to progression of the primary tumor.

DISCUSSION

It was revealed that combining endobiliary RFA with standard percutaneous interventions contributes to a shorter treatment course and a reduction in complications, and that endobiliary RFA is an effective and safe treatment option for patients with resistant biliary strictures. Endoscopic retrograde cholangiopancreatography (ERCP) is the first-line modality for the diagnosis and treatment of biliary strictures. Repeated aggressive endoscopic interventions and placement of multiple plastic stents are generally considered the initial step in management (6–8). When endoscopic access to the biliary system is not feasible, percutaneous techniques serve as an alternative approach (9,10). The percutaneous approach is typically employed in cases where endoscopic access is not possible due to prior surgery or after failed endoscopic treatment (11). The cornerstone of percutaneous management consists of long-term biliary drainage and repeated balloon dilatation procedures (11–17). Metallic stents are not considered appropriate or preferred for the treatment of benign biliary strictures because of frequent recurrent cholangitis and occlusion of the stent lumen (18). Although the use of removable covered stents has been recommended, high rates of stent migration have been reported, particularly in short stricture segments (19,20). Another alternative is the placement of biodegradable stents; however, stent availability is limited, and data regarding their use remain scarce (21). If endoscopic and percutaneous interventions fail, open surgical revision remains the final definitive treatment option. However, surgical management is associated with high complication and recurrence rates (2,22). In the present study, an alternative treatment modality to those reported in the literature was applied for the management of benign biliary strictures. Percutaneous endobiliary RFA was found to be an effective and safe therapeutic option for biliary strictures.

Hu et al. applied balloon dilatation followed by temporary stent placement after endoscopic endobiliary RFA in stenotic segments (4). Supporting these findings, they reported rapid improvement of strictured biliary segments without serious adverse effects after RFA. Similarly, Ozdemir M. et al. applied percutaneous endobiliary RFA and balloon dilatation in 22 patients with benign biliary strictures and achieved a clinical success rate of 88.9% (5). In the study by Akinci D, et al., catheter removal was successfully achieved in all seven patients who could not be liberated from catheterization despite repeated balloon dilatations and long-term drainage after endobiliary RFA (3). In that study, the technical success rate was 100%, and the clinical success rate was 95.2%. In the present study, we achieved a technical success rate of 100% and a clinical success rate of 95.45%. Our results regarding technical success, clinical success, complication rates, and recurrence rates are consistent with those reported in the literature. We believe that the use of large-caliber biliary drainage catheters (14F) with prolonged catheterization, together with the effectiveness of endobiliary RFA, contributed to the high clinical success rate observed in our study. When high-frequency electrical current is applied to tissue via RFA probes, intracellular ions move in opposite directions. This ionic movement generates frictional

heat around the probe, resulting in thermal destruction of scar tissue (23,24). We believe that this destruction of scar tissue enhances the response to balloon dilatation and long-term catheterization and prolongs their effectiveness. Procedure-related complications associated with endobiliary RFA performed via both endoscopic and percutaneous routes, including bleeding, perforation, bile leakage, pancreatitis, and cholecystitis, have been reported more frequently in malignant biliary strictures (25,26). Wener Dolak et al. reported complications such as hepatic infarction, cholangitis, cholangiosepsis, gallbladder empyema, hepatic coma, and newly diagnosed left bundle branch block following endoscopic endobiliary RFA performed for malignant biliary strictures (27). In the present study, three patients experienced abdominal pain that responded to analgesics, and no major complications were observed. We believe that the use of a lower power output (7 W) instead of the 10 W commonly applied in malignant strictures may have prevented thermal injury severe enough to cause complications in the bile ducts and anastomotic region. Further studies are warranted to substantiate this hypothesis with stronger evidence.

Biliary strictures after liver transplantation occur either as proximal strictures at the anastomotic site or as peripheral strictures resulting from ischemic cholangiopathy related to hepatic artery anastomosis. End-to-end anastomotic strictures occur in approximately 8–30% of liver transplant recipients and are typically reported to arise from scar formation at the suture line (28). In the two liver transplant recipients included in our study, endobiliary RFA was performed following unsuccessful endoscopic interventions, based on a multidisciplinary board decision. Complete technical and clinical success was achieved without any significant complications. Moreover, shortening the catheterization period reduces the risk of infection and serious morbidity in immunosuppressed patients. In patients with large and multiple intrahepatic bile duct stones accompanied by recurrent episodes of cholangitis, treatment options extending as far as hepatectomy or even transplantation have been reported in the literature (29). Intrahepatic stones can be removed using percutaneous lithotripsy (30). In this study, we benefited from our experience with percutaneous lithotripsy. After fragmenting bile stones using pneumatic and laser lithotripsy and removing them percutaneously, endobiliary RFA, balloon dilatation, and catheterization for one month were applied to the existing stricture. The patient's benign biliary stricture responded well to treatment, and symptoms regressed. No biliary stone formation, cholestasis, or cholangitis was observed during follow-up. This study demonstrates that patients with a high intrahepatic stone burden secondary to benign biliary stricture can be successfully treated using minimally invasive techniques without the need for surgery.

The primary limitation of this study is its retrospective design. A second limitation is the relatively small sample size and the inclusion of patients with different etiologies within the same study cohort. At present, there are no large-scale studies with substantial case numbers on this topic, and randomized controlled trials are needed. Recurrence remains the most significant challenge in the treatment of benign biliary strictures. Meta-analyses comparing the success rates of different techniques, including surgery, percutaneous treatment, multiple plastic stent placement, and covered metallic stents, have not demonstrated a significant difference among these modalities (3). Recurrence rates remain unacceptably high across all procedures, at approximately 20% (2). In this study, the mean symptom-free period after endobiliary RFA and catheter removal was 587 days (range: 210–1170 days). The addition of endobiliary RFA to standard percutaneous intervention shortened the overall treatment duration and prolonged the symptom-free interval. In standard percutaneous approaches, prolonged catheterization adversely affects patient comfort and may lead to catheter-related infections and cholangitis. The findings of this study indicate that combining endobiliary RFA with standard percutaneous interventions contributes to a reduction in complications.

CONCLUSION

Due to variability in recurrence rates, there is currently no established standard definitive treatment for benign biliary strictures. This study demonstrates that, in a selected group of patients who were treated with percutaneous interventions but could not be liberated from catheterization despite the benign etiology and experienced significant impairment in quality of life, endobiliary RFA is a safe adjunctive technique that enhances the effectiveness of percutaneous treatment.

DECLARATIONS

Conflict of Interest: *The authors declare no conflict of interest.*

Financial Disclosure: *The authors declare that there is no financial conflict of interest related to this study*

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RESEARCH ARTICLE

Investigation of The Anti-İnflammatory Effect of İsotretinoin in Patients with Acne Vulgaris, A New İndicator: Systemic İnflammation Aggregate İndex

Akne Vulgaris Hastalarında İzotretinoinin Antiinflamatuar Etkisinin Araştırılması, Yeni Bir Gösterge: Sistemik İnflamasyon Agregat İndeksi

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ABSTRACT

Objective: Acne vulgaris is a chronic inflammatory skin disease, and isotretinoin. The vitamin A derivative, is widely used in its treatment. The effects of isotretinoin on systemic inflammation remain controversial. Neutrophil-lymphocyte ratio (NLR), systemic inflammatory response index (SIRI), systemic immune-inflammatory index (SII), and total index of systemic inflammation (AISI) are inexpensive and easily calculated biomarkers derived from complete blood counts. These markers are used to assess the presence of inflammation in systemic and dermatological inflammatory diseases. This study aimed to evaluate changes in these markers during isotretinoin therapy in acne vulgaris.

Materials and Methods: The study included 183 patients receiving isotretinoin. Complete blood counts were retrospectively recorded at 0, 3, and 6 months, and NLR, SII, SIRI, and AISI values were analyzed.

Results: The absolute neutrophil count decreased at 6 months compared to baseline (p=0.032), and the lymphocyte count increased at 3 and 6 months (p=0.003 and p=0.043, respectively). The platelet count increased at the end of the 3rd month and decreased at the end of the 6th month compared to baseline (p=0.002, p=0.012, respectively). NLR, SIRI, SII, and AISI values have continued to decrease during treatment, and a significant decrease has observed at the end of the 6th month (p=0.001, p=0.006, p=0.016, p=0.029, respectively).

Conclusion: Systemic isotretinoin therapy in patients with acne vulgaris is associated with significant reductions in NLR, SIRI, SII, and AISI. These findings support the presence of a systemic anti-inflammatory effect of isotretinoin and contribute to the ongoing debate regarding its impact on systemic inflammation.

Keywords: Aggregate index of systemic inflammation, isotretinoin, neutrophil-lymphocyte ratio, systemic inflammatory response index, systemic immune-inflammatory index

ÖZET

Amaç: Akne vulgaris, kronik inflamatuar bir hastalıktır. Bir A vitamini türevi olan izotretinoin, akne tedavisinde yaygın olarak kullanılmaktadır. İzotretinoinin sistemik inflamasyon üzerindeki etkileri literatürde çelişkili sonuçlara sahiptir. Nötrofil-lenfosit oranı (NLR), sistemik inflamatuar yanıt indeksi (SIRI), sistemik immün-inflamatuar indeksi (SII) ve sistemik inflamasyonun toplam indeksi (AISI), tam kan sayımından elde edilen, ucuz ve kolay hesaplanabilen biyobelirteçlerdir ve sistemik ve dermatolojik inflamatuar hastalıklarda inflamasyonun varlığını değerlendirmek için kullanılmaktadır. Bu çalışmanın amacı, akne vulgaris hastalarında izotretinoin tedavisi sırasında bu sistemik inflamatuar belirteçlerdeki değişiklikleri değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya, akne vulgaris tedavisi için izotretinoin tedavisi gören 183 hasta dahil edildi. Tam kan sayımları 0, 3 ve 6. aylarda retrospektif olarak kaydedildi ve NLR, SII, SIRI ve AISI değerleri analiz edildi.

Bulgular: Mutlak nötrofil sayısı, başlangıç değerine kıyasla 6. ayda azaldı (p=0,032) ve lenfosit sayısı 3. ve 6. aylarda arttı (sırasıyla p=0,003 ve p=0,043). Trombosit sayısı, 3. ayın sonunda arttı ve 6. ayın sonunda başlangıç değerine kıyasla azaldı (sırasıyla p=0,002 ve p=0,012). NLR, SIRI, SII ve AISI değerleri tedavi sırasında azalmaya devam etmiş ve 6. ayın sonunda önemli bir azalma gözlemlenmiştir (sırasıyla p=0,001, p=0,006, p=0,016, p=0,029).

Sonuç: Akne vulgaris hastalarında sistemik izotretinoin tedavisi, NLR, SIRI, SII ve AISI'da önemli azalmalarla ilişkilidir. Bu bulgular, izotretinoinin sistemik antiinflamatuar etkisinin varlığını desteklemekte ve sistemik inflamasyon üzerindeki etkisine ilişkin süregelen tartışmaya katkıda bulunmaktadır.

Anahtar Kelimeler: Sistemik inflamasyon agregat indeksi, izotretinoin, nötrofil-lenfosit oranı, sistemik inflamatuar yanıt indeksi, sistemik immün-inflamatuar indeks

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INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit that commonly begins during the second and third decades of life and affects approximately 85% of the population worldwide (1). Clinically, acne is characterized by comedones, papules, and pustules, while severe or untreated cases may result in post-inflammatory hypo- or hyperpigmentation and permanent atrophic or hypertrophic scarring. The etiopathogenesis of acne vulgaris involves four main mechanisms: increased sebum production, follicular hyperkeratinization, Cutibacterium acnes colonization, and inflammation (2). Treatment strategies vary according to disease severity. Topical therapies are generally sufficient for mild acne, whereas systemic treatments are required in moderate to severe cases. Oral isotretinoin is considered the most effective systemic agent, as it targets all major pathogenic mechanisms involved in acne development (3). Despite its well-documented efficacy, isotretinoin is associated with a range of adverse effects involving multiple organs and systems, including xerosis, cheilitis, dry eyes, myalgia, dyslipidemia, photosensitivity, and hepatotoxicity. Additionally, inflammatory conditions such as pancreatitis, inflammatory bowel disease, and arthritis have been reported during isotretinoin therapy (4).

Although acne vulgaris is fundamentally an inflammatory disorder, the impact of isotretinoin on systemic inflammation remains controversial. Previous studies evaluating changes in inflammatory markers during isotretinoin treatment have yielded conflicting results (5,6). Hareedy et al. suggested that isotretinoin may increase systemic inflammatory activity (5), where as Semiz et al. demonstrated a potential anti-inflammatory effect of isotretinoin therapy (6). These inconsistent findings highlight the need for further investigation into the systemic inflammatory effects of isotretinoin.

In recent years, several hematological indices derived from routine complete blood counts have emerged as practical, inexpensive, and reliable markers of systemic inflammation. The neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI) have been increasingly used to assess inflammatory burden in various dermatological diseases in which inflammation plays a key role (7–9). The Aggregate Index of Systemic Inflammation (AISI) is a more comprehensive composite marker that incorporates neutrophil, lymphocyte, monocyte, and platelet counts, based on the concept that integrated inflammatory indices provide a more accurate representation of systemic inflammatory status than single parameters alone (7).

To date, there are limited studies evaluating the relationship between isotretinoin therapy and these systemic inflammatory indices. Therefore, the present study aimed to investigate whether systemic inflammation is reduced in patients with acne vulgaris treated with isotretinoin by analyzing changes in inflammatory response markers, with particular emphasis on AISI, alongside NLR, SIRI, and SII.

MATERIALS AND METHODS

The study was designed retrospectively, and included acne vulgaris patients who used isotretinoin between January 2023 and November 2024. Ethics committee approval has been obtained. (2024/5380 ID: 21974). Patients older than 18 years of age who received at least 3 months of isotretinoin 0.5-1 mg/kg/day treatment for acne vulgaris were included in the study. Complete blood count data at the end of the 0th, 3rd and 6th months of treatment were recorded from the patients' files. NLR, SIRI, SII, AISI were calculated using the following formulas.

NLR= neutrophil count /lymphocyte count (×103/μL)

SIRI = neutrophil count x monocyte count/lymphocyte count (×103/μL)

SII = platelet count x neutrophil count/lymphocyte count, (×103/μL)

AISI=neutrophils count x platelets count x monocytes count /lymphocytes count (×103/μL)

Patients with inflammatory, autoimmune or active infectious diseases, malignancy or pregnancy, and those using additional anti-inflammatory drugs or antibiotics in addition to isotretinoin treatment were not included in the study.

The Statistical Package for the Social Sciences (SPSS), version 20.0 for Windows (SPSS Inc., Chicago, IL) was used for the statistical analysis. Continuous data were expressed as mean ± standard deviation, and the categorical data were expressed as percentages. Kolmogorov– Smirnov test was used to check the distribution of pre-treatment and posttreatment values for normality. Paired sample t-test was used to compare normally distributed values. Statistical significance was described as $p<0.05$.

RESULTS

A total of 183 patients were included in the study, comprising 148 females (80.9%) and 35 males (19.1%). The mean age of the cohort was 26.15 ± 6.61 years (range: 18–45 years). No statistically significant changes were observed in total white blood cell (WBC) counts during isotretinoin treatment. However, the absolute neutrophil count showed a significant decrease at the 6-month follow-up compared with baseline ($p = 0.032$). In contrast, lymphocyte counts significantly increased at both the 3rd and 6th months of treatment ($p = 0.003$ and $p = 0.043$, respectively). Monocyte counts did not demonstrate significant changes throughout the treatment period. Platelet counts exhibited a biphasic pattern, with a significant increase at the 3rd month of treatment followed by a significant decrease at the 6th month compared with baseline ($p = 0.002$ and $p = 0.012$, respectively). Inflammatory indices derived from complete blood count parameters, including the NLR, SIRI, SII, and AISI, demonstrated a progressive decline throughout isotretinoin therapy. Statistically significant reductions in all indices were observed at the end of the 6-month treatment period ($p = 0.001$, $p = 0.006$, $p = 0.016$, and $p = 0.029$, respectively). Detailed laboratory and inflammatory marker

Table 1. Changes in complete blood count and inflammation parameters according to measurement time during the treatment process.

	0. Month	3. Month	6. Month	P1	P2
WBC ($\times10^3/\mu L$)	6.90±1.47	6.99±1.45	6.65±1.36	0.414	0.303
Neutrophils count ($\times10^3/\mu L$)	3.87±1.19	3.84±1.08	3.58±1.01	0.756	0.032
Lymphocyte count ($\times10^3/\mu L$)	2.31±0.55	2.42±0.56	2.35±0.56	0.003	0.043
Monocyte count ($\times10^3/\mu L$)	0.53±0.16	0.53±0.16	0.52±0.14	0.423	0.851
Platelets count ($\times10^3/\mu L$)	283.89±55.75	291.81±53.41	280.70±52.58	0.002	0.012*
NLR	1.76±0.66	1.64±0.51	1.57±0.49	0.022	0.001
SIRI	0.93±0.48	0.88±0.38	0.83±0.35	0.126	0.006
SII	500.05±213.05	478.88±175.79	440.92±151.93	0.157	0.016
AISI	269.71±152.80	258.15±124.23	235.42±109.01	0.310	0.029

WBC: White blood cell NLR: Neutrophil lymphocyte ratio, SIRI: systemic inflammation response index, SII: systemic immune-inflammation index, AISI: Aggregate index of systemic inflammation.
The data are presented with the mean ± standard deviation.
P1: value for the difference between 0th month and 3rd month group
P2: value for the difference between 0th month and 6th month group
*: platelet level decreased at month 6 of treatment compared to month 0.

values are presented in Table 1.

DISCUSSION

In the present study, we demonstrated a significant reduction in inflammatory markers derived from complete blood count parameters during isotretinoin treatment in patients with acne vulgaris. Although isotretinoin is widely and effectively used in the treatment of acne vulgaris, its impact on systemic inflammation remains controversial, with both pro-inflammatory and anti-inflammatory effects reported in the literature (5,6,10,11). Several experimental and clinical studies have supported the immunomodulatory and anti-inflammatory properties of isotretinoin. Dispenza et al. reported that isotretinoin inhibits Toll-like receptor 2 and 4 expression, reduces T helper cell activity, and exerts immunomodulatory effects (11). Similarly, Karadağ et al. demonstrated that isotretinoin decreases the release of pro-inflammatory cytokines such as TNF-α, IL-4, IL-17, and IFN-γ from T lymphocytes, suggesting a regulatory effect on adaptive immune responses (10). In contrast, Hareedy et al. reported increases in erythrocyte sedimentation rate, C-reactive protein, and ferritin levels, acute phase reactants, indicating a potential pro-inflammatory effect of isotretinoin (5). These conflicting findings underline the complexity of isotretinoin's systemic effects and the need for further investigation using accessible inflammatory markers.

Changes in complete blood count parameters and derived inflammatory indices during isotretinoin therapy have been widely studied; however, results remain inconsistent. Ataseven et al. reported a decrease in platelet counts after at least three months of isotretinoin treatment (12), whereas Kutlu et al. observed no significant changes in platelet or neutrophil counts but reported increased lymphocyte counts and decreased NLR values (13). Tamer et al. found an increase in platelet counts, no change in neutrophil or monocyte counts, and a decrease in lymphocyte counts (14). Similarly, Seçkin et al. reported increased platelet counts without significant changes in NLR after at least five months of treatment (15). Önder et al. found a decrease in neutrophil counts but no significant changes in lymphocyte counts, monocyte counts, or NLR (16). In contrast, Hareedy et al. observed decreases in both platelet counts and NLR values (5), while Demirci et al. reported increased platelet counts accompanied by decreased neutrophil counts and NLR after six months of treatment (17). Esen et al. demonstrated no significant changes in lymphocyte, monocyte, or platelet counts but observed a decrease in NLR due to reduced neutrophil counts after at least three months of isotretinoin therapy (18). In our study, platelet counts showed a transient increase at the third month of treatment, followed by a decreasing trend at the sixth month. Concurrently, lymphocyte counts increased, neutrophil counts decreased, and NLR values significantly declined throughout the treatment period. These findings support the hypothesis that isotretinoin exerts a time-dependent modulatory effect on hematological inflammatory parameters.

Recently, multicomponent inflammatory indices derived from routine blood counts have gained increasing attention as prognostic and monitoring tools in various inflammatory diseases (9,19). Turan et al. reported no changes in neutrophil, monocyte, or platelet counts during isotretinoin treatment but observed increased lymphocyte counts and decreased SII values, and also demonstrated that patients with acne vulgaris had higher baseline neutrophil, monocyte, platelet, and SII values compared with healthy controls (20). Çoşansu et al. found increased platelet and lymphocyte counts along with decreased NLR, SII, and SIRI levels after at least three months of isotretinoin treatment. In the same study, platelet counts were higher in patients with acne vulgaris than in healthy controls prior to treatment, while no differences were observed in neutrophil or lymphocyte counts or inflammatory indices between the two groups (21).

AISI, which integrates neutrophil, monocyte, platelet, and lymphocyte counts, has recently emerged as a comprehensive marker of systemic inflammation (22,23). Zorlu et al. demonstrated decreases in neutrophil and monocyte counts after six months of isotretinoin treatment, along with an increase in lymphocyte percentage despite a decrease

in absolute lymphocyte counts. Platelet counts increased, particularly during the early phase of treatment, while SII, SIRI, and AISI values significantly decreased over the treatment course (24). In line with these findings, our study showed a continuous decrease in neutrophil counts during isotretinoin therapy, an early increase followed by a later decline in platelet counts, stable monocyte counts, and increased lymphocyte counts, ultimately resulting in significant reductions in NLR, SIRI, SII, and AISI.

Taken together, our findings suggest that isotretinoin therapy is associated with a systemic anti-inflammatory effect as reflected by multiple hematological inflammatory indices. The observed reductions in composite markers such as AISI, SII, and SIRI may provide a more comprehensive understanding of isotretinoin's immunomodulatory role in acne vulgaris.

Limitation

This study has several limitations that should be acknowledged. First, its retrospective design may limit the ability to establish causal relationships. Second, acute-phase reactants such as C-reactive protein and erythrocyte sedimentation rate were not simultaneously evaluated, which may have restricted a more comprehensive assessment of systemic inflammation. In addition, the potential effects of different isotretinoin dosing regimens could not be analyzed. Finally, the absence of a healthy control group precluded direct comparisons between patients with acne vulgaris and the general population. Despite these limitations, we believe that the findings of the present study contribute valuable data regarding the systemic inflammatory effects of isotretinoin therapy. Further well-designed prospective studies incorporating acute-phase reactants, dose–response analyses, and appropriate control groups are warranted to clarify the relationship between isotretinoin treatment, systemic inflammation, and hematological parameters.

CONCLUSION

The findings of the present study indicate that systemic isotretinoin therapy is associated with a significant reduction in blood-count-derived inflammatory markers, including NLR, SII, SIRI, and particularly the Aggregate Index of Systemic Inflammation (AISI), in patients with acne vulgaris. These results support the anti-inflammatory effect of isotretinoin at the systemic level and suggest that composite inflammatory indices may better reflect treatment-related changes than single hematological parameters. Given their low cost, wide availability, and ease of calculation, these indices, especially AISI, may serve as practical tools for monitoring inflammatory response and treatment efficacy in patients receiving isotretinoin therapy. Future prospective studies are warranted to further validate their clinical utility.

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RESEARCH ARTICLE

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Association of Selenoprotein P Levels with Proteinuria Severity in Newly Diagnosed Type 2 Diabetes Mellitus

Selenoprotein P Düzeylerinin Yeni Tanı Konmuş Tip 2 Diabetes Mellitus Hastalarında Proteinüri Şiddeti ile İlişkisi

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ABSTRACT

Objective: Diabetic nephropathy is one of the leading causes of chronic kidney disease and progression to end-stage renal failure. Identifying new biomarkers that correlate with nephropathy severity may improve risk stratification and clinical decision-making processes. The aim of this study was to evaluate the relationship between serum selenoprotein levels, renal function parameters, and proteinuria severity in newly diagnosed diabetes mellitus patients.

Materials and Methods: Ninety patients with diabetes mellitus were divided into three groups according to their proteinuria status: those without proteinuria (n=30), those with microalbuminuria (30–300 mg/g, n=30), and those with macroalbuminuria (>300 mg/g, n=30). Demographic characteristics, glycemic indicators, renal function tests, and serum selenoprotein P concentrations were evaluated.

Results: Selenoprotein P levels showed a gradual increase across groups (1,61 [1,23–2,10], 3,28 [2,79–4,07], and 7,13 [5,51–8,34], respectively; p < 0,001). Proteinuria severity showed a strong positive correlation with selenoprotein P (r=0.794, p<0.001), creatinine (r=0.532, p<0.001), and HbA1c (r=0.406, p<0.001), and negatively correlated with GFR (r=−0.681, p<0.001).

Conclusion: Increased selenoprotein P concentrations are closely associated with worsening proteinuria and renal dysfunction and support its potential as an early biomarker of diabetic nephropathy.

Keywords: Diabetic nephropathy, Selenoprotein P, Proteinuria severity

ÖZET

Amaç: Diyabetik nefropati, kronik böbrek hastalığının ve son dönem böbrek yetmezliğine gidişin önde gelen nedenlerinden biridir. Nefropati şiddeti ile paralellik gösteren yeni biyobelirteçlerin tanımlanması, risk sınıflandırması ve klinik karar verme süreçlerini geliştirebilir. Bu çalışmanın amacı yeni tanı almış diyabetes mellitus hastalarında serum selenoprotein P düzeylerinin, böbrek fonksiyon parametreleri ve proteinüri şiddeti ile ilişkisini değerlendirmektir.

Gereç ve Yöntemler: Doksan diyabetes mellitus hastası proteinüri durumlarına göre üç gruba ayrıldı: proteinürisi olmayanlar (n=30), mikroalbüminürisi olanlar (30–300 mg/g, n=30) ve makroalbüminürisi olanlar (>300 mg/g, n=30). Demografik özellikler, glisemik göstergeler, böbrek fonksiyon testleri ve serum selenoprotein P konsantrasyonları değerlendirildi.

Bulgular: Selenoprotein P düzeyleri gruplar arasında kademeli olarak artış gösterdi (sırasıyla 1,61 [1,23-2,10], 3,28 [2,79-4,07] and, 7,13 [5,51-8,34], p <0,001). Proteinüri şiddeti; selenoprotein P (r=0,794, p<0,001), kreatinin (r=0,532, p<0,001) ve HbA1c (r=0,406, p<0,001) ile güçlü pozitif korelasyon, GFR (r=−0,681, p<0,001) ile ise negatif korelasyon sergiledi.

Sonuç: Artmış selenoprotein P konsantrasyonları, kötüleşen proteinüri ve böbrek fonksiyon bozukluğu ile yakından ilişkilidir ve diyabetik nefropatinin erken biyobelirteci olma potansiyelini desteklemektedir.

Anahtar Kelimeler: Diyabetik nefropati, Selenoprotein P, Proteinüri şiddeti

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INTRODUCTION

Diabetes mellitus (DM) is a major global health problem with increasing prevalence in both developed and developing countries (1). Characterized by chronic hyperglycemia, DM is closely associated with the development of vascular complications. These complications include microvascular manifestations (retinopathy, neuropathy, and nephropathy) and macrovascular disorders, which significantly increase cardiovascular morbidity and mortality. Among these, diabetic nephropathy (DN) stands out as the primary cause of chronic kidney disease (CKD) and the most important predictor of end-stage renal disease (ESRD) worldwide, placing a serious burden on both patients and healthcare systems (2).

Early detection and effective monitoring of DN are critical for improving renal and cardiovascular outcomes. Proteinuria, especially albuminuria, is among the classic early markers of diabetic kidney damage. Microalbuminuria indicates the onset of nephropathy, while macroalbuminuria is a strong indicator of advanced kidney damage and adverse cardiovascular events. However, the predictive power of albuminuria is limited and does not fully reflect the underlying pathophysiological mechanisms of DN. Therefore, research continues into new and more sensitive biomarkers that can more accurately reflect disease activity and progression (3–5).

Selenoproteins are a unique family of proteins containing selenocysteine in their structure and perform essential functions in antioxidant defense, immune response regulation, and cellular redox balance (6, 7). Enzymes such as glutathione peroxidases and thioredoxin reductases play a critical role in protecting kidney tissue against oxidative stress, one of the main mechanisms of diabetic renal damage (8). Impaired selenoprotein expression may increase oxidative damage, endothelial dysfunction and progressive nephron loss (9). Selenoprotein P, in particular, has been associated with renal function loss and diabetic complications in recent years (10, 11). However, data on the direct relationship between circulating selenoprotein levels and proteinuria severity in DN are limited, and further studies in this area are needed.

The aim of this study was to investigate whether selenoprotein levels are associated with proteinuria severity in newly diagnosed with type 2 diabetes mellitus (DM). As a secondary objective, the relationship between selenoprotein levels and glycemic control (HbA1c) and renal function indicators (GFR, creatinine, urea) was planned to be evaluated. Thus, their potential as candidate biomarkers in diabetic nephropathy was attempted to be elucidated.

MATERIALS AND METHODS

Study Population

This cross-sectional study included 90 patients with newly diagnosed type 2 diabetes who were diagnosed between September 2024 and December 2025. Individuals with acute infections, chronic inflammatory diseases, advanced chronic kidney disease (stages 4–5), or other systemic diseases that could affect kidney function were excluded from the study.

Patients were divided into three groups based on their proteinuria status:

Group 1: Those without proteinuria (n=30)

Group 2: Microalbuminuria (30–300 mg/g, n=30)

Group 3: Macroalbuminuria (>300 mg/g, n=30)

Demographic and clinical data were recorded (age, gender, body mass index [BMI]), and biochemical parameters were evaluated (fasting glucose, HbA1c, urea, creatinine, estimated glomerular filtration rate [GFR], and selenoprotein levels). Selenoprotein measurement was performed by ELISA according to the manufacturer's instructions.

Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Necmettin Erbakan University Faculty of Medicine (Approval No: 2025/6052, Date: October 10, 2025).

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Continuous data were presented as mean ± standard deviation. Normal distribution was assessed using the Shapiro–Wilk test. The Kruskal–Wallis test was used for group differences; the Bonferroni-corrected Mann–Whitney U test was applied for pairwise comparisons. Categorical data were evaluated using the chi-square test. The relationships between proteinuria severity and biochemical parameters were examined using Spearman correlation analysis. $p<0.05$ was considered statistically significant.

RESULTS

Ninety newly diagnosed type 2 DM patients were included in the study. Thirty (33.3%) had no proteinuria, 30 (33.3%) had microalbuminuria, and 30 (33.3%) had macroalbuminuria. The mean age was similar across groups (p=0.804). No significant differences were found between groups in terms of gender distribution (male/female, p=0.670) and BMI (p=0.981). Group comparisons of clinical and laboratory data are summarized in Table 1. Serum creatinine levels were significantly higher in the macroalbuminuria group compared to both the microalbuminuria and proteinuria-free groups (p<0.001). HbA1c values were significantly higher in the macroalbuminuria group (9.74±2.61%) compared to microalbuminuria (7.80±0.86%) and non-proteinuric (7.64±0.87%) patients (p<0.001). Estimated GFR gradually decreased as proteinuria severity increased (101.47±12.99, 90.96±15.03, and 70.93±10.87 mL/min/1.73 m^2; p<0.001).

Selenoprotein levels showed a gradual and statistically significant increase across the three groups (1.88±1.17, 3.44±1.08, and 6.56±2.12; p<0.001). The highest levels were detected in the macroalbuminuria group (Figure 1).

Table 2 summarizes the correlation analyses. A strong positive correlation was found between proteinuria severity and selenoprotein (r=0.794, p<0.001), creatinine (r=0.532, p<0.001), and HbA1c (r=0.406, p<0.001). In contrast, a strong negative correlation was found with GFR (r=-0.681, p<0.001). No significant relationship was found between proteinuria severity and age, BMI, fasting glucose, or urea levels (p>0.05 for all comparisons). Additionally, the inverse correlation between

Table 1. Comparison of Clinical and Laboratory Parameters Between Groups

Parameters	No proteinuria (n=30)	Microalbuminuria (n=30)	Macroalbuminuria (n=30)	p-value
Age (years)	58.0 (54.5–65.0)	58.5 (52.3–63.8)	58.0 (54.3–65.0)	0.804
BMI (kg/m²)	28.2 (26.2–30.4)	28.4 (26.2–30.0)	28.3 (26.4–30.2)	0.981
Urea (mg/dL)	25.1 (21.0–32.5)	24.0 (20.1–31.4)	24.0 (20.5–30.2)	0.676
Creatinine (mg/dL)	0.83 (0.70–0.93)[a]	0.83 (0.69–0.91)[a]	1.17 (1.02–1.33)[b]	<0.001
Glucose (mg/dL)	159.8 (130.9–194.7)	158.9 (132.3–188.2)	179.9 (145.8–191.1)	0.445
HbA1c (%)	7.5 (6.9–8.2)[a]	7.7 (7.1–8.5)[a]	8.6 (8.1–11.2)[b]	<0.001
GFR (mL/min/1.73m²)	100.6 (94.1–105.8)[c]	93.4 (77.4–105.5)[b]	70.1 (65.1–77.7)[a]	<0.001
Selenoprotein P	1.61 (1.23–2.10)[a]	3.28 (2.79–4.07)[b]	7.13 (5.51–8.34)[c]	<0.001

Bold p values indicate statistical significance ($p < 0.05$).
Data are presented as median (25^{th}-75^{th} percentiles/interquartile range). Overall group comparisons were performed using the Kruskal–Wallis test. Post-hoc pairwise comparisons were conducted with Bonferroni-adjusted Mann–Whitney U tests. Different superscript letters ([a], [b], [c]) indicate statistically significant differences between groups ($p < 0.05$); identical letters denote no significant difference.
For creatinine and HbA1c: b>a. For GFR: c> b>a. For selenoprotein: c> b>a.

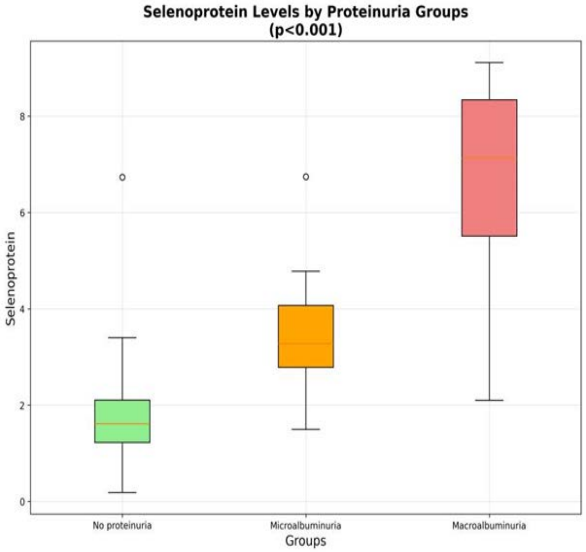

Figure 1. Serum selenoprotein concentrations across proteinuria groups in newly diagnosed type 2 diabetic patients. Box plots illustrate median values, interquartile ranges, and outliers. A progressive and significant increase in selenoprotein levels was observed from patients without proteinuria to those with microalbuminuria and macroalbuminuria (p<0.001).

Table 2. Correlation Analysis Between Proteinuria Severity and Parameters

Parameters	Correlation (r)	p-value
Age	0.019	0.861
BMI	0.020	0.849
Urea	-0.085	0.421
Creatinine	0.532	<0.001
Glucose	0.101	0.340
HbA1c	0.406	<0.001
GFR	-0.681	<0.001
Selenoprotein	0.794	<0.001

Bold p values indicate statistical significance ($p < 0.05$)

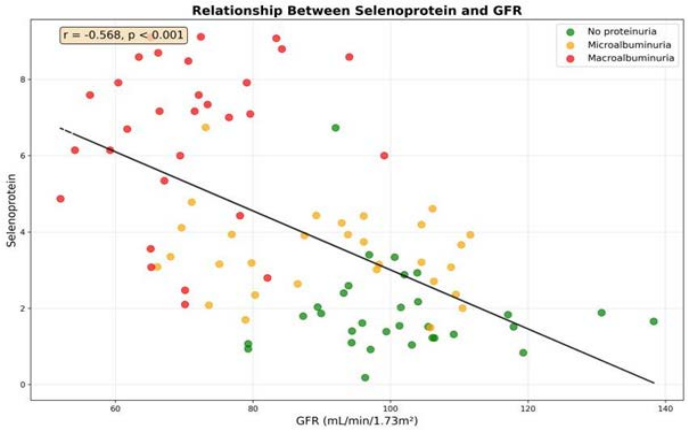

Figure 2. Scatter plot showing the relationship between serum selenoprotein P levels and estimated glomerular filtration rate (GFR). Each point represents an individual patient stratified by proteinuria status (green: no proteinuria, yellow: microalbuminuria, red: macroalbuminuria). Selenoprotein levels demonstrated a strong inverse correlation with GFR (r = –0.681, p < 0.001).

selenoprotein and GFR was demonstrated by a scatter plot; increased selenoprotein levels were consistently associated with decreased renal function (Figure 2).

DISCUSSION

The present study demonstrates that higher proteinuria levels in newly diagnosed DM are significantly associated with impaired renal function, suboptimal glycemic control, and altered selenoprotein concentrations. Patients with macroalbuminuria exhibited significantly higher creatinine and HbA1c levels and lower GFR values compared to patients with microalbuminuria and those without proteinuria. Furthermore, serum selenoprotein levels showed a progressive and significant increase with increasing severity of proteinuria.

Correlation analysis confirmed strong positive relationships between proteinuria severity and selenoprotein, creatinine, and HbA1c, while GFR showed a strong negative relationship. Among all parameters evaluated, selenoprotein showed the closest correlation with kidney impairment, highlighting its potential role in monitoring disease progression.

Diabetic nephropathy is one of the leading causes of chronic kidney disease and end-stage renal failure on a global scale. Traditional clinical markers such as albuminuria, serum creatinine, and estimated glomerular filtration rate (eGFR) remain the most commonly used tools for diagnosis and staging (12). The current findings are consistent with previous studies showing that more advanced proteinuria is associated with reduced kidney function and poor glycemic control. These results support the role of HbA1c as a critical factor in nephropathy progression and confirm the clinical utility of GFR and creatinine as traditional markers of kidney damage (13, 14).

A novel finding of this study is the strong association between selenoprotein levels and proteinuria severity. Selenoproteins play a role in redox regulation and defense against oxidative stress; these mechanisms are closely linked to both diabetes mellitus and kidney damage (10). High selenoprotein levels may reflect an adaptive response to increased oxidative load in diabetic nephropathy. On the other hand, altered selenoprotein homeostasis may contribute to kidney damage through disruption of antioxidant pathways. This dual interpretation highlights the need for mechanistic studies to clarify whether the observed elevation is protective or pathogenic (7).

Clinically, the elevation of selenoprotein levels in stages of proteinuria and their strong correlation with renal function parameters suggest that this protein may be a promising biomarker for diabetic nephropathy. Detecting its increase early could provide clinicians with an additional tool to identify patients at higher risk of progressive renal failure, thereby guiding closer monitoring and more targeted interventions (15).

Study Limitations

This study is subject to several limitations that need to be taken into account. First, the cross-sectional design does not allow for causal inference, thereby constraining the interpretation of observed associations. Second, the modest sample size limits statistical power and reduces the generalizability of the findings. Third, selenoprotein P concentrations were measured at a single time point, without serial assessments to capture longitudinal variation. Lastly, dietary selenium intake, a potential determinant of serum levels, was not assessed. Future investigations should employ prospective designs with larger and more diverse populations to validate these findings and to elucidate underlying mechanisms more comprehensively.

CONCLUSION

In conclusion, elevated serum selenoprotein P concentrations are closely linked to worsening proteinuria and renal dysfunction in diabetic patients, supporting their potential role as an early biomarker of nephropathy. Larger prospective cohorts are needed to confirm these findings.

DECLARATIONS

Conflict of Interest: *The authors declare that there is no conflict of interest related to this study.*

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OPEN

RESEARCH ARTICLE

Medial Meniscus Extrusion on MRI: A Critical Indicator for High-Risk Tears and Associated Intra-Articular Pathologies

Manyetik Rezonans Görüntülemede Medial Menisküs Ekstrüzyonu: Yüksek Riskli Yırtıklar ve Eşlik Eden İntra-Artiküler Patolojiler için Kritik Bir Gösterge

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ABSTRACT

Objective: To evaluate the relationship between medial meniscus (MM) tear morphology and meniscal extrusion, and to determine whether extrusion can be used as an indicator for identifying high-risk tears based on knee MRI findings.

Materials and Methods: This retrospective study included 183 knee examinations from 160 patients. MM pathologies were classified as degeneration, horizontal-oblique tear, radial tear at the root region, and complex tear. Lateral meniscal pathologies, chondromalacia, joint effusion, and anterior cruciate ligament (ACL) status were recorded. Meniscal extrusion was measured on coronal proton-density–weighted images. Intergroup differences were analyzed using the chi-square and Kruskal–Wallis tests. Receiver operating characteristic (ROC) analysis was performed to predict high-risk tears. A multivariate logistic regression model was used to investigate independent predictors of extrusion ≥3 mm.

Results: Radial root tears and complex tears demonstrated significantly greater extrusion compared with other pathologies. Chondromalacia and joint effusion were significantly more frequent in knees with extrusion ≥3 mm. ACL rupture was associated with both increased extrusion and complex MM tears. ROC analysis identified a threshold value of 3.27 mm (clinically approximated as 3 mm) for discriminating high-risk tears (sensitivity 84.4%, specificity 70.2%, AUC 0.82). In the regression analysis, low-risk and high-risk tear groups as well as chondromalacia were identified as independent predictors of pathological extrusion.

Conclusion: MM extrusion, particularly values ≥3 mm, is a strong radiological indicator of radial root and complex tears and reflects accompanying degenerative changes. Quantitative assessment of extrusion may contribute to the early diagnosis of surgically significant meniscal tears.

Keywords: Meniscus tear, meniscal extrusion, MRI, anterior cruciate ligament rupture, chondromalacia

ÖZET

Amaç: Medial menisküs (MM) yırtık morfolojisi ile menisküs ekstrüzyonu arasındaki ilişkiyi ve ekstrüzyonun yüksek riskli yırtıkların belirlenmesinde bir gösterge olarak kullanılıp kullanılamayacağını diz MRG bulguları üzerinden değerlendirmek.

Gereç ve Yöntemler: Bu retrospektif çalışmaya 160 hastaya ait 183 diz değerlendirmesi dahil edilmiştir. MM patolojileri dejenerasyon, horizontal-oblik, kök bölgesinde radyal yırtık ve kompleks yırtık olarak sınıflandırılmıştır. Lateral menisküs patolojileri, kondromalazi, efüzyon ve ön çapraz bağ (ÖÇB) durumu kaydedilmiştir. Menisküs ekstrüzyonu koronal proton-ağırlıklı kesitlerde ölçülmüştür. Gruplar arası farklar Ki-kare ve Kruskal-Wallis testleri ile değerlendirilmiş; yüksek riskli yırtıkları öngörmek için ROC analizi yapılmıştır. Multivaryant lojistik regresyon modeli ≥3 mm ekstrüzyonun bağımsız belirleyicilerini araştırmıştır.

Bulgular: Radyal kök yırtığı ve kompleks yırtıklar diğer patolojilere göre belirgin derecede daha yüksek ekstrüzyon göstermiştir. Kondromalazi ve efüzyon, ≥3 mm ekstrüzyonu olan dizlerde anlamlı olarak daha sık görülmüştür. ÖÇB rüptürü, hem yüksek ekstrüzyon hem de kompleks MM yırtıkları ile ilişkili bulunmuştur. ROC analizinde yüksek riskli yırtıkları ayırt etmek için 3,27 mm (klinik olarak 3 mm) eşik değeri belirlenmiştir (duyarlılık %84,4; özgüllük %70,2; AUC 0,82). Regresyon analizinde düşük-risk ve yüksek-risk yırtık grupları ile kondromalazi, patolojik ekstrüzyonun bağımsız belirleyicileri olarak bulunmuştur.

Sonuç: MM ekstrüzyonu özellikle 3 mm ve üzerindeki değerlerde, radyal kök ve kompleks yırtıkların güçlü bir radyolojik göstergesidir ve eşlik eden dejeneratif değişiklikleri yansıtır. Ekstrüzyonun nicel değerlendirilmesi, cerrahi açıdan önemli yırtıkların erken tanısına katkı sağlayabilir.

Anahtar Kelimeler: Menisküs yırtığı, menisküs ekstrüzyonu, MRG, ön çapraz bağ yırtığı, kondromalazi

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INTRODUCTION

Magnetic Resonance Imaging (MRI) is a reliable method in the diagnosis of knee pathologies. Since 1985, when Reiche et al first used MRI for knee pathologies, MRI has become a non-invasive alternative to knee arthroscopy with its day-by-day increasing sensitivity and specificity (1). Ability to have images in three planes, having no radiation, high contrast in soft tissue, allowing elaborate examination in cartilage tissue besides the bony structures, and superiority in different scans for tissue characterization, MRI plays an important role in musculoskeletal imaging, especially for knee imaging (2). This positioning establishes MRI as the principal or exclusive imaging technique for evaluating suspected internal knee derangements, given that traditional radiography and CT arthrography exhibit limitations in thoroughly assessing the capsule, collateral ligaments, menisci, and tendons (3).

The menisci in the knee are crucial for load transmission, shock absorption, joint stability, nutrient supply, lubrication, and proprioception (4). They also enhance joint congruency and load transmission by increasing the contact area. While meniscal tears are prevalent knee pathologies, other conditions affecting connective tissues and bones can present with symptoms mimicking meniscal injuries (5). MRI provides the physician with proper diagnostic information in meniscus injuries and accompanying knee pathologies. This comprehensive imaging capability allows for a detailed assessment of meniscal integrity, including the identification of various tear types and associated extrusions, which are crucial for determining appropriate management strategies (6).

This study aims to explore the relation of knee pathologies, which may be seen in knee joint effusion, cartilage damage, anterior cruciate ligament rupture, and the relationship of these signs with meniscus degeneration, different tear types, and meniscus shift. Our hypothesis is that major medial extrusion amounts could be a sign of high-risk tears of medial meniscus tears and even can be related with lateral meniscal and other intraarticular pathologies.

MATERIAL AND METHODS

After obtaining the ethical board approval from our institution (2009/324,26-02-2009, Selçuk University Meram School of Medicine), a total of 183 knees from 160 patients who presented to our clinic with a knee MRI request between January 2009 and August 2010 were included in this study. Patients reported by the same musculoskeletal radiologist were searched retrospectively. All knee MRI reports during this period were screened in the PACS archive, and meniscal pathologies were identified using the keywords "radial", "complex", "horizontal", "discoid", and "degeneration. The patients were stratified based on meniscal pathology, comprising 40 knees with medial meniscal degeneration, 40 with horizontal or horizontal oblique medial meniscal tears, 50 with medial meniscal radial tears of the root, 40 with complex medial meniscal tears, and 13 with discoid lateral menisci. Cases with more than one tear were evaluated in the complex tear group. Patient selection was consecutive within each predefined pathology subgroup: the first eligible examinations that met all imaging and reporting criteria were included until the intended sample size (40–50 knees) was reached. This approach was chosen to avoid subjective case picking while maintaining analytically meaningful subgroup sizes. Lateral meniscus pathologies of the patients were also recorded. The 13 knees with discoid lateral menisci were analyzed as a separate group for LM pathology; however, any co-existing medial meniscal pathologies within this group were also included in the corresponding MM pathology subgroups for analysis. Radiographic Kellgren–Lawrence grading was not available in this retrospective MRI-based dataset. Exclusion criteria were applied to minimize confounding factors and included: prior knee surgery (such as meniscectomy or ligament reconstruction), acute fractures or bone tumors, clearly documented inflammatory arthropathies, and inadequate image quality or missing sequences that prevented accurate extrusion measurement.

The imaging of all of the patients were performed by 1,5 Tesla MRI device (Symphony, Siemens, Germany) with knee coil using a protocol of Proton density plus T2A turbo spin echo (TE: 14 ve101, TR: 3450, Matrix: 183x256, FOV: 160, slice thickness 3,5 mm) sagittal; T2-A turbo spin-echo fat sat (TE: 88, TR:3300, Matrix: 183x256, FOV: 160, slice thickness 4 mm) coronal; Proton density turbo spin-echo (TE: 22, TR: 3300, Matrix: 183x256, FOV: 160, slice thickness 4 mm) coronal; proton density turbo spin-echo fat sat (TE: 14, TR: 3800, Matrix: 180x 256, FOV: 160, slice thickness 4 mm) transverse images. Images were evaluated on the PACS system (Enlil Paks, Eroglu software, Eskisehir). Tear types and degeneration condition of medial and lateral menisci, extrusion amounts of medial and lateral menisci, anterior cruciate ligament, synovial effusion condition, and periarticular cartilage and bone were evaluated. The anterior cruciate ligament is evaluated in three groups as normal, mucinous degeneration, and tear. Synovial effusion is evaluated especially on the T2A and PD images, and chondromalacia is evaluated on the coronal images. Medial and lateral menisci extrusion amounts were measured on the magnified coronal PD images on radiological monitors, from the most distal point of the meniscus to the tibial plate. Measurement was performed perpendicular to the tibial plateau, from the outer margin of the meniscal body to the edge of the tibial cortex at the level of the medial compartment (Figure 1).

Statistical Analysis

Meniscus status and extrusion rates of the groups; ACL conditions, joint effusions, and development of chondromalacia were compared. Chi-square test was performed to reveal the relationship between anterior cruciate ligament, effusion, and chondromalacia conditions with lateral and medial meniscus pathologies and MM deviation amounts. The amount of medial and lateral meniscus extrusion according to tear types was determined by Kruskal-Wallis one-way analysis of variance. If the result was significant, the Bonnferroni-corrected Mann-Whitney U test was applied. A multivariable binary logistic

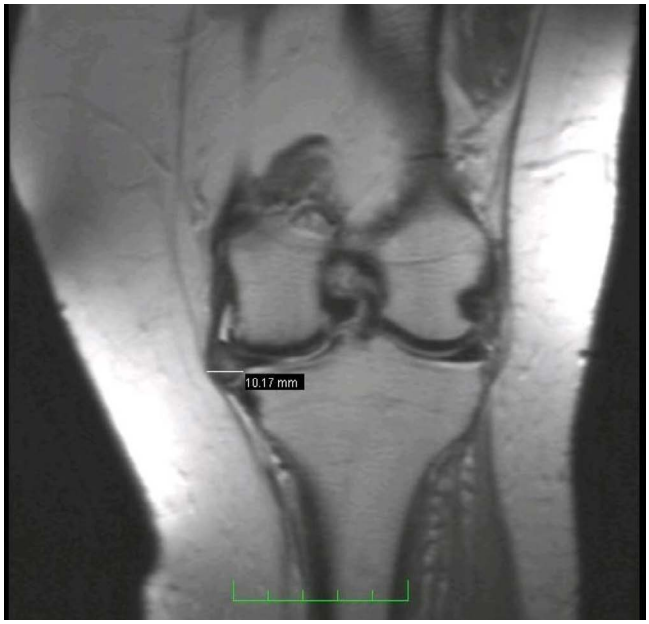

Figure 1. Measurement of the amount of extrusion in the medial meniscus in the coronal proton-weighted knee MRI image. The horizontal distance between the edge of the tibial plateau and the outermost edge of the meniscus was measured.

regression model was constructed to identify independent factors associated with pathological MME. The dependent variable was pathological MME (≥ 3 mm). Independent variables entered the model were age (years, continuous), sex (male vs. female), presence of chondromalacia (yes/no), presence of joint effusion (yes/no), presence of ACL pathology (yes/no), and meniscal risk group (low risk and high risk vs. degenerative). Odds ratios (ORs) with 95% confidence intervals (CIs) and p values were calculated. Statistical significance was set at $p < 0.05$.

RESULTS

The patients were between 18 and 62 years old, and their average age was 43. There were 85 women and 75 men. Ages of the females and males in each of the MM pathologies groups was not significant ($p>0.05$).

Distribution of Meniscal Pathologies

Medial meniscus (MM) pathologies included 6 normal (3.2%), 44 degeneration (24.0%), 43 horizontal–oblique (HO) tears (23.0%), 50 radial tear of the root (27.8%), and 40 complex tears (22.0%). Lateral meniscus (LM) pathologies comprised 113 normal (62.1%), 23 degeneration (12.6%), 27 HO tears (14.8%), 5 complex tears (2.7%), and 14 discoid menisci (7.7%).

Joint Effusion

Effusion was present in 52 of 183 knees (28.4%).

Effusion was present at all ages. In younger age groups, effusion was often associated with acute traumatic pathology (ACL tear, root tear, high grade meniscal tears). In older groups, effusion was more frequently seen together with chondromalacia and degenerative meniscal tears, reflecting chronic synovial irritation rather than only acute trauma.

• Association by LM pathology: Effusion occurred in 24.8% of normal LM, 43.5% of degeneration, 33.3% of HO, 40.0% of complex, and 21.4% of discoid.

The association was not statistically significant ($\chi^2=3.41$, $p=0.49$).

• Association by MM pathology: Effusion was 0% in normal MM, 9.1% in degeneration, 21.4% in HO, 43.1% in radial root, and 42.5% in complex. The distribution was significant ($\chi^2=14.28$, $p=0.0065$).

Effusion was significantly more frequent in radial root and complex tears compared to normal MM.

• Association by MM extrusion severity: Effusion was 17.6% with no extrusion, 17.1% with <3 mm, and 36.1% with ≥3 mm. The association was significant ($\chi^2=7.68$, $p=0.022$).

Effusion was significantly more common in ≥3 mm extrusion compared to both 0 mm and <3 mm groups.

Chondromalacia

Chondromalacia was observed in 98/183 knees (53.6%). Across the entire cohort, knees with chondromalacia were older on average than those without chondromalacia.

• Association by LM pathology: It was present in 82.6% of degeneration, 74.1% of HO, 100% of complex, 45.1% of normal, and 21.4% of discoid LMs. The distribution was significant ($\chi^2=18.97$, $p=0.0008$).

LM degeneration and LM complex groups had significantly higher chondromalacia than LM discoid and LM normal groups. LM discoid showed significantly lower chondromalacia than all other LM groups.

• Association by MM pathology: Chondromalacia was 16.7% in normal MM, 36.4% in degeneration, 33.3% in HO, 74.5% in radial root, and 72.5% in complex.

The association was highly significant ($\chi^2=34.77$, $p<0.001$).

Radial root and complex tears had significantly higher chondromalacia compared to normal and degenerative MM. Differences between radial root and HO, and between complex and HO, were also significant.

• Association by MM extrusion severity: Chondromalacia was 38.2% with 0 mm, 24.4% with <3 mm, and 70.4% with ≥3 mm extrusion.

The association was highly significant ($\chi^2=29.53$, $p<0.001$). ≥3 mm extrusion had significantly higher chondromalacia than both 0 mm and <3 mm groups (Figure 2).

Anterior Cruciate Ligament (ACL)

ACL was normal in 101 knees (55.2%), degenerated in 61 (33.3%), and ruptured in 21 (11.5%). Patients <30 and 30–39 categories had the highest proportion of ACL tears, consistent with trauma related injuries. In the ≥50 groups, ACL tears were relatively infrequent, whereas degenerative ACL changes constituted a higher proportion of findings.

• Association by LM pathology: With normal ACL, LM was usually normal (68.3%).

With ACL degeneration, LM was more often with HO (18.3%). With ACL rupture, LM degeneration and HO were frequent

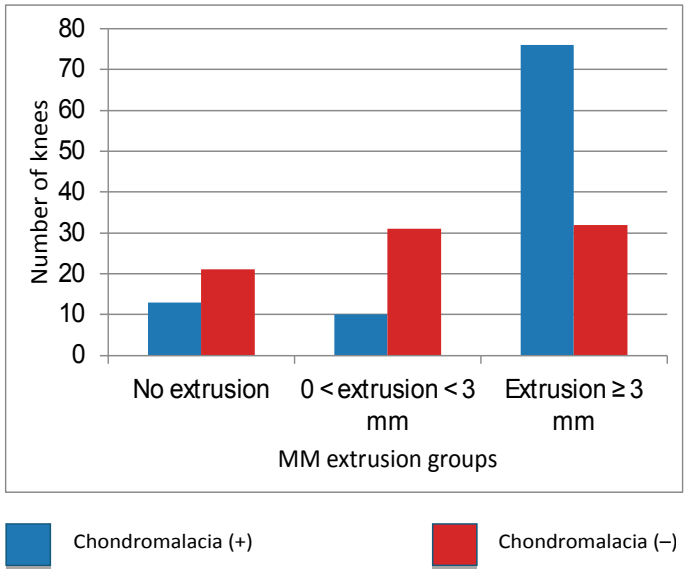

Figure 2. Extrusion amounts of MM according to chondromalacia. Chondromalacia was seen more common in knees with major medial meniscus extrusions. MM: Medial meniscus.

(both 28.6%). The association was significant (χ^2=17.49, p=0.025). LM degeneration and HO groups were significantly more common in ACL rupture compared to normal ACL.

• Association by MM pathology: With normal ACL, MM most often showed degeneration (28.7%) or HO (25.7%).
With ACL degeneration, MM radial root was most common (45.9%).

With ACL rupture, MM complex was most common (47.6%). The association was highly significant (χ^2=42.03, p<0.001).
Radial tear of the root was significantly associated with ACL degeneration. Complex tears were significantly associated with ACL rupture. Normal MM was significantly associated with normal ACL compared to degeneration/rupture groups.

• Association by MM extrusion severity: ACL rupture was 11.8% with 0 mm, 2.4% with <3 mm, and 14.8% with ≥3 mm extrusion. The association was significant (χ^2=12.15, p=0.016). ACL rupture was significantly more common in ≥3 mm extrusion compared to <3 mm.

Extrusion Measurements

Mean MM extrusion was 3.79 ± 2.82 mm (range 0–11.6). Mean LM extrusion was 0.27 ± 0.91 mm (range 0–6).

• Association by LM pathology: MM extrusion was 3.27 ± 2.53 mm in normal, 5.24 ± 3.16 in degeneration, 5.25 ± 2.78 in HO, 5.66 ± 3.71 in complex, and 2.12 ± 2.04 in discoid LM. Kruskal–Wallis showed significance (χ^2=19.3, p<0.001).
MM extrusion was significantly higher in LM degeneration, HO, and complex compared to LM discoid; complex was also higher than LM normal.

LM extrusion (0.16–2.09 mm) did not differ significantly (p=0.27).

• Association by MM pathology: MM extrusion was 1.08 ± 1.37 mm in normal, 1.40 ± 1.77 in degeneration, 3.34 ± 1.98 in HO, 5.92 ± 2.56 in radial root, and 4.67 ± 2.51 in complex. Kruskal–Wallis showed strong significance (χ^2=92.6, p<0.001). Radial root and complex tears had significantly higher extrusion than all other MM groups. HO was significantly higher than degeneration and normal MM. LM extrusion across MM pathologies (0.18–0.53 mm) showed no significant differences (p=0.47).

• Association by LM pathology distribution across extrusion categories: ≥3 mm extrusion was more frequent in LM degeneration (78%) and HO (81%) compared to normal (52%) and discoid (29%). The association was significant (χ^2=18.93, p=0.041).

• Association by MM pathology distribution across extrusion categories: ≥3 mm extrusion occurred in 92% of radial root and 80% of complex tears, but only 17% of normal, 23% of degeneration, and 43% of HO.

The association was highly significant (χ^2=91.86, p<0.001) (Figure 3).

ROC Analysis-Cut off point for extrusion

ROC analysis was performed to distinguish high-risk MM lesions (defined as radial root and complex tears, n=90) from low-risk lesions (normal, degeneration, and horizontal oblique tears, n=93). A 3.27 mm extrusion was found to be the optimal cut-off point to differentiate these two categories with the following results (Figure 4). AUC: 0.82, Sensitivity: 84.4%, Specificity: 70.2%, PPV: 73.1%, NPV: 77.2%. This indicates that MM extrusion ≥3.27 mm reliably discriminates against high-risk meniscal tears.

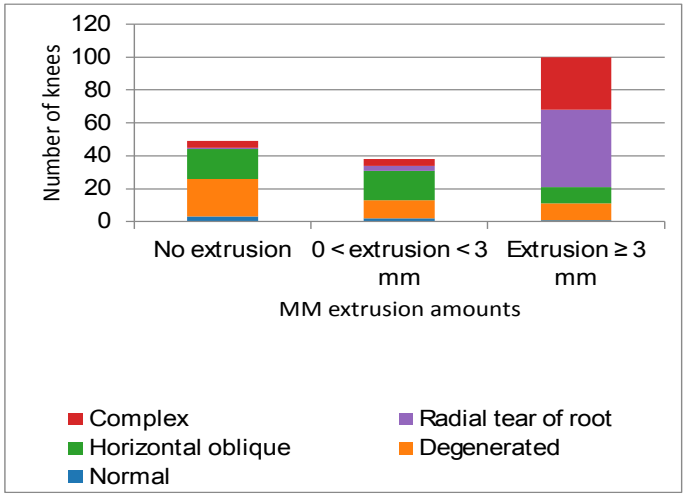

Figure 3. MM pathology types according to extrusion amounts. Knees with medial meniscus extrusion equal to and more than 3 mm had significantly more risk of radial and complex medial meniscus tears on knee MRI. MM: Medial meniscus.

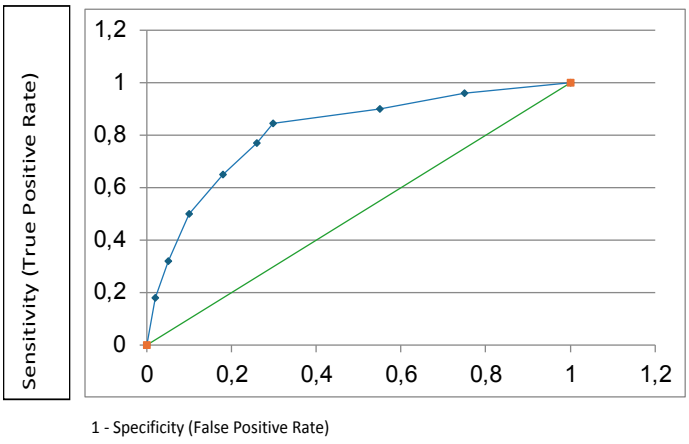

Figure 4. ROC curve to explore the optimum extrusion amount to use as a cut-off point in between tear types. AUC: 0.82, Sensitivity: 84.4%, Specificity: 70.2%, PPV: 73.1%, NPV: 77.2%. Cut-off for medial meniscus extrusion ≥3.27 mm reliably discriminates high-risk meniscal tears.

Multivariance analysis

After evaluating the variables with basic statistics, we performed multivariant logistic regression to find the independent effects of the variables on MM extrusion, searching for each one's variance analysis. In the multivariable logistic regression model, meniscal tear risk group and chondromalacia were independently associated with pathological medial meniscal extrusion (MM Extrusion ≥ 3 mm) (Table 3). Compared with degenerative meniscal changes, both low risk and high risk tear types demonstrated significantly higher odds of pathological MM Extrusion (low risk vs. degenerative: OR 7.34, 95% CI 1.78–30.17, p = 0.006; high risk vs. degenerative: OR 4.90, 95% CI 1.49–16.12, p = 0.009). The presence of chondromalacia was also associated with an increased likelihood of pathological MM Extrusion (OR 3.83, 95% CI 1.42–10.32, p = 0.008).

Male sex was associated with a lower odd of pathological MME compared with female sex (OR 0.29, 95% CI 0.10–0.84, p = 0.022). Age, joint effusion, and ACL pathology were not significantly associated with pathological MM Extrusion after adjustment for other variables in the model (all p > 0.05).

DISCUSSION

Effusion

Fifty-two of the 183 (28%) knees who were all patients with medial meniscus pathologies had synovial effusion. Specifically, the presence of effusion often accompanies advanced meniscal tears and degenerative changes, suggesting a reactive synovitis (7,8). Academic literature indicates that synovial inflammation, frequently observed as effusion, is strongly associated with meniscal pathology and represents a substantial risk factor for the worsening of structural joint deterioration in osteoarthritis (9). This correlation underscores the significance of evaluating joint effusion in conjunction with meniscal extrusion, as it may function as a clinical indicator of ongoing intra-articular pathology and a prognostic marker for patient outcomes (10).

Effusion is found to be significantly more common in patients with 3 mm or more extrusion (p=0.022). This observation suggests that significant meniscal extrusion may serve as an indicator of increased intra-articular inflammation, contributing to synovial fluid accumulation. Most patients with medial meniscus degeneration, without any tears, did not have effusion. This might imply that while degeneration can occur without significant inflammatory exudates, the mechanical disruption and instability caused by meniscal extrusion are more directly linked to the induction of a synovial inflammatory response and subsequent effusion (11,12). Because detailed clinical data such as trauma mechanism, symptom duration, and whether presentations were acute or chronic were not systematically documented in the retrospective records, effusion could not be analyzed separately for acute versus chronic knee pain. This lack of clinical stratification should be considered when interpreting the effusion findings and is acknowledged as a limitation of the study.

Chondromalacia

It is known that osteoarthritis changes are related to the degree of the meniscal extrusion, and MM extrusion is an independent predictor for both cartilage loss and osteoarthritic changes (7,11,13). Meniscal extrusion itself likely represents a

Table 3. Logistic regression between pathological medial meniscus extrusion and other variables.

Variable	OR	95% CI	p-value
Intercept	0.14	0.01–3.94	0.250
Meniscal risk group: low vs. degenerative	7.34	1.78–30.17	0.006
Meniscal risk group: high vs. degenerative	4.90	1.49–16.12	0.009
Age (per 1-year increase)	1.01	0.97–1.05	0.560
Sex: male vs. female	0.29	0.10–0.84	0.022
Chondromalacia: present vs. absent	3.83	1.42–10.32	0.008
Joint effusion: present vs. absent	1.03	0.33–3.18	0.964
ACL pathology: present vs. absent	1.23	0.42–3.63	0.706

Binary logistic regression between pathological MME (≥ 3 mm) as the dependent variable and, given independent variables.
MME, medial meniscal extrusion; OR, odds ratio; CI, confidence interval; ACL, anterior cruciate ligament.

complex interplay of joint tissue degradation and mechanical stressors within the osteoarthritic process, highlighting its role as both a consequence and a contributor to disease progression (13). Similarly, our study demonstrated that 71% of the patients with MM extrusion had chondromalacia, which is consistent with the previous studies (11,14). A study with 548 cadavers revealed that cadavers with a radial tear of the posterior horn had more cartilage damage (15). The authors suggested early repair of posterior horn radial tears to protect the joint from subsequent possible degeneration. In a parallel way, in our study, patients with radial tear of the MM root having chondromalacia (37/50, 74%) and knees with chondromalacia having radial tears of the root compared to the other pathologies (37/98, 38%) are shown to be statistically significant. This finding reinforces the notion that specific meniscal tear patterns, particularly radial tears, significantly predispose the knee to early chondral degeneration (Figure 5). Lateral meniscus degeneration and chondromalacia were seen together significantly in our series. The lateral meniscus carries 70% of the load applied to the lateral compartment (16). As a result, in a patient with LM degeneration, a diminished function of LM may reflect the load to the cartilage more than in a patient with normal LM and can cause degenerative changes of the cartilage (8).

It is also shown that discoid LM is associated with the absence of chondromalacia. Conversely, the normal morphology of a discoid lateral meniscus, despite its atypical shape, may offer a broader contact area, thereby distributing forces more evenly across the articular cartilage and mitigating localized wear. This situation reveals that increased meniscal volume in the discoid meniscus causes a decreased load reflecting to the cartilage. This study is notable for demonstrating that discoid meniscus may be a protective factor from chondromalacia, although it can cause knee complaints itself. The larger surface area of a discoid meniscus may help it dissipate compressive forces across the tibiofemoral joint, reducing localized stress on the articular cartilage (17,18).

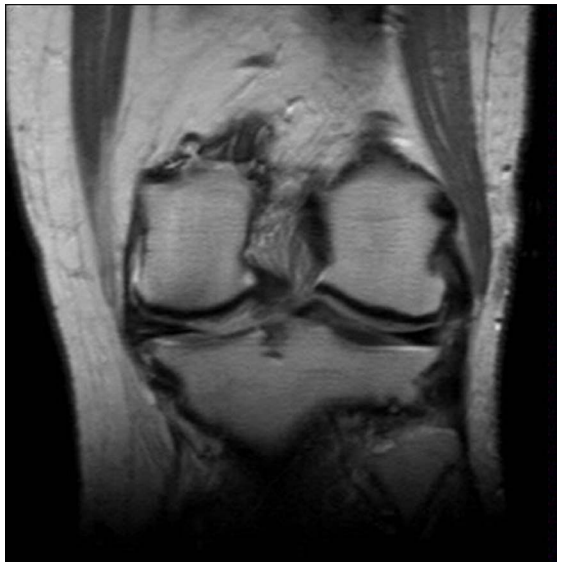

Figure 5. Proton Density Coronal image demonstrating the chondromalacia and cartilage irregularity concomitant with radial tear of root of medial meniscus.

ACL pathologies

Studies were showing and denying the relation between MM extrusion and ACL tears (19,20). In this study, patients with extrusion had 40% and patients without a major or minor extrusion had 20% percent mucinous degeneration of ACL, and this relation was significant. This finding suggests that substantial meniscal displacement may contribute to altered knee kinematics, potentially predisposing the anterior cruciate ligament to degenerative changes (11). Similarly, ACL tear had a significant relation with major extrusion (16/21). This indicates that the mechanical instability induced by significant meniscal extrusion may predispose the ACL to injury or accelerate its degeneration, thereby contributing to broader knee joint pathology (13,16). This study revealed consistent results with previous studies regarding ACL and meniscal tears (36%). Furthermore, the presence of an ACL tear often exacerbates meniscal extrusion due to increased joint laxity, creating a vicious cycle of instability and accelerated cartilage degradation (19). This result could be anticipated due to the close relation of ACL and MM and the coexistence of their pathologies (10).

There was not any normal MM in the degenerated or ruptured ACL group. We observed that the presence of a complex tear in the half of the patients with ruptured ACL and a radial tear of the root in the patients with degenerated ACL was significant according to chi square test($p<0,005$). This observation underscores the critical role of ACL stability in maintaining meniscal integrity and preventing the progression of complex meniscal tears.

LM-MM Extrusion difference

It is reported that MM is more prone to extrusion due to the movements of the medial capsule (21). In our study, we found a mean extrusion of 3,8 at MM and 0,27 mm at LM. Consistent with prior research, a statistically significant difference in extrusion between the medial and lateral menisci has been observed (22). Whereas Rennie, with his younger study group, said that there is no significant difference between MM and LM extrusions (12). This can be a clue that extrusion may be developing mostly after degenerative changes instead of acute traumas, which are more commonly seen in the younger patient group (23). This age-related disparity in extrusion prevalence suggests that chronic biomechanical stresses and degenerative processes likely play a more substantial role in medial meniscal extrusion than acute traumatic events. Furthermore, the anatomical differences in capsular attachments and meniscotibial ligaments contribute to the greater mobility of the lateral meniscus compared to the more rigidly fixed medial meniscus, inherently predisposing the medial compartment to higher extrusion rates under chronic loading (11). A key finding of this study, distinct from

Table 1. Lateral and medial meniscus extrusion amounts in mm, according to medial meniscus pathologies.

Mm Condition	Mm*	Lm
Normal	1,078	0,53
Degenerated	1,401	0,19
Horizontal Oblique Tear	3,341	0,39
Radial Tear Of Root	5,920	0,18
Complex Tear	4,672	0,30
Total	3,796	0,27

Medial meniscus extrusion significantly alters in between MM pathologies.

previous research, was the differential effect of meniscal pathologies on extrusion. While both LM and MM pathologies were significantly associated with an increase in MM extrusion, neither pathology type significantly affected LM extrusion. This suggests the lateral meniscus is more resilient to extrusive forces, likely due to its greater mobility, whereas the more fixed medial meniscus is susceptible to extrusion resulting from pathology in either compartment.

Meniscal pathologies-meniscal extrusion

Costa et al. showed a relation between minor extrusion of less than 3 mm and oblique tear (22). There are studies demonstrating the relation of radial tear, complex tear, and root avulsion with major extrusion (20,24,25). Magee et al showed that when MRI is compared with arthroscopy, patients having 3mm or more extrusion on MRI had severe degeneration, complex tear, or radial tear of the MM root arthroscopically. Among these patients 55% had radial tears displayed both on MRI and arthroscopically (26). Distinct from previous studies, this study searched for the effect of LM pathologies apart from MM pathologies on LM and MM extrusion. There was a significant relation between LM tear types and MM extrusion, but it was not true for LM tear types and LM extrusion (Table1). Similarly, while MM pathologies are not found to be affecting LM extrusion whereas there was a significant relation between MM extrusion amount and MM pathologies (Table2). This can be interpreted as LM is less sensitive to MM and LM pathologies in the aspect of extrusion due to its increased mobility shown in dynamic studies (16). Likewise, because of its anatomical configuration and close relation with the capsule, MM is more prone to extrusion as a result of MM and LM pathologies as

Table 2. Lateral and medial meniscus extrusion amounts in mm, according to lateral meniscus pathologies.

Lm Condition	Mm*	Lm
Normal	3,268	0,16
Degenerated	5,238	0,43
Horizontal Oblique Tear	5,253	0,29
Complex Tear	5,660	2,09
Discoid Meniscus	2,123	0,23
Total	3,789	0,27

Medial meniscus extrusion significantly alters in between LM pathologies.

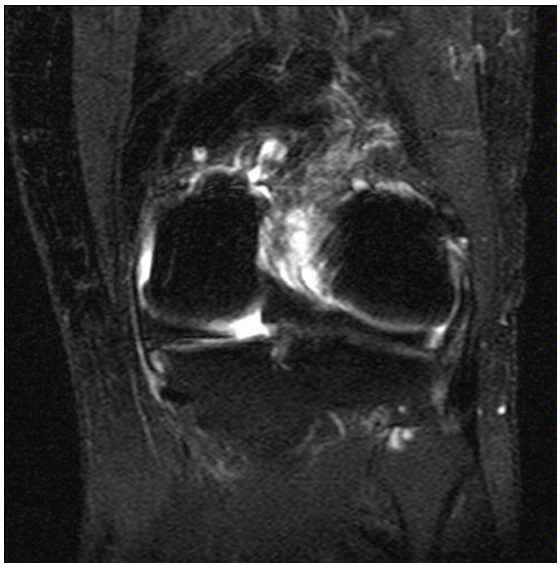

Figure 6. T2 Fat Saturated coronal MRI image of knee. There is a radial tear at the root of the medial meniscus.

tears and degeneration (27). A cut-off value of MM extrusion amount is tried to find to predict the MM pathologies. We found that 3mm or more of extrusion of MM can be used as a reliable tool in differentiating the degeneration and HO tear patients from complex tear and radial tear of the root group, with a sensitivity of 84% and specificity of 70% (Figure 6). Costa et al showed that advanced meniscal degeneration, which is a close entity to a tear, is related to the major extrusion (22). However, most of the patients with any degree of degeneration did not demonstrate extrusion in the current study.

MM posterior root tears are a form of avulsion fracture occurring within the 1st cm of the tibial bony attachment (28). MM root tear is known to increase osteoarthritic changes in the knee (29). This could be due to the disruption of the continuity of circumferential fibers and resulting in loss of hoop tension and meniscal extrusion, which is a cause of rapid osteoarthritic changes (30). MM root tears can be overlooked arthroscopically if a detailed examination is not performed, especially if the tear is close to the tibial insertion site. For this reason, recognizing radial tears of the root by MRI is important in the aspect of enlightening the physician during the arthroscopy (28). Studies show that diagnosing radial tears of the root on MRI is difficult (28,31). These tears are often seen at the knees, with osteoarthritis and coexisting degeneration can mask the tear (24). Also, it is shown that extrusion develops very shortly after the root tear (32). Extrusion of MM can be used as a helpful tool in evaluating the radial tear of the root, and it can provide the chance of early diagnosis and treatment before the development of osteoarthritic changes (24,29). There are biomechanical studies show that repair of radial tears of the root at the MM is successful in sustaining the normal biomechanics of the knee (33). For this reason, early diagnosis

and repair of radial tear of the root as a treatable disease are important (34).

In this study, meniscal tear morphology and chondromalacia emerged as the strongest independent predictors of pathological medial meniscal extrusion (MME). Both low-risk and high-risk meniscal tear groups showed markedly increased odds of MME ≥ 3 mm compared with degenerative changes alone. And high-risk tears resulting in even more severe extrusions. This finding supports the concept that structural disruption of the meniscal hoop fibers, even in so-called "low-risk" tear patterns, can lead to loss of meniscal containment and medial displacement of the meniscus. Also, it is demonstrated that radial, root, complex, and bucket-handle tears are associated with greater meniscal extrusion and altered tibiofemoral contact mechanics, which in turn accelerates cartilage degeneration and osteoarthritis progression (17,22,35). The strong association between chondromalacia and pathological MME in our model is also in line with previous reports linking meniscal extrusion to cartilage damage and knee osteoarthritis severity (11,17). Meniscal extrusion reduces the effective load-bearing surface of the meniscus, increases focal cartilage stress, and may reflect an advanced stage of menisco-chondral disease. Our results therefore reinforce the idea that MME is not only a marker of meniscal pathology but also a potential imaging marker of early degenerative joint change.

Interestingly, male sex was associated with lower odds of pathological MME compared with female sex, even after adjustment for meniscal tear type and chondromalacia. Although sex differences in knee osteoarthritis prevalence and pain perception have been described, the relationship between sex and meniscal extrusion is less clear (36). Potential explanations include sex-related differences in knee alignment, ligamentous laxity, or hormonal influences on soft tissue and cartilage biomechanics; however, these hypotheses require further investigation. Despite sole meaningful, joint effusion, and ACL pathology were not independently associated with pathological MM Extrusion in our multivariable model. While ACL rupture and chronic instability have been related to meniscal tears and secondary osteoarthritic changes, our results suggest that, when meniscal tear morphology and chondromalacia are considered, ACL abnormalities per se may not be the primary determinant of extrusion (37). The lack of association with age may reflect the predominance of structural factors (tear pattern and cartilage damage) over chronological age in driving MME in our cohort. Overall, our findings highlight the importance of carefully characterizing meniscal tear morphology and assessing MME and cartilage status in routine knee MRI. Early recognition of tear patterns prone to extrusion, together with the presence of chondromalacia, may have implications for treatment decisions and prognosis.

Clinical variables such as body mass index, activity level, and detailed injury mechanism were not available in the radiology archive and therefore could not be included in the analysis. The single observer measurements planning of the study is a limitation that should be mentioned. Also, the absence of arthroscopic correlation can be considered a limitation of this study. However, we aimed to evaluate meniscal extrusion, not the recognizability of tears on MRI, so tear diagnosis by arthroscopy was not included in the study plan. Future prospective studies incorporating direct arthroscopic correlation would be valuable to further validate the 3 mm extrusion threshold as a definitive diagnostic sign.

CONCLUSION

This study demonstrates a correlation between extrusion and important tears as the root tear of the posterior horn and complex tear, highlighting the importance of its diagnosis via MRI. An extrusion of 3 mm or more can serve as an indicator of radial tear of the root, prompting closer examination of the root to avoid overlooking this treatable condition. Furthermore, significant extrusion is indicative of concurrent degenerative changes, underscoring the clinical value of quantitatively assessing meniscal extrusion through imaging as a critical early sign of substantial intra-articular pathologies, especially those that are surgically manageable.

DECLARATIONS

Conflict of Interest: *We would like to declare that there isn't any conflict of interest in this study.*

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RESEARCH ARTICLE

Endocrine Complications in Long-Term Survivors of Allogeneic Hematopoietic Stem Cell Transplantation: Prevalence and Risk Factors

Allojenik Hematopoetik Kök Hücre Nakli Sonrası Uzun Dönem Sağ Kalan Hastalarda Endokrin Komplikasyonlar: Sıklık ve Risk Faktörleri

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ABSTRACT

Objective: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers a potentially curative treatment for a range of hematologic disorders. However, long-term survivors of the treatment are increasingly affected by late-onset complications, particularly endocrine dysfunction, which considerably impair quality of life. This study aimed to establish the prevalence and risk factors of late endocrine complications in patients who survived at least 1 year without disease following allo-HSCT.

Materials and Methods: We conducted a retrospective cohort analysis of 79 recipients of allo-HSCT at a single tertiary referral center. Patients with disease relapse or those who died within the first year after allo-HSCT were excluded. Data on demographic and transplant characteristics, graft-versus-host disease, immunosuppressive therapy, and endocrine outcomes were analyzed. Patients with such conditions before transplantation were excluded from the corresponding outcome analyses. Risk factors were evaluated using statistical methods.

Results: The median follow-up duration was 38 months. New-onset endocrine complications were observed in a substantial proportion of patients: dyslipidemia (77.3%), osteopenia or osteoporosis (58.2%), hypogonadism (27.8%), thyroid dysfunction (hypothyroidism or hyperthyroidism: 36.2%), and hypertension (33.5%). Significant risk factors included female sex, corticosteroid exposure, short-term cyclosporine use, and acute graft-versus-host disease. Avascular necrosis was detected in 13.9% of patients and associated with bisphosphonate, mycophenolate mofetil, and steroid use.

Conclusion: Endocrine complications are highly prevalent among patients who have survived beyond 1 year after allo-HSCT. Regular and comprehensive endocrine surveillance is essential, particularly in patients with specific risk factors. Early identification and management of these complications could improve quality of life in this patient population.

Keywords: Allogeneic stem cell transplantation, endocrine complications, graft-versus-host disease

ÖZET

Amaç: Allojenik hematopoietik kök hücre nakli (AKHN), çeşitli hematolojik hastalıklar için potansiyel olarak küratif bir tedavi seçeneğidir. Ancak uzun dönem sağ kalan hastalar, yaşam kalitesini belirgin şekilde bozabilen geç başlangıçlı komplikasyonlardan, özellikle endokrin disfonksiyonlardan, giderek daha fazla etkilenmektedir. Bu çalışmanın amacı, AKHN sonrası en az bir yıl hastalıksız sağ kalan hastalarda geç dönem endokrin komplikasyonların sıklığını ve risk faktörlerini belirlemektir.

Gereç ve Yöntemler: Tek bir üçüncü basamak merkezde AKHN uygulanmış 79 hastayı içeren retrospektif bir kohort analizi yapıldı. Nakil sonrası ilk yıl içinde hastalık nüksü gelişen ve kaybedilen hastalar çalışmaya dahil edilmedi. Demografik ve nakille ilişkili özellikler, graft-versus-host hastalığı, immünsüpresif tedaviler ve endokrin sonuçlara ait veriler analiz edildi. Nakil öncesinde ilgili endokrin hastalığı bulunan hastalar, ilgili endokrin komplikasyon gelişim risk analizlerinden dışlandı. Risk faktörleri tek değişkenli istatistiksel yöntemlerle değerlendirildi.

Bulgular: Medyan takip süresi 38 aydı. Yeni gelişen endokrin komplikasyonlar hastaların önemli bir kısmında saptandı: dislipidemi (%77.3), osteopeni/osteoporoz (%58.2), hipogonadizm (%27.8), tiroid disfonksiyonu (hipotiroidi veya hipertiroidi: %36.2) ve hipertansiyon (%33.5). Anlamlı risk faktörleri arasında kadın cinsiyet, kortikosteroid maruziyeti, kısa süreli siklosporin kullanımı ve akut graft-versus-host hastalığı yer aldı. Avasküler nekroz %13.9 oranında saptandı ve bifosfonat, mikofenolat mofetil ve steroid kullanımı ile ilişkili bulundu.

Sonuç: Endokrin komplikasyonlar, uzun dönem AKHN sağ kalanlarında oldukça yaygındır. Özellikle belirli risk faktörlerine sahip hastalarda düzenli ve kapsamlı endokrin izlem büyük önem taşımaktadır. Bu komplikasyonların erken tanınması ve yönetimi, bu hasta grubunda yaşam kalitesini artırabilir.

Anahtar Kelimeler: Allojenik kök hücre nakli, endokrin komplikasyonlar, graft-versus-host hastalığı

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for various malignant and non-malignant hematological disorders (1, 2). Enhancements in transplant techniques and supportive care have markedly improved survival rates (1, 2). Nonetheless, patients who survive long-term after allo-HSCT encounter late complications, particularly endocrine dysfunctions that can remain for many years post-transplantation (2, 3). Various endocrine complications, such as thyroid problems, infertility, growth retardation, metabolic syndrome and bone disorders have been observed in patients who have received allo-HSCT (2, 4). Many risk factors, including the use of immunosuppressive medications, ongoing graft-versus-host disease (GVHD), exposure to glucocorticoids, and therapies administered before transplant (eg, total body irradiation: TBI), are associated with these complications (2–5). Recent studies indicate that endocrine sequelae can affect up to 60% of long-term allo-HSCT survivors, resulting in heightened morbidity and diminished quality of life (2, 4).

In pediatric and young adult populations, these issues further affect growth, pubertal development, fertility, and psychosocial wellbeing (4, 5). However, despite increased awareness, standardized guidelines for long-term endocrine surveillance in allo-HSCT recipients remain absent. In this context, our study aimed to evaluate the prevalence and risk factors of late-onset endocrine complications in patients who survived at least 1 year without disease following allo-HSCT. By identifying high-risk categories and prevalent endocrine sequelae, we aimed to facilitate the formulation of effective follow-up techniques and early treatments to improve long-term outcomes.

MATERIALS AND METHODS

Design and Participants:

This retrospective, observational cohort study was performed at a tertiary referral center. The 10-year medical data of patients who underwent allo-HSCT was systematically reviewed. The eligibility criteria were: (a) having received allo-HSCT, (b) disease-free survival for a minimum of 12 months post-transplant, and (c) the availability of comprehensive clinical and laboratory follow-up records. The exclusion criteria were the recurrence or mortality within the first year after transplantation. Between December 2003, and September 2012, a total of 520 HSCTs were performed for 474 patients at our center. Among these procedures, 275 were allo-HSCTs and 245 were autologous HSCTs. For the purposes of our study, only allo-HSCT recipients who survived at least 1 year without disease relapses were considered eligible. After exclusions, 79 allo-HSCT recipients met the inclusion criteria and constituted the study cohort. Endocrine complications were defined using international guidelines. Obesity was classified as a body mass index (BMI) ≥30 kg/m^2. Diabetes was diagnosed according to the American Diabetes Association 2010 criteria (ie, fasting plasma glucose ≥126 mg/dL, random glucose ≥200 mg/dL, or HbA1c ≥6.5%). Hypertension was defined according to the Joint National Committee 7 criteria as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medication. Metabolic syndrome and dyslipidemia were classified according to the International Diabetes Federation criteria. Thyroid dysfunction was diagnosed according to the Turkish Endocrinology and Metabolism Society guidelines based on abnormal thyroid-stimulating hormone and thyroid hormone levels. Bone metabolism disorders were defined according to World Health Organization criteria based on bone mineral density measurements (T-score or Z-score). Gonadal dysfunction was diagnosed based on clinical symptoms and abnormal sex hormone levels.

Patients with pre-existing endocrine disorders were not excluded from the overall cohort description. However, for each specific endocrine outcome analysis, patients with the condition before transplantation were excluded to allow for the evaluation of de novo post-transplant complications. The date of diagnosis of the endocrine disorder was considered the event time for time-to-event analyses. Pre-transplant bone mineral density and gonadal function assessments were not available; therefore, the onset of obesity, osteoporosis, osteopenia, or hypogonadism was assessed using post-transplantation measurements. Annual bone mineral density results obtained after transplantation were used to determine the presence of low bone density. Demographic data (eg, age and sex), transplant-related variables (eg, underlying diagnosis, conditioning regimen, donor type, and TBI use), and post-transplant clinical parameters (eg, acute and chronic GVHD, immunosuppressive therapies, and endocrine follow-up records) were obtained from the institutional database and patient files. Conditioning regimens were categorized as myeloablative or non-myeloablative, and TBI exposure was recorded for all patients.

Ethical Approval:

This retrospective study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the institutional ethical committee (SBE-07/2013-58). The ethics committee waived the need for individual informed consent because of the retrospective nature of the study that used anonymized patient data. The study strictly protected the privacy of the patients.

Statistical Analysis:

Statistical analyses were performed using SPSS software version 16.0 (IBM Corp, Armonk, NY, USA). Continuous variables were assessed for normality using histograms, Q–Q plots and Kolmogorov–Smirnov or Shapiro–Wilk tests. Variables with a normal distribution were expressed as mean ± standard deviation, whereas non-normally distributed variables were presented as median with minimum and maximum values. Categorical variables were summarized as frequencies and percentages. Comparisons between categorical variables were performed using the Chi-squared (χ^2) test or Fisher's exact test, where appropriate. Comparisons of non-normally distributed continuous variables between two independent groups were performed using the Mann–Whitney U test.

Time-to-event analyses were performed for each endocrine outcome using survival analysis methods. Event was defined as post-transplant development of the endocrine complication. Time was measured from the date of allo-HSCT (day 0) to the first documented diagnosis, or to the date of last follow-up in patients without the event. Time-to-event distributions were estimated using the Kaplan–Meier method, risk factors were evaluated using Cox's proportional hazards regression, and results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). A two-sided p-value of <0.05 was deemed statistically significant.

Because the retrospective dataset lacked complete documentation of GVHD severity and organ involvement, GVHD was analyzed as a binary variable, indicating its presence or absence. The duration of cyclosporine A (CsA) treatment in months, served as the continuous variable in Cox's regression models. Tacrolimus was not administered to this particular cohort. Univariable Cox's regression analyses were performed for each endocrine outcome to evaluate potential risk factors, including age, sex, the presence of acute and chronic GVHD, the duration of CsA exposure, the use of corticosteroids after transplantation, and the use of mycophenolate mofetil. Since the study cohort was retrospectively derived from a dataset originally designed in 2013 and as several endocrine outcomes had limited event numbers, multivariable analyses were not performed to avoid model overfitting. Therefore, risk factor assessment was based on univariable Cox's regression analyses.

RESULTS

A total of 79 patients who underwent allo-HSCT and survived at least 1 year without disease relapse were included in the study. The median age at transplantation was 27 years (15–64 years), and 30.4% were female. The median follow-up duration was 38 months (11–98 months). Baseline demographic and transplant-related characteristics, including conditioning regimen intensity and TBI exposure, are summarized in Table 1. Overall Incidence of Endocrine Complications During Follow-up Endocrine complications were common among long-term survivors. The most frequent complications were

Table 1. Baseline characteristics of patients

Characteristic	n=79
Sex, n (%)	
Female	24 (30.4%)
Male	55 (69.6%)
Median age, years (range)	27 (15–64)
Primary diagnosis, n (%)	
Acute myeloid leukemia	31 (39.2%)
Aplastic anemia	15 (19.0%)
Acute lymphoblastic leukemia	14 (17.5%)
Myelodysplastic syndrome	4 (5.1%)
Non-Hodgkin's lymphoma	3 (3.8%)
Others	12 (15.4%)
Pre-transplant radiotherapy, n (%)	7 (8.9%)
Conditioning regimen, n (%)	
Myeloablative	52 (65.8%)
Non-myeloablative	27 (34.2%)
Total body irradiation-based regimen, n (%)	14 (17.7%)
Donor type, n (%)	
Matched related donor	70 (88.6%)
Mismatched related donor	3 (3.8%)
Matched unrelated donor	2 (2.5%)
Mismatched unrelated donor	4 (5.1%)
Graft-versus-host disease prophylaxis regimen, n (%)	
Cyclosporin A + methotrexate	74 (93.7%)
Cyclosporin A + mycophenolate mofetil	5 (6.3%)
Median follow-up duration, months (range)	38 (11–98)
Pre-transplant endocrine diseases, n (%)	
Obesity	12 (15.2%)
Hypertension	5 (6.3%)
Diabetes	3 (3.8%)
Metabolic syndrome	5 (6.3%)
Dyslipidemia	57 (72.2%)
Thyroid disorders	10 (12.7%)
Hypothyroidism (overt or subclinical)	3 (3.8%)
Hyperthyroidism (subclinical)	7 (8.9%)

dyslipidemia (77.3%), bone metabolism disorders (osteopenia or osteoporosis; 58.2%), thyroid dysfunction (hypothyroidism and hyperthyroidism; 36.2%), hypertension (33.5%), and hypogonadism (27.8%). Less frequent complications included diabetes (11.8%), metabolic syndrome (6.8%), and obesity (4.5%). Newly developed endocrine complications after allo-HSCT are summarized in Table 2.

Metabolic Complications:

De novo post-transplant dyslipidemia occurred in a substantial proportion of patients without pre-transplant lipid abnormalities (77.3%). A shorter duration of CsA exposure was significantly associated with an increased risk of post-transplant dyslipidemia (HR 0.919, 95% CI 0.857–0.985, p = 0.018). Post-transplant hypertension developed in approximately one-third of patients (33.5%). Older age (HR 1.038, 95% CI 1.005–1.073, p = 0.024), male sex (HR 3.77, 95% CI 1.14–12.53, p = 0.030), and post-transplant corticosteroid use (HR 3.10, 95% CI 1.19–8.85, p = 0.017) were significantly associated with an increased risk of hypertension. Diabetes, metabolic syndrome and obesity were observed less frequently. Due to the limited number of events, formal risk factor analyses were not performed for these outcomes.

Thyroid Dysfunction:

Post-transplant thyroid dysfunction occurred in 36.2% of patients. Hypothyroidism (17.4%) mostly developed later during follow-up, whereas hyperthyroidism (18.9%) occurred earlier and was often transient. A longer duration of CsA exposure was significantly associated with a reduced risk of post-transplant hyperthyroidism (HR 0.784, 95% CI 0.675–0.911, p = 0.001; Table 3). No other transplant-related variables were significantly associated with thyroid dysfunction.

Bone Metabolism Disorders and Avascular Necrosis:

Post-transplant bone metabolism disorders were observed in 58.2% of long-term allo-HSCT survivors. Osteoporosis was diagnosed in 12 patients (15.2%) and osteopenia in 34 patients (43.0%). For univariable analysis, a shorter duration of CsA

Table 2. Incidence of newly developed endocrine complications after allo-HSCT

Endocrine complication	Patients (n)	Percentage (%)
Dyslipidemia	17	77.3
Bone metabolism disorders (osteopenia or osteoporosis)	46	58.2
Thyroid dysfunction (overall)	25	36.2
Hypothyroidism	12	17.4
Hyperthyroidism	13	18.9
Hypertension	27	33.5
Hypogonadism	22	27.8
Diabetes mellitus	9	11.8
Metabolic syndrome	5	6.8
Obesity	3	4.5
Avascular necrosis	11	13.9

Only patients without the respective condition before transplantation were included in each analysis. Percentages were calculated based on the number of evaluable patients for each complication. Abbreviations: allo-HSCT= allogeneic hematopoietic stem cell transplantation.

Table 3. Univariable cox's regression analysis of risk factors for post-transplantation endocrine complications

Variable	Dyslipidemia		Hypertension		Hypothyroidism		Hyperthyroidism		Bone metabolism disorder		Avascular necrosis		Hypogonadism	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	P	HR (95% CI)	P
Age (years)	1.02(0.98-1.06)	0.51	1.04(1.01–1.07)	**0.024**	1.00(0.94–1.06)	0.999	1.04(1.00–1.09)	**0.053**	1.00(0.97–1.03)	0.80	1.00(0.94–1.06)	0.954	1.00(0.96–1.04)	0.93
Female sex	0.50(0.11-2.28)	0.37	3.77(1.14–12.53)	**0.030**	2.58(0.83–7.99)	0.101	2.25(0.50–10.14)	0.292	0.88(0.47–1.64)	0.687	1.58(0.46–5.40)	0.470	6.40(2.64–15.56)	**<0.00**
Acute GVHD	0.64(0.21-1.97)	0.44	0.97(0.39–2.39)	0.939	2.88(0.84–9.81)	0.092	0.49(0.15–1.60)	0.236	1.64(0.69–3.89)	0.262	2.95(0.86–10.14)	0.085	2.57(1.04–6.34)	**0.041**
Chronic GVHD	1.76(0.64-4.83)	0.270	0.55(0.24–1.21)	0.137	1.85(0.56–6.14)	0.316	1.67(0.55–5.11)	0.369	1.04(0.58–1.85)	0.904	3.27(0.70–15.19)	0.130	1.17(0.50–2.71)	0.718
CsA duration (months)	0.92(0.86-0.99)	**0.018**	0.99(0.97–1.02)	0.551	0.96(0.90–1.02)	0.195	0.78(0.68–0.91)	**0.001**	0.95(0.90–0.99)	**0.032**	1.01(0.98–1.04)	0.484	0.94(0.89–0.99)	**0.019**
Post-transplant steroids	1.06(0.39-2.87)	0.904	3.10(1.19–8.85)	**0.017**	2.39(0.76–7.56)	0.139	0.67(0.21–2.17)	0.503	1.04(0.54–2.01)	0.910	25.93(3.31–203.11)	**0.002**	1.25(0.53–2.99)	0.611
MMF	0.54(0.19-1.47)	0.226	1.84(0.82–4.09)	0.773	1.50(0.40–5.59)	0.546	0.82(0.23–2.99)	0.767	1.49(0.66–3.34)	0.335	7.27(2.11–24.99)	**0.002**	1.07(0.40–2.91)	0.893

Univariable Cox's regression analyses were performed separately for each outcome. A p<0.05 was considered statistically significant (higlighted as bold font). Abbreviations: GVHD=graft-versus-host disease. CsA=cyclosporine A. MMF= mycophenolate mofetil. HR= hazard ratio. CI= confidence interval.

exposure was significantly associated with an increased risk of post-transplant bone metabolism disorders (HR 0.95, 95% CI 0.900-0.990, p = 0.032; Table 3). Avascular necrosis developed in 13.9% of patients. For univariable analyses, post-transplant corticosteroid use (HR 25.93, 95% CI 3.31–203.11, p = 0.002), mycophenolate mofetil use (HR 7.27, 95% CI 2.11–24.99, p = 0.002), and bisphosphonate exposure (HR 6.02, 95% CI 1.82–19.12, p = 0.003) were associated with avascular necrosis (Table 3).

Hypogonadism:

Post-transplant hypogonadism occurred in 27.8% of patients, predominantly within the first year after transplantation. Female sex was associated with an increased risk of hypogonadism (HR 6.40, 95% CI 2.64–15.56, p <0.001). The presence of acute GVHD was also significantly associated with hypogonadism (HR 2.57, 95% CI 1.04–6.34, p = 0.041). A shorter duration of CsA exposure was associated with increased hypogonadism risk in univariable analysis (HR 0.935, 95% CI 0.885–0.989, p = 0.019; Table 3). Univariable Cox's regression analyses for all newly developed endocrine complications are summarized in Table 3, while detailed outcome-specific analyses are provided in the Supplementary Material (Supplementary Tables 1–9).

Hypogonadism usually developed within the first year after transplantation, tended to occur earlier during follow-up, and was often transient. In contrast, hypothyroidism generally developed later, while bone metabolism disorders were more frequently identified during long-term follow-up.

DISCUSSION

Patients who have received allo-HSCT and are surviving longer than 1 year at risk of developing late-onset complications, particularly endocrine disorders. Our study of 79 allo-HSCT recipients showed a markedly higher incidence of endocrine complications. Osteopenia and osteoporosis (58.2%), hypogonadism (27.8%), hypothyroidism (17.4%), and dyslipidemia (77.3%) were the most common complications. These findings correlate with other studies reporting that 60% of long-term transplant survivors have endocrine complications (2, 4). Hypertension developed in 33.5% of patients in our cohort; significant risk variables were post-transplant corticosteroid use, male sex, and age. This finding correlates with other data indicating that steroids induce salt retention and vascular remodeling, hence increasing patients' hypertension risk (6, 7). Long-term survivors show higher sensitivity due to endothelial degradation resulting from extended glucocorticoid administration and conditioning protocols (8). In our cohort, thyroid dysfunction (observed in 36.2% of the patients) was one of the most frequently reported endocrine abnormalities. Hypothyroidism and hyperthyroidism both indicate complex immunological dysregulation and the potential for post-transplant autoimmune thyroiditis (9, 10). Both TBI exposure and chronic GVHD could contribute to thyroid dysfunction (9, 11).

In our group, 15.2% exhibited osteoporosis and 43% had osteopenia, both of which are highly common disorders of bone metabolism. Additionally, 13.9% had avascular necrosis, likely due to treatments with bisphosphonates, mycophenolate mofetil (MMF), and corticosteroids. These findings correlate with the corpus of research identifying the primary causes of bone loss as inadequate calcium and vitamin D metabolism, prolonged corticosteroid exposure, and reduced physical activity (12, 13). Additionally, the capacity of MMF to influence bone remodeling and blood vessel structure might contribute to its correlation with avascular necrosis (14). Some associations, particularly for avascular necrosis, were associated with wide confidence intervals, reflecting the limited number of events and reduced statistical precision. These findings should therefore be interpreted with caution.

Gonadal dysfunction, identified in 27.8% of our patients, remains a major concern, particularly in younger patients. Our hypogonadism findings illustrate the vulnerability of the gonadal axis to several injuries related to transplantation. In the literature, acute GVHD, the use of CsA, and female sex are all associated with hypogonadism (15). The gonadotoxic effects of the alkylating chemical busulfan have been well-documented, particularly in women with diminished ovarian reserves (16). Our study contributes to the literature by providing real-world data from a single-center cohort. These data indicate that long-term surveillance of endocrine systems is crucial. Current guidelines indicate that 1-year post-transplantation, patients who have undergone gonadotoxic treatments or TBI should receive annual evaluations for thyroid function, bone quality, reproductive health, and metabolic parameters (17–19).

Our study revealed that endocrine complications, including post-transplant dyslipidemia and gonadal dysfunction, were more prevalent in patients with shorter duration of CsA exposure. Nonetheless, the standardization of starting doses among all patients using CsA prompts an inquiry into why a short period of treatment increases the incidence of complications. Currently, it is believed that the effects of CsA on the endocrine system might be associated with both cumulative toxicity and rebound effects after the discontinuation of immunological modulation, and inadequate adaptation in hepatic lipid metabolism. A preclinical study shows that CsA affects lipoprotein clearance, resulting in the accumulation of low-density lipoprotein and very low-density lipoprotein, and inhibition of lipoprotein lipase function (20). Accordingly, patients are able to achieve an equilibrium in lipid homeostasis with prolonged use; the early cessation of CsA can interfere with this adaptive mechanism and could cause increased dyslipidemia. In CsA-induced hypogonadotropic hypogonadism (as shown in animal models) early withdrawal of CsA rather than prolonged use could disturb hypothalamic-pituitary feedback pathways, resulting in increased hormonal imbalance (21). Short-term use of CsA could result in a triggering effect on the endocrine system rather than having a protective effect.

When interpreting statistically significant results, it is important to consider the possibility of a type I error, especially when multiple univariable comparisons are used.

Study Limitations:

This study has several limitations. The retrospective design and the fact that it was conducted at a single center could have introduced selection bias, thereby potentially restricting the generalizability of the findings. Additionally, the median follow-up duration of 38 months might not fully capture very late endocrine complications that can occur many years after transplantation. Some biochemical or imaging parameters, particularly related to gonadal function and bone density, could have been inconsistently documented. Furthermore, although the temporal patterns of endocrine complications were described, detailed stratification according to predefined time intervals (eg, 0–1 year, 1–3 years, and >3 years) could not be performed due to the retrospective design and limited number of events for some outcomes.Detailed information regarding specific conditioning agents (eg, busulfan and cyclophosphamide) was not consistently available due to the retrospective nature of the dataset, which might limit the assessment of agent-specific effects on endocrine outcomes. Additionally, detailed information regarding GVHD severity (eg, grading of acute GVHD and classification of chronic GVHD) and organ involvement was not consistently available; therefore, GVHD was analyzed as a binary variable, which could limit the interpretability of its impact on endocrine outcomes. Detailed information regarding CsA dose intensity and therapeutic drug monitoring levels was also not consistently available in this retrospective dataset, potentially limiting a more comprehensive evaluation of immunosuppressive exposure. Lastly, the study cohort was treated between 2003–2012; thus, changes in transplant practices since then could affect comparability with contemporary outcomes.

CONCLUSION

In conclusion, our study reveals that endocrine complications are common in long-term survivors of allo-HSCT. In particular, dyslipidemia, bone loss, and hypogonadism were the common complications and their risk increases with shorter duration or early discontinuation of CsA rather than cumulative exposure and GVHD. These findings suggest that long-term monitoring of endocrine complications is important for these patients.

DECLARATIONS

Conflict of Interest: *The authors declare no conflicts of interest.*

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OPEN

RESEARCH ARTICLE

Association Between Obstructive Sleep Apnea Severity and Cardiometabolic Index in the Context of Cardiovascular Risk

Obstrüktif Uyku Apne Şiddeti ile Kardiyometabolik İndeks Arasındaki İlişki: Kardiyovasküler Risk Bağlamında

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ABSTRACT

Objective: This study aimed to evaluate the relationship between the cardiometabolic index (CMI) and obstructive sleep apnea (OSA) and to investigate its potential clinical relevance in cardiovascular risk assessment.

Materials and Methods: A total of 158 patients who underwent polysomnography (PSG) with a preliminary diagnosis of sleep apnea between January 2022 and July 2023 were included. Demographic characteristics, anthropometric measurements, comorbidities, biochemical parameters, and CMI values were analyzed.

Results: Of the 158 patients, 112 (70.9%) were male. CMI values increased significantly with increasing OSA severity (p=0.03). A weak but statistically significant positive correlation was found between the apnea–hypopnea index (AHI) and CMI (r=0.21, p<0.001, 95% CI: 0.001–0.020). An absolute difference of 0.88 units in CMI was observed between patients with severe OSA and those with simple snoring. Although CMI values were higher in patients with cardiovascular disease, this difference did not reach statistical significance (p = 0.385).

Conclusion: There is a significant positive association between OSA severity and CMI. CMI may serve as a simple and practical marker reflecting an adverse cardiometabolic profile associated with cardiovascular risk in patients with OSA.

Keywords: Cardiometabolic index, cardiovascular disease, obstructive sleep apnea.

ÖZET

Amaç: Çalışmamız, Kardiyometabolik İndeks (KMİ) ile Obstrüktif Uyku Apne (OUA) arasındaki ilişkiyi değerlendirmeyi ve kardiyovasküler risk değerlendirmesindeki potansiyel klinik önemini araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Ocak 2022 ile Temmuz 2023 tarihleri arasında uyku apnesi ön tanısıyla polisomnografi (PSG) uygulanan toplam 158 hasta çalışmaya dahil edildi. Demografik veriler, antropometrik ölçümler, eşlik eden hastalıklar, biyokimyasal parametreler ve KMİ değerleri analiz edildi.

Bulgular: Çalışmaya 112'si erkek (%70,9) olmak üzere toplam 158 hasta alındı. Kardiyometabolik indeks değerlerinin, OUA şiddeti arttıkça anlamlı derecede yükseldiği saptandı (p=0,03). Apne-hipopne indeksi ile KMİ arasında düşük düzeyde pozitif korelasyon bulundu (r=0,21, p<0,001, %95 GA: 0,001-0,020). Ağır OUA olan hastalar ile basit horlama olan hastalar arasında KMİ değerlerinde 0,88 birimlik mutlak fark tespit edildi. Kardiyometabolik indeks, kardiyovasküler hastalığı olan hastalarda daha yüksek saptanmasına rağmen, aralarında anlamlı derecede fark bulunmadı (p=0,385).

Sonuç: Obstrüktif uyku apnesi şiddeti ile KMİ arasında anlamlı pozitif bir ilişki saptadık. Kardiyometabolik indeksin, uyku apnesi olan hastalarda kardiyovasküler riskle ilişkili olumsuz kardiyometabolik profili yansıtan basit ve pratik bir belirteç olarak kullanılabileceğini öne sürüyoruz.

Anahtar Kelimeler: Kardiyometabolik indeks, kardiyovasküler hastalık, obstrüktif uyku apnesi,

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INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by recurrent episodes of upper airway obstruction during sleep, leading to intermittent hypoxemia and sleep fragmentation (1). Epidemiological data indicate that OSA affects approximately 4% of men and 2% of women aged 30–60 years who present with significant daytime sleepiness, with prevalence expected to increase further in the aging population, particularly among individuals aged 65 years and older (2,3). The development of OSA is influenced by multiple anatomical and physiological factors that promote upper airway narrowing or instability. Among these, male sex and obesity represent the most prominent risk factors, while smoking, alcohol consumption, and the use of sedative or hypnotic agents further contribute to disease susceptibility (4). Clinically, OSA is characterized by loud snoring, witnessed apneas, excessive daytime sleepiness, nocturnal choking, and disrupted sleep architecture (5–7).

The pathophysiology of OSA is complex and involves a combination of intermittent hypoxia, oxidative stress, and systemic inflammation. Chronic intermittent hypoxemia and sleep fragmentation trigger inflammatory pathways and oxidative injury, which play a central role in disease progression (8). Importantly, these mechanisms are also implicated in the development of cardiovascular and metabolic disorders. A growing body of evidence has demonstrated that OSA severity is closely associated with major cardiovascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and physical inactivity (9). These shared risk factors converge on common biological pathways, such as endothelial dysfunction, increased sympathetic activity, and accelerated atherosclerosis, thereby establishing OSA as an independent contributor to cardiovascular morbidity (10).

The cardiometabolic index (CMI) is a new measure first introduced by Wakabayashi et al. This index is calculated using the waist-to-height ratio (WHtR), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C), which are routinely measured in clinical practice (11). CMI is calculated as: CMI = (Triglycerides/HDL-cholesterol) x (Waist circumference/ Height). Given the shared cardiometabolic risk profile between OSA and cardiovascular disease, CMI appears to be a relevant marker for reflecting the adverse metabolic profile in these patients (12,13). By integrating measures of central adiposity and lipid metabolism, CMI provides a comprehensive assessment of cardiometabolic risk.

Given the substantial overlap between the pathophysiological mechanisms of OSA and cardiometabolic disorders, CMI may represent a clinically relevant marker for identifying adverse metabolic profiles in patients with OSA (12,13). In this context, the present study was designed to evaluate the relationship between CMI and OSA severity and to explore its potential role in cardiovascular risk assessment.

MATERİALS AND METHODS

This retrospective study included patients who were evaluated for suspected sleep apnea in the Chest Diseases Clinic and underwent overnight polysomnography (PSG) between January 2022 and July 2023. Demographic characteristics, anthropometric measurements, smoking status, comorbidities, complete blood count, lipid profile, hyperlipidemia treatment status, and PSG findings were obtained from the hospital's electronic medical records system and systematically analyzed. Patients were categorized into four groups according to their apnea–hypopnea index (AHI): simple snoring (AHI<5), mild OSA (AHI 5–15), moderate OSA (AHI 15–30), and severe OSA (AHI > 30). The primary objective was to investigate the relationship between OSA severity and the cardiometabolic index. The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to its retrospective design, informed consent was not required. Ethical approval was obtained from the Health Sciences Ethics Committee of Balıkesir University Faculty of Medicine (Decision No: 2024/24, Date: 21/02/2024).

Statistical Analysis

All statistical analyses were performed using SPSS version 23.0. A priori power analysis conducted using G*Power indicated that a sample size of 158 patients would provide 85% power for the primary outcome (α=0.05, Cohen's f=0.54), while the power for secondary outcomes ranged between 70% and 75%. Continuous variables were expressed as mean ± standard deviation for normally distributed data and as median (IQR) for non-normally distributed data. Categorical variables were presented as counts and percentages. Normality was assessed using the Kolmogorov–Smirnov test. Comparisons between categorical variables were performed using the chi-square test, with Pearson's $\chi 2$ or Fisher's exact test applied as appropriate. For comparisons among more than two independent groups, one-way ANOVA was used for normally distributed variables, while the Kruskal–Wallis test was used for non-normally distributed variables. When overall group differences were statistically significant, post-hoc analyses were conducted to identify the specific groups contributing to the difference.

Correlation analyses were performed to evaluate relationships between continuous variables, using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-normally distributed data. For comparisons between two independent groups with non-normally distributed variables, the Mann–Whitney U test was applied. A critical α value of 0.05 was considered significant.

RESULTS

A total of 158 patients were included in the study, of whom 112 (70.9%) were male. The baseline characteristics of the study population are presented in Table 1. According to OSA severity, 22 patients were classified as simple snoring, 37 as mild OSA, 37 as moderate OSA, and 62 as severe OSA. There was no significant difference in sex distribution across the groups (p= 0.79) (Table 2). However, age differed significantly among groups (p= 0.01), with post hoc analysis (Tukey HSD) indicating that patients in the simple snoring group were significantly younger than those in the moderate and severe OSA groups (M=-9.38 p=0.014, M=-8.20 p=0.023, respectively)

Table 1. General characteristics of all patients

Variable	n= 158
Age	52.91±11.7
Gender (M/F)	116/42
Comorbidity (Yes/No)	115/43
BMI	32.54±6.2
CMI	2.68±1.57

Data are presented as mean ± standard deviation. BMI: Body mass index, CMI: Cardiometabolic Index

(Table 4). A history of smoking was present in 22.1% (n = 35) of the study population, with no significant differences between OSA severity groups (p= 0.753) or according to cardiovascular disease status (p= 0.410).

Hyperlipidemia treatment was more frequently observed in patients with OSA compared to the control group; however, this difference did not reach statistical significance when all patients were considered (p= 0.514). Similarly, no significant differences were observed in treatment rates across OSA severity subgroups (p= 0.745). In contrast, hyperlipidemia treatment was significantly more common among patients with cardiovascular disease (p< 0.001). Comorbidities were present in 73.4% (n= 116) of patients. Cardiovascular disease was identified in 34.2%, hypertension in 58.9%, and diabetes mellitus in 30.4% of the cohort. The prevalence of cardiovascular disease did not differ significantly across OSA severity groups (p=0.151) (Table 2). The distribution of cardiovascular diseases according to groups is shown in Figure 1. Although CMI values were higher in patients with a history of cardiovascular disease

Table 2. Comparison of gender and comorbidities between groups

Variable	Simple snoring	Mild OSA	Moderate OSA	Severe OSA	p value
Gender (F/M)	6/16	11/26	13/24	16/46	0.796
Hypertension n (%)	7 (31.8)	23 (62.4)	24 (64.8)	39 (62.9)	0.051
Diabetes Mellitus n (%)	8 (36.3)	6 (16.2)	13 (35.1)	20 (33.8)	0.201
Cardiovascular Disease n (%)	4 (19.2)	11 (29.7)	12 (32.4)	27 (43.5)	0.151

Table 3. Comparison of age, laboratory parameters, and indices between groups

Variable	Simple snoring (n=22)	Mild OSA (n=37)	Moderate OSA (n=37)	Severe OSA (n=62)	p value
Age	45.86±11.99	52.84±12.50	55.24±11.01	54.06±10.80	0.017
BMI	27.51 (26.43-31.23)	29.9 (27.58-35.15)	31.14 (28.85-35.22)	33.14 (29.67-37.39)	0.003
CMI	1.91 (1.45-2.74)	2.27 (1.51-3.63)	2.05 (1.29-3.57)	2.79 (1.96-3.82)	0.031
HDL	47.09±9.56	46.64±8.08	52.10±13.02	45.37±8.66	0.012
LDL	125.50±36.25	131±24.14	118.02±40.63	132.39±35.19	0.435
Cholesterol	197.18±37.14	208.73±39.49	208.25±42.70	214.62±42.70	0.403
Triglyceride	144 (113.50-191.75)	178 (122-223.50)	162 (106.50-227)	173.50 (127.75-241.25)	0.219
Hemoglobin	14.42±1.07	14.07±1.50	13.76±1.64	14.03±1.90	0.535
Lymphocyte	2.40±0.77	2.48±0.78	2.47±0.60	2.42±0.95	0.971
Platelet	258.63±46.16	260.89±66.06	284.35±63.16	278.71±63.65	0.230

Data are presented as mean ± standard deviation, median (25th Percentile – 75th Percentile), BMI: Body mass index, CMI: Cardiometabolic Index, HDL: High density lipoprotein, LDL: Low density lipoprotein

Table 4. Tukey HSD Post-hoc test results for age and HDL across OSA Groups

Variable	Mean difference	%95 CI	p value
Age			
Simple snoring - Moderate OSA	-9.38	-(17.38 - 1.38)	0.014
Simple snoring - Severe OSA	-8.20	-(15.57 - 0.83)	0.023
HDL			
Moderate OSA - Severe OSA	6.74	0.36 – 13.11	0.035

HDL: High density lipoprotein

Table 5. Comparison of CMI with comorbidity, hypertension, and cardiovascular disease variables

Variable	Yes median (IQR)	No median (IQR)	p value
Comorbidity	2.10 (1.40-3.31)	3.02 (2.19-3.89)	0.002
Hypertension	2.12 (1.34-3.25)	2.76 (1.85-3.80)	0.022
Cardiovascular Disease	2.44 (1.57-3.66)	2.31 (1.60-3.18)	0.385

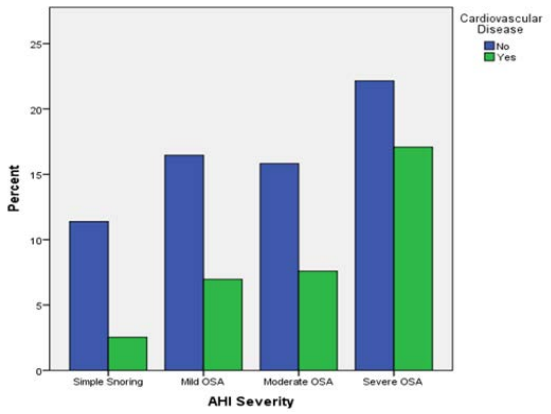

Figure 1. Incidence of cardiovascular disease by case group

[2.44 (1.57–3.66)] compared to those without [2.31 (1.60–3.18)], no significant difference was observed between the groups. In addition, no association was found between the number of comorbidities and CMI (p= 0.88).

Body mass index (BMI) differed significantly across groups (p = 0.03), with higher values observed in patients with more severe OSA. Post hoc analysis demonstrated that patients with severe OSA had significantly higher BMI compared to those with simple snoring (p< 0.001). Additionally, BMI was significantly higher in patients with hypertension and cardiovascular disease (p= 0.00, p= 0.00, respectively), and a weak positive correlation was observed between BMI and the number of comorbidities (r=0.26, p=0.00). No significant association was found between BMI and CMI (p= 0.25). CMI values differed significantly according to OSA severity (p= 0.03) (Table 3). Post hoc analysis revealed that patients with severe OSA had significantly higher CMI values compared to those with simple snoring (p<0.001), whereas no significant differences were observed between other group pairs. No significant difference in CMI was found between patients receiving and not receiving hyperlipidemia treatment (p=0.842).

A low-level, positive, and statistically significant correlation was found between AHI and CMI (r=0,21, p<0,001, 95% CI: 0,001-0,020). No statistically significant differences were observed between OSA severity groups in terms of LDL cholesterol, total cholesterol, or triglyceride levels (p=0.435, p=0.403, p=0.219, respectively) (Table 3). However, HDL cholesterol levels differed significantly across groups (one-way ANOVA, p=0.012). Post hoc analysis using the Games–Howell test demonstrated that HDL levels were significantly higher in the moderate OSA group compared to the severe OSA group (p = 0.035) (Table 4), while no other pairwise differences reached statistical significance.

DISCUSSION

In the present study, the relationships between obstructive sleep apnea (OSA) severity, cardiometabolic index (CMI), and related clinical parameters were comprehensively evaluated. Our findings demonstrated a significant association between OSA severity and CMI, with higher CMI values observed in patients with more severe disease. In addition, a weak but statistically significant positive correlation between the apnea–hypopnea index (AHI) and CMI was identified, suggesting that increasing disease severity is accompanied by a progressively adverse cardiometabolic profile. OSA is increasingly recognized not only as a sleep-related breathing disorder but also as a systemic condition with substantial cardiovascular implications. The underlying pathophysiological mechanisms include chronic intermittent hypoxemia, oxidative stress, systemic inflammation, and sustained sympathetic nervous system activation. These processes contribute to endothelial dysfunction and accelerated atherosclerosis, thereby increasing cardiovascular risk independently of traditional risk factors (10). Furthermore, these mechanisms are closely linked to disturbances in lipid metabolism; OSA-related hypoxemia and sympathetic overactivity may promote dyslipidemia, particularly through alterations in HDL metabolism and triglyceride clearance (8,14). In this context, CMI, which integrates measures of central adiposity and lipid parameters, appears to be a relevant composite marker reflecting the adverse cardiometabolic milieu in patients with OSA.

In our cohort, the prevalence of cardiometabolic comorbidities was notably high, with 34.2% of patients having cardiovascular disease, 58.9% hypertension, and 30.4% diabetes mellitus. These findings are consistent with previous reports demonstrating a higher prevalence of such conditions among patients with OSA compared to the general population (10). Moreover, prior studies have reported a direct relationship between OSA severity and the prevalence of cardiometabolic diseases (15). In line with this evidence, our data also indicated an increasing prevalence of cardiovascular disease with increasing OSA severity, although this trend did not reach statistical significance. Body mass index (BMI) was significantly associated with OSA severity in our study, with higher BMI values observed in more severe disease groups. This finding supports the well-established role of obesity as a major predisposing factor for OSA (10,15–17). Increased adiposity contributes to upper airway collapsibility and plays a central role in the pathogenesis of OSA (18). Additionally, we observed that BMI was significantly higher in patients with hypertension and cardiovascular disease, and that the number of comorbidities showed a weak positive correlation with BMI. These results suggest that excess body weight represents a shared and important risk factor linking OSA and cardiovascular disease. Consistent with this, Drager et al. reported that OSA and obesity synergistically increase cardiovascular risk (13). In contrast, no statistically significant relationship was found between the number of comorbidities and CMI in our study. This finding suggests that cardiometabolic risk may not be solely determined by the presence of comorbid conditions, but also by their severity and management. Although higher CMI values were observed in patients with cardiovascular disease, this difference did not reach statistical significance.

One possible explanation is the more frequent use of lipid-lowering therapies in these patients, which may have attenuated differences in CMI values. Taken together, these findings suggest that CMI may still have potential utility as a marker for cardiometabolic risk, particularly in patients with OSA.

A key finding of our study is the significant association between OSA severity and CMI. Post hoc analysis revealed an absolute difference of 0.88 units in CMI between patients with severe OSA and those with simple snoring. In addition, the presence of a weak but significant linear correlation between AHI and CMI further supports this relationship. The role of CMI as a predictor of cardiovascular risk has been increasingly investigated in recent years. Wakabayashi et al. originally defined CMI as a composite marker reflecting both adiposity and lipid abnormalities (19), while Shi et al. reported its utility in predicting coronary artery disease risk (20). In this context, our findings suggest that increasing OSA severity is associated with a more unfavorable cardiometabolic profile, as reflected by elevated CMI values. Previous studies have identified OSA as a risk factor for cardiovascular, cerebrovascular, and metabolic diseases (13). In a longitudinal study, Cai et al. demonstrated that CMI is an effective predictor of cardiovascular disease risk in patients with OSA and hypertension, with a mean follow-up of 6.83 years (12). These findings support our results and further indicate that CMI may provide additional value in cardiovascular risk stratification among patients with OSA.

Interestingly, our lipid profile analysis did not reveal significant differences in LDL cholesterol, total cholesterol, or triglyceride levels across OSA severity groups, whereas HDL cholesterol levels differed significantly. This finding contrasts with some previous studies reporting lipid abnormalities in OSA patients. The relationship between OSA and lipid metabolism is complex and likely influenced by multiple factors, including obesity, insulin resistance, systemic inflammation, and pharmacological treatments (8,13). Although intermittent hypoxemia may theoretically impair lipid metabolism via increased sympathetic activity (14), our findings suggest that concurrent treatments, particularly lipid-lowering therapies in a population with a high burden of cardiovascular disease, may have mitigated these differences. CMI has been described as a marker reflecting both abdominal obesity and dyslipidemia (11). In our study, no significant association was observed between BMI and CMI, suggesting that CMI may capture aspects of cardiometabolic risk that are not fully reflected by general adiposity measures. Supporting this, Wang et al. reported that CMI may better reflect visceral adiposity and may therefore be a more sensitive indicator of cardiometabolic risk compared to BMI (21). In addition, our study also revealed a significant association of BMI with cardiovascular disease and hypertension. All these findings support the importance of obesity in patients with OSA and its potential role in increasing cardiovascular risk.

From a clinical perspective, CMI offers several practical advantages. It is derived from routinely measured clinical parameters—waist circumference, height, triglycerides, and HDL cholesterol—without requiring additional diagnostic procedures. Moreover, the lack of association between CMI and BMI in our findings suggests that CMI may provide complementary information beyond traditional anthropometric indices. Therefore, CMI may represent a simple, accessible, and clinically useful tool for evaluating cardiometabolic risk in patients with OSA, particularly in resource-limited settings.

Study Limitations

Nevertheless, several limitations should be acknowledged. The retrospective, single-center, and cross-sectional design limits the ability to establish causal relationships. Although the sample size was sufficient for the primary outcome, the statistical power for secondary analyses was moderate, and thus these findings should be interpreted with caution. In addition, the high prevalence of comorbidities and the potential confounding effects of lipid-lowering therapies may have influenced the observed associations. Finally, the long-term prognostic value of CMI in patients with OSA was not assessed.

CONCLUSION

In conclusion, our study demonstrated that increasing OSA severity is associated with higher CMI values and a more adverse cardiometabolic profile. These findings support the potential role of CMI as a simple and practical marker for cardiovascular risk assessment in patients with OSA. However, further large-scale, prospective studies are needed to better define its independent predictive value and clinical applicability.

DECLARATIONS

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OPEN

RESEARCH ARTICLE

Cutaneous Symptoms Observed in Patients Hospitalized in Gastroenterology Service: A 207-Case Single-Center Study

Gastroenteroloji Servisinde Yatan Hastalarda Gözlenen Kutanöz Belirtiler: 207 Olguluk Tek Merkezli Bir Çalışma

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ABSTRACT

Objective: To characterize the spectrum of cutaneous findings observed in adult patients hospitalized for gastroenterological diseases who required dermatology consultation.

Materials and Methods: In this single-center, prospective, cross-sectional descriptive study, adult patients hospitalized in the Gastroenterology Service of Gaziantep University Faculty of Medicine between September 2022 and September 2023 were evaluated when dermatologic findings were present. Demographic and clinical data, underlying gastroenterological diagnoses, medications, dermatologic symptoms, lesion morphology, distribution, duration and final dermatologic diagnoses were recorded. Diagnoses were based on history and complete dermatologic examination, supplemented by potassium hydroxide microscopy, wound culture and histopathologic examination when clinically indicated. Data were analyzed descriptively.

Results: A total of 207 patients were included (107 men [51.69%] and 100 women [48.31%]; mean age, 54.30 ± 18.75 years). The most frequent underlying diagnoses were pancreatic diseases (26.09%), hepatobiliary disorders (23.67%), liver cirrhosis (19.81%), gastrointestinal malignancy (16.43%) and inflammatory bowel disease (8.21%). The most common cutaneous findings were pruritus (60.38%), skin color changes, mainly icterus or pallor (56.52%), xerosis cutis (45.41%), hyperkeratotic changes (43.47%) and infections (35.26%). Dermatologic diagnoses were most often established clinically by history and physical examination.

Conclusion: Dermatologic findings in hospitalized gastroenterology patients are heterogeneous and include disease-related clues as well as nonspecific findings related to age, nutritional status, systemic illness or treatment. In this selected consultation-based cohort, pruritus, color change and xerosis were the leading findings. These data support dermatologic assessment when cutaneous symptoms are present in gastroenterology wards, but should not be interpreted as prevalence estimates for all gastroenterology inpatients.

Keywords: Gastroenterological diseases, xerosis cutis, pruritus, pigmentary changes, hepatobiliary disease, inflammatory bowel disease.

ÖZET

Amaç: Gastroenterolojik hastalık nedeniyle yatırılan ve dermatoloji konsültasyonu gerektiren erişkin hastalarda saptanan kutanöz bulguların dağılımını ve klinik özelliklerini değerlendirmek.

Gereç ve Yöntemler: Bu tek merkezli, prospektif, kesitsel tanımlayıcı çalışmada, Eylül 2022 ile Eylül 2023 arasında Gaziantep Üniversitesi Tıp Fakültesi Gastroenteroloji Servisi'nde yatan ve dermatolojik bulgusu bulunan erişkin hastalar değerlendirildi. Demografik veriler, mevcut gastroenterolojik tanı, kullanılan ilaçlar, deri semptomları, lezyonların yerleşimi, morfolojisi, süresi ve dermatolojik tanıları kaydedildi. Tanılar öykü ve dermatolojik muayene temelinde konuldu; gerekli olgularda KOH ile direkt mikroskobik inceleme, yara kültürü ve histopatolojik inceleme kullanıldı. Veriler tanımlayıcı olarak sunuldu.

Bulgular: Çalışmaya 207 hasta dahil edildi (107 erkek [%51,69] ve 100 kadın [%48,31]; ortalama yaş 54,30 ± 18,75 yıl). En sık altta yatan tanılar pankreas hastalıkları (%26,09), hepatobiliyer hastalıklar (%23,67), karaciğer sirozu (%19,81), gastrointestinal malignite (%16,43) ve inflamatuvar bağırsak hastalığı (%8,21) idi. En sık kutanöz bulgular kaşıntı (%60,38), başlıca ikter veya solukluk şeklinde renk değişikliği (%56,52), kserozis kutis (%45,41), hiperkeratotik değişiklikler (%43,47) ve enfeksiyonlar (%35,26) olarak saptandı.

Sonuç: Gastroenteroloji servisinde yatan hastalarda dermatolojik bulgular geniş bir klinik yelpaze göstermektedir. Bu konsültasyon temelli seçilmiş kohortta kaşıntı, renk değişikliği ve kserozis öne çıkmıştır. Bulgular, gastroenteroloji servislerinde kutanöz semptomu olan hastalarda dermatolojik değerlendirmenin önemini desteklemekle birlikte, tüm gastroenteroloji hastaları için prevalans verisi olarak yorumlanmamalıdır.

Anahtar Kelimeler: Gastroenterolojik hastalıklar, kserozis kutis, kaşıntı, pigment değişiklikleri, hepatobiliyer hastalık, inflamatuvar bağırsak hastalığı.

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INTRODUCTION

The skin may provide important clinical clues to systemic disease, and gastrointestinal, hepatobiliary and pancreatic disorders are among the systemic conditions in which cutaneous findings are frequently encountered. These manifestations range from nonspecific findings such as pruritus and xerosis to more disease-related clues, including jaundice, vascular changes, paraneoplastic dermatoses and inflammatory bowel disease (IBD)-associated mucocutaneous lesions (1-6). The clinical relevance of these findings is not uniform. Some lesions reflect the pathophysiology of the underlying disease, such as cholestasis-associated pruritus or IBD-related reactive dermatoses; others may be secondary to malnutrition, advanced age, prolonged hospitalization, infection risk or medications. In patients with malignancy, selected paraneoplastic dermatoses may occasionally precede the diagnosis, whereas many common findings, such as xerosis or seborrheic keratosis, require cautious interpretation (2,3).

Most published data focus on specific disease groups, particularly IBD or chronic liver disease. Studies evaluating the overall dermatologic spectrum in hospitalized gastroenterology patients remain limited, especially in single-center inpatient settings (7). The present study aimed to describe the frequency, distribution and clinical characteristics of dermatologic findings in adult patients hospitalized in a gastroenterology ward who had cutaneous findings requiring dermatology consultation.

MATERIALS AND METHODS

This was a single-center, prospective, cross-sectional descriptive observational study. Adult patients aged 18 years or older who were hospitalized in the Gastroenterology Service of Gaziantep University Faculty of Medicine between September 2022 and September 2023 were included if they had dermatologic findings requiring dermatology consultation. Only patients with evident cutaneous or mucosal findings were evaluated. Therefore, the study population represents a selected consultation-based subgroup and not all hospitalized gastroenterology patients. Demographic data (age and sex), primary gastroenterological diagnosis, duration of the underlying disease, medications used for the underlying condition, lesion location, morphology, duration, associated symptoms and final dermatologic diagnosis were recorded. Dermatologic diagnoses were established using clinical history and dermatologic examination. Potassium hydroxide microscopy, wound culture and histopathologic examination were performed when clinically indicated.

Statistical analyses were performed using IBM SPSS Statistics software. Because the study was descriptive, continuous variables were summarized as mean ± standard deviation (SD), and categorical variables were presented as number and percentage. No comparative or inferential statistical analyses were performed. The study was approved by the ethics committee on 31 August 2022 (approval code: 2022/288). All patients were informed about the study, and written informed consent was obtained.

RESULTS

The study included 207 adult patients hospitalized with gastroenterological diseases. Of these, 107 patients (51.69%) were male and 100 (48.31%) were female. The mean age of the cohort was 54.30 ± 18.75 years. The distribution of primary gastroenterological diagnoses is shown in Figure 1, and mean age by diagnostic group is summarized in Table 1. A total of 49 patients were hospitalized with hepatobiliary disorders other than liver cirrhosis. Most of these patients had gallbladder or biliary tract disease (n=43, 87.75%); toxic hepatitis was identified in 3 patients (6.12%), hydatid cyst disease in 2 patients (4.08%) and autoimmune hepatitis in 1 patient (2.04%).

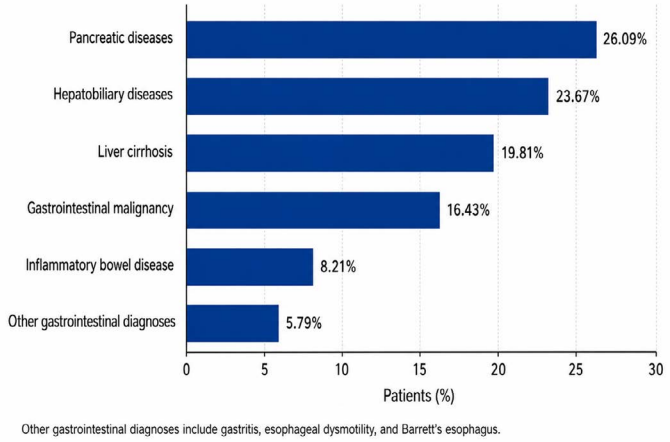

Figure 1. Distribution of primary gastroenterological diagnoses among hospitalized patients (n=207).

Table 1. Mean age and standard deviation by primary gastroenterological diagnosis

Primary diagnosis	n (%)	Age, mean ± SD (years)
Liver cirrhosis	41 (19.81)	58.12 ± 16.73
Hepatobiliary diseases	49 (23.67)	53.98 ± 18.58
Gastrointestinal malignancy	34 (16.43)	61.68 ± 14.22
Pancreatic diseases	54 (26.09)	55.24 ± 19.48
Inflammatory bowel disease	17 (8.21)	33.35 ± 13.20
Other (gastritis, esophageal dysmotility, Barrett's esophagus)	12 (5.79)	47.25 ± 20.22

SD: standard deviation.

Table 2. Distribution of cutaneous findings in the study cohort

Cutaneous finding	Number of patients	%
Pigmentation changes	44	21.25
Skin color changes	117	56.52
Xerosis cutis	94	45.41
Infections	73	35.26
Hair changes	37	17.87
Hyperkeratotic changes	90	43.47
Pruritus	125	60.38
Nail changes	32	15.45
Vascular changes	53	25.60
Eczema	20	9.66
Oral mucosal findings	11	5.31
Autoimmune/immune-mediated dermatoses	5	2.41
Drug eruptions	3	1.44
Other findings	111	53.62
Ascites/pretibial edema	40	19.32*
Rosacea	29	14.01*

Note: More than one dermatologic finding could be recorded in the same patient; therefore, percentages may exceed 100%. Pigmentation changes included lentigo/hyperpigmentation. Skin color changes included icterus/pallor. *Within the "other findings" category, ascites/pretibial edema accounted for 36.03% and rosacea for 26.12%.

Among the 34 patients with gastrointestinal malignancy, pancreatic cancer was the most common diagnosis (n=10, 29.41%), followed by hepatocellular carcinoma (n=8, 23.52%), colon cancer (n=5, 14.70%), cholangiocarcinoma (n=4, 11.76%) and gastric cancer (n=3, 8.82%). Metastatic gastrointestinal malignancy was present in 2 patients (5.88%), and gallbladder adenocarcinoma and esophageal cancer were each observed in 1 patient (2.94%). Pancreatic diseases accounted for 54 admissions. Acute pancreatitis was the predominant diagnosis (n=46, 85.18%), whereas chronic pancreatitis was diagnosed in 8 patients (14.81%). Seventeen patients had IBD; Crohn's disease was more frequent (n=13, 76.47%) than ulcerative colitis (n=4, 23.52%).

The distribution of dermatologic findings is presented in Table 2. Because more than one dermatologic finding could be recorded in the same patient, percentages are not mutually exclusive. The most common findings were pruritus (n=125, 60.38%), skin color changes (n=117, 56.52%), xerosis cutis (n=94, 45.41%), hyperkeratotic changes (n=90, 43.47%) and infections (n=73, 35.26%). On detailed assessment, solar lentigo was the most common pigmentation change (77.27%). Among patients with color change, icterus (51.28%) and pallor (39.31%) were the leading findings. All patients with xerosis had diffuse xerosis cutis. Fungal infection was the most common infectious diagnosis (58.90%). Androgenetic alopecia was the dominant hair finding (89.18%). Localized hyperkeratosis was the most common hyperkeratotic change (67.77%), followed by seborrheic keratosis (25.55%). Most patients with pruritus had generalized pruritus (94.40%).

Among patients with nail changes, onychomycosis was the most common diagnosis (81.25%), followed by yellow nail discoloration (56.25%). Telangiectasia was the most frequent vascular change (69.81%), followed by varicosities (45.28%). Oral aphthae accounted for most oral mucosal findings (81.81%). Autoimmune or immune-mediated dermatoses were observed in 5 patients: psoriasis vulgaris in 3, hidradenitis suppurativa in 1 and dermatitis herpetiformis in 1. Within the "other findings" category, ascites or pretibial edema and rosacea were the leading subcategories.

DISCUSSION

This study describes the dermatologic spectrum observed in a selected group of adult patients hospitalized in a gastroenterology ward and referred for dermatologic evaluation. The leading findings were pruritus, color change, xerosis cutis, hyperkeratotic changes and infections. Because the cohort included only patients with dermatologic findings requiring consultation, these results should be interpreted as the distribution of findings within a symptomatic inpatient subgroup rather than the prevalence of skin disease among all gastroenterology inpatients. Our findings partly overlap with the limited inpatient literature from Türkiye. Karabay et al. reported skin findings among patients hospitalized in a gastroenterology clinic and emphasized that most findings were nonspecific, while a smaller proportion were more directly related to gastrointestinal disease (7). In the present cohort, pancreatic and hepatobiliary disorders were the most frequent underlying diagnostic groups, which likely reflects the case mix of the ward during the study period rather than a disease-specific predisposition to dermatologic consultation.

Hepatobiliary disease and liver cirrhosis together represented 90 patients in the cohort. In this group, pruritus, xerosis and icteric discoloration were prominent. These findings are clinically plausible, as liver disease may be accompanied by jaundice, pruritus, pigmentary change, vascular lesions, palmar erythema, spider angioma, nail findings and xerosis (1,8,12). The comparison with primary biliary cholangitis/cirrhosis literature should be made carefully: Koulentaki et al. evaluated a specific primary biliary cirrhosis population and reported high rates of pruritus, xerosis, dermographism and

fungal infections (9). Our lower rate of infections and absence of dermographism likely reflect differences in diagnostic composition, inpatient selection and the consultation-based design. Cholestasis-associated pruritus is multifactorial. Older explanations emphasized endogenous opioids, whereas more recent work has also focused on bile acid-related signaling, autotaxin-lysophosphatidic acid pathways and nonhistaminergic neural mechanisms (10,11). In this context, the high rate of generalized pruritus in hepatobiliary disease is consistent with clinical experience, but our descriptive design does not allow mechanistic interpretation. Palmar erythema and spider angioma were observed in a limited number of cirrhosis patients; these lesions are classically linked to chronic liver disease and altered vascular or hormonal regulation (12).

Patients with gastrointestinal malignancy also showed a broad dermatologic spectrum. Paraneoplastic dermatoses, direct infiltration, metastasis and treatment-related reactions are well recognized in gastrointestinal cancers (2,13). In our malignancy subgroup, pruritus was frequent. Large clinical data have shown an association between pruritus and malignancy, particularly hepatobiliary, hematologic and skin cancers; however, such associations do not imply that pruritus is specific for cancer in an individual hospitalized patient (14). In our cohort, concomitant xerosis and older age may have contributed substantially to itch burden. Several common or potentially paraneoplastic findings in the malignancy group require cautious interpretation. Xerosis was frequent and has also been described among patients with internal malignancies, but it remains common in older and systemically ill patients and should not be overinterpreted (15). Seborrheic keratoses were observed, but no patient had a convincing Leser-Trélat sign; the association between seborrheic keratoses and internal malignancy remains controversial (16). One patient with colon adenocarcinoma had acquired hypertrichosis lanuginosa, a rare paraneoplastic clue that has been reported with gastrointestinal malignancies, including colorectal cancer (17,18). Nail changes were less frequent than in some chemotherapy-focused series, probably because not all patients had received chemotherapy at the time of dermatologic evaluation (19,20). Rosacea was also observed in the malignancy subgroup. Although population-based data have reported associations between rosacea and certain cancers, our study had no control group and cannot support any inference regarding cancer risk (21).

Pancreatic diseases formed the largest primary diagnostic group. Pruritus and icterus were common in these patients, which may reflect biliary obstruction or hepatobiliary involvement in a subset of cases. Two patients had xanthomas. Specific cutaneous signs of severe acute pancreatitis, such as Cullen, Grey Turner, Fox or Bryant signs, were not observed. These hemorrhagic signs are rare but clinically important because they may point to severe pancreatic or retroperitoneal pathology (22,23). IBD accounted for a relatively small subgroup. Oral aphthae and perianal fistulas were the most relevant mucocutaneous findings in Crohn's disease. Erythema nodosum and pyoderma gangrenosum, which are among the best-known IBD-associated dermatoses, were not observed. This is most likely related to the limited number of IBD patients, the timing of hospitalization and the consultation-based design rather than a true absence of these manifestations in the local IBD population (3-6,24-26). One Crohn's disease patient had psoriasis. The epidemiologic association between psoriasis and IBD is well established, but a single case in this cohort cannot be used to draw any conclusion regarding directionality or risk (27).

A considerable proportion of findings, including xerosis cutis, eczema, solar lentigines, seborrheic keratoses, onychomycosis, androgenetic alopecia, rosacea and nonspecific nail changes, are not specific to gastrointestinal disease. In hospitalized patients, these findings may reflect age, nutritional status, systemic inflammation, reduced mobility, hygiene-related factors, immunosuppression or drug exposure. Their documentation remains clinically useful, but they should be separated from disease-specific or diagnostically suggestive dermatoses in the interpretation of the study. This study has several limitations. It was conducted in a single center and included only hospitalized patients with dermatologic findings requiring consultation; therefore, it is subject to selection bias and does not represent all gastroenterology inpatients. The absence of a control group and the use of descriptive statistics preclude causal inference or prevalence estimation. Disease activity scores, nutritional parameters and standardized pruritus or quality-of-life measures were not systematically evaluated. Finally, some common dermatologic findings may have been influenced by age, hospitalization and comorbid conditions rather than the primary gastrointestinal diagnosis.

CONCLUSION

Dermatologic findings in hospitalized gastroenterology patients encompass a wide clinical spectrum. In this selected cohort, pruritus, color change and xerosis cutis were the most frequent findings, while hepatobiliary disease, gastrointestinal malignancy, pancreatic disease and IBD each showed clinically distinct but partly overlapping dermatologic patterns. Collaboration between dermatology and gastroenterology may facilitate recognition of disease-related skin clues, management of symptomatic findings and identification of treatment-related adverse events. Larger multicenter studies with control groups and standardized clinical measures are needed to clarify the diagnostic and prognostic value of these associations.

DECLARATIONS

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OPEN

RESEARCH ARTICLE

Diagnostic Utility of the Corpus Callosum Index in Mild and Moderate Alzheimer's Disease and Its Relationship with Mini Mental State Examination Subcomponents

Hafif ve Orta Evre Alzheimer Hastalığında Korpus Kallozum İndeksinin Tanısal Değeri ve Mini Mental Durum Değerlendirmesi Alt Bileşenleriyle İlişkisi

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ABSTRACT

Objective: This study evaluated the utility of the corpus callosum index (CCI) as a discriminative biomarker between the mild and moderate stages of Alzheimer's disease (AD).

Materials and Methods: A total of 168 individuals were included, comprising two patient groups diagnosed with mild and moderate AD and a control group. CCI values and Mini-Mental State Examination (MMSE) subcomponent scores were compared. Statistical analyses assessed correlations between MMSE subdomains and CCI, group differences, optimal cutoff values using receiver operating characteristic (ROC) analysis, and logistic regression models.

Results: Significant differences in CCI values were observed among the groups ($p < 0.001$). CCI values decreased progressively with increasing dementia severity. A positive correlation was identified between CCI and total MMSE score, as well as orientation, attention-calculation, and language subtests. In the univariate logistic regression analysis, age, CCI, and education level were significant variables; in the multivariate logistic regression model, both CCI and age remained independent predictors of dementia severity ($p < 0.001$ for both). In the ROC analysis, CCI demonstrated high discriminative power between controls and patients with mild dementia (AUC = 0.922) and acceptable discriminative power between mild and moderate dementia (AUC = 0.756).

Conclusion: The findings suggest that CCI may be a useful measure for the early assessment of AD severity. Its high sensitivity in distinguishing controls from patients with mild dementia indicates potential clinical utility as an adjunctive assessment tool. However, larger multicenter prospective studies are needed to draw definitive conclusions regarding the prognostic value and clinical applicability of CCI.

Keywords: Alzheimer's disease, cognitive decline, corpus callosum index, magnetic resonance imaging,mini-mental state examination,

ÖZET

Amaç: Bu çalışma, korpus kallozum indeksinin (KKİ) Alzheimer hastalığının (AH) hafif ve orta evreleri arasında ayırt edici bir biyobelirteç olarak kullanılabilirliğini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: Hafif ve orta evre AH tanısı alan iki hasta grubu ile bir kontrol grubundan oluşan toplam 168 birey çalışmaya dahil edilmiştir. KKİ değerleri ve Mini-Mental Durum Muayenesi (MMSE) alt bileşen puanları karşılaştırılmıştır. İstatistiksel analizlerde MMSE alt alanları ile KKİ arasındaki korelasyonlar, grup karşılaştırmaları, ROC analizi ile optimal kesim noktaları ve lojistik regresyon modelleri değerlendirilmiştir.

Bulgular: Gruplar arasında KKİ değerlerinde anlamlı farklılıklar saptanmıştır ($p < 0.001$). Demans şiddeti arttıkça KKİ değerleri basamaklı olarak azalmıştır. KKİ ile toplam MMSE puanı arasında pozitif bir korelasyon bulunmuş olup yönelim, dikkat-hesaplama ve dil alt testleri ile ilişkiler gözlenmiştir. Tek değişkenli lojistik regresyon analizinde yaş, KKİ ve eğitim anlamlı bulunmuş; çok değişkenli lojistik regresyon modelinde ise hem KKİ hem de yaş demans şiddetinin bağımsız belirleyicileri olarak kalmıştır (her ikisi için $p < 0.001$). ROC analizinde KKİ, kontroller ile hafif demans arasında yüksek ayırt edicilik (AUC = 0.922) ve hafif ile orta evre demans arasında kabul edilebilir düzeyde ayırt edicilik (AUC = 0.756) göstermiştir.

Sonuç: Bu çalışmanın bulguları, KKİ'nin AH'nin erken evrelerinin değerlendirilmesinde destekleyici bir yapısal ölçüt olabileceğini göstermektedir. Kontroller ile hafif demansı ayırt etmedeki yüksek duyarlılığı, klinik değerlendirmelere potansiyel katkı sağlayabileceğini düşündürmektedir. Ancak KKİ'nin prognostik değeri ve klinik uygulanabilirliği hakkında kesin sonuçlara varılabilmesi için daha geniş örneklemli, çok merkezli prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Alzheimer hastalığı, bilişsel gerileme, korpus kallozum indeksi, manyetik rezonans görüntüleme, mini-mental durum muayenesi

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INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disorder leading to dementia and is characterized in its early stages by memory impairment, particularly affecting episodic memory, deterioration in executive functions, and reduced decision-making ability (1). AD pathology progresses through the accumulation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles, resulting in neuronal and synaptic loss and consequently widespread brain atrophy (2,3).

The corpus callosum (CC) is the largest white matter structure facilitating information transfer between the right and left hemispheres and plays a critical role in the integrated organization of cognitive functions (1). Regional atrophy, accompanied by demyelination and microstructural alterations in the CC, has been reported in patients with AD (4). Structural changes, particularly in the midanterior and central segments, have been associated with the degree of cognitive impairment and may reflect disease severity (4). The presence of these changes in both AD patients and individuals with mild cognitive impairment (MCI), compared with healthy controls, suggests that the CC may be affected from the early stages of the Alzheimer spectrum (4). Previous studies have reported pronounced changes in shape-based morphometric features of the CC during the early stages of AD, suggesting that these changes may be more sensitive indicators of disease severity and progression than volumetric measurements (5). Structural reductions observed in different CC segments in patients with amnestic MCI and mild AD have also been proposed as early indicators of disease progression (6). In their magnetic resonance imaging (MRI)–based review, Di Paola et al. stated that atrophy in the anterior (genu) segment of the CC is related to myelin degradation in late-myelinating fibers, whereas atrophy in the posterior (splenium) segment is associated with Wallerian degeneration (7). Similarly, morphometric changes in the genu and midbody segments of the CC observed in various neurological disorders have been reported to reflect disruption of transcallosal connections associated with executive functions and attentional networks (8). These findings suggest that segmental morphometric evaluation of the CC may represent a sensitive imaging approach for identifying structural involvement specific to cognitive systems.

In recent years, shape-based morphometric analyses have been more sensitive than conventional volumetric measurements. Ardekani et al. (5) reported that the CC circularity index could discriminate between very mild and mild stages of AD. These findings support the notion that shape- and ratio-based CC measurements may serve as potential biomarkers during the early stages of AD progression. However, heterogeneity in diagnostic criteria and Mini-Mental State Examination (MMSE) cutoff values across Alzheimer's clinical studies limits comparability between disease stages (9). Das et al. (6) demonstrated that CC atrophy is an effective morphometric marker for differentiating patients with mild and moderate AD from healthy individuals. Nevertheless, that study did not include a direct comparison between disease stages and did not specifically focus on distinguishing the Clinical Dementia Rating (CDR) 1 and CDR 2 groups. In this respect, the present study aims to address an important gap in the literature.

The primary aim of this study was to evaluate the potential role of the CC index (CCI) in differentiating disease stages in mild and moderate AD. By examining the extent to which CCI may contribute to clinical classification, we explored whether this structural measurement could serve as a potential biomarker for early diagnosis and follow-up. Additionally, we aimed to analyze the relationships between CCI and MMSE subcomponents (orientation, registration, attention and calculation, recall, and language) to clarify potential associations between cognitive performance and structural changes.

MATERIALS AND METHODS

This retrospective cross-sectional study included individuals aged ≥50 yr who presented to the Neurology Clinic of Aksaray University Training and Research Hospital with complaints of cognitive decline between December 5, 2019, and July 9, 2025. Data were obtained from the hospital's digital archive system. A total of 7,099 patient records were screened, and after duplicate entries were removed, 1,660 unique patient records remained. Among these, 112 patients who met the inclusion and exclusion criteria were enrolled in the study. In addition, 56 healthy controls who fulfilled the imaging and clinical criteria were included, resulting in a total sample of 168 individuals. Demographic characteristics and accompanying comorbidities were recorded for all participants. Eligible individuals were required to have at least a primary school education and sufficient proficiency in Turkish to complete cognitive assessments. Education level was coded in SPSS as a three-level categorical variable (1 = primary school, 2 = middle school, and 3 = high school or higher).

Patients were included if they had an AD diagnosis based on neurological ICD diagnostic codes, complete MMSE and MMSE subcomponent scores in the archive records (orientation, registration, attention and calculation, recall, and language), and cranial MRI obtained at the time of diagnosis. In addition, individuals diagnosed with moderate-stage AD during follow-up who had cranial MRI scans recorded during clinical visits and treatment modifications were also included.

Healthy controls were selected from age-matched individuals who underwent MRI for noncognitive complaints, such as headache or vertigo, and whose imaging findings were reported as normal. The study population was divided into three groups: mild-stage AD (n = 54), moderate-stage AD (n = 58), and healthy controls (n = 56). Because of the retrospective design, individuals with major metabolic or vascular disorders known to substantially affect brain structure, such as poorly controlled diabetes mellitus or uncontrolled hypertension, were excluded from the control group. However, common age-related chronic conditions were not considered exclusion criteria because completely comorbidity-free elderly

individuals are rarely encountered in retrospective cohorts.

Diagnosis and Staging

Alzheimer's disease diagnosis was established according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (9,10). Disease staging was determined through combined evaluation of total MMSE scores, MMSE subcomponent distributions, activities of daily living, treatment protocols, and clinical examination findings. For clinical standardization, staging was matched to Clinical Dementia Rating (CDR) scores of 1 and 2, respectively.

Mild-stage Alzheimer's dementia: Individuals with MMSE scores ranging from 19 to 23, largely preserved functional independence, and clinical findings consistent with CDR = 1 were classified as having mild-stage dementia. In some participants with low educational attainment, an MMSE score of 19 was categorized as mild-stage dementia based on preserved functional independence and concordant clinical evaluation. This approach is consistent with previous reports indicating that the MMSE alone may have limited discriminative capacity (11,12).

Moderate-stage Alzheimer's dementia: Individuals with MMSE scores ranging from 10 to 19 who required substantial assistance with activities of daily living, demonstrated clinical findings compatible with moderate-stage disease, and were managed according to moderate-stage treatment protocols were classified as having moderate-stage dementia, corresponding to CDR = 2.

Inclusion and Exclusion Criteria

Inclusion criteria: Evaluation in the neurology clinic; diagnosis of mild or moderate AD established by a neurology specialist; complete MMSE administration; technically adequate cranial MRI obtained at the time of diagnosis or within 3–4 months after diagnosis; and at least primary school-level education with the ability to complete cognitive tests in Turkish.

Exclusion criteria: History of cranial surgery, cerebrovascular disease, head trauma, neurodevelopmental disorders, psychiatric disorders affecting cognitive function, incomplete clinical records, and causes of dementia other than AD, including vascular dementia.

Corpus Callosum Index Measurement

The CCI was measured on midsagittal T1-weighted MRI sections. CCI was calculated using the following ratio-based formula: (aa'/ab + bb'/ab + cc'/ab) (Figure 1) (13). All measurements were performed twice by a radiologist blinded to the clinical and cognitive data, and the measurements were subsequently confirmed.

Ethical Approval

This retrospective study was approved by the Aksaray University Health Sciences Scientific Research Ethics Committee (Decision No. 2025/173; Meeting Date: 11.09.2025; Protocol No. SAGETIK 2025-114). All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25. The distributional characteristics of continuous variables were assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Comparisons between two nonnormally distributed groups were performed using the Mann–Whitney U test. Variables with three categories that did not show normal distribution were analyzed using the Kruskal–Wallis H test. When significant differences were identified, post hoc multiple comparisons were conducted using Dunn's test with Bonferroni correction. Categorical variables were analyzed using Pearson's chi-square test. Spearman correlation analysis was performed to evaluate the relationships between CCI and age and between CCI and MMSE subcomponents. Binary logistic regression analysis was used to determine the effects of independent variables on discrimination between the mild- and moderate-stage dementia groups. Receiver operating characteristic (ROC) analysis was performed to identify discriminative parameters and determine optimal cutoff values. Continuous variables were presented as median (interquartile range [IQR]) and minimum–maximum values, whereas categorical variables were expressed as number (n) and percentage (%). A two-tailed p value <0.05 was considered statistically significant.

RESULTS

A total of 168 individuals were included in the study, comprising 54 patients with mild dementia, 58 with moderate dementia, and 56 healthy controls. The median age of the entire cohort was 75 yr (IQR: 68–82; range: 51–95 yr). Median age was

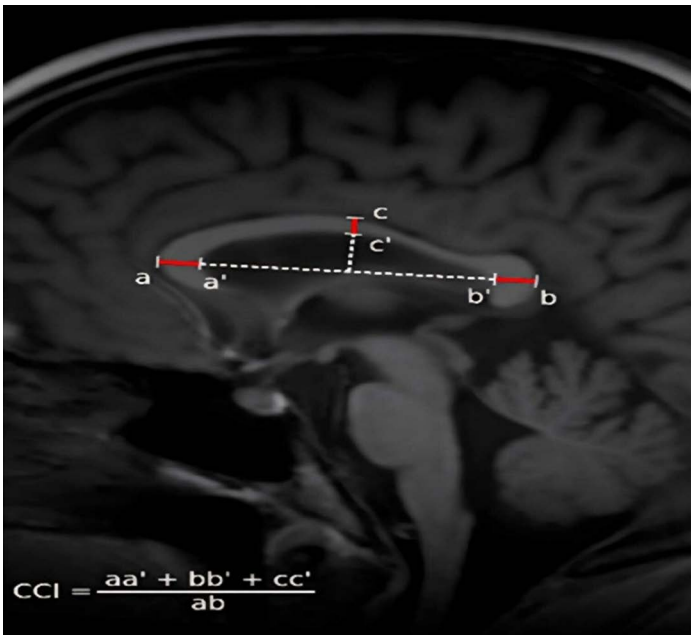

Figure 1. The corpus callosum index (CCI) was measured from midsagittal T1 weighted MRI images and calculated using the ratio of anteroposterior length to segmental heights according to the formula (aa'/ab + bb'/ab + cc'/ab).

72 yr (IQR: 65–80; range: 51–85 yr) in the control group, 75 yr (IQR: 70–80; range: 60–99 yr) in the mild dementia group, and 80 yr (IQR: 75–85; range: 57–95 yr) in the moderate dementia group. Kruskal–Wallis analysis demonstrated a significant difference in age among the groups ($H = 29.753$, $p < 0.001$). Bonferroni-corrected Dunn post hoc analyses indicated that age increased significantly with advancing dementia stage (Table 1).

Among all participants, 72 were male (42.9%), and 96 were female (57.1%). The mild dementia group included 24 males (44.4%) and 30 females (55.6%), whereas the moderate dementia group included 19 males (32.8%) and 39 females (67.2%). In the control group, 29 participants were male (51.8%), and 27 were female (48.2%). No statistically significant difference in sex distribution was observed among the groups ($p = 0.117$). The CCI values differed significantly among the groups (Figure 2). The median CCI was 0.38 (IQR: 0.35–0.41; range: 0.29–0.44) in the control group, 0.29 (IQR: 0.26–0.32; range: 0.16–0.38) in the mild dementia group, and 0.25 (IQR: 0.22–0.28; range: 0.17–0.34) in the moderate dementia group. The median CCI value for the entire cohort was 0.30 (IQR: 0.27–0.35; range: 0.17–0.44). Kruskal–Wallis analysis showed a significant difference in CCI values among the groups ($H = 104.279$, $p < 0.001$). Post hoc analyses demonstrated a progressive decrease in CCI values with increasing dementia severity (Table 1).

Mini-Mental State Examination scores also differed significantly between the dementia groups. The median MMSE score was 20 (IQR: 19–21; range: 19–23) in the mild dementia group and 12 (IQR: 11–14; range: 10–18) in the moderate dementia group. The median MMSE score for the overall dementia cohort was 16 (IQR: 13–19; range: 10–23). Because MMSE is not routinely administered to healthy controls, MMSE subcomponent analyses were performed only between the mild and moderate dementia groups. Patients with mild dementia had significantly higher scores in orientation ($p < 0.001$), attention and calculation ($p < 0.001$), recall ($p < 0.001$), and language ($p < 0.001$) subtests compared with those with moderate dementia. A significant difference was also observed in the registration subtest ($p = 0.007$; Table 2).

Table 1. Comparison of age and CCI values among healthy controls, mild dementia, and moderate dementia groups

Variable	Control (n=56) Median (IQR)	Control Min–Max	Mild Dementia (n=54) Median (IQR)	Mild Min–Max	Moderate Dementia (n=58) Median (IQR)	Moderate Min–Max	Test Statistic (H)*	P
Age (yr)	72 (65–80)[a]	51–85	75 (70–80)[b]	60–99	80 (75–85)[c]	57–95	29.753	<0.001
CCI	0.38 (0.35–0.41)[a]	0.29–0.44	0.29 (0.26–0.32)[b]	0.16–0.38	0.25 (0.22–0.28)[c]	0.17–0.34	104.279	<0.001

a–c: Groups sharing the same letter do not differ significantly from each other, whereas groups with different letters show statistically significant differences (Dunn's test with Bonferroni correction, $p<0.05$). Post-hoc Comparison Explanation (with Test Statistics) Age: Control vs. Mild dementia: Test statistic = 24.225, Std. Test = 2.615, $p = 0.027$. Control vs. Moderate dementia: Test statistic = 49.627, Std. Test = 5.453, $p < 0.001$. Mild vs. Moderate dementia: Test statistic = –25.401, Std. Test = –2.765, $p = 0.017$. CCI: Moderate vs. Mild dementia: Test statistic = 32.205, Std. Test = 3.501, $p = 0.001$. Moderate vs. Control: Test statistic = –91.893, Std. Test = –10.084, $p < 0.001$. Mild vs. Control: Test statistic = –59.688, Std. Test = –6.434, $p < 0.001$. Pairwise comparisons were conducted using Dunn's test with Bonferroni adjustment. CCI: Corpus callosum index; IQR: Interquartile range. * Kruskal–Wallis test statistic.

Comorbidity distributions were evaluated using Pearson's chi-square test. Significant between-group differences were identified for hypertension, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and renal failure (all $p < 0.05$). In contrast, no significant differences were observed for atrial fibrillation, hyperlipidemia, hypothyroidism, or hearing loss (all $p > 0.05$; Table 3). Spearman correlation analysis demonstrated a significant negative correlation between CCI and age ($r = –0.467$, $p < 0.001$), indicating that CCI values decreased with increasing age. A significant positive correlation was observed between CCI and total MMSE score ($r = 0.470$, $p < 0.001$). At the MMSE subcomponent level, significant positive correlations were found between CCI and orientation ($r = 0.391$, $p < 0.001$), attention and calculation ($r = 0.429$, $p < 0.001$), and language scores ($r = 0.357$, $p < 0.001$). However, no significant correlations were identified between CCI and registration ($r = 0.107$, $p = 0.262$) or recall scores ($r = 0.145$, $p = 0.127$).

Logistic regression analysis was performed using mild and moderate dementia groups as dependent variables. The overall model demonstrated a significant fit (Omnibus test: $\chi^2 = 25.324$, $p < 0.001$; Nagelkerke $R^2 = 0.270$), with a classification accuracy of 71.4%. In univariate analyses, age, CCI, and education level were significantly associated with the likelihood of moderate dementia. In the multivariable logistic regression model, age (OR = 1.05, 95% CI, 1.01–1.10; $p = 0.018$) and scaled CCI (OR

Table 2. Comparison of MMSE subcomponents between mild and moderate dementia groups

MMSE Subcomponent	Mild Dementia (n=54) Median (IQR)	Mild Min–Max	Moderate Dementia (n=58) Median (IQR)	Moderate Min–Max	U	P*
Orientation	6 (4–7)	2–9	4 (3–6)	2–8	141.000	<0.001
Registration	3 (3–3)	0–3	3 (3–3)	0–3	1299.000	0.007
Attention & Calculation	1 (0–4)	0–5	0 (0–2)	0–5	147.000	<0.001
Recall	0 (0–1)	0–3	0 (0–0)	0–2	1122.000	<0.001
Language	6 (5–7)	3–7	5 (4–6)	3–7	400.000	<0.001

MMSE: Mini-Mental State Examination; IQR: Interquartile range; Min–Max: Minimum–maximum values. * Mann–Whitney U test

Table 3. Distribution of comorbidities in control, mild, and moderate dementia groups (Pearson Chi-square test results)

Comorbidity	Control (n=56)	Mild (n=54)	Moderate (n=58)	χ^2	p
Hypertension	18 (32.1%)	47 (87.0%)	48 (82.8%)	47.281	<0.001
AF	3 (5.4%)	7 (13.0%)	12 (20.7%)	5.887	0.053
Hyperlipidemia	12 (21.4%)	18 (33.3%)	21 (36.2%)	3.277	0.194
CHF	0 (0%)	6 (11.1%)	9 (15.5%)	8.903	0.012
COPD	2 (3.6%)	12 (22.2%)	16 (27.6%)	12.235	0.002
Hypothyroidism	6 (10.7%)	4 (7.4%)	2 (3.4%)	2.276	0.320
Hearing loss	0 (0%)	5 (9.3%)	4 (6.9%)	5.063	0.080
DM	4 (7.1%)	18 (33.3%)	14 (24.1%)	11.586	0.003
Renal failure	1 (1.8%)	10 (18.5%)	8 (13.8%)	8.218	0.016

Comparisons between the three groups were performed using the Pearson Chi square test. AF: Atrial fibrillation; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus.

Table 4. Univariable and multivariable logistic regression analysis results for distinguishing mild and moderate dementia groups

Variable	Univariate OR (95% CI)	Univariate p	Multivariable OR (95% CI)	Multivariable p
Age (yr)	1.07 (1.02–1.12)	0.010	1.05 (1.01–1.10)	0.018
Sex (male)	0.61 (0.28–1.32)	0.205	0.74 (0.30–1.80)	0.510
Education: Middle school vs primary	1.58 (1.06–2.80)	0.025	1.40 (0.80–2.45)	0.230
Education: High school vs primary	0.58 (0.36–0.94)	0.023	0.62 (0.35–1.10)	0.098
CCI (scaled)	0.98 (0.97–0.99)	<0.001	0.97 (0.95–0.99)	0.004
Hypertension	0.72 (0.25–2.00)	0.530	—	—
AF	1.75 (0.63–4.85)	0.280	—	—
Hyperlipidemia	1.14 (0.50–2.00)	0.750	—	—
CHF	1.47 (0.50–4.30)	0.496	—	—
COPD	1.33 (0.60–2.60)	0.513	—	—
Hypothyroid	0.45 (0.08–2.40)	0.364	—	—
Hearing loss	0.73 (0.18–2.80)	0.647	—	—
DM	0.64 (0.28–1.45)	0.283	—	—
Renal failure	0.70 (0.25–2.00)	0.498	—	—

OR: Odds ratio; CI: Confidence interval; CCI (scaled): Corpus callosum index divided by 1000 for interpretability; AF: Atrial fibrillation; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus. Education was modeled using primary school as the reference category. Variables included in the multivariable model were selected based on clinical relevance and prior literature rather than univariable p-values. Omnibus $\chi^2 = 25.324$, $p < 0.001$; Nagelkerke $R^2 = 0.270$. Note: In logistic regression analysis, the dependent variable was coded as 0 = mild dementia and 1 = moderate dementia.

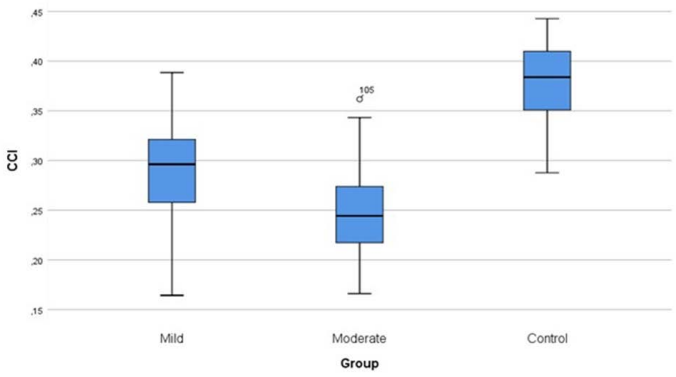

Figure 2. Boxplots showing the distribution of corpus callosum index (CCI) across the control, mild dementia, and moderate dementia groups.

= 0.97, 95% CI, 0.95–0.99; p = 0.004) remained independent predictors of moderate dementia, whereas sex and education level were not significant after adjustment. Other comorbidities were evaluated in univariate analyses but were not included in the multivariable model because they did not reach statistical significance (Table 4).

Receiver operating characteristic analysis demonstrated that CCI had high discriminative ability for differentiating healthy controls from patients with mild dementia (AUC = 0.922, 95% CI, 0.874–0.970). The optimal cutoff value was 0.2886 (sensitivity: 98.2%, specificity: 46.3%, Youden index: 0.445); CCI values below this threshold were more indicative of mild dementia (Figure 3). For discrimination between mild and moderate dementia, CCI showed acceptable discriminative performance (AUC = 0.756, 95% CI, 0.664–0.848). The optimal cutoff value was 0.2446 (sensitivity: 81.5%, specificity: 50.0%, Youden index: 0.315); CCI values below this threshold were more indicative of moderate dementia (Figure 4).

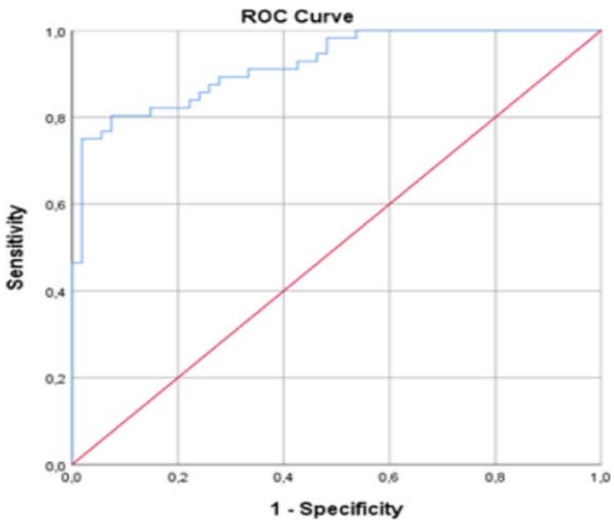

Figure 3. Receiver operating characteristic (ROC) curve of the corpus callosum index (CCI) for distinguishing control and mild dementia groups. The analysis yielded an AUC of 0.922 (95% CI, 0.874–0.970). The optimal cutoff value was 0.2886, with a sensitivity of 98.2%, specificity of 46.3%, and a Youden index of 0.445.

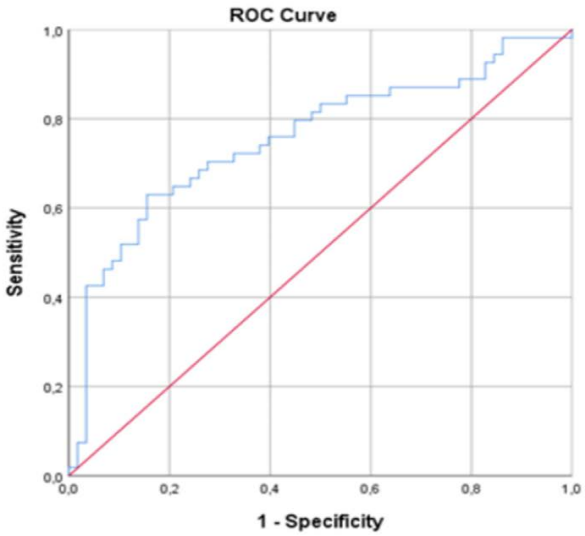

Figure 4. Receiver operating characteristic (ROC) curve of the corpus callosum index (CCI) for distinguishing mild and moderate dementia groups. The analysis yielded an AUC of 0.756 (95% CI, 0.664–0.848). The optimal cutoff value was 0.2446, with a sensitivity of 81.5%, specificity of 50.0%, and a Youden index of 0.315.

DISCUSSION

This study investigated the relationship between the CCI, dementia stages, and MMSE subcomponents and evaluated the potential diagnostic utility of CCI in differentiating mild and moderate dementia. Our findings demonstrated that CCI values decreased progressively with advancing dementia severity and showed particularly high discriminative performance in distinguishing patients with mild dementia from healthy controls. Although increasing dementia severity is known to be associated with advancing age, a significant negative correlation between age and CCI was also observed. This finding suggests that aging may contribute to the structural vulnerability of the CC during the dementia process. In addition, positive correlations between MMSE scores and CCI were most pronounced for the orientation, attention-calculation, and language subtests, indicating a close association between CC structural integrity and cognitive performance.

In logistic regression analyses, age, CCI, and education level were significant in the univariate model. After adjustment for covariates, age and scaled CCI remained independent predictors of moderate dementia, whereas education level and sex were no longer significant. These findings suggest that CCI provides diagnostic value beyond demographic characteristics, while the independent contribution of age is consistent with the established association between aging and dementia severity. Furthermore, reevaluation of the multivariable model confirmed that CCI remained a significant independent predictor even after adjustment for age, indicating that the observed association was not solely attributable to age-related structural alterations.

Receiver operating characteristic analysis demonstrated that CCI had particularly high sensitivity for differentiating healthy controls from patients with mild dementia and acceptable discriminative ability for distinguishing mild from moderate dementia. This high sensitivity suggests that CCI may detect early-stage dementia even when cognitive impairment remains relatively mild. Such structural changes may precede more apparent clinical decline, highlighting the potential role of CCI as an early-stage screening marker. Early identification of mild dementia is clinically important because it may facilitate timely intervention and management planning. However, despite the high sensitivity of CCI in differentiating controls from mild dementia, specificity remained relatively low, indicating a greater likelihood of false-positive classifications in the early stages. Therefore, the clinical applicability of CCI should be considered within a multimodal diagnostic framework rather than as a standalone diagnostic tool. Overall, our findings support the potential utility of CCI as a supportive biomarker in AD. Segmental morphometric alterations reported by Liu et al. (14) and Zhou et al. (8) suggest that different CC regions may exhibit varying sensitivity during disease progression. Consistent with these observations, structural reductions in the genu and midbody regions described in poststroke cognitive impairment studies have been associated with executive dysfunction (8). In the present study, CCI differences reflecting frontal and midbody segments showed significant associations with MMSE subcomponents, particularly attention-calculation and language, supporting the clinical relevance of regional callosal vulnerability. Collectively, the observed relationships between CCI and orientation, attention-calculation, and language functions suggest that callosal structural compromise may clinically manifest as impairments in attentional control, executive processing, and language-related cognitive functions. These findings are consistent with the established role of anterior and midbody callosal fibers in interhemispheric integration of frontal cognitive networks.

The detailed anatomy of the anterior CC and septal region demonstrates dense interhemispheric connections between frontal and limbic cortical areas (15). Recent systematic reviews and meta-analyses have associated this structural organization with executive function, attention, and social cognition (8,16,17). Accordingly, the correlations identified between CCI and orientation and attention subtests may reflect the functional consequences of these anatomical connections. Large-scale systematic reviews and meta-analyses further indicate that morphological changes in the CC are associated with the clinical spectrum and degree of cognitive involvement in AD (16). Wang et al. (18) reported an anterior-to-posterior atrophy pattern, and our findings showing relative preservation of CCI in mild dementia and marked reduction in moderate dementia are consistent with this model. Methodological approaches such as the shape-on-scalar regression model proposed by Dogra et al. (19), which account for confounding factors including age, sex, and education, are also methodologically consistent with our multivariable findings demonstrating that CCI remained an independent predictor. These findings further support the practical utility of CCI as a morphometric marker in clinical settings.

Studies investigating biomarkers have also provided insight into the pathophysiological basis of structural CC changes. Shaji et al. (20) reported that CC abnormalities were associated with phosphorylated tau (p-tau), whereas associations with amyloid-β were less consistent. The limited significant correlations between CCI and memory-related subtests observed in our study may be compatible with this heterogeneous relationship. In addition, multimodal findings summarized by Talwar et al. (21), including hippocampal atrophy, default-mode network hypoconnectivity, and parietal hypometabolism, suggest that CCI may have greater diagnostic utility when evaluated alongside other imaging modalities and biomarkers rather than in isolation. Furthermore, considering the limitations of traditional morphometric indices such as the Evans Index and callosal angle, our findings suggest that CCI may represent a more sensitive and clinically practical metric (14). Overall, our results indicate that CC morphometry provides meaningful information for dementia staging and that CCI may serve as a practical supportive tool in this context. However, the pathological and clinical heterogeneity of AD may limit the generalizability of these findings. Therefore, validation of the prognostic value and multimodal applicability of CCI will require larger prospective studies supported by biomarker integration.

Limitations

This study has several limitations. First, the cross-sectional design precludes definitive conclusions regarding the temporal trajectory of CCI alterations and causal relationships. Therefore, the prognostic utility of CCI can only be confirmed through prospective longitudinal studies. Second, the relatively limited sample size and single-center design may restrict the generalizability of the findings. In addition, because of the retrospective design, MMSE assessments were not available for the control group, limiting objective confirmation of their cognitive status. Third, integration of multimodal imaging and biomarker data was limited. Simultaneous evaluation of CCI together with positron emission tomography, MRS, or cerebrospinal fluid biomarkers would strengthen pathophysiological interpretation of the findings. Fourth, measurement and segmentation procedures may be susceptible to human- or software-related errors.

Finally, the pathological heterogeneity of AD and potential confounding factors, including concomitant vascular changes, may complicate the interpretation of the relationship between CCI and cognitive performance. Although age was adjusted for in multivariable analyses, the marked age differences between groups may still have resulted in residual confounding. Additionally, although CCI measurements were performed twice by the same radiologist, the intraclass correlation coefficient was not calculated, limiting formal assessment of intra-rater reliability.

CONCLUSION

The present study demonstrates that CCI provides meaningful information for dementia staging and has particularly high discriminative ability in distinguishing healthy controls from patients with mild dementia. The consistent associations observed between CCI and MMSE subcomponents further support the relationship between CC morphometry and clinical cognitive function. These findings suggest that CCI may serve as a practical, rapid, and cost-effective morphometric index to complement clinical assessment.

Nevertheless, definitive conclusions regarding the prognostic value and biological specificity of CCI require larger multicenter prospective studies incorporating multimodal imaging and biomarker integration. Future investigations should evaluate CCI across diverse demographic populations, at-risk early-stage groups, and treatment-monitoring settings to further clarify its clinical applicability and utility.

DECLARATIONS

Conflict of Interest: *The authors declare that there is no conflict of interest.*

Financial Disclosure: *The authors report no financial conflicts of interest related to this study.*

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RESEARCH ARTICLE

Comparison of Monocyte/High-Density Lipoprotein Cholesterol Ratio Between Patients with First-Episode and Chronic Schizophrenia

İlk Epizod ve Kronik Şizofreni Hastalarında Monosit/Yüksek Yoğunluklu Lipoprotein Kolesterol Oranı Karşılaştırması

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ABSTRACT

Objective: To investigate the monocyte/high-density lipoprotein ratio (MHR), which has been shown in the literature to be a novel inflammatory marker in patients with first-episode (FES) and chronic (CS) schizophrenia.

Materials and Methods: The study involved 38 patients with FES, 65 patients with CS and 40 healthy controls (HC). Retrospective investigations of blood parameters were carried out using the database and associated records. The monocyte count was divided by the HDL-C level to determine the MHR.

Results: Monocyte levels were significantly higher and platelet and HDL-C levels were significantly lower in both the FES and CS groups compared with the HC group. MHR levels were significantly higher in both the FES and CS groups compared with healthy controls, although no statistically significant difference was detected between the two groups. Correlation analyses revealed several modest associations between MHR and certain clinical variables, though no consistent relationship with illness duration or hospitalisation-related variables was observed.

Conclusion: The findings of this study demonstrate that MHR is significantly increased in patients with schizophrenia, supporting the notion that schizophrenia is associated with inflammatory activation. These results suggest that MHR may be associated with the inflammatory alterations observed in schizophrenia.

Keywords: Schizophrenia, inflammation, monocyte-to-high-density-lipoprotein ratio

ÖZET

Amaç: Literatürde ilk atak (İEŞ) ve kronik (KŞ) şizofreni hastalarında yeni bir inflamasyon belirteci olduğu gösterilen monosit/yüksek yoğunluklu lipoprotein oranını (MHO) araştırmaktır.

Gereç ve Yöntemler: Çalışmaya 38 IEŞ hastası, 65 KŞ hastası ve 40 sağlıklı kontrol (SK) dahil edildi. Kan parametrelerinin retrospektif incelemeleri, veri tabanı ve ilgili kayıtlar kullanılarak gerçekleştirilmiştir. MHO'yu belirlemek için monosit sayısı HDL-K düzeyine bölünmüştür.

Bulgular: Monosit düzeyleri önemli ölçüde daha yüksekken, trombosit ve HDL-K düzeyleri hem İEŞ hem de KŞ gruplarında sağlıklı kontrollere kıyasla önemli ölçüde daha düşüktü. MHO düzeyleri hem İEŞ hem de KŞ hastalarında sağlıklı kontrollere kıyasla önemli ölçüde daha yüksekti, ancak iki gurup arasında istatistiksel olarak anlamlı bir fark tespit edilmedi. Korelasyon analizleri, MHO ile belirli klinik değişkenler arasında birkaç mütevazı ilişki olduğunu gösterdi, ancak hastalık süresi veya hastaneye yatışla ilgili değişkenlerle tutarlı bir ilişki gözlemlenmedi.

Sonuç: Bu çalışmanın bulguları, şizofreni hastalarında MHO'nun önemli ölçüde arttığını göstermekte ve şizofreninin inflamatuar aktivasyonla ilişkili olduğu görüşünü desteklemektedir. Bu sonuçlar, MHO'nun şizofrenide gözlenen inflamatuar değişikliklerle ilişkili olabileceğini düşündürmektedir.

Anahtar Kelimeler: Şizofreni, inflamasyon, monosit/yüksek yoğunluklu lipoprotein oranı

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INTRODUCTION

Schizophrenia is a severe and chronic psychiatric disorder characterized by disturbances in perception, thought processes, emotional regulation, and behavior, and it affects approximately 1% of the global population (1, 2). In addition to its profound impact on functional outcomes and quality of life, schizophrenia is associated with complex and multifactorial pathophysiological mechanisms involving genetic, neurodevelopmental, and environmental factors. In recent years, increasing evidence has indicated that immune dysregulation and inflammatory processes may be important in the pathophysiology of schizophrenia (3, 4). Several lines of evidence support the involvement of inflammatory mechanisms in schizophrenia. Studies have demonstrated alterations in peripheral immune markers, including increased levels of pro-inflammatory cytokines and changes in immune cell profiles in patients with schizophrenia (5–8). Neuroinflammatory processes, particularly microglial activation and dysregulated immune signalling within the central nervous system, have also been suggested as potential causes of neuronal dysfunction and symptom development in schizophrenia (9). These findings have led to growing interest in identifying accessible peripheral biomarkers that may reflect the inflammatory alterations associated with the disorder.

In recent years, routine blood-based inflammatory indices derived from standard hematological and biochemical parameters have gained attention as potential biomarkers in psychiatric research. Among these markers, the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR) and the monocyte-to-lymphocyte ratio (MLR) have been investigated as potential indicators of systemic inflammation in patients with schizophrenia. Several studies have reported elevated NLR and PLR levels in patients with schizophrenia compared to healthy controls, suggesting the presence of low-grade systemic inflammation in the condition (10–12). Additionally, composite biomarkers derived from routine laboratory parameters, such as C-reactive protein-based indices and other haematology-derived inflammatory markers, have been increasingly explored to better characterise immune dysregulation in psychiatric disorders. The monocyte-to-high-density lipoprotein cholesterol ratio (MHR) is one of the emerging inflammatory biomarkers that has recently attracted considerable attention as a composite marker reflecting the balance between pro-inflammatory and anti-inflammatory processes. Monocytes are key components of the innate immune system and play a crucial role in inflammatory responses through the secretion of pro-inflammatory cytokines and oxidative mediators (13). In contrast, high-density lipoprotein cholesterol (HDL-C) exerts anti-inflammatory, antioxidant, and endothelial-protective effects, partly by inhibiting monocyte activation and reducing oxidative stress (14, 15). Consequently, the MHR, which is calculated by dividing the monocyte count by the HDL-C level, has been suggested as an effective indicator of systemic inflammatory burden.

Previous studies have shown that MHR is associated with inflammatory activity and disease severity in several cardiovascular, metabolic, and inflammatory disorders (16,17-20). These findings suggest that MHR may serve as a practical and accessible biomarker reflecting immune and inflammatory processes in various clinical conditions. Given the growing evidence linking schizophrenia with immune dysfunction and chronic low-grade inflammation, investigating MHR in patients with schizophrenia may provide additional insight into the inflammatory mechanisms underlying the disorder. Only a limited number of studies have examined MHR levels in patients with schizophrenia. Previous studies have reported higher MHR levels in patients with schizophrenia compared with healthy controls and have suggested that this marker may be associated with disease severity or clinical characteristics (21-24). However, the existing literature remains limited, with most studies have evaluated schizophrenia patients as a single group without considering potential differences across illness stages.

From an inflammatory perspective, comparing patients with first-episode schizophrenia (FES) and chronic schizophrenia (CS) may provide valuable insights into whether inflammatory alterations represent an early feature of the disorder or develop progressively during the course of the illness. Previous studies examining inflammatory biomarkers such as cytokines and hematological ratios have reported increased inflammatory markers both in first-episode and chronic stages of schizophrenia, although findings regarding differences across disease stages remain inconsistent (25-27). Therefore, further research is needed to clarify whether inflammatory markers differ between early and chronic phases of schizophrenia. Based on this background, the present study aimed to investigate serum monocyte-to-HDL cholesterol ratio (MHR) levels as a potential inflammatory biomarker in patients with first-episode and chronic schizophrenia and to compare these findings with healthy controls. It was hypothesised that MHR levels would be higher in patients with schizophrenia than in healthy individuals, and that any differences between patients experiencing their first episode of the disorder and those with chronic schizophrenia might reflect stage-related inflammatory alterations in the disorder.

MATERIALS AND METHODS

Design and Participants

This retrospective study reviewed the medical records of patients hospitalized with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), at the Psychiatry Clinic of the University of Health Sciences Beyhekim Training and Research Hospital between January 2018 and July 2020. Patient inclusion was performed consecutively among eligible individuals who met the study criteria during the study period in order to minimize potential selection bias. A total of 103 male patients aged between 18 and 65 years were included in the study. The patients were divided into two groups: those with first-episode schizophrenia (FES) and those with chronic schizophrenia (CS). The CS group consisted of patients previously diagnosed with

schizophrenia who had not used any antipsychotic medication within the last six months and were followed through the hospital automation system. This criterion was applied to minimize the potential effects of antipsychotic medications on inflammatory markers and lipid metabolism.

To reduce biological variability related to hormonal fluctuations that may influence lipid metabolism and inflammatory parameters, only male participants were included in the study. In particular, variations in estrogen levels and menstrual cycle phases may affect HDL-C levels and inflammatory markers; therefore, restricting the sample to male participants was intended to improve the homogeneity of the study population. Clinical information regarding the patients, including duration of illness, number of episodes, and number of hospitalizations, was obtained from the hospital automation system.

Control Group

The control group consisted of healthy male individuals who attended routine health examinations during the same time. The control group was matched to the patient group in terms of age and smoking status. Individuals in the control group were required to have no history of psychiatric disorders, chronic inflammatory diseases, metabolic disorders, cardiovascular diseases, or other systemic illnesses that could affect inflammatory or lipid parameters.

Exclusion Criteria

Participants with an acute infection, autoimmune disease, chronic inflammatory disorder, metabolic syndrome, liver or kidney disease, malignancy, or a substance use disorder were excluded from the study. Additionally, individuals who had recently used medications known to influence inflammatory markers or lipid metabolism were excluded. These medications included systemic corticosteroids, anti-inflammatory drugs, lipid-lowering agents, and immunomodulatory medications. Smoking status was obtained from medical records and recorded as a potential confounding variable.

Laboratory Measurements

A retrospective analysis of demographic characteristics, clinical data, and laboratory findings was performed using the hospital's computerized medical database. Venous blood samples were obtained from all participants after overnight fasting. Hematological parameters, including monocyte counts, and biochemical parameters, including high-density lipoprotein cholesterol (HDL-C), were measured using standard automated laboratory methods. The monocyte-to-high-density lipoprotein cholesterol ratio (MHR) was calculated by dividing the absolute monocyte count (10^3/μL) by the HDL-C level (mg/dL). As a ratio, MHR was expressed as a unitless index.

Ethical Approval: The research had the approval of the Faculty of Medicine's clinical research ethics committee, KTO Karatay University (approval number E.2345-41901325-050.99, date: 17 July 2020). Research was conducted according to the standards of the Declaration of Helsinki. No invasive procedures were performed.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), version 18.0, was used for data analysis. Categorical variables were presented as numbers and percentages, whereas continuous variables were expressed as the mean ± standard deviation (SD). The chi-square test was used to assess the associations between the categorical variables. The Kolmogorov–Smirnov test was applied to evaluate normality. One-way analysis of variance (ANOVA) was used to compare normally distributed continuous variables among the three groups, while the Kruskal–Wallis test was used for non-normally distributed variables. Post-hoc pairwise comparisons were performed using the Tukey test when the assumption of homogeneity of variances was met, and the Games–Howell test when this assumption was violated. A p-value of less than < 0.05 was considered statistically significant. Although most continuous variables were normally distributed and analyzed using parametric tests, correlation analyses were conducted using Spearman's rank correlation coefficient. This decision was made because several clinical variables (e.g., disease duration, number of hospitalizations) demonstrated skewed distributions and/or potential non-linear relationships. Therefore, a non-parametric correlation method was preferred to provide a more robust assessment of associations across variables with heterogeneous distributional properties.

Sample size estimation was performed using G*Power software (version 3.1.9.7). An a priori power analysis was conducted based on the comparison of MHR values among the three independent groups using the F-tests family and one-way ANOVA fix fixed effects, omnibus, one-way statistical test. Assuming an effect size of $f = 0.30$, an alpha error probability of 0.05, a power of 0.80 and three groups, the minimum total sample size required was calculated to be 111 participants. The present study included a total of 143 participants, indicating that the sample size was sufficient for the planned analyses.

RESULTS

The study sample consisted of 143 male participants, including 38 patients with first-episode schizophrenia (FES), 65 patients with chronic schizophrenia (CS), and 40 healthy controls (HC). For categorical variables, chi-square statistics (χ^2) are reported alongside p-values. For continuous variables analyzed using ANOVA, F-statistics are presented to provide a complete description of the statistical analyses. A statistically significant difference in age was observed between the groups ($F = 18.76$, $p < 0.001$) (see Table 1). The younger age observed in the FES group was consistent with the earlier onset of first-episode schizophrenia. Smoking status did not differ significantly between the FES and CS groups ($p = 0.081$). In the CS group, the mean duration of illness was 115.6±68.1 months. The mean number of hospitalizations was 3.4±2.0, and the mean number of relapses was 3.9±2.1. Demographic and clinical characteristics of groups are presented in Table 1.

Comparisons of hematological and biochemical parameters among the three groups are shown in Table 2. There were significant differences among the groups in platelet levels ($F = 25.04$, $p < 0.001$), monocyte levels ($F = 17.82$, $p < 0.001$), HDL-C levels ($F = 31.19$, $p < 0.001$), and MHR ($F = 34.02$, p

Table 1. Clinical and demographic characteristics of patients with schizophrenia

	FES (n=38)	CS (n=65)	HC (n=40)	χ^2/F (overal	p (overall)	χ^2/t (FES vs CS)	p (FES vs CS)
Age (years)	25±6.3	34.8±8.4	30.6±8.1	18.76	<0.001	6.21	<0.001
Smoking							
Yes	29 (76.3%)	58 (89.2%)	22 (55%)	12.23	0.002	3.05	0.081
No	9 (23.7%)	7 (10.8%)	18 (45%)				
Marital Status							
Single	35 (92.1%)	39 (60%)	-			13.67	<0.001
Married	2 (5.3%)	25(38.5%)	-				
Other	1(2.6%)	1(1.5%)	-				
Education Status							
≤8 years	16 (42.1%)	52 (80%)	-			15.65	<0.001
>8 years	22 (57.9%)	13 (20%)	-				
Disease duration	-	115.6±68.1	-				
Number of Hospitalizations	-	3.4±2.0	-				
Number of Episodes	-	3.9±2.1	-				

FES: First-episode schizophrenia; CS: Chronic schizophrenia; HC: Healthy control.
Continuous variables were expressed as mean±SD and compared using one-way ANOVA for overall group comparisons and independent samples t-test for pairwise comparisons (FES vs CS).
Categorical variables were expressed as n (%) and analyzed using the chi-square test (χ^2) for both overall and pairwise comparisons. p<0.05 was considered statistically significant.

Table 2. Comparison of blood count parameters between patients with schizophrenia and healthy controls.

	FES (n=38)	CS (n=65)	HC (n=40)	F	p	post hoc
WBC (10^3/μL)	7.1±1.2	7.4±1.3	6.8±1.6	2.33	0.100	
Hemoglobin (g/dL)	15±1.3	15.1±1.1	14.3±1.1	5.25	0.006	
Platelets (10^3/μL)	226.6±50.8	221.3±49.6	284.2±34.9	25.04	<0.001	HC > FES, HC >CS
Neutrophils (10^3/μL)	3.7±1.1	4.2±1.1	4.1±1.2	1.88	0.156	
Monocytes (10^3/μL)	0.7±0.1	0.7±0.1	0.5±0.1	17.82	<0.001	FES>HC, CS> HC
Lymphocytes (10^3/μL)	2.5±0.8	2.4±0.6	2.3±0.5	0.83	0.434	
Triglyceride (mg/dL)	102.8±38.6	112.2±41.3	101.2±32.9	1.28	0.279	
LDL-C (mg/dL)	100.7±32.9	99.4±30.7	104.8±25.5	0.40	0.666	
HDL-C (mg/dL)	41.7±9.4	38.3±7.7	50.8±6.5	31.19	<0.001	HC > FES, HC>CS
MHR	17.5±4.6	19.4±6.6	10.9±2.2	34.02	<0.001	FES>HC, CS > HC

FES: First-episode schizophrenia; CS: Chronic schizophrenia; HC: Healthy control; WBC: White blood cell; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MHR: Monocyte-to-high-density lipoprotein ratio. Statistics: One-way ANOVA was used for group comparisons. Results are presented with F-statistics and corresponding p-values. Post-hoc comparisons were performed using the Tukey test. Data are expressed as mean ± SD. p < 0.05 was considered statistically significant.
MHR was calculated as monocyte count (10^3/μL) divided by HDL-C (mg/dL) and expressed as a unitless ratio.

< 0.001). Compared with the HC group, both FES and CS patients exhibited significantly higher monocyte counts and significantly lower platelet and HDL-C levels. Mean MHR values were 17.5 ± 4.6 in the FES group, 19.4 ± 6.6 in the CS group, and 10.9 ± 2.2 in the HC group. MHR levels were significantly higher in both the FES and CS patients compared with healthy controls (p < 0.001). Given the significant age difference between the groups, an analysis of covariance (ANCOVA) was conducted with age as a covariate to control for its potential confounding effect. After adjustment for age, the difference in MHR levels between the groups remained statistically significant (p < 0.001). Post hoc pairwise comparisons using the Tukey test showed that MHR levels were significantly higher in both the FES and CS groups than in the HC group. However, no statistically significant difference was detected between the FES and CS groups. Although the mean MHR value was numerically higher in the CS group than in the FES group, no statistically significant difference was detected between these two groups. The mean difference between the CS and FES groups was 1.9, indicating a higher MHR value in the CS group; however, no evidence of a statistically significant between-group difference was detected. Comparisons of MHR and other hematological parameters among the three groups are presented in Table 2.

Correlation analyses were performed to examine the relationship between MHR levels and clinical variables in patients with chronic schizophrenia. A statistically significant positive correlation was observed between disease duration and age in the FES, CS and FES+CS groups (p<0.01). A weak positive correlation was also observed between age and MHR in the healthy control (HC) group (p: 0.03). The results of the correlation analysis showed no statistically significant

Table 3. Spearman's correlation coefficients for the groups

	Correlations	Correlation coefficient (r)	Level	p value
Patients (FES+CS)				
(n: 103)	Age-Disease duration	0.79	Strong	p<0.01
	WBC-MHR	0.31	Weak	p<0.01
FES (n: 38)	Age-Disease duration	0.43	Moderate	p<0.01
CS (n: 65)	Age-Disease duration	0.71	Strong	p<0.01
	WBC-Disease duration	0.25	Weak	0.04*
HC (n: 40)	WBC-MHR	0.53	Moderate	p<0.01
	Age-MHR	0.35	Weak	0.03*

FES: First Episode schizophrenia, CS: Chronic schizophrenia, HC: Healthy control, Statistics: Spearman's correlation test, *p<0.05, **p<0.01, For correlation analyses, the Spearman correlation coefficient (r) was considered as an effect size indicator.

link between MHR levels and either the number of hospital admissions or the number of relapses. The detailed results of the correlation analyses are presented in Table 3.

DISCUSSION

The present study demonstrated that MHR levels were significantly higher in both first-episode schizophrenia (FES) and chronic schizophrenia (CS) patients compared with healthy controls. These findings indicate that alterations in the balance between pro-inflammatory monocytes and anti-inflammatory HDL-C may be associated with schizophrenia. However, no statistically significant difference was detected between the FES and CS groups, suggesting that within the limits of the present sample size, we did not observe evidence of stage-related differences in MHR levels. Recent research suggests that inflammatory responses may contribute to the development of, and worsen the prognosis for several mental illnesses (28). Pro-inflammatory cytokines contribute to the activation of microglia. However, as cytokines and other direct inflammatory mediators were not measured in the present study; therefore, these mechanisms should be considered biologically plausible hypotheses rather than mechanisms demonstrated by the current data. This activation is strongly correlated with initiating and progressing the inflammatory process. The possibility that an aberrant immunological response contributes to the development of schizophrenia is often raised (29,30). In many clinical studies of schizophrenia patients, the detection of elevated peripheral cytokine levels in plasma is accepted as an indicator of an increased peripheral immune response (31-33). Numerous studies have consistently shown a significant increase in monocyte levels (they secrete proinflammatory and prooxidant cytokines) and total white blood cell counts (13,23). These findings have prompted the search for simple and reliable inflammatory markers that may reflect immune dysregulation in schizophrenia (10,21).

In this context, hematological inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) have been investigated as potential biomarkers in schizophrenia (10-12). Several inflammatory ratios such as NLR, PLR, and MLR have been reported to be elevated in schizophrenia and are considered indirect indicators of systemic inflammation. These findings provide a broader context for investigating composite inflammatory markers such as the MHR. Monocytes and macrophages are the cells responsible for pro-inflammatory and pro-oxidative responses. These cells are central to the initiation and regulation of inflammatory responses. Their activation triggers the production and release of inflammatory cytokines (34). On the other hand, HDL-C modulates monocyte activation and adhesion, controls the proliferation of progenitor cells that differentiate into monocytes, and increases nitric oxide synthase expression in endothelial tissue. These properties give it antioxidant and anti-inflammatory activity (35). Taken together, MHR has been proposed as a potentially useful composite inflammatory index reflecting the balance between pro-inflammatory monocytes and anti-inflammatory HDL-C (36).

Consistent with this conceptual framework, MHR has been investigated as a systemic inflammatory marker in various chronic inflammatory and vascular conditions, where elevated levels were generally interpreted as reflecting an increased inflammatory burden (16,17,37). These findings from different clinical contexts support the rationale for examining MHR in psychiatric disorders characterized by potential immune dysregulation, such as schizophrenia. However, studies evaluating MHR in schizophrenia remain limited, particularly in patients at different stages of the illness. Only a small number of studies have examined MHR in patients with schizophrenia. Sahpolat et al. reported significantly higher MHR levels in patients with schizophrenia compared to healthy controls and demonstrated a positive correlation between MHR and total PANSS scores, suggesting a relationship between inflammation and disease severity (23). In another study, Wei et al. found higher MHR levels in patients with schizophrenia compared to HC. In addition, they emphasized that MHR may be a predictor for differentiating schizophrenia patients from HC (24). Similar to our study, a 2023 study comparing the MHR levels of 85 patients with schizophrenia and 50 healthy controls and reported that the patient group had significantly higher MHR and platelet levels, and significantly lower HDL-C levels, compared to the control group (21). In another study conducted in the same year, 214 schizophrenia patients were divided into 2 groups as aggressive and non-aggressive, and it was reported that platelet, monocyte, and MHR levels of the aggressive patients were significantly higher than the non-aggressive schizophrenia group, and MHR levels may be used

to predict aggressive behavior in schizophrenia patients. They also did not compare these results with the HC (22). However, in these two studies, which were similar to our study, they did not evaluate the patient group by dividing them into two different groups as FES and CS as in our study.

According to the results of our research, MHR levels were significantly higher in people diagnosed with schizophrenia compared to HC. These findings are consistent with previous studies and are compatible with the presence of systemic inflammatory alterations reported in schizophrenia, although the present design does not allow for causal inferences regarding the role of inflammation in the pathophysiology of the disorder. However, there was no scale in the medical records to indicate the severity of the attacks. Therefore, we could not investigate the possible effect of episode severity on inflammation. In addition, age differences between the groups may have affected the results. Contrary to the findings of Sahpolat et al., no correlation was found between other clinical characteristics that might indicate disease severity and MHR levels in CS patients (23). Further studies may be needed to clarify this relationship. Unlike most previous studies, this study compared MHR levels between first-episode schizophrenia (FES) and chronic schizophrenia (CS) patients. Although the mean MHR value was numerically higher in the CS group than in the FES group, no statistically significant between-group difference was detected. Therefore, within the limits of the present sample, we did not observe any of stage-related differences in MHR levels. However, the study was not specifically powered to detect differences between patient subgroups, so the possibility of a type II error cannot be excluded. Further adequately powered prospective studies are required to determine whether inflammatory alterations differ across illness stages.

Correlation analyses revealed several associations between MHR levels and certain clinical variables. However, these relationships were modest and should be interpreted cautiously given the retrospective design and potential residual confounding. Previous studies have also reported elevated inflammatory markers in both first-episode and chronic schizophrenia, although findings regarding changes across disease progression remain inconsistent (25-27). The differences between the present findings and those reported by Sahpolat et al. (23) may be due to methodological factors such as variations in sample composition or study design, or the absence of standardized psychopathology severity scales in the present study.

Study Limitations

This study has several limitations that should be considered when interpreting the findings. Firstly, the retrospective design may introduce potential selection bias. As the sample of patients consisted of individuals who were hospitalised, the study population may represent patients with more severe clinical presentations, which may limit the generalisability of the findings to all individuals with schizophrenia. Secondly, the healthy control group was recruited from individuals attending routine health examinations, which may introduce a potential health-seeking bias. Thirdly, although smoking status was available and considered in the analyses, other potential confounding factors that may influence inflammatory markers and lipid metabolism, such as physical activity, dietary habits, and socioeconomic status, were not systematically recorded in the medical records and therefore could not be included in the analysis.

Finally, the study included only male participants in order to minimize hormonal variability that could influence lipid and inflammatory parameters. While this approach improved sample homogeneity, it may limit the generalizability of the findings to female patients with schizophrenia. Future research should employ prospective longitudinal designs that include repeated MHR measurements across relapse and remission phases, standardized psychopathology scales (e.g., PANSS or BPRS), and multivariable models adjusting for metabolic and lifestyle-related covariates. Despite these limitations, this study contributes to the limited literature examining MHR in schizophrenia and provides additional evidence to support the potential role of this accessible biomarker in inflammatory alterations associated with the disorder.

CONCLUSION

Previous studies have suggested that a high MHR may be a new biomarker for inflammatory disorders. Our study showed that MHR is significantly elevated in patients with schizophrenia. The findings of the present study demonstrate that MHR levels are significantly higher in patients with schizophrenia compared to healthy controls, supporting the growing body of evidence that schizophrenia is associated with inflammatory activation. Moreover, this study is among the first to evaluate MHR levels in patients with first-episode schizophrenia, indicating that inflammatory alterations may be present even in the early stages of the disease. Although no significant difference was observed between the first-episode and chronic schizophrenia groups, the overall elevation of MHR in patients with schizophrenia suggests that this marker may be compatible with the presence of persistent low-grade inflammatory alterations reported in schizophrenia. Future longitudinal and multicenter studies with larger and more diverse populations, incorporating standardized clinical assessments and comprehensive inflammatory panels, including cytokine profiling, are needed to clarify whether MHR reflects a stable trait marker or varies according to clinical state and treatment response, and to further evaluate its potential clinical utility as an accessible inflammatory marker.

DECLARATIONS

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RESEARCH ARTICLE

Direct Anterior Versus Posterolateral Approaches in Total Hip Arthroplasty: A Comparative Evaluation of Early and Late Clinical Outcomes

Total Kalça Artroplastisinde Direkt Anterior ve Posterolateral Yaklaşımların Karşılaştırılması: Erken ve Geç Dönem Klinik Sonuçların Değerlendirilmesi

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ABSTRACT

Objective: The direct anterior approach (DAA) and posterolateral approach (PLA) are commonly used in total hip arthroplasty (THA). This study aimed to compare these approaches in terms of complication rates and functional outcomes.

Materials and Methods: This retrospective study included 130 patients who underwent THA for primary hip osteoarthritis (DAA: 53; PLA: 77). All patients underwent preoperative radiological and comorbidity assessments. Clinical outcomes were evaluated using the Harris Hip Score (HHS), University of California Los Angeles (UCLA) Activity Score, and Visual Analog Scale (VAS) for pain preoperatively, at 3 months, and at final follow-up. Patients were followed at regular intervals for at least 1 year.

Results: There were no significant differences between groups in intraoperative blood loss, transfusion requirements, or hospital stay. Operative time was longer in the DAA group (p=0.008). The overall complication rate was higher in the DAA group (p=0.049). Both groups showed significant improvement in clinical scores over time. HHS was significantly higher in the DAA group at 3 months, but this difference diminished at final follow-up. The DAA group demonstrated higher UCLA scores at final follow-up. Multivariable regression analysis identified preoperative UCLA score as an independent predictor of final UCLA score (B=0.371; p<0.001).

Conclusions: DAA was associated with longer operative time but showed no significant disadvantage in major perioperative outcomes compared to PLA. While DAA provided an early functional benefit, long-term outcomes were comparable. Final outcomes appeared to be influenced more by patient-related factors than surgical approach. Therefore, surgical approach selection should be individualized based on patient characteristics and surgeon experience.

Keywords: Total hip arthroplasty, posterolateral approach, direct anterior approach, primary hip osteoarthritis, complications

ÖZET

Amaç: Total kalça artroplastisinde (TKA) direkt anterior yaklaşım (DAA) ve posterolateral yaklaşım (PLA) sık kullanılan tekniklerdir. Bu çalışmanın amacı, bu iki yaklaşımı komplikasyon oranları ve fonksiyonel sonuçlar açısından karşılaştırmaktır.

Gereç ve Yöntemler: Primer kalça osteoartriti nedeniyle TKA uygulanan 130 hasta retrospektif olarak incelendi (DAA: 53; PLA: 77). Tüm hastalar preoperatif radyolojik değerlendirme ve komorbiditeler açısından analiz edildi. Klinik değerlendirmede Harris Kalça Skoru (HHS), UCLA Aktivite Skoru ve Görsel Analog Skala (VAS) ağrı skoru preoperatif dönemde, postoperatif 3. ayda ve son kontrolde değerlendirildi. Hastalar en az 1 yıl süreyle düzenli aralıklarla takip edildi.

Bulgular: Gruplar arasında intraoperatif kanama miktarı, transfüzyon ihtiyacı ve hastanede kalış süresi açısından anlamlı fark saptanmadı. Operasyon süresi DAA grubunda daha uzundu (p=0.008). Toplam komplikasyon oranı DAA grubunda daha yüksekti (p=0.049). Her iki grupta da klinik skorlar zamanla anlamlı şekilde iyileşti. HHS, postoperatif 3. ayda DAA grubunda daha yüksekken, bu fark son kontrolde ortadan kalktı. Son kontrolde UCLA skorları DAA grubunda daha yüksekti. Çok değişkenli regresyon analizinde preoperatif UCLA skoru, son kontrol UCLA skorunun bağımsız belirleyicisi olarak saptandı (B=0.371; p<0.001).

Sonuç: DAA, daha uzun ameliyat süresi ile ilişkili olmakla birlikte, temel perioperatif sonuçlar açısından PLA'ya göre belirgin bir dezavantaj göstermemiştir. DAA erken dönemde fonksiyonel avantaj sağlasa da uzun dönem sonuçlar benzerdir. Nihai sonuçların cerrahi yaklaşımdan çok hasta özelliklerinden etkilendiği görülmektedir. Bu nedenle cerrahi yaklaşım seçimi, belirli bir tekniğin üstünlüğünden ziyade cerrah deneyimi ve hasta profiline göre bireyselleştirilmelidir.

Anahtar Kelimeler: Total kalça artroplastisi, posterolateral yaklaşım, direkt anterior yaklaşım, primer kalça osteoartriti, komplikasyonlar

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INTRODUCTION

Total hip arthroplasty (THA) is a frequently performed surgical procedure that improves the quality of life in patients with functional loss due to arthritic hip pain. However, it has been reported that 7%–15% of patients who undergo THA experience persistent complaints after surgery, preventing them from returning to full function and activity levels. Reasons for postoperative patient dissatisfaction include fixation failure, instability, and tissue damage related to the surgical procedure. Choosing the optimal surgical approach can help reduce these risks and improve THA outcomes (1). Although numerous studies have been conducted on this issue in recent years, the most appropriate surgical approach for THA remains debatable. The direct anterior approach (DAA) and posterolateral approach (PLA) are commonly used in THA. These approaches have their own advantages and disadvantages. The PLA is preferred because it provides an excellent field of view of the femoral shaft and has a low risk of femoral fracture. Furthermore, it can be easily expanded distally when needed. A potential disadvantage of the posterior approach is an increased risk of posterior dislocation due to cutting of the external rotator muscles (2). However, this risk can be reduced with improved closure techniques. Although there is a risk of sciatic nerve damage with the PLA, the incidence of this complication is low (2,3).

The DAA is a less invasive approach that, in theory, reduces these complications by using the intermuscular and internervous planes between the rectus femoris and tensor fascia lata muscles. It is thought that this muscle-sparing approach leads to faster, easier postoperative recovery, and better functional outcomes (4). For these reasons, the use of DAA with THA has become increasingly popular. As it has become more widespread among surgeons, the number of studies on this approach has also increased. Many researchers have reported advantages, including lower dislocation risk, less postoperative pain, shorter hospital stays, and faster functional recovery, in patients undergoing THA with DAA (5). Although good short-term results have been reported in the literature, some recent studies have shown that DAA does not provide superior long-term results compared with other approaches. In fact, some studies have reported higher rates of complications, such as nerve injuries, fractures, and infections, associated with DAA (6). Within the scope of this research, we aimed to elucidate and compare surgical approaches with respect to complication rates and functional outcomes. Briefly, early- and late-phase functional outcomes and the safety of DAA were compared with those of PLA.

MATERIALS AND METHODS

Patients

This retrospective analysis was conducted between 2018 and 2024. A total of 130 patients (58 women and 72 men) underwent THA for primary hip osteoarthritis. All patients underwent radiological evaluation, including preoperative and postoperative anteroposterior (AP) pelvic radiographs and lateral hip radiographs. Preoperative AP pelvic radiographs were used to determine limb length and offset planning, with the contralateral side as a reference. Template creation was performed using preoperative AP and lateral hip radiographs. Postoperative radiographs were obtained during routine follow-up visits to assess implant position, lateral offset difference, limb length discrepancy, and potential implant-related complications. The acetabular cup version was measured on standardized AP hip radiographs according to the method described by Lewinnek et al. (7) (Figure 1a). The acetabular cup inclination angle (Figure 1b), lateral offset difference (Figure 2a), and limb length discrepancy (Figure 2b) were assessed on postoperative AP pelvic radiographs, as demonstrated in the corresponding figures.

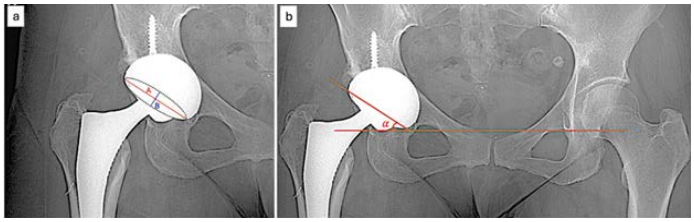

Figure 1. (a) A: The length of the long axis of the acetabular component and B: The length of the short axis of the projected ellipse, reflecting the maximum diameter of the implant. (b) The acetabular cup inclination: angle between the inter-teardrop line and the line connecting the superior and inferior rims of the acetabular component.

Each patient was evaluated for additional comorbidities preoperatively and classified according to the Charlson Comorbidity Index (CCI). For clinical evaluation, the Harris

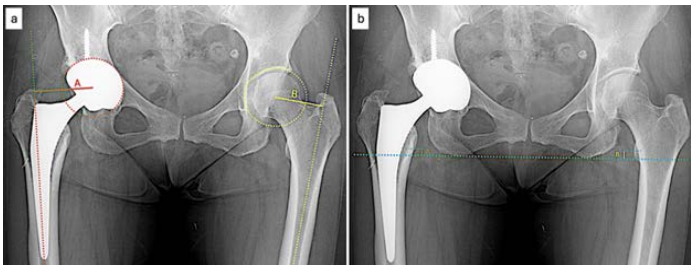

Figure 2. (a) Lateral offset difference: The perpendicular horizontal distance from the center of the femoral head to the anatomical axis of the femoral shaft (A) The same measurement was performed on the contralateral hip (B), and the difference was calculated. (b) Limb length discrepancy: The perpendicular distance from the center of the lesser trochanter to a horizontal line passing through the ischial tuberosities on operated side (A) and same measurement for contralateral hip (B), and the difference was calculated.

Hip Score (HHS), University of California, Los Angeles (UCLA) Activity Score, and Visual Analog Scale (VAS) – pain score were used preoperatively, at 3 months postoperatively, and at the final follow-up. Patients were followed up at 2 weeks, 4 weeks, 3 months, 6 months, and then at 6-month intervals for at least 1 year after surgery, and treatment success was evaluated clinically and functionally.

In addition to these data, the following data were recorded: age, sex, side of the affected area, follow-up time, surgical approach, surgical duration, use of intraoperative fluoroscopy, amount of intraoperative bleeding, need for blood transfusion, length of hospital stay, body mass index (BMI), smoking status, development of complications, and need for secondary surgery.

Surgical Procedure

In total, 53 patients underwent DAA, and 77 underwent PLA. All surgeries were performed by a single, experienced surgeon in both DAA and PLA approaches, who had completed the learning curve for these techniques during the study period. PLA was performed using the capsular closure technique described by Pellicci et al. (8). The Smith–Petersen approach, in which the anterior capsule is excised, was used for DAA. All patients received standard prophylactic antibiotics during the intraoperative and postoperative periods. The same implants were used in all patient groups, and all implants are uncemented. (Polarstem Hip Reconstruction System Smith & Nephew, Cordova, USA) Intraoperative fluoroscopy was used for appropriate component placement. During surgery, the surgeon performed the shuck test, kick test, and hip pistoning maneuvers in each patient to confirm hip stability. In the postoperative period, all patients received thromboprophylaxis, antiembolic stockings, and early mobilization to prevent venous thrombosis. The same pain control protocols were used in all patients. Patients were allowed to walk with a walker or crutches on the first postoperative day and to bear weight to the extent tolerated. Lower extremity isometric contraction exercises, hip and knee flexion-extension exercises, and exercises involving craniocaudal reciprocal movements of the pelvis were initiated in the second week postoperatively.

Patients in the PLA group were informed about the precautions to prevent posterior hip dislocation; for 1 month postoperatively, crossing the legs, hip flexion greater than 90°, and internal rotation on the operated side were not allowed. These precautions constituted the only difference in the rehabilitation protocols between the two groups. After achieving the functional range of motion, muscle strength, and stability, light sports activities were started 3 months postoperatively. To objectively evaluate the length of hospital stay, discharge criteria such as the ability to perform daily living activities without assistance, controllable pain with analgesics, no discharge from the wound site, and no abnormal findings in postoperative blood tests were applied.

Inclusion Criteria

Patients aged 50 years or older who underwent THA for primary hip osteoarthritis were included in this retrospective analysis. Patients who met the inclusion criteria underwent surgical treatment with a DAA or PLA.

Exclusion Criteria

Patients with inflammatory arthritis, hip osteonecrosis, degenerative hip dysplasia, femoral deformity, neuromuscular pathology, BMI >40 kg/m^2, previous ipsilateral hip surgery, failure to attend regular follow-up visits, or incomplete clinical records were excluded from the study.

Ethics Approval

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Declaration of Helsinki (1975, as revised in 2008). Our institution has granted ethics committee approval with protocol number (E-67961857-050.04-167783), and informed consent has been obtained from all participants.

Statistical Analysis

The distribution characteristics of continuous variables were evaluated using the Kolmogorov–Smirnov test, histogram analysis, and consideration of skewness and kurtosis values (±2). Categorical variables are presented as numbers and percentages [n (%)]. In contrast, continuous variables are presented as mean ± standard deviation for normally distributed variables and as median (interquartile range, IQR) for non-normally distributed variables. For intergroup comparisons, the Student's t-test was used for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Pearson chi-square test or Fisher's Exact test, where appropriate, was used for comparisons of categorical variables. Time-dependent changes in clinical functional scores across surgical techniques were evaluated using a mixed-design analysis of variance (mixed ANOVA), with time as the within-subject factor and surgical technique as the between-subject factor. The assumption of sphericity was evaluated using the Mauchly test. The Greenhouse–Geisser correction was applied when the assumption was not met. To control for potential confounding effects of observed differences in baseline characteristics between groups, factors affecting the final control clinical scores were evaluated using multivariable linear regression analyses. Surgical technique was included as the primary independent variable, and the relevant preoperative score, follow-up time, BMI, and CCI were used as covariates. In all statistical analyses, a two-sided p-value <0.05 was considered statistically significant.

RESULTS

Table 1 presents the distribution of demographic and surgical characteristics. No significant differences were found between the DAA and PLA groups in age, gender, BMI, smoking status, or CCI (p>0.05). The side distribution differed between the groups (p=0.011). The follow-up time was longer in the PLA group than in the DAA group (p=0.002). When surgical characteristics were evaluated, the surgical time was longer in the DAA group than in the PLA group (p=0.008). No significant differences were observed between the groups in terms of intraoperative bleeding volume, transfusion requirements, or length of hospital stay (p>0.05).

Table 1. Distribution of Demographic and Surgical Characteristics

Variables (N=130)	Total	DAA (n=53)	PLA (n=77)	P-value
Gender				0.899
Male	72 (55.4)	29 (54.7)	43 (55.8)	
Female	58 (44.6)	24 (45.3)	34 (44.2)	
Age (years)	55±11	54±11	55±10	0.356
BMI (kg/m²)	26.5±3.8	27.2±3.7	26±3.9	0.083
Side	0.011			
Right	61 (46.9)	32 (60.4)	29 (37.7)	
Left	69 (53.1)	21 (39.6)	48 (62.3)	
Smoking	15 (11.5)	5 (9.4)	10 (13)	0.533
CCI	0.810			
0	58 (44.6)	22 (41.5)	36 (46.8)	
1	57 (43.8)	25 (47.2)	32 (41.6)	
2	15 (11.5)	6 (11.3)	9 (11.7)	
Follow-up period (months)	51.7±16.5	46.3±14	55.4±17.1	0.002
Surgery time (min)	103 (97-115)	110 (100-120)	101 (97-111)	0.008
Intraoperative bleeding amount (mL)	373.3±75.6	383.4±74.3	366.4±76.2	0.208
Transfusion requirement	22 (16.9)	12 (22.6)	10 (13)	0.149
Hospital stay (days)	2.9±0.9	2.8±0.9	3±0.9	0.089

Categorical variables are presented as numbers and percentages [n (%)], and continuous variables are presented as mean ± standard deviation for normally distributed variables and as median (interquartile range, IQR) for non-normally distributed variables. † BMI: Body mass index; ‡ CCI: Charlson comorbidity index

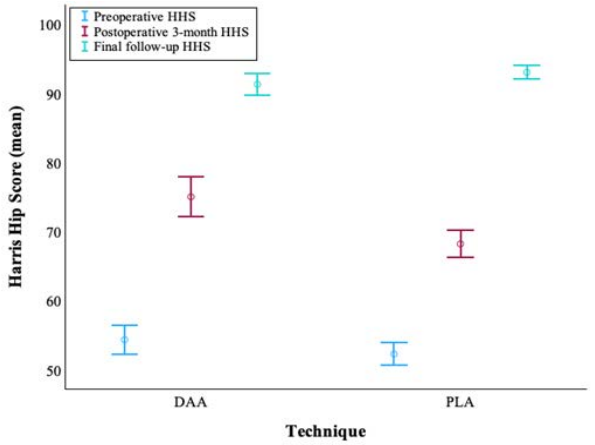

Figure 3. Time-dependent changes in mean HHS according to surgical technique. Error bars represent 95% confidence intervals.

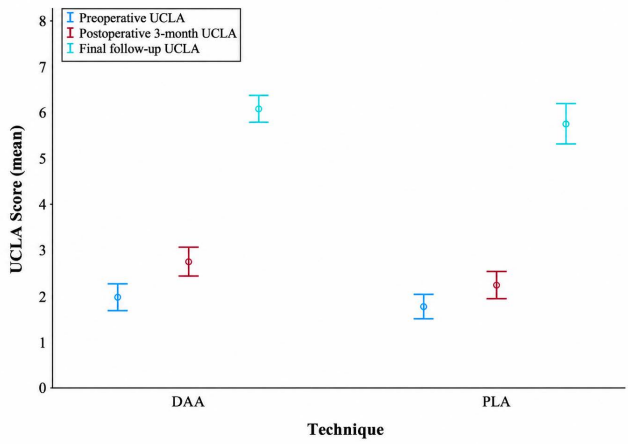

Figure 4. Time-dependent changes in mean UCLA score according to surgical technique. Error bars represent 95% confidence intervals.

Table 2 shows the time-dependent changes in clinical functional scores according to the surgical techniques applied to the patients. When evaluated using HHS (Figure 3), a significant increase over time was observed in both groups in the postoperative period (time effect, p<0.001). A significant difference was found between the DAA and PLA techniques in the overall intergroup assessment (group effect, p=0.010). Furthermore, the significant group-by-time interaction (p<0.001) indicates that the functional recovery pattern differs across surgical techniques. Looking at the mean values, HHS were higher in the DAA group, especially at the 3rd postoperative month, compared with the PLA group, and the difference between the groups decreased at the last follow-up. When UCLA activity scores (Figure 4) were examined, a significant increase was observed in both groups over time (p<0.001). A significant difference was found between the DAA and PLA groups in overall scores (p=0.008), and the group-by-time interaction was also significant (p=0.008). At the last follow-up measurements, the mean UCLA scores in the DAA group were higher than those in the PLA group. In terms of VAS

Table 2. Time-Dependent Changes in Clinical Scores

Variables (N=130)	DAA (n=53)	PLA (n=77)	P-value (Group)	P-value (Time)	P-value (Group x Time)
HHS			0.010	<0.001	<0.001
Before surgery	54.4±7.4	52.3±7.4			
3rd month post-operative	75.1±10.5	68.3±8.5			
Final follow-up	91.4±5.5	93.1±4.4			
UCLA activity score			0.008	<0.001	0.008
Before surgery	1.93±0.59	1.78±0.46			
3rd month post-operative	2.72±0.74	2.24±0.68			
Final follow-up	6.06±0.63	5.75±0.99			
VAS			<0.001	<0.001	0.142
Before surgery	5.9±0.7	6.5±1.1			
3rd month post-operative	1.3±0.9	1.5±0.8			
Final follow-up	0.4±0.2	0.8±0.7			

Changes over time were analyzed using repeated measures ANOVA. † HHS: Harris Hip Score; †† UCLA: University of California Los Angeles; ††† VAS: Visual Analog Scale

Table 3. Radiological Evaluation

Variables (N=130)	Total	DAA (n=53)	PLA (n=77)	P-value
Anteversion	18.5±4.2	16.2±4	20±3.7	<0.001
Inclination	43.4±3.3	45.3±2.5	42±3.2	<0.001
Lateral offset difference (mm)	0.4±1.5	0.3±1.5	0.5±1.5	0.478
Limb length discrepancy (mm)	0.3±1.6	0±1.7	0.5±1.5	0.068

Categorical variables are presented as numbers and percentages [n (%)], and continuous variables are presented as mean ± standard deviation

Table 4. Complications

	DAA Group n (%)	PLA Group n (%)	Total n (%)	P- value
Complications	8 (15.1)	3 (3.9)	11 (8.5)	0.049
Dislocation	-	1 (1.3)	1 (0.8)	
Infection	2 (3.8)	-	2 (1.5)	
Intraoperative fracture	1 (1.9)	1 (1.3)	2 (1.5)	
Wound healing problem	5 (9.4)	1 (1.3)	6 (4.6)	
Secondary surgery	2 (3.8)	-	2 (1.5)	0.164

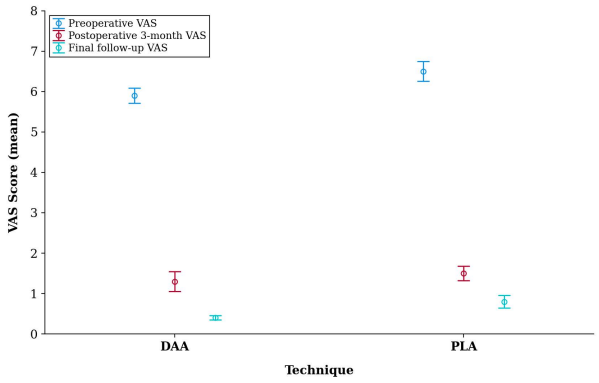

Figure 5. Time-dependent changes in mean VAS score according to surgical technique. Error bars represent 95% confidence intervals.

pain scores (Figure 5), a significant decrease was observed in both groups in the postoperative period (time effect, p<0.001). Although a significant difference was found between the groups in overall pain levels (group effect, p<0.001), the lack of a significant group-by-time interaction (p=0.142) indicates that the reduction in pain occurred similarly across the surgical techniques over time.

Radiological evaluations are presented in Table 3. Significant differences were found between the groups in terms of anteversion and inclination angles on radiological evaluation (p<0.001). However, no significant difference was observed between the groups in terms of lateral offset difference and limb length discrepancy (p>0.05). Complications are presented in Table 4. The total complication rate was higher in the DAA group than in the PLA group (p=0.049). No significant difference was found between the groups regarding the need for secondary surgery (p=0.164). Low rates of dislocation, infection, intraoperative fracture, and wound healing problems

Table 5. Multivariable Linear Regression Analysis of Factors Affecting the Final Control Clinical Score

Variables	B	Standard Error	t	P-value
HHS				
Pre-operative HHS	0.025	0.060	0.420	0.675
Technique (DAA vs PLA)	1.610	0.953	1.690	0.094
Follow-up time	0.472	0.568	0.348	0.278
BMI	0.009	0.028	0.323	0.747
CCI	0.382	0.898	0.425	0.671
Model Summary: R=0.183; R^2=0.034; Adjusted R^2=0.003; F=1.086; p=0.366				
UCLA activity score				
Pre-operative UCLA	0.371	0.086	4.329	<0.001
Technique (DAA vs PLA)	0.908	0.661	1.374	0.172
Follow-up time	0.648	0.382	0.442	0.536
BMI	-0.003	0.019	-0.176	0.860
CCI	0.793	0.624	1.270	0.206
Model Summary: R=0.411; R^2=0.169; Adjusted R^2=0.142; F=6.334; p<0.001				
VAS				
Pre-operative VAS	-0.100	0.064	-1.576	0.117
Technique (DAA vs PLA)	0.478	0.134	3.564	<0.001
Follow-up time	0.694	0.824	0.126	0.745
BMI	-0.003	0.004	-0.673	0.502
CCI	0.057	0.122	0.463	0.644
Model Summary: R=0.323; R^2=0.104; Adjusted R^2=0.076; F=3,643; p=0.008				

† HHS: Harris Hip Score; †† UCLA: University of California Los Angeles; ††† VAS: Visual Analog Scale; †††† BMI: Body mass index; ††††† CCI: Charlson comorbidity index
Technique was entered as a categorical factor variable (Reference: DAA).

were observed in both groups.

Table 5 presents the results of the multivariable linear regression analysis evaluating the factors affecting the final control clinical scores. The model created was found to be statistically insignificant (F=1.086; p=0.366) for HHS. No independent effects of preoperative HHS, surgical technique, follow-up time, BMI, and CCI variables were found on the final control HHS (p>0.05). However, the models created for the UCLA activity score (F=6.334; p<0.001) and VAS score (F = 3.643; p = 0.008) were found to be statistically significant. According to the analysis results, the preoperative UCLA score was identified as an independent predictor of the final control UCLA score (B=0.371; p<0.001). No independent effects of surgical technique, follow-up time, BMI, and CCI variables on final control UCLA scores were observed (p>0.05). The analysis revealed that the surgical technique was an independent predictor of the final control VAS score (B=0.478; p<0.001). Preoperative VAS score, follow-up time, BMI, and CCI variables did not have an independent effect on the final control VAS scores (p >0.05).

DISCUSSION

In our study, the lack of differences between the DAA and PLA groups in terms of age, sex, body mass index (BMI), smoking status, and CCI in patients undergoing THA is consistent with the literature, which shows that these two approaches are generally applied in similar patient populations. Retrospective cohort and meta-analysis studies, in particular, have reported that surgical approach preference is largely determined by the surgeon's experience and center preference, while demographic and comorbidity profiles do not differ significantly (9, 10). Although the difference in side distribution points to a possible methodological bias, there is no strong evidence that it directly affects clinical outcomes; therefore, while reporting it is important in interpreting the results, it does not appear to be a major confounding variable. The longer follow-up period in the PLA group can be explained by the fact that DAA is a relatively new technique with a more pronounced learning curve, as reported in the literature. The fact that the PLA approach has been used as a "traditional" method for a longer time in many centers results in PLA cohorts with longer follow-up data. This situation requires careful interpretation, especially when comparing late-stage complications and revision rates. This is because shorter follow-up periods in the DAA group can cause late-onset problems to appear lower than they actually are. Meta-analyses also highlight that a significant portion of studies on DAA focus on short- and medium-term outcomes, while long-term data are relatively limited.

The finding that surgical time was significantly longer in the DAA group is consistent with the existing literature. Both in single-surgeon series and multicenter studies, DAA has been reported to be associated with longer operation times than PLA, especially in the early stages of the learning curve, and that this difference may decrease but not completely disappear as experience increases (10-12). While some studies have shown that DAA is associated with greater intraoperative blood loss in addition to longer surgical time (13), it is noteworthy that no difference was found in the amount of bleeding and transfusion needs in our series. This finding is further supported

by recent studies reporting comparable perioperative blood loss between different surgical approaches (14-16). It may be related to the surgeon's experience, hemostasis techniques, anesthesia protocols, and blood transfusion thresholds applied in our center, and suggests that DAA is not necessarily associated with "greater blood loss," and that this disadvantage can be minimized with appropriate surgical and perioperative management. The lack of difference between the groups in terms of length of stay is somewhat at odds with some meta-analyses and cohort studies in the literature. Many studies have reported that DAA is associated with shorter hospital stays and faster early functional recovery (10,15); however, this advantage can be diminished in centers with standardized rehabilitation protocols, early mobilization policies, and strict discharge criteria. Our data suggest that similar rehabilitation and discharge algorithms were applied to both approaches in our center, and that the surgical approach alone did not determine the length of stay. From this perspective, this study provides a nuanced contribution, consistent with the literature, showing that the theoretical advantages of DAA become clinically apparent only when considered in conjunction with organizational and rehabilitation processes.

These results reflect the functional outcomes of THA between the DAA and PLA groups, consistent with the literature; however, this remains a topic of debate. Our study showed that HHS increased significantly over time in both groups. However, a clear superiority of the DAA group was observed, particularly at 3 months postoperatively, with the difference decreasing at the final follow-up. This pattern aligns with numerous studies reporting an early functional gain advantage for DAA, with scores converging in the medium-to long-term. A 2025 review reported that DAA provided a significant advantage over the posterior approach in terms of HHS, especially at early follow-ups (2–6 weeks); however, the difference disappeared by 6–12 months (12,17,18). Similarly, in the retrospective study by Wang et al. [10], HHS were significantly higher in the DAA group than in the PLA group at 6 weeks, 3 months, and 6 months; but the long-term difference was minimized. In our findings, the significant difference in favor of DAA at 3 months and the decrease in this difference at the last follow-up can be interpreted as a typical pattern reflecting the muscle-sparing and early mobilization advantages of DAA, as well as the "catch-up" potential of the PLA group over time. The significant group × time interaction statistically confirms this "early advantage–late convergence" pattern described in the literature.

The significant increase in UCLA activity scores over time in both groups is an expected result, consistent with pain reduction and increased functional capacity after TKA. However, the fact that the DAA group demonstrated higher UCLA scores than the PLA group at the final follow-up can be explained by the literature, even though the UCLA activity score has been evaluated in a limited number of studies. This may be explained by the muscle-sparing nature of DAA, which uses an intermuscular interval without detaching muscles, whereas the posterior approach involves splitting the gluteus maximus and releasing the short external rotators, leading to greater soft-tissue disruption. Wang et al. (10) reported that the DAA group achieved lower early postoperative muscle damage, higher muscle strength, and better hip joint function (including pain level, activity capacity, activities of daily living, and overall activity degree). In that study, postoperative creatine kinase (CK) levels were significantly lower in the DAA group than in the PLA group, and a significant negative correlation was identified between CK levels measured at 48 h and the 6-month HHS. This finding suggests that early muscle damage may be associated with long-term functional outcomes. Furthermore, the study reported that muscle strength values were significantly higher in the DAA group on postoperative days 4 and 7; on day 7, pain level, activity capacity, activities of daily living, and overall hip function were also superior in the DAA group compared with those in the PLA group. These early advantages may translate into a positive impact on long-term functional capacity. Accordingly, the higher late-term UCLA activity scores observed in the DAA group in our study support this interpretation. Although many studies have reported comparable overall functional scores in the long term (12,15,17), a sustained advantage in favor of DAA may be evident in measures that more sensitively assess activity level. Therefore, the higher end-stage UCLA scores in the DAA group can be considered a unique and hypothesis-generating finding of our study; it would be appropriate to discuss this alongside factors such as patient profile, rehabilitation protocols, and surgeon experience (13,19).

The significant decrease in VAS pain scores over time in both groups and the insignificant group × time interaction indicate that the pattern of pain improvement follows a similar course, independent of the surgical approach. Although differences in general pain levels were observed between the groups, the parallelism of the time-course curves suggests that the long-term effects of DAA and PLA are similar. Some studies have reported that DAA is associated with lower VAS pain scores on postoperative days 1 and 2 compared to the posterior approach (14,17). In contrast, other investigations have found no significant difference between surgical approaches during the early postoperative period (days 1 and 2) (20). Furthermore, Peng et al. (17) reported no difference in pain scores between the groups at the 1-year postoperative follow-up. Although detailed VAS data for the early postoperative period are not reported in our study, the strong time effect and insignificant interaction are consistent with the "small early advantage – equalization in the long term" model in the literature. In this respect, the general opinion that the choice of surgical approach affects early postoperative comfort and rehabilitation speed more than the long term in terms of pain is supported.

The significant differences in the anteversion and inclination angles between the DAA and PLA groups in our study suggest that the placement of the acetabular component is particularly sensitive to the surgical approach. While Sun et al.'s (9) meta-analysis comparing DAA and PLA did not report a significant difference in inclination, it highlighted that acetabular component anteversion was higher in the PLA group in some

studies and that a more "controlled" anteversion could be achieved with DAA. Surgeons who prefer the anterior approach avoid excessive anteversion to reduce the risk of anterior dislocation. Nevertheless, conflicting results exist in the literature; some studies have reported greater cup anteversion with the DAA, although this difference did not reach statistical significance (21). In contrast, Barrett et al. (22) found a greater inclination and lower anteversion with DAA, suggesting that these differences are likely surgeon-dependent. From this perspective, the anteversion and inclination differences observed in our study are consistent with the literature, suggesting that fluoroscopy use and patient positioning may influence component placement.

Furthermore, these findings may reflect the deliberate component positioning strategies adopted by the surgeon to remain within the safe zone and minimize the risk of dislocation associated with the selected surgical approach. Although DAA has been theoretically suggested to provide superior component control and limb length restoration, no significant differences were observed between the groups regarding lateral offset difference or limb length discrepancy in our study. This finding is consistent with the current literature (9,13,21). The absence of significant differences between the groups in terms of lateral offset restoration and limb length discrepancy, both of which are known to affect hip biomechanics and postoperative function, together with the fact that the mean anteversion and inclination values in both groups were within the accepted safe zones, suggest that the observed radiological differences may not have had a clinically meaningful impact on functional outcomes. Overall, our findings support the prevailing view in the literature that both approaches can provide comparable radiological and clinical outcomes when performed by experienced surgeons using modern planning and measurement techniques.

Complications occurred in 8.5% (n=11) of the patients included in the study. Early infections requiring secondary surgical intervention were observed in two patients in the DAA group, which is consistent with previous studies reporting that prolonged operative time is associated with an increased risk of surgical site infection (23,24). Although the posterior approach has classically been associated with a higher risk of dislocation, this difference has been reported to decrease significantly with the development of capsular and soft-tissue repair techniques. (8) The absence of a significant difference between the groups in terms of the need for secondary surgery suggests that most complications were minor in nature.

The low rates of dislocation, infection, intraoperative fracture, and wound-healing problems observed in both groups in our series are consistent with the data reported from high-volume centers and are likely related to surgeon experience, appropriate patient selection, and the standardization of perioperative protocols (9,13). This finding supports the literature suggesting that complication rates can be kept low when proper surgical techniques and perioperative protocols are applied, regardless of the surgical approach (2). Nevertheless, in our study, the significantly higher overall complication rate observed in the DAA group than in the PLA group (p=0.049) is consistent with studies highlighting the technical challenges associated with the DAA approach (9). Previous studies have shown that the risk of postoperative complications may increase during the surgeon's learning curve when performing DAA (25,26). In the large-scale meta-analysis by Sun et al. [9], although all surgeons performing THA via DAA were reported to have extensive experience, higher complication rates were still observed in the DAA group than in the PLA group. Therefore, it has been emphasized that DAA is a technically more demanding approach that should be performed by experienced hip surgeons and may be associated with higher complication rates during the initial adoption phase.

In our study, the significant positive effect of the preoperative UCLA activity score on postoperative activity levels indicates that patients with higher preoperative activity levels tend to achieve higher levels of physical activity in the postoperative period. This finding is consistent with previous studies reporting that insufficient physical activity prior to total hip or knee arthroplasty is a strong predictor of persistent limitations in physical activity at 6 and 12 months after surgery (27-29). Therefore, we believe that interventions aimed at increasing physical activity in the preoperative period may have significant potential for improving postoperative activity levels. Current evidence has shown that preoperative rehabilitation improves muscle strength and gait function and facilitates earlier postoperative mobilization in patients (30,31).

Strengths and Limitations

This study has several strengths. First, all procedures were performed by a single experienced surgeon who had completed the learning curve for both approaches, thereby minimizing variability related to the surgical technique. Second, perioperative management, rehabilitation protocols, pain control strategies, and discharge criteria were standardized for all patients, reducing potential confounding factors associated with postoperative care. In addition, both clinical (HHS, UCLA, and VAS) and radiological parameters were comprehensively evaluated, allowing a multidimensional assessment of surgical outcomes. The use of multivariable regression analysis to evaluate factors affecting final clinical outcomes further strengthened the analytical framework of the study.

Nevertheless, several limitations should be acknowledged. The retrospective design may have introduced selection bias and limited causal inferences. The study was conducted at a single center with a relatively moderate sample size, which may have affected the generalizability of the findings. Finally, the lack of randomization in surgical approach selection may have introduced treatment allocation bias.

CONCLUSION

This study demonstrated that both approaches in THA can provide safe and satisfactory clinical, functional, and radiological outcomes when appropriate surgical planning is applied. Although DAA provided some early functional advantages, long-term outcomes were largely comparable

between the two approaches. Therefore, neither approach could be considered clearly superior based on the findings of the present study.

DECLARATIONS

Conflict of Interest: *The authors declare that they have no conflict of interest.*

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OPEN

RESEARCH ARTICLE

Pertrochanteric Femur Fractures in Adults Younger Than 65: A Retrospective Analysis of Outcomes After Proximal Femoral Nailing

Altmış Beş Yaşından Küçük Erişkinlerde Pertrokanterik Femur Kırıkları: Proksimal Femur Çivileme Sonrası Sonuçların Retrospektif Analizi

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ABSTRACT

Objective: This study aimed to evaluate fracture healing patterns and factors affecting outcomes in patients under 65 years of age who were treated with proximal femoral nail (PFN) fixation for pertrochanteric femur fractures.

Materials and Methods: A retrospective analysis was conducted on 158 patients under 65 years of age treated with PFN fixation between 2013 and 2024. Demographic data, trauma mechanisms, fracture classifications, reduction quality, bone quality, presence of femoroacetabular impingement (FAI), osteoarthritis progression, and complication rates were evaluated.

Results: The mean age was 51.1 years and 63.3% of the patients were male. High-energy trauma was the leading mechanism (43%), particularly in male patients ($p<0.01$). Good reduction quality was significantly associated with earlier mobilization ($p<0.05$). FAI lesions were present in 39.9% of patients, and cam- or pincer-type FAI was more frequently associated with low-energy trauma ($p=0.06$). Osteoarthritis progression was observed in 35.4% of patients, but no significant associations were found with reduction quality, bone quality, or the presence of coxa valga. The complication rate was 24.1%, with heterotopic ossification being the most common type of complication. Smoking was significantly associated with delayed healing ($p<0.05$).

Conclusions: Pertrochanteric femur fractures in patients younger than 65 are more commonly associated with high-energy trauma and occur more frequently in male individuals. Reduction quality was significantly associated with earlier mobilization. Although preoperative FAI was more frequently observed in patients with low-energy trauma, the association was not statistically significant. These findings highlight the importance of fracture characteristics and reduction quality for functional recovery in younger patients.

Keywords: Pertrochanteric femur fracture, proximal femoral nail, young adult, femoroacetabular impingement

ÖZET

Amaç: Bu çalışmanın amacı, pertrokanterik femur kırığı nedeniyle proksimal femoral çivi (PFN) ile tedavi edilen 65 yaş altı hastalarda kırık kaynama paternlerini ve klinik sonuçları etkileyen faktörleri değerlendirmektir.

Gereç ve Yöntemler: 2013–2024 yılları arasında PFN ile tedavi edilen 65 yaş altı 158 hasta retrospektif olarak incelendi. Hastaların demografik verileri, travma mekanizması, kırık sınıflaması, redüksiyon kalitesi, kemik kalitesi, femoroasetabular impingement (FAİ) varlığı, osteoartrit progresyonu ve komplikasyon oranları değerlendirildi.

Bulgular: Hastaların ortalama yaşı 51.1 yıl olup, %63.3'ü erkekti. En sık travma mekanizması yüksek enerjili travma (%43) olup, özellikle erkek hastalarda daha sık görüldü ($p<0.01$). Ortalama kırık kaynama süresi 2.3 ay olarak saptandı. İyi redüksiyon kalitesi, erken mobilizasyon ile anlamlı olarak ilişkiliydi ($p<0.05$). Hastaların %39.9'unda FAİ lezyonu mevcuttu ve cam veya pincer tipi FAİ'nin düşük enerjili travma ile daha sık ilişkili olduğu görüldü ($p=0.06$). Osteoartrit progresyonu hastaların %35.4'ünde izlenmiş olup; redüksiyon kalitesi, kemik kalitesi veya coxa valga varlığı ile anlamlı bir ilişki saptanmadı. Komplikasyon oranı %24.1 olup, en sık görülen komplikasyon heterotopik ossifikasyondu. Sigara kullanımı gecikmiş kaynama ile anlamlı olarak ilişkili bulundu ($p<0.05$).

Sonuçlar: 65 yaş altı hastalarda pertrokanterik femur kırıkları daha sıklıkla yüksek enerjili travma ile ilişkilidir ve erkeklerde daha sık görülür. Redüksiyon kalitesi, daha erken mobilizasyon ile anlamlı derecede ilişkiliydi. Ameliyat öncesi FAI düşük enerjili travma geçiren hastalarda daha sık gözlemlenmiş olsa da, bu ilişki istatistiksel olarak anlamlı değildi. Bu bulgular, genç hastalarda fonksiyonel iyileşmede kırık özelliklerinin ve redüksiyon kalitesinin önemini vurgulamaktadır.

Anahtar Kelimeler: Pertrokanterik femur kırığı, proksimal femoral çivi, genç yetişkin, femoroasetabüler sıkışma

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INTRODUCTION

Hip fracture is a serious public health issue, causing disability in more than four million individuals annually. Approximately half of these fractures occur in the trochanteric region (1,2). The incidence varies according to bone quality, the morphological characteristics of the bone, and age (3). Since individuals between the ages of 70 and 80 years are at highest risk, studies in the literature have primarily focused on pertrochanteric fractures in the elderly population (4). In these patients, various complications may occur due to the quality of reduction, comorbidities, and smoking habits, which in turn affect remobilization and the healing duration of the fracture (5).

As nearly all studies in the literature focus on the elderly population, we have not encountered previous research analyzing pertrochanteric fractures in younger populations. The aim of this study is to examine the healing patterns of fractures in patients under the age of 65 who were treated with proximal femoral nail (PFN) fixation due to pertrochanteric fracture and to identify the factors influencing those patterns.

MATERIALS AND METHODS

Patients under the age of 65 diagnosed with pertrochanteric fractures between 2013 and 2024, who had at least 6 months of follow-up and were treated with PFN fixation, were included in this study. Patients with pathological fractures, insufficient follow-up duration, missing data, preoperative immobility, previous surgery on the contralateral hip, or hip joint conditions such as Perthes disease or developmental dysplasia were excluded.

The study was approved by the institutional ethics committee and all procedures were conducted in accordance with the Declaration of Helsinki. Informed consent for the academic use of clinical data was obtained from all patients at the time of hospitalization. Demographic data were recorded for all patients. Mechanisms of trauma were categorized into two groups: simple falls from the same level and high-energy trauma. Fractures were confirmed via radiographs and classified according to the Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification. The quality of reduction was graded based on the Baumgartner criteria (6). The degree of osteoporosis in the contralateral hip was assessed using the Singh index. Bone mineral density was primarily assessed from radiographs using the Singh index. Dual-energy X-ray absorptiometry (DEXA) measurements were not routinely available for all patients due to the retrospective nature of the study. Therefore, DEXA data were analyzed only for patients for whom prior measurements were available. The collodiaphyseal angle and center–edge angle (CEA) of the contralateral hip were measured. The presence and type of femoroacetabular impingement (FAI), as well as the presence or progression of osteoarthritis in the fractured hip, were evaluated preoperatively and at the final follow-up according to the Kellgren–Lawrence classification. FAI was evaluated using preoperative and postoperative anteroposterior and lateral hip radiographs. Cam-type FAI was identified by the asphericity of the femoral head–neck junction, while pincer-type FAI was defined by radiographic signs of acetabular overcoverage. Osteoarthritis progression was evaluated using the Kellgren–Lawrence classification by comparing radiographs obtained at the time of fracture with those at the final follow-up visit. Progression was defined as an increase in Kellgren–Lawrence grade between baseline and the last available radiographic assessment. Follow-up duration was not standardized across patients, and all available final follow-up radiographs were used for analysis.

In cases of ambiguity in radiographic interpretation, all images were independently reviewed by two authors and a consensus was reached through joint evaluation. All surgical procedures were performed by experienced orthopedic surgeons within the same clinic. A single type of PFN was used for all patients. Data on complications during follow-up, comorbidities, smoking status, the season in which the trauma occurred, time to unsupported mobilization, Charlson Comorbidity Index (CCI) (7), and fracture healing time were also recorded. Healing was defined radiographically by callus formation or clinically by the patient's ability to mobilize without support and the absence of hip pain during movement. Comorbidities were categorized as follows: Group 1 included patients without any comorbid conditions; Group 2 included patients with systemic diseases such as hypertension, diabetes, or heart failure; Group 3 included patients with neurological diseases such as multiple sclerosis, cerebrovascular events, or Parkinson's disease; and Group 4 included patients with other conditions not fitting the previous categories, such as hypo/hyperthyroidism.

Statistical Analyses

Data were analyzed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA). Chi-square tests were conducted to assess qualitative parameters. Parametric variables were compared using Student's t-test, while non-parametric variables were analyzed using the Mann–Whitney U test or Kruskal–Wallis test as appropriate. Spearman's correlation coefficient was employed to assess relationships between quantitative variables, while Pearson's correlation coefficient was utilized to evaluate associations among categorical variables. A value of 1 signifies a perfect positive correlation, whereas a value of -1 indicates a perfect negative correlation. Quantitative variables were expressed as mean ± standard deviation and minimum and maximum values. Qualitative variables were expressed as frequencies or ratios. Values of $p<0.05$ were accepted as indicating statistical significance.

RESULTS

A total of 158 patients were included in this study, comprising 58 female patients (36.7%) and 100 male patients (63.3%). The mean age of all patients was 51.1 years (range: 17–65); the mean age was 55 years for female patients and 48.8 years for male patients. The mean follow-up duration was 20.8 months. The mean time to union was 2.3 months (range: 1–16). The distribution of patients according to the AO classification is presented in Table 1. Seasonal distribution analysis revealed that 25.3% of the fractures occurred in winter, 20.9% in spring,

Table 1. Number of patients in AO classification groups

AO classification	n (%)
3A11	5 (3%)
3A12	25 (15%)
3A13	9 (5%)
3A21	8 (5%)
3A22	38 (24%)
3A23	22 (13%)
3A31	20 (12%)
3A32	10 (6%)
3A33	21 (13%)

Table 2. Patient characteristics and FAI findings

Parameter	Category	Number of patients
FAI lesions	No lesion	95
FAI lesions	Pincer-type	31
FAI lesions	Cam-type	32
Smoking status	Non-smoker	89
Smoking status	Smoker	69
DEXA results (n=35)	Osteopenia	19
DEXA results (n=35)	Osteoporosis	16

Table 3. Comorbidity distribution

Comorbidity category	n (%)
No comorbidities	72 (45.5%)
Systemic diseases *	58 (36.7%)
Neurological diseases **	14 (8.9%)
Others	14 (8.9%)

*: Hypertension, diabetes mellitus, heart failure
**: Cerebrovascular events, multiple sclerosis, Parkinson's disease

Table 4. Complication rates

Complication type	n (%)
No complications	120 (75.9%)
Screw-related complications	6 (3.8%)
Peri-implant fractures	4 (2.5%)
Wound drainage or infection	3 (1.9%)
Heterotopic ossification	22 (13.9%)
Nonunion	3 (1.9%)

32.9% in summer, and 20.9% in autumn. Ninety patients (57%) sustained fractures due to low-energy trauma (simple falls), while 68 patients (43%) sustained high-energy trauma.

The distribution of FAI types, smoking status, and bone mineral density findings are summarized in Table 2. The distribution of patient comorbidities is summarized in Table 3. The mean collodiaphyseal angle was 137.9° (range: 123–156°) and the mean CEA was 42.6° (range: 21.5–67.5°). The mean time to unsupported mobilization was 2.3 months (range: 1–12 months). The encountered complications are shown in Table 4. No complications were observed in 120 patients (75.9%). Coxa valga was present in 62 patients (39.2%). All complications except heterotopic ossification were observed in patients aged

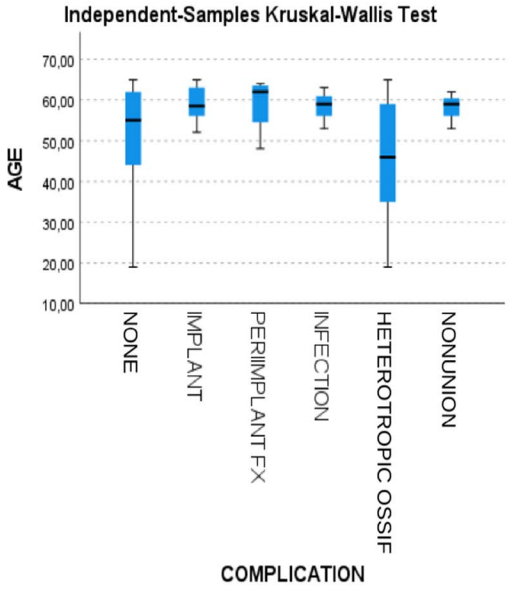

Figure 1. Relationship between age and complications

50 years or older (Figure 1). Comparing trauma mechanisms by gender, it was observed that 22% of female patients experienced high-energy trauma compared to 55% of male patients. This difference was statistically significant (chi-square test, $p<0.001$) (Figure 2). Analyzing the relationship between trauma mechanism and age, the mean age of patients who sustained injuries from simple falls was found to be 57 years, while the mean age of those who sustained high-energy trauma was 43 years, and this difference was statistically significant (Mann–Whitney U test, $p<0.001$).

When trauma mechanisms were analyzed according to FAI type, low-energy trauma was observed in 48 patients (50%)

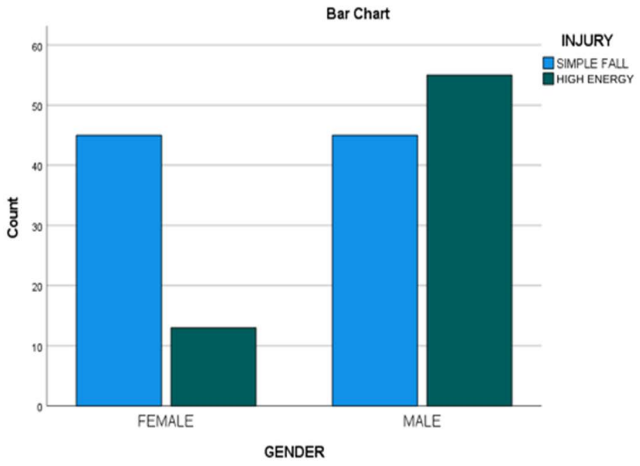

Figure 2. Relationship between gender and trauma mechanism

Table 5. Relationship between Singh index grade and trauma mechanism

Singh index grade	Low-energy trauma, n (%)	High-energy trauma, n (%)	Total	p
Grade 1	6 (75%)	2 (25%)	8	
Grade 2	22 (88%)	3 (12%)	25	
Grade 3	22 (66%)	11 (33%)	33	
Grade 4	36 (56%)	28 (43%)	64	
Grade 5	4 (14%)	24 (85%)	28	
Total	90	68	158	<0.050

Table 6. Factors associated with osteoarthritis (OA) progression

Variable	OA progression, n (%)	No OA progression, n (%)	p
Overall	56 (35.4%)	102 (64.6%)	—
Coxa valga			
Present	35.5%	64.5%	0.990
Absent	35.4%	64.6%	
Reduction quality			
Good	28 (50%)	64 (62%)	
Moderate	27 (48%)	37 (36%)	
Poor	1 (2%)	1 (2%)	0.291
Singh index grade			
Grade 1	4 (7%)	4 (3%)	
Grade 2	7 (12%)	18 (17%)	
Grade 3	10 (17%)	23 (22%)	
Grade 4	25 (44%)	39 (38%)	
Grade 5	10 (17%)	18 (17%)	0.729

without FAI, 23 patients (74%) with pincer-type FAI, and 19 patients (59%) with cam-type FAI, whereas high-energy trauma occurred in 47, 8, and 13 patients, respectively. No statistically significant association was found between trauma mechanism and FAI type (chi-square test, p=0.060).

Low-energy trauma occurred in 75% of patients with Singh grade 1, 88% with grade 2, 66% with grade 3, 56% with grade 4, and 14% with grade 5 bone quality. Thus, a statistically significant association was found between Singh index grade and trauma mechanism (chi-square test, p<0.050), with lower Singh grades being more frequently associated with low-energy trauma (Table 5). According to the Baumgartner classification, 92 patients had good reduction, 64 had moderate reduction, and 2 had poor reduction. Time to mobilization differed significantly among the reduction quality groups (Kruskal–Wallis test, p<0.001). Patients with good reduction experienced the shortest mobilization time (mean rank: 63.24), followed by those with moderate reduction (mean rank: 101.43) and poor reduction (mean rank: 125.50), respectively. The mean time to union was 1.98±1.03 months for non-smokers and 2.93±2.24 months for smokers, reflecting a significantly prolonged healing time among smokers (Mann–Whitney U test, p=0.002).

Regarding postoperative changes in osteoarthritis, 56 patients (35.4%) demonstrated progression in osteoarthritic grading. Osteoarthritis progression occurred in 35.5% of patients with coxa valga and 35.4% without coxa valga; thus, no significant association was detected (chi-square test, p=0.990) (Table 6). Osteoarthritis progression occurred in 28 patients (50%) with good reduction, 27 patients (48%) with moderate reduction, and one patient (2%) with poor reduction. No statistically significant association was found between reduction quality and osteoarthritis progression (chi-square test, p=0.291) (Table 6). However, osteoarthritis progression was numerically more frequent in patients with moderate or poor reduction. No statistically significant association was found between Singh index grade and osteoarthritis progression (chi-square test, p=0.729) (Table 6). Similarly, CCI scores did not differ significantly between patients with and without osteoarthritis progression (mean ranks: 74.95 vs. 82.00; Mann–Whitney U test, p=0.344).

When the relationship between complications and the Singh index was evaluated, no statistically significant difference was found (chi-square test, p=0.478). No complications occurred in 59% of patients with high Singh grades (grades 4 and 5) and 41% of patients with low Singh grades (grades 1, 2, or 3). Similarly, when complications were compared according to CCI scores, no statistically significant difference was found (Mann–Whitney U test, p=0.118), although numerically higher CCI scores were observed in patients with complications. No significant correlation was found between CCI and time to mobilization (Spearman's rho test, p=0.673).

DISCUSSION

While pertrochanteric femoral fractures are a particularly significant health issue in the elderly population, they are also

an important cause of disability in younger individuals. These fractures have been extensively evaluated in patients over the age of 65, but studies focusing exclusively on younger populations while excluding elderly patients, and particularly studies investigating healing outcomes and associated factors, remain limited in the literature (4). In the elderly, low-energy traumas such as simple falls are the most common mechanisms of injury, whereas in younger individuals, high-energy traumas are predominant. The high rate of high-energy trauma cases observed in the present study is attributable to the fact that the study population consisted of younger patients. Furthermore, although many studies have shown that pertrochanteric femoral fractures are more common in women, the majority of our patients were men (8,9). This may be due to the overlap of the higher involvement of men in high-energy activities and the predominance of high-energy trauma mechanisms in the younger population. Seasonal analysis of fracture occurrence in this study revealed a higher incidence during the summer months. In contrast, studies focusing on elderly patients frequently report peak incidence during the winter months (9). Our findings suggest a different seasonal pattern in the younger population, which may provide useful insight for the planning of preventive measures and healthcare resource allocation (10).

In the literature to date, osteoarthritis progression has not been extensively evaluated in younger patients with pertrochanteric fractures. In our study, no significant associations were found, which may be related to the study's relatively short and heterogeneous follow-up durations. Although no significant association was found between Singh index and osteoarthritis progression in this study, bone quality is known to play an important role in fracture characteristics and clinical outcomes. The lack of association in our study may again be related to the relatively short and heterogeneous follow-up durations. Although many studies have explored the association between FAI and femoral neck fractures, the relationship between FAI and pertrochanteric fractures has not been clearly defined (11,12). In the present study, low-energy trauma was more frequently observed in patients with FAI, but this difference did not reach the level of statistical significance. Backer et al. reported a mean CEA of 43° in patients with pertrochanteric fractures and noted the presence of underlying osteoarthritis in such cases (12). Similarly, our study showed a mean CEA of 42.6°, with 62% of patients demonstrating grade 2 or 3 osteoarthritis according to the Kellgren–Lawrence classification.

Consistent with other studies (8,9), the average age of female patients was higher than that of male patients in this study. The mean time to postoperative mobilization in our study was 2.3 months, and this was found to be significantly associated with reduction quality according to the Baumgartner classification. In a study by Schneider et al., the average CCI score was found to be higher in patients without complications (13). In contrast, our findings showed that, excluding heterotopic ossification, patients who developed complications had a numerically higher mean CCI score (p=0.1), suggesting that increasing CCI scores may be associated with a greater risk of complications in younger patients.

Study Limitations

We acknowledge several limitations of this study. Preoperative radiographs were obtained in the emergency department, and due to fracture-related pain, standard pelvic radiographs could not always be achieved. Since not all types of hip fractures were included, results pertaining to other fracture types could not be provided. The relatively small sample size and retrospective design constitute further limitations of our study. Another limitation of this study is the lack of formal intra- and interobserver reliability analysis for radiographic measurements. Evaluations were performed independently by two experienced observers. Although these evaluations were finalized by consensus between the observers, the absence of reliability testing may have affected the reproducibility of the findings.

Furthermore, osteoarthritis progression was assessed in this study based on comparisons between baseline and final follow-up radiographs without standardized follow-up intervals. Given that osteoarthritis is a time-dependent process, longer and more uniform follow-up periods would be necessary for more accurate evaluations of disease progression.

CONCLUSION

Pertrochanteric femoral fractures are known to be a significant cause of morbidity and mortality in elderly populations. Evaluating these fractures in a younger patient cohort, we identified both similarities to the elderly patient population and distinct factors affecting treatment outcomes for younger patients. We found that this fracture type was more commonly observed in men within the younger population and was predominantly caused by high-energy trauma. Moreover, we demonstrated that the presence of preoperative FAI was associated with an increased incidence of fractures resulting from low-energy trauma.

DECLARATIONS

Conflict of Interest: *The authors declare that they have no competing interests.*

Financial Disclosure: *The authors declare that there is no financial conflict of interest related to this study.*

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OPEN

RESEARCH ARTICLE

Electrophysiological and Functional Effects of Neuromuscular Electrical Stimulation Compared with Sham Stimulation in Children with Cerebral Palsy and Dysphagia: A Randomized Controlled Trial

Serebral Palsili ve Disfajili Çocuklarda Nöromüsküler Elektrik Stimülasyonunun Elektrofizyolojik ve Fonksiyonel Etkileri: Sham Stimülasyon ile Karşılaştırmalı Randomize Kontrollü Bir Çalışma

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ABSTRACT

Objective: To examine the functional and electrophysiological effects of NMES in children with cerebral palsy presenting with dysphagia.

Materials and Methods: This prospective, randomized, sham-controlled clinical trial was conducted in children with cerebral palsy presenting with oropharyngeal dysphagia. A total of 26 children (mean age: 7.02 ± 2.40 years) were randomly allocated to either the NMES group (n = 16) or the sham-NMES group (n = 10). Both groups received conventional swallowing rehabilitation. Outcome measures included the Pediatric Eating Assessment Tool (PEDI-EAT-10), Penetration-Aspiration Scale (PAS), Karaduman Chewing Performance Scale (KCPS), Swallowing Ability and Function Evaluation (SAFE), and electrophysiological assessment of suprahyoid activity during four consistencies. The trial was registered at ClinicalTrials.gov (Identifier: NCT07329387; registered September 30, 2025).

Results: PEDI-EAT-10 scores improved in both groups (NMES: p = 0.001, d = 0.92; sham-NMES: p = 0.012, d = 0.71) without a significant between-group difference (p=0.318). PAS decreased in both groups (NMES: p = 0.002, d = 0.88; sham-NMES: p = 0.021, d = 0.69; between-group p = 0.274). The SAFE oral phase improved in both groups, whereas the pharyngeal phase improved only in the NMES group (p < 0.001, d = 1.12). KCPS improved only with NMES (p=0.043, d = 0.64). Suprahyoid activation increased significantly with NMES during spontaneous, liquid, and solid swallowing, with the greatest improvement observed for solid swallowing. Swallowing duration favored NMES (p = 0.013–0.027).

Conclusion: Functional gains were similar between groups; however, NMES provided additional benefits in pharyngeal function and suprahyoid activation, particularly during solid swallowing.

Keywords: Cerebral Palsy, Dysphagia, Neuromuscular Electrical Stimulation, Suprahyoid Muscle

ÖZET

Amaç: Bu çalışmanın amacı, disfajisi olan serebral palsili çocuklarda NMES'in fonksiyonel ve elektrofizyolojik etkilerini incelemektir.

Gereç ve Yöntemler: Bu prospektif, randomize, sham kontrollü klinik çalışmaya orofaringeal disfajisi olan serebral palsili 26 çocuk (yaş ortalaması: 7.02 ± 2.40 yıl) dahil edildi. Katılımcılar NMES grubu (n = 16) ve sham-NMES grubu (n = 10) olarak randomize edildi. Her iki gruba da konvansiyonel yutma rehabilitasyonu uygulandı. Değerlendirmede Pediatric Eating Assessment Tool (PEDI-EAT-10), Penetrasyon-Aspirasyon Skalası (PAS), Karaduman Çiğneme Performans Skalası (KCPS), Swallowing Ability and Function Evaluation (SAFE) ve dört farklı besin kıvamında yutma sırasında suprahyoid kas aktivitesinin elektrofizyolojik değerlendirmesi kullanıldı. Çalışma ClinicalTrials.gov veri tabanına kaydedildi (Kayıt Numarası: NCT07329387; kayıt tarihi: 30 Eylül 2025).

Bulgular: PEDI-EAT-10 skorları her iki grupta da anlamlı düzeyde iyileşti (NMES: p = 0.001; Sham: p = 0.012), ancak gruplar arasında anlamlı fark bulunmadı (p = 0.318). PAS skorlarında her iki grupta azalma gözlendi (NMES: p = 0.002; Sham: p = 0.021; gruplar arası p = 0.274). SAFE değerlendirmesinde oral faz her iki grupta iyileşirken, farengeal fazda anlamlı iyileşme yalnızca NMES grubunda saptandı (p < 0.001). KCPS skorlarında iyileşme yalnızca NMES grubunda görüldü (p = 0.043). Elektrofizyolojik değerlendirmede NMES grubunda spontan, sıvı ve katı yutma sırasında suprahyoid kas aktivitesinde anlamlı artış saptandı ve bu özellikle katı kıvamda daha belirgindi. Ayrıca yutma süresi NMES grubunda daha kısa bulundu (p = 0.013–0.027).

Sonuç: Her iki grupta fonksiyonel iyileşmeler gözlemlenmiş, NMES özellikle farengeal fonksiyon ve suprahyoid kas aktivasyonu açısından ek faydalar sağlamıştır. Bu etkiler özellikle katı kıvamlı besinlerin yutulması sırasında daha belirgin bulunmuştur.

Anahtar Kelimeler: Serebral Palsi, Disfaji, Nöromüsküler Elektrik Stimülasyonu, Suprahyoid Kas

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INTRODUCTION

Swallowing function consists of automatic and sequential processes involved in the passage of food from the oral cavity to the stomach (1). Dysphagia refers to an impairment in one or more phases of this process and is common in children with cerebral palsy (CP) (2). Among these comorbidities, oropharyngeal dysphagia (OPD) is highly prevalent, impacting up to 85% of children with CP and resulting in significant nutritional deficits (3). This condition negatively affects nutritional status and respiratory health and increases caregiver burden. Common clinical features include poor cervical control, inadequate lip closure, impaired bolus formation and propulsion, delayed swallowing reflex, insufficient laryngeal elevation, and laryngeal penetration or aspiration (4-5). Electrical stimulation is increasingly used in children with CP, although outcomes remain inconsistent. Electrical stimulation is thought to enhance muscle strength and facilitate the swallowing reflex via motor and sensory pathways and is commonly applied in neurological populations to improve muscle function and reduce atrophy (6). It induces muscle contraction and cortical activation through afferent input and has been associated with improved hyoid movement and reduced aspiration (7-8).

Suprahyoid muscles play a key role in laryngeal elevation; insufficient activation of these muscles compromises airway protection. Neuromuscular electrical stimulation (NMES) applied to the suprahyoid muscle group aims to enhance hyoid elevation and improve swallowing safety in patients with dysphagia. The effectiveness of NMES in dysphagia was first demonstrated in stroke patients by Freed et al. Although electrophysiological evaluations of suprahyoid muscle activity have been conducted in adults with various conditions and in healthy children, studies combining clinical and electrophysiological assessments in children with CP and dysphagia are lacking (7,9). To our knowledge, this is the first study to evaluate the effects of NMES on swallowing function in children with CP using electrophysiological analyses. This study aimed to investigate the effects of NMES on suprahyoid muscle activation, swallowing duration, and aspiration severity in children with CP and dysphagia. We hypothesized that NMES, in addition to conventional oromotor exercises and thermal-tactile stimulation, would result in greater improvements in both clinical and electrophysiological swallowing outcomes compared with conventional therapy alone.

MATERIALS AND METHODS

Design and Participants

This study was conducted at Necmettin Erbakan University. A total of 63 children with CP were screened for eligibility. The study was designed as a randomized controlled trial comparing neuromuscular electrical stimulation (NMES) plus conventional swallowing rehabilitation with sham-NMES plus conventional therapy.

Ethical Approval

The study protocol was approved by the Non-Invasive Clinical Research Ethics Committee of Selçuk University (Decision No: 2017/22). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants, and assent was obtained from the children when appropriate, based on their age and cognitive status.

Participants and Data Collection

Participants were children with CP aged between 4 and 18 years who scored above 4 on the Turkish version of the Pediatric Eating Assessment Tool (Pedi-EAT-10) and were able to sit with or without support. A total of 63 children were screened for eligibility. Of these, 12 did not meet the age criteria, and 19 were unable to adhere to the treatment schedule and were therefore excluded. The remaining 32 children were included in the study. Six participants withdrew from the study, and a total of 26 patients completed the study (mean age: 7.02 ± 2.40 years), with 16 in the treatment group and 10 in the Sham-NMES group (Figure 1). Demographic, clinical, and feeding history data were collected through face-to-face interviews with the parents or caregivers.

Diagnostic Criteria

Dysphagia was diagnosed based on a clinical swallowing examination and videofluoroscopic swallowing study (VFSS). Electrophysiological evaluations were utilized for assessment rather than diagnosis. Dysphagia severity was evaluated using the Penetration–Aspiration Scale (PAS).

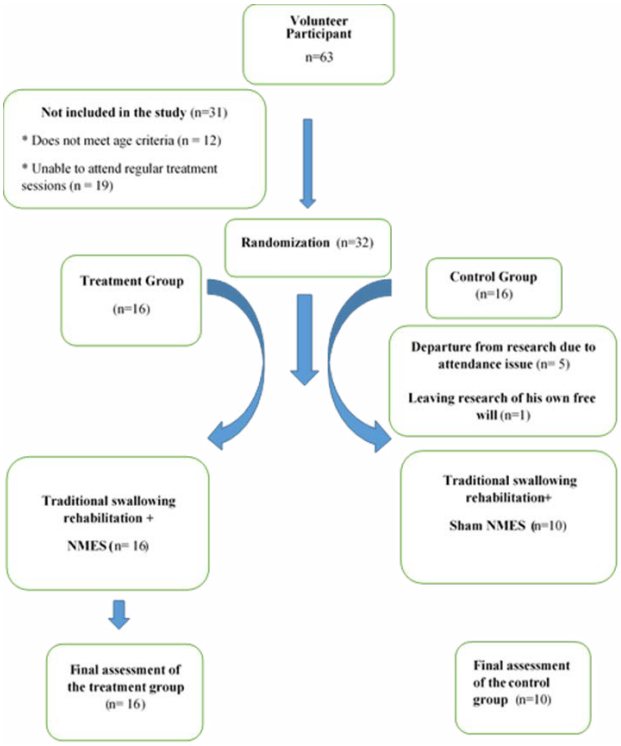

Figure 1. CONSORT flow diagram showing the enrollment, allocation, follow-up, and analysis of participants.

Clinical Assessment Tools

The Swallowing Ability and Function Evaluation (SAFE) was employed to assess the oropharyngeal phase of swallowing. Chewing performance was evaluated using the Karaduman Chewing Performance Scale (KCPS).

Inclusion Criteria

The inclusion criteria were: (1) a diagnosis of CP, (2) age between 4 and 18 years, (3) a Pedi-EAT-10 score > 4, and (4) the ability to sit with or without support.

Exclusion Criteria

Exclusion criteria included: history of maxillofacial, head, or neck surgery; recent botulinum toxin injection (within the last 3 months); structural oropharyngeal abnormalities; gastroesophageal reflux disease; history of previous medical or physical therapy interventions for dysphagia; severe cognitive, visual, auditory, or sensory impairments; current use of pharmacological treatment for spasticity; serious pulmonary or cardiac disease; and coagulation disorders.

Study Procedures

The study was conducted by independent experts blinded to treatment allocation. Physical examination, VFSS, and electrophysiological assessments were performed by an otorhinolaryngologist who was blinded to group allocation. Follow-up evaluations were conducted by a second otorhinolaryngologist who was blinded to group allocation four weeks after the intervention. This trial was prospectively registered at ClinicalTrials.gov (Identifier: NCT07329387).

Randomization

Randomization was performed by an independent researcher who was not involved in participant recruitment, assessment, or treatment. A computer-generated random allocation sequence was created using block randomization with a fixed block size of four to ensure balanced group allocation. The allocation sequence was concealed using sequentially numbered, opaque, sealed envelopes prepared in advance. After baseline assessments were completed, participants were assigned to either the NMES group or the sham-NMES group according to the predefined randomization sequence. Six participants allocated to the control group discontinued the intervention due to poor adherence to the rehabilitation schedule and were excluded from the final analysis. These withdrawals occurred after randomization and are detailed in the CONSORT flow diagram.

Rehabilitation methods

All participants underwent a 4-week swallowing rehabilitation program (3 sessions per week, 12 sessions in total) administered by a physiotherapist with 10 years of clinical experience in pediatric rehabilitation and clinical expertise in dysphagia management. All rehabilitation practices were carried out with the primary caregiver, and after 12 sessions, the family was trained to continue the treatment as a home program. Conventional swallowing rehabilitation approaches were applied to both groups, including oral motor exercises such as tongue traction performed by the physiotherapist using a gloved finger or a tongue depressor, tongue protrusion against resistance, passive and/or active tongue movements performed laterally and superiorly, lip closure exercises, and blowing exercises performed in front of a mirror. Each exercise was performed for 20 repetitions (10). For laryngeal mobilization, the larynx was moved in mediolateral (right–left) and superior (upward) directions for approximately 1 minute without causing discomfort or erythema, especially to facilitate laryngeal elevation during swallowing (11). For thermal-tactile stimulation, cold stimuli were applied to the anterior pharyngeal area with thermal stimulation probes in 5–6 contacts, which were considered one application, and 200 applications were performed on each side during each session (12). Gingival massage; Circular massage was performed digitally using a gloved finger from the front teeth towards the back on the upper and lower gums. Gum massage was applied for approximately 8–10 minutes in treatment sessions.

In addition to conventional therapy, the treatment group received NMES targeting the suprahyoid muscle group (80 Hz, 300–400 µs pulse width) using VitalStim for 40 minutes per session, while the control group received sham NMES with identical electrode placement but with no current output. To address ethical considerations, NMES was offered to the sham group after data collection. NMES and surface electromyography (s-EMG) parameters were selected based on previously established safe and effective protocols in pediatric dysphagia and CP populations (9,13).

Data Collection

Demographic and clinical characteristics (including sex, birth history, gestational age, birth weight, Neonatal Intensive Care Unit (NICU) history, feeding history, Gross Motor Function Classification System (GMFCS) level, and clinical type of CP) were recorded via face-to-face interviews.

Clinical evaluation

Dysphagia severity was assessed using the PAS based on VFSS performed by experienced radiologists (14). Children were evaluated in a seated position while swallowing 3 mL of liquid three times, and bolus movement in the sagittal plane was scored on an 8-point scale. Chewing performance was assessed using the KCPS during consumption of a standard biscuit without physical or verbal assistance (15). Signs of respiratory distress (e.g., dyspnea, cyanosis, coughing, and voice changes) observed during feeding were recorded. Oral motor function was evaluated using the SAFE battery through inspection and palpation in a seated position (16). In children with cognitive impairment, verbal and visual cues were provided as needed. The sensory and cognitive evaluation subscales of SAFE were excluded from statistical analyses, as they were not considered essential for determining swallowing severity.

Electrophysiological evaluation

Prior to recording, the skin over the submental region was cleaned with alcohol to reduce impedance, and self-adhesive surface electrodes (1 × 2.5 cm) were placed over the submental region, symmetrically on either side of the midline. Electrodes and cables were secured with adhesive tape to minimize movement artifacts. Swallowing-related muscle activity was recorded using a dual-channel s-EMG system (Digital Swallowing Workstation Model 7245C, Kay Pentax,

Lincoln Park, NJ) integrated with Noraxon MyoResearch XP software. Signals were recorded in microvolts, band-pass filtered between 20 Hz and 2 kHz, and amplified with a gain of 200. Electromyographic recordings were obtained during four swallowing conditions: spontaneous swallowing, liquid (3 mL water), semi-solid (5 mL yogurt), and solid (biscuit); in children with chewing difficulties, the solid bolus was mechanically altered for safety. To standardize head position, participants wore a soft cervical collar. Each condition was recorded three times with 1-minute rest intervals, and the highest mean and peak values were analyzed. Assessments were performed before and after the 12-session intervention. Peak amplitude was defined as the maximum muscle contraction; baseline and resting amplitudes reflected resting muscle tone; and burst duration represented the total time of swallowing activity.

Sample size

The sample size was determined using an a priori power analysis (G*Power v3.1.9.2). An effect size of d = 0.5 was selected based on clinical relevance and previous literature (17). The analysis indicated that a minimum sample size of 32 participants would be required to achieve 90% power at an alpha level of 0.05.

Statistical Analysis

Statistical analyses were conducted using SPSS version 21.0 for Windows (IBM Corp., Armonk, NY, USA). The distribution of the data was assessed using the Shapiro–Wilk test. Descriptive data are presented as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. To evaluate the effect of the intervention over time and to directly test the group × time interaction, linear mixed-effects models were applied. In these models, group (NMES vs. sham-NMES), time (pre- and post-treatment), and their interaction (group × time) were included as fixed effects, while subjects were treated as a random effect to account for within-subject correlations. Within-group comparisons (pre–post treatment) were performed separately for each group using the Wilcoxon signed-rank test. Between-group comparisons were analyzed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test. Statistical significance was set at $p < 0.05$. Effect sizes and 95% confidence intervals were calculated for significant findings.

RESULTS

The study included a total of 26 participants, with 16 allocated to the NMES group and 10 to the sham-NMES group. At baseline, no significant differences were observed between the NMES and sham-NMES groups in PEDI-EAT-10 or PAS scores ($p > 0.05$), indicating baseline homogeneity regarding swallowing severity (Tables 1 and 2).

Clinical Outcomes

Linear mixed-effects analysis revealed no significant group × time interaction for PEDI-EAT-10 ($p = 0.421$, $\eta^2 = 0.037$), indicating that the change over time was similar in both the NMES and sham-NMES groups. Similarly, no significant group × time interaction was observed for PAS scores ($p = 0.362$, $\eta^2 = 0.048$). Following the 12-session intervention, no statistically significant between-group differences were found in PEDI-EAT-10 or PAS scores ($p>0.05$). However, within-group analyses revealed significant post-treatment improvements in both groups for PEDI-EAT-10 and PAS scores ($p<0.05$), demonstrating a large treatment effect (Tables 1 and 2). Although both groups demonstrated significant improvements, the magnitude of change did not differ significantly between the NMES and Sham-NMES groups. For SAFE scores, no significant group × time interaction was found for physical ($p = 0.118$, $\eta^2 = 0.09$), oral ($p = 0.482$, $\eta^2 = 0.03$), and pharyngeal phase evaluations ($p = 0.091$, $\eta^2 = 0.11$). No significant between-group differences

Table 1. Comparison of pre- and post-treatment PEDI-EAT-10 scores.

Pedi-Eat 10	Within-Group Changes		Mean Difference	95% CI	Between-Group Differences	Group × Time
	NMES group (n=16) Mean ± SD / Median (Min–Max)	Sham-NMES group (n=10) Mean ± SD / Median (Min–Max)			p	
Pre-treatment	25.56±9.69/ 25.50 (10-40)	19.10±6.57/ 18.50 (8-40)	6.46	[-0.48, 13.40]	0.096**	P=0.421
Post-treatment	20.93±8.9/ 20.00 (6-38)	17.00±7.48/ 16.50 (7-38)	3.93	[-2.88, 10.74]	0.413**	$\eta^2 = 0.037$
Δ (Post–Pre)	−4.63 ± 6.20 /−4.00	−2.10 ± 4.80 /−2.00	−2.53	[−7.10, 2.04]	0.318**	
z	-3.073	-2.408				
p	0.002*	0.017*				
r	0.768	0.761				

CI: Confidence Interval, SD; Standard Deviation, * Wilcoxon test **Mann-Whitney U test, Δ (change score) was calculated as post-treatment minus pre-treatment values. The group × time interaction effect was evaluated using a linear mixed-effects model including group, time, and group × time interaction as fixed effects and subject as a random effect. Effect size (r) was calculated using the formula $r = z / \sqrt{N}$. Values of 0.1, 0.3, and 0.5 indicate small, medium, and large effects, respectively. Statistically significant p-values are presented in bold.

Table 2. Comparison of pre- and post-treatment Penetration-Aspiration Scale (PAS) scores.

PAS	Within-Group Changes		Between-Group Differences		Group × Time
	NMES group (n=16) Mean ± SD / Median (Min–Max)	Sham-NMES group (n=10) Mean ± SD / Median (Min–Max)	Mean Difference	95% CI p	
Pre-treatment	5.41±2.10/ 5.50 (2 – 8)	5.71±2.32/ 5.50 (2 – 8)	-0.30	[-2.14, 1.54] 0.096**	P= 0.362
Post-treatment	3.56±1.63/ 3.00 (1 – 7)	3.60±1.26/ 3.50 (2 – 7)	-0.04	[-1.18, 1.10] 0.213**	
Δ (Post–Pre)	−1.85 ± 1.50 / −2.00	−2.11 ± 1.40 / −2.00	0.26	[−1.10, 1.62] 0.274**	η^2 = 0.048
Z	-3.073	-2.307			
P	0.002*	0.016*			
r	0.768	0.758			

CI: Confidence Interval , PAS: Penetration Aspiration Scale * Wilcoxon test **Mann-Whitney U test, Δ (change score) was calculated as post-treatment minus pre-treatment values. The group × time interaction effect was evaluated using a linear mixed-effects model including group, time, and the group × time interaction as fixed effects, with subject as a random effect.. Effect size (r) was calculated using the formula r = z / √N. Values of 0.1, 0.3, and 0.5 indicate small, medium, and large effects, respectively. Statistically significant p-values are presented in bold.

Table 3. Comparison of pre- and post-treatment Swallowing Ability and Function Evaluation (SAFE) scores.

SAFE		Within-Group Changes (Pre- Post-treatment)		Between-Group Differences	Group × Time
		NMES group (n=16)	Sham-NMES group (n=10)	p	
Physical Evaluation	Pre-treatment	68.50±12.29	68.00±9.68	0.369**	
	Post-treatment	66.87±13.60	65.30±10.17	0.398**	
					P= 0.118
	z	-2.794*	-1.809*		η^2 = 0.09
	p	0.005*	0.071*		
	r	0.698	0.272		
Oral Phase Evaluation	Pre-treatment	14.87±5.34	15.20±2.14	0.873**	p = 0.482
	Post-treatment	16.50±5.46	16.20±2.09	0.208**	η^2 = 0.034
	z	-3.125*	-2.368*		
	p	0.002*	0.018*		
	r	0.781	0.748		
Pharyngeal Phase Evaluation	Pre-treatment	12.93±3.71	14.60±4.24	0.958**	p = 0.091
	Post-treatment	14.62±3.05	15.30±3.43	0.978**	η^2 = 0.112
	z	-3.550*	-1.370*		
	p	p < 0.001 *	0.171*		
	r	0.887	0.433		

SAFE: Swallowing Ability and Functional Evaluation * Wilcoxon test **Mann-Whitney U test, The group × time interaction effect was evaluated using a linear mixed-effects model including group, time, and the group × time interaction as fixed effects, with subject as a random effect. Effect size (r) was calculated using the formula r = z / √N. Values of 0.1, 0.3, and 0.5 indicate small, medium, and large effects, respectively. Statistically significant p-values are presented in bold.

Table 4. Comparison of pre- and post-treatment Karaduman Chewing Performance Scale (KCPS) scores.

KCPS	Within-Group Changes *				Between-Group Differences **	
	NMES group (n=16)		Sham-NMES group (n=10)		Pre-treatment	Post-treatment
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	p	p
Level 1	2 (12.5%)	2 (12.5%)	1 (10%)	1 (10%)	0.585	0.085
Level 2	2 (12.5%)	5 (31.25%)	2 (20%)	3 (30%)		
Level 3	7 (43.75%)	6 (37.5)	5 (50%)	4 (40%)		
Level 4	5 (31.25%)	3 (18.75%)	2 (20%)	2 (20%)		
z	-3.004		-1.200			
p	0.043*		0.245			
r	0.751		0.379			

* Marginal homogeneity test ** Mann Whitney U test, Effect size (r) was calculated using the formula r = z / √N. Values of 0.1, 0.3, and 0.5 indicate small, medium, and large effects, respectively. Statistically significant p-values are presented in bold.

were observed in SAFE scores at baseline or post-treatment (p>0.05) (Table 3). Within-group analysis showed significant improvements in the NMES group in the oral (p=0.002) and pharyngeal phases (p<0.001), whereas the Sham-NMES group demonstrated a significant improvement only in the oral phase (p=0.018).

No significant between-group differences were found in KCPS scores at baseline or post-treatment (p>0.05) (Table 4). A significant within-group improvement was observed in the NMES group (p=0.043), while the change in the Sham-NMES group was not significant (p=0.245).

Maximum Activation Amplitude of Suprahyoid Muscle (Muscle Performance)

NMES led to a statistically significant increase in muscle performance for all consistencies except semi-solids (spontaneous: p=0.004; liquid: p=0.003; solid: p=0.035). Analysis of between-group differences revealed a significant difference only for solid consistency (p=0.002) (Table 5).

Suprahyoid Muscle Burst Duration

The activation amplitude of the suprahyoid muscle determined by the onset of laryngeal elevation was not significantly altered by either intervention. Differences in bolus

Table 5. Comparison of suprahyoid s-EMG parameters before and after treatment.

s-EMG	Within-Group Changes *						Between-Group Differences**	
	NMES group (n=16)			Sham-NMES group (n=10))			Before	After
	Pre-treatment	Post-treatment	z /p/r	Pre-treatment	Post-treatment	z /p/r	p	p
Spontaneous								
MIN	11.10±8.15	9.57±6.05	z:-0.284 p:0.776 r: 0.071	9.62±6.92	7.68±6.23	z:-0.766 p:0.444 r: 0.242	0.895	0.476
MAX	39.91±12.25	57.23±19.61	z:-2.897 p:0.004 r: 0.724	50.90±17.42	46.55±10.78	z:-0.664 p:0.507 r: 0.210	0.206	0.091
TIME	645.22±117.95	516.12±67.81	z:-2.783 p:0.005 r: 0.696	570.67±41.21	559.54±57.32	z:-1.277 p:0.202 r: 0.404	0.235	0.027
Liquid								
MIN	10.75±6.93	8.07±4.74	z:-1.162 p:0.245 r: 0.290	10.80±4.71	12.74±5.78	z:-1.277 p:0.202 r: 0.403	0.890	0.080
MAX	42.68±13.5	60.83±25.25	z:-2.229 p:0.026 r: 0.557	46.49±14.70	59.28±16.33	z:-2.809 p:0.005 r: 0.888	0.174	0.978
TIME	620.95±91.7	561.13±94.66	z:-1.852 p:0.064 r: 0.463	582.10±25.00	478.00±21.58	z:-2.809 p:0.005 r: 0.888	0.421	0.013
Viscous								
MIN	11.01±8.86	10.23±6.60	z:-0.315 p:0.753 r: 0.078	9.94±4.40	10.80±4.33	z:-0.970 p:0.332 r: 0.306	0.930	0.334
MAX	57.80±20.60	64.13±21.81	z:-0.454 p:0.650 r: 0.656	51.89±10.35	52.55±15.29	z:0.357 p:0.721 r: 0.888	0.333	0.334
TIME	626.84±90.77	534.38±74.19	z:-2.622 p:0.009 r:0.655	578.37±20.05	483.08±31.42	z:-2.809 p:0.005 r:0.088	0.464	0.057
solid								
MIN	10.57±8.20	7.21±4.44	z:-1.401 p:0.161 r: 0.350	13.86±5.91	10.40±3.21	z:-1.123 p:0.261 r: 0.355	0.193	0.053
MAX	57.57±28.25	87.42±19.33	z:-2.103 p:0.035 r:0.526	59.10±17.33	54.24±14.09	z:0.000 p:1.000 r:0.000	0.809	0.002
TIME	645.14±127.81	473.53±51.30	z:-2.240 p:0.025 r:0.560	588.88±25.90	576.46±84.53	z:-0.140 p:0.888 r:0.044	0.736	0.017

Wilcoxon test **Mann-Whitney U test, Effect size (r) was calculated using the formula r = z / √N. Values of 0.1, 0.3, and 0.5 indicate small, medium, and large effects, respectively. Min: Resting amplitüde, Max: Peak amplitüde, Time; Swallow duration. Statistically significant p-values are presented in bold.

consistency did not significantly alter the amplitude required to initiate suprahyoid muscle activation (p>0.05) (Table 5).

Suprahyoid Muscle Activation Duration

In both groups, swallowing duration was reduced across all consistencies. However, this reduction was not statistically significant for all consistencies. In within-group analyses, NMES did not significantly alter the duration of liquid swallowing (p>0.05). Regarding between-group comparisons, a statistically significant difference was observed in swallowing duration for consistencies other than semi-solids (spontaneous: p=0.027; liquid: p=0.013; solid: p=0.017). The absence of a between-group difference after treatment for semi-solid consistency suggests that NMES did not affect the electrophysiology of swallowing for this bolus type (Table 5). Correlation analysis revealed a positive correlation between GMFCS level and dysphagia severity as well as aspiration–penetration risk, and a negative correlation with swallowing ability and function. No correlation was found between GMFCS level and post-treatment KCPS. A negative correlation was observed between GMFCS level and maximal suprahyoid muscle contraction amplitude during liquid swallowing.

In the Sham-NMES group, electrophysiological parameters did not show any statistically significant changes during dry and solid swallowing. In contrast, in the NMES group, a statistically significant difference was observed between groups in electrophysiological parameters during spontaneous and solid swallowing (spontaneous: p=0.004; solid: p=0.035) (Table 5). Therefore, NMES treatment resulted in significant electrophysiological improvements, particularly during spontaneous swallowing and solid food consumption.

DISCUSSION

NMES has increasingly been used as an adjunct to traditional dysphagia rehabilitation in children with CP (18). There are conflicting findings regarding the treatment efficacy of NMES for dysphagia (19,20). In many recent adult studies, NMES included in conventional dysphagia rehabilitation has been reported to yield superior electrophysiological results in the treatment of swallowing function compared to either NMES alone or conventional dysphagia rehabilitation alone (21,22). To our knowledge, this study is the first randomized controlled trial in a pediatric CP population to simultaneously evaluate both clinical swallowing outcomes and electrophysiological suprahyoid muscle activation parameters in a sham-controlled design. By integrating instrumental VFSS-based clinical assessment with surface electromyographic analysis, this study provides a more comprehensive evaluation of NMES effects in children with dysphagia. While NMES did not demonstrate superiority over sham stimulation in overall clinical swallowing scales, it resulted in significantly greater improvements in maximal suprahyoid muscle activation during spontaneous and solid swallowing. These findings suggest that electrophysiological gains may precede or exceed measurable clinical scale improvements in pediatric populations. Although between-group differences were not significant for several clinical scales, the within-group improvements observed in PEDI-EAT-10, PAS, and SAFE scores may still have clinical relevance. The decrease in PEDI-EAT-10 scores may reflect reduced caregiver-perceived swallowing difficulties during daily feeding. Similarly, improvements in PAS scores may indicate safer swallowing with a lower risk of penetration and aspiration. Improvements in SAFE scores, particularly in the oral and pharyngeal phases, may suggest better bolus control and improved swallowing function. Therefore, these findings may have practical implications for feeding safety and daily swallowing performance in children with cerebral palsy.

Previous research has indicated that the prevalence of oropharyngeal dysphagia increases markedly with higher GMFCS levels in children with CP (23). In addition, Ma et al. demonstrated that NMES treatment in children with CP and dysphagia classified as GMFCS levels IV and V reduced the risk of aspiration by decreasing PAS scores for both solid and liquid consistencies (13). Unlike previous research, our sample included children across all GMFCS levels. Our analysis revealed a positive association between GMFCS level and both PAS and Pedi-EAT-10 scores after treatment. Consistent with the findings of Benfer et al., increased functional limitation was associated with greater swallowing impairment and reduced treatment benefit. No significant relationship was observed between GMFCS level and chewing performance after treatment, which may be attributable to the lack of stratification based on baseline chewing ability. Oral and pharyngeal phases are closely linked in swallowing function. Therefore, the improvement of oral functions will facilitate the reflex phase of swallowing. Song et al. reported that NMES application to the suprahyoid muscle in children with CP and dysphagia significantly improved functions related to the oral phase compared to the Sham group. In contrast, using the modified SAFE battery to evaluate the oral phase, we found that both groups benefited from the treatment, with no significant difference between them. This may be attributed to the administration of oral exercises in both groups.

Chewing and swallowing are integral components of the stomatognathic system. Therefore, the muscles involved in these two functions are interrelated. Giannas et al. reported that they treated sleep apnea by applying NMES to the masticatory muscles in 13 adult CP patients, hypothesizing that it enhanced muscle activation and motor unit recruitment in the upper respiratory tract (24). The results of the present study offer reciprocal support for this hypothesis. There was no difference between the effects of the treatments applied to both groups on masticatory function. Although no significant between-group difference was observed in masticatory function, within-group analysis indicated significant improvement in the NMES group. As hypothesized by Giannas et al., it can be suggested that the increase in motor units or sensory gain from NMES in muscles related to the hyolaryngeal complex outside the target muscle may have contributed to the improvement in chewing function. Mishra et al. reported that children with CP exhibited significantly more suprahyoid muscle activity during the ingestion of semisolid and solid foods compared to healthy children. This is attributed to the increased demand

for muscle contraction and additional muscle strength during the chewing and swallowing of solids (25). In our study, as the viscosity of food increased before and after treatment, peak muscle amplitude increased in both groups. Xia et al. reported that NMES administration in combination with conventional dysphagia rehabilitation in adult hemiplegic dysphagia patients was significantly superior in both FEES assessment results and electrophysiological outcomes compared to NMES or conventional rehabilitation alone (26). Our study also found that NMES administration increases muscle contraction performance during spontaneous swallowing and the ingestion of liquid and solid boluses, consistent with these findings. When examining the effect of NMES on maximum muscle contraction performance between the two groups, we found that it was significantly greater only during solid food swallowing. Accordingly, we can conclude that strengthening the suprahyoid muscle with electrical stimulation in solid foods may be beneficial.

During voluntary muscle contraction, type I motor units, specifically slow-twitch fibers, are recruited first, whereas type II motor units are activated only when greater force is required. In contrast, NMES recruits motor units in a non-physiological reverse order, contrary to Henneman's size principle (7). Therefore, potential improvements in muscle activation or strength may not fully translate into significant functional swallowing performance. For this reason, evaluating the effectiveness of NMES requires assessment of both myoelectric activity and functional swallowing outcomes. The pharyngeal phase of swallowing lasts approximately 500–600 ms, and prolonged suprahyoid muscle activation has been reported in dysphagia (27).Vaiman et al. demonstrated that in healthy children aged 4–12 years, swallowing duration increases with bolus consistency and is longer than in adults, indicating slower swallowing patterns (27).In the present study, activation duration decreased across all consistencies in both groups; however, NMES did not demonstrate superiority for semi-solid boluses. Christiaanse et al. reported that NMES application had no significant therapeutic effect in their study on pediatric dysphagia patients (28). However, these results were assessed using the functional oral intake level. In our study, aspiration risk was assessed by a blinded radiologist, while other clinical parameters were evaluated by independent researchers to minimize bias. The use of objective instrumental assessment (VFSS) and blinded evaluators in our study strengthens the validity and reliability of the results. Nevertheless, the interpretation of these findings should take into account the relatively small final sample size and the participant attrition that occurred after randomization, particularly in the sham-NMES group. Although the sample size was determined through an a priori power analysis, the target sample size could not be fully achieved due to withdrawals related to difficulties in adhering to the rehabilitation schedule. This reduction in sample size may have decreased the statistical power of the study and limited the detection of additional between-group differences in some clinical outcomes. Therefore, larger randomized controlled trials with adequate sample sizes are needed to confirm the present findings.

Recent studies have reported electrophysiological analyses of the submental muscle in adult patient populations and in healthy children (1,2,6-8); however, no study has combined clinical and electrophysiological evaluations in children with CP. To our knowledge, this is the first study to assess the effectiveness of NMES in children with CP and dysphagia using electromyographic analysis, making the evaluation of both clinical dysphagia outcomes and submental muscle EMG parameters particularly important. A primary strength of this study is its novelty as the first randomized controlled trial to show the effect of NMES on submental muscle performance and clinical dysphagia evaluation parameters by comparing it with conventional oromotor exercises in dysphagia rehabilitation. Second, the evaluation techniques chosen to assess clinical dysphagia and suprahyoid muscle activations are all valid and reliable, and the study was conducted using a single-blind design. Third, sham-NMES was administered to the control group to control for potential placebo effects and standardize sensory input between groups. Another strength is the baseline homogeneity of the groups regarding clinical involvement, type, GMFCS levels, head control values, dysphagia scores, chewing scores, penetration-aspiration levels, and swallowing ability and function assessment scores, which supports the robustness of group comparisons.

Study Limitations: One limitation of this study is the lack of a control group receiving NMES alone, which restricts the ability to isolate the effects of NMES on swallowing and electrophysiological outcomes. Additionally, for safety reasons, mechanically altered solid food was used in some children with inadequate lip closure and chewing ability, which may have altered physiological chewing mechanics and affected suprahyoid muscle activation during solid swallowing. Therefore, EMG findings for solid consistencies should be interpreted with caution. Another limitation is the relatively small final sample size. Although the sample size was estimated through an a priori power analysis, the planned sample size was not fully achieved because several participants withdrew after randomization, particularly in the sham-NMES group. This attrition may have reduced the statistical power of the study and limited the ability to detect significant between-group differences for some outcomes.

CONCLUSION

The findings of this study suggest that adding NMES to conventional swallowing rehabilitation did not result in additional significant improvements in overall swallowing function. However, NMES appears to provide electrophysiological benefits, particularly in children who experience difficulty in solid food consumption. These patients often exhibit prolonged spontaneous swallowing durations during solid bolus management. Therefore, NMES may be considered an adjunctive modality of swallowing rehabilitation in this population.

DECLARATIONS
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RESEARCH ARTICLE

Persistent Papilledema After Cerebral Venous Sinus Thrombosis: A Prospective Observational Cohort Study

Serebral Venöz Sinüs Trombozu Sonrası Persistan Papilödem: Prospektif Gözlemsel Kohort Çalışması

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ABSTRACT

Objective: Papilledema is a clinically significant manifestation of cerebral venous sinus thrombosis (CVST) and reflects intracranial hypertension resulting from impaired venous outflow. However, its severity and longitudinal course have not been adequately characterized. This study aimed to evaluate the longitudinal course of papilledema in patients with CVST and to identify clinical and radiological factors associated with persistent papilledema.

Materials and Methods: This prospective observational study included 37 adult patients with radiologically confirmed CVST. Papilledema severity was assessed at baseline and at six months using the Frisén grading scale. Persistent papilledema was defined as the presence of papilledema of any grade (≥1) at follow-up. Clinical and radiological variables, including venous sinus involvement and recanalization status, were analyzed.

Results: Papilledema was present in 14 patients (37.8%) at baseline. At six months, papilledema had resolved in 5 patients but persisted in 9 patients (24.3% of the cohort). The frequency of baseline Frisén grade 3–4 papilledema was significantly higher among patients with persistent papilledema than among those without persistent papilledema (66.7% vs. 7.1%; $p < 0.001$). Magnetic resonance imaging (MRI) data were available for 25 patients, and complete recanalization was observed more frequently in patients without persistent papilledema ($p = 0.007$). No significant associations were identified between persistent papilledema and demographic, clinical, or other radiological variables.

Conclusion: Papilledema may persist in a substantial proportion of patients with CVST. Higher baseline papilledema grades were more frequently observed among patients with persistent papilledema, whereas complete recanalization was more common among those without persistent papilledema. These findings support the importance of structured neuro-ophthalmological follow-up in patients with CVST.

Keywords: Cerebral venous sinus thrombosis, Intracranial hypertension, Papilledema, Prognosis

ÖZET

Amaç: Papilödem, serebral venöz sinüs trombozunun (SVST) klinik açıdan önemli bir bulgusudur ve bozulmuş venöz dönüşe bağlı intrakraniyal hipertansiyonu yansıtır. Ancak şiddeti ve zaman içindeki seyri yeterince tanımlanmamıştır. Bu çalışmada, SVST hastalarında papilödemin uzunlamasına seyrinin değerlendirilmesi ve persistan papilödem ile ilişkili klinik ve radyolojik faktörlerin belirlenmesi amaçlandı.

Gereç ve Yöntemler: Bu prospektif gözlemsel çalışmaya, radyolojik olarak doğrulanmış SVST tanılı 37 erişkin hasta dahil edildi. Papilödem şiddeti başlangıçta ve altıncı ayda Frisén derecelendirme ölçeği kullanılarak değerlendirildi. Persistan papilödem, takipte herhangi bir derecede papilödem varlığı (≥1) olarak tanımlandı. Venöz sinüs tutulumu ve rekanalizasyon durumu dahil olmak üzere klinik ve radyolojik değişkenler analiz edildi.

Bulgular: Başlangıçta 14 hastada (%37,8) papilödem mevcuttu. Altıncı ayda 5 hastada düzeldi, 9 hastada ise devam etti (kohortun %24,3'ü). Başlangıçta Frisén evre 3–4 papilödem görülme sıklığı, persistan papilödemi olan hastalarda olmayan hastalara göre anlamlı derecede daha yüksekti (%66,7'ye karşı %7,1; $p<0,001$). Manyetik rezonans görüntüleme (MRG) verileri 25 hastada mevcuttu ve tam rekanalizasyon, persistan papilödem olmayan hastalarda daha sık görüldü ($p = 0,007$). Demografik, klinik veya diğer radyolojik değişkenlerle anlamlı ilişki saptanmadı.

Sonuç: Papilödem, SVST'li hastaların önemli bir kısmında persiste edebilir. Daha yüksek başlangıç papilödem dereceleri, persistan papilödemi olan hastalarda daha sık gözlenirken; tam rekanalizasyon, persistan papilödemi olmayan hastalarda daha sık görüldü. Bu bulgular, SVST'de yapılandırılmış nöro-oftalmolojik takibin önemini desteklemektedir.

Anahtar Kelimeler: İntrakraniyal hipertansiyon, Papilödem, Prognoz, İntrakraniyal sinüs trombozu

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INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is an uncommon cerebrovascular disorder, accounting for approximately 0.5–3% of all stroke cases and occurring more frequently among young adults and women (1, 2). The clinical presentation of CVST is highly heterogeneous and primarily reflects impaired cerebral venous drainage (3-5). Headache, seizures, and focal neurological deficits represent the most common presenting manifestations, whereas symptoms associated with intracranial hypertension constitute another important component of the disease spectrum (1, 4, 6). Among these manifestations, papilledema is a clinically significant finding resulting from elevated intracranial pressure secondary to venous outflow obstruction (7).

Papilledema in CVST develops predominantly because increased venous pressure impairs cerebrospinal fluid absorption at the arachnoid granulations (3, 4, 8). Although this pathophysiological mechanism differs from direct parenchymal injury, persistent intracranial hypertension may nevertheless lead to progressive optic nerve damage and visual impairment if not adequately recognized and monitored (2, 7). Despite its clinical relevance, papilledema in CVST has frequently been reported only as a dichotomous finding, with limited attention paid to its severity or temporal evolution (9). Recent studies have suggested that signs of intracranial hypertension may persist in a subset of patients despite apparent clinical stabilization (10). This observation indicates that papilledema may not always represent a transient manifestation confined to the acute phase of the disease and may instead necessitate ongoing follow-up (7, 10). However, longitudinal studies assessing papilledema severity using standardized grading systems remain scarce.

Furthermore, the relationship between specific patterns of venous sinus involvement and the clinical course of papilledema remains inadequately characterized. Thrombosis involving major venous outflow pathways may alter intracranial pressure dynamics and contribute to the persistence of papilledema in certain patients (4, 10). Therefore, a more comprehensive understanding of the longitudinal course of papilledema in CVST is of considerable clinical importance, as sustained intracranial hypertension may place patients at risk of progressive and potentially preventable visual impairment. The present study aimed to evaluate the longitudinal course of papilledema in patients with CVST using the Frisén papilledema grading scale at baseline and after six months of follow-up. Additionally, we sought to determine the frequency of persistent papilledema and to investigate its potential associations with clinical and radiological characteristics.

MATERIALS AND METHODS

Study Design and Participants

This prospective observational study included consecutive adult patients diagnosed with CVST who were admitted to Ankara Etlik City Hospital between July 2023 and December 2024. The diagnosis of CVST was established on the basis of the clinical presentation and was confirmed by neuroimaging findings, including magnetic resonance imaging (MRI) combined with magnetic resonance venography (MRV) or computed tomography venography (CTV) (1). Eligible participants were adults (≥18 years of age) with radiologically confirmed CVST who underwent ophthalmological and/or neurological assessment for papilledema at the time of diagnosis and were available for follow-up evaluation at six months. Patients were excluded if they had pre-existing optic nerve disorders, ocular diseases that could interfere with the assessment of papilledema, or incomplete clinical or neuroimaging data.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ankara Etlik City Hospital Ethics Committee (approval number: Ankara Etlik City Hospital-EK1-2023-243). Written informed consent was obtained from all participants prior to study enrollment.

Clinical Assessment and Follow-up

Baseline demographic and clinical characteristics were recorded at the time of presentation. These data included age, sex, presenting symptoms, and neurological examination findings. Particular emphasis was placed on manifestations associated with intracranial hypertension, including headache and visual symptoms. For analytical purposes, comorbidities and risk factors were categorized into predefined groups. Metabolic and endocrine comorbidities included conditions such as diabetes mellitus, hypertension, hyperlipidemia, and thyroid disorders. Potential predisposing factors comprised smoking, migraine, polycystic ovary syndrome (PCOS), high-dose vitamin A exposure, and obesity. Transient provoking risk factors included oral contraceptive use, pregnancy, the postpartum period, and active sinusitis. Persistent provoking risk factors included malignancy, inherited or acquired thrombophilia (including antiphospholipid syndrome), and Behçet's disease.

All patients were followed for a period of six months following the initial diagnosis. Clinical evaluations were performed both at baseline and at the six-month follow-up visit.

Papilledema Assessment

The severity of papilledema was evaluated using the Frisén papilledema grading scale, a standardized clinical classification system ranging from grade 0 (normal optic disc) to grade 5 (severe papilledema). Fundoscopic examinations were performed at baseline and repeated at the six-month follow-up visit. All papilledema assessments were conducted by a single ophthalmologist with expertise in neuro-ophthalmology. Both eyes were evaluated separately, and Frisén grades were recorded individually for each eye at baseline and at the six-month follow-up assessment. For patient-level analyses, the highest papilledema grade observed in either eye was used as the representative measure of papilledema severity. Persistent papilledema was defined as the presence of any degree of papilledema (Frisén grade ≥1) at the six-month follow-up visit and was considered the primary outcome of the study.

Neuroimaging Evaluation

All patients underwent neuroimaging at the time of diagnosis. The diagnosis of CVST was confirmed by magnetic resonance imaging (MRI) combined with magnetic resonance venography (MRV) or by computed tomography venography (CTV).

All neuroimaging studies were reviewed by an interventional neurologist with expertise in cerebrovascular diseases. The anatomical location of venous sinus thrombosis was recorded for each patient. Venous sinus involvement was categorized according to the affected sinus segments, including the superior sagittal sinus, transverse sinus, sigmoid sinus, straight sinus, and other venous structures. The presence of single-sinus and multiple-sinus involvement was also documented.

Treatment

All patients received treatment in accordance with current clinical guidelines for cerebral venous sinus thrombosis (1). Anticoagulation therapy was initiated unless contraindicated, and additional therapeutic interventions were administered when clinically indicated. Treatment decisions were made by the treating physicians as part of routine clinical practice and were not influenced by the study protocol. Treatment-related variables were not included in the statistical analyses of the present study.

Statistical Analysis

Statistical analyses were performed using jamovi version 2.6.45 (The jamovi Project, Sydney, Australia). The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test. Non-normally distributed variables were presented as median (interquartile range [IQR]) and compared using the Mann–Whitney U test.

Categorical variables were expressed as frequencies and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. A two-sided p value < 0.05 was considered statistically significant. Multivariable logistic regression analysis was not performed because of the limited sample size and the low number of outcome events.

RESULTS

Baseline Characteristics of the Study Population

A total of 37 patients with CVST were included in the study. The median age was 31 years (IQR 24–45; range, 18–71 years), and 67.6% (n = 25) were female. The median number of emergency department or outpatient clinic visits related to CVST prior to diagnosis was 1 (IQR 0–3). Headache and other nonspecific symptoms, including dizziness and nausea, constituted the most common initial presentation (73.0%), followed by focal neurological deficits (13.5%), encephalopathy (10.8%), and visual symptom–predominant presentation (2.7%). Seizures occurred in 21.6% of patients, while status epilepticus was observed in 5.4%. Papilledema was present at baseline in 14 patients. Metabolic and endocrine comorbidities were identified in 18.9% of the cohort. Potential predisposing factors were present in 51.4% of patients, whereas transient and persistent precipitating factors were observed in 51.4% and 62.2% of patients, respectively. Radiologically, multiple-sinus thrombosis was the most common finding, occurring in 86.5% of patients. Among individual venous sinus involvements, transverse sinus thrombosis was the most frequent (83.8%), followed by superior sagittal sinus thrombosis (37.8%). Venous infarction was detected in 32.4% of patients, and hemorrhagic components were present in 8.1%. The baseline demographic, clinical, and radiological characteristics of the study population are summarized in Table 1.

Persistent Papilledema

Among the 14 patients with papilledema at baseline, papilledema resolved during follow-up in 5 patients, whereas it persisted in 9 patients. Overall, persistent papilledema was observed in 9 of 37 patients (24.3%) at the six-month follow-up assessment. No significant associations were identified between persistent papilledema and age, sex, seizure occurrence, clinical presentation at symptom onset, venous infarction, or multiple-sinus thrombosis (all $p > 0.05$). However, the prevalence of high-grade papilledema at baseline (Frisén grades 3–4) was significantly greater among patients with persistent papilledema than among those without persistent papilledema without persistent papilledema (66.7% vs. 7.1%, $p < 0.001$).

Six-month MRI data were available for 25 of 37 patients (8/9 patients with persistent papilledema and 17/28 patients without persistent papilledema). Among these patients,

Table 1. Baseline demographic, clinical, and radiological characteristics of the study population

Characteristics	n (%) / median (IQR)
Demographics	
Age, years (median IQR)	31 (24–45)
Female sex, n (%)	25 (67.6)
Presenting symptoms	
Headache/nonspecific symptoms	27 (73.0)
Focal neurological deficit	5 (13.5)
Encephalopathy	4 (10.8)
Visual-symptom–predominant onset	1 (2.7)
Neurologic features	
Seizure, n (%)	8 (21.6)
Status epilepticus, n (%)	2 (5.4)
Papilledema at presentation, n (%)	14 (37.8)
Risk factors	
Metabolic/endocrine comorbidities, n (%)	7 (18.9)
Potential predisposing factors, n (%)	19 (51.4)
Transient precipitating factors, n (%)	19 (51.4)
Persistent precipitating factors, n (%)	23 (62.2)
Radiological findings	
Transverse sinus thrombosis, n (%)	31 (83.8)
Superior sagittal sinus thrombosis, n (%)	14 (37.8)
Multi-sinus thrombosis, n (%)	32 (86.5)
Venous infarction, n (%)	12 (32.4)
Hemorrhagic component, n (%)	3 (8.1)

Note: IQR: interquartile range. Visual-symptom–predominant onset refers to patients presenting primarily with visual complaints.

Table 2. Comparison of clinical and radiological features according to persistent papilledema status

Variable	Without Persistent Papilledema (n=28)	Persistent Papilledema (n=9)	p value
Age, years (median IQR)	32 (24.8-44.3)	26 (20-51)	0.357
Female, n (%)	20 (71.4%)	5 (55.6%)	0.432
Seizure, n (%)	7 (25.0%)	1 (11.1%)	0.649
Venous infarction, n (%)	11 (39.3%)	1 (11.1%)	0.220
Multi-sinus thrombosis, n (%)	24 (85.7%)	8 (88.9%)	1.000
Baseline papilledema Frisén grade 3-4, n (%)	2 (7.1%)	6 (66.7%)	<0.001
Complete recanalization, n (%)	13 (76.5%)	1 (12.5%)	0.007*
Incomplete recanalization, n (%)	4 (23.5%)	7 (87.5%)	

Note: Recanalization data were available for 25 patients and were evaluated based on six-month MRI findings. Incomplete recanalization comprised both partial recanalization and absence of recanalization. The p value was calculated using Fisher's exact test.
*Complete and incomplete recanalization represent complementary categories of the same variable; therefore, a single p value is reported.

Table 3. Comparison of patients with and without baseline papilledema

Variable	Without Papilledema (n=23)	Papilledema (n=14)	p value
Age, years (median IQR)	33 (25.5-43.5)	27 (21.5-45.0)	0.357
Female, n (%)	18 (78.3%)	7 (50.0%)	0.146
Seizure, n (%)	4 (17.4%)	4 (28.6%)	0.445
Superior sagittal sinus thrombosis, n (%)	6 (26.1%)	8 (57.1%)	0.085
Multi-sinus thrombosis, n (%)	20 (86.9%)	12 (85.7%)	1.000
Venous infarction, n (%)	8 (34.8%)	4 (28.6%)	1.000

Note: IQR: interquartile range. Age is presented as median (IQR); other variables are presented as n (%).

complete recanalization was significantly more common in those without persistent papilledema than in those with persistent papilledema (76.5% vs. 12.5%; Fisher's exact test, p = 0.007). Comparisons between patients with and without persistent papilledema are presented in Table 2.

Comparison Between Patients With and Without Baseline Papilledema

Of the 37 patients included in the study, 14 presented with papilledema at admission, whereas 23 had no evidence of papilledema. No significant differences were observed between the two groups regarding age, sex, seizure occurrence, venous infarction, multiple-sinus thrombosis, clinical presentation, or the distribution of risk factors (all p > 0.05). Superior sagittal sinus thrombosis was numerically more frequent among patients with papilledema than among those without papilledema (57.1% vs. 26.1%); however, this difference did not reach statistical significance (p = 0.085). Comparisons according to baseline papilledema status are summarized in Table 3.

DISCUSSION

In this prospective cohort of patients with CVST, papilledema was present at the time of diagnosis in more than one-third of patients. At the six-month follow-up, papilledema had resolved in most cases; however, it persisted in approximately one-quarter of the cohort. The frequency of baseline high-grade papilledema (Frisén grades 3–4) was significantly higher among patients with persistent papilledema than among those without persistent papilledema (66.7% vs. 7.1%, p < 0.001). In addition, differences in recanalization status were observed between patients with and without persistent papilledema. Complete recanalization at six months was more frequently observed in patients without persistent papilledema. No significant associations were identified between persistent papilledema and demographic characteristics, clinical presentation, seizure occurrence, or the radiological parameters evaluated, including venous infarction and multiple-sinus involvement. Taken together, these findings support careful follow-up of patients presenting with high-grade papilledema. The prevalence of papilledema in our cohort was consistent with the broad range reported in previous studies (4, 11-13). Papilledema was observed in 37.8% of patients at presentation. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), papilledema was reported in 28.3% of 624 patients (14). Similarly, the large multicenter VENOST study reported papilledema in approximately 28% of 1,144 patients (9). The slightly higher prevalence observed in our cohort may be attributable to the systematic neuro-ophthalmological assessment performed at baseline. Both eyes were evaluated, and papilledema severity was graded using the standardized Frisén scale. This approach may have increased the detection of mild or early-stage optic disc edema in routine clinical practice.

Our findings indicate that papilledema may persist beyond the acute phase in a subset of patients with CVST. Nearly one-quarter of patients exhibited persistent papilledema at the six-month follow-up assessment. Although persistent papilledema does not necessarily indicate ongoing intracranial hypertension, previous studies have suggested that intracranial hypertension may persist in a subset of

patients following CVST and that the mean time required for papilledema resolution is approximately six months (3). Schuchardt et al. demonstrated that neuroimaging markers of intracranial hypertension, including optic nerve sheath enlargement and partial empty sella, may persist for several months despite clinical stabilization (10). Likewise, Wei et al. reported that severe intracranial hypertension at presentation, including papilledema and visual symptoms, was associated with poorer visual outcomes during follow-up (4). Collectively, these observations suggest that papilledema should not be regarded solely as a transient acute manifestation and support continued neuro-ophthalmological surveillance during follow-up (7). The most notable finding of our study was that baseline high-grade papilledema (Frisén grades 3–4) was significantly more frequent among patients with persistent papilledema at six months than among those without persistent papilledema. One possible explanation is that patients presenting with more severe papilledema may experience slower resolution of optic disc edema during follow-up. This observation suggests that the initial severity of papilledema may be associated with its subsequent clinical course. However, the mechanisms underlying this association could not be directly evaluated in the present study. Previous investigations have demonstrated that structural and hemodynamic changes within the optic nerve head may persist even after clinical improvement (7, 10, 15).

Recanalization status differed significantly between patients with and without persistent papilledema. Complete recanalization at six months was more frequently observed in patients without persistent papilledema than in those with persistent papilledema (76.5% vs. 12.5%, $p = 0.007$). Previous studies have suggested that persistent impairment of venous outflow may contribute to prolonged venous hypertension and delayed resolution of papilledema (2–4, 7). In this context, our findings suggest a potential relationship between recanalization status and the persistence of papilledema. However, intracranial pressure was not directly measured in our cohort, and the mechanisms underlying this association remain speculative. We did not identify significant associations between persistent papilledema and several clinical or radiological factors. Variables such as seizure occurrence, venous infarction, and multiple-sinus thrombosis were not associated with papilledema persistence. Although superior sagittal sinus thrombosis was numerically more frequent among patients with papilledema at presentation, this difference did not reach statistical significance. The superior sagittal sinus is a major site of cerebrospinal fluid (CSF) absorption through the arachnoid granulations, and its occlusion has been associated with more pronounced intracranial hypertension (4). Recent systematic reviews have likewise emphasized impaired CSF drainage at this location as an important mechanism contributing to optic disc swelling (2, 3). Nevertheless, the lack of statistical significance should be interpreted cautiously given the limited sample size of our cohort.

We found no clear association between papilledema and seizure occurrence. This finding supports the concept that CVST may manifest through distinct pathophysiological pathways. Recent clinical classifications distinguish between isolated intracranial hypertension syndromes and focal parenchymal syndromes in CVST (6). Seizures and focal neurological deficits are commonly associated with parenchymal injury, hemorrhagic infarction, or cortical vein involvement (16). In contrast, papilledema primarily reflects generalized intracranial pressure elevation resulting from impaired venous drainage. Recent studies have similarly reported that papilledema is not strongly associated with seizure occurrence in patients with CVST (17, 18). These findings have important clinical implications. Papilledema in CVST should not be considered merely a transient manifestation of the acute disease phase. Persistent papilledema may occur in a substantial proportion of patients and may threaten vision if not adequately monitored. Patients presenting with high-grade papilledema may benefit from closer neuro-ophthalmological follow-up, including regular funduscopic examinations and visual field assessments (4, 7). Accordingly, these findings may contribute to risk stratification and guide the intensity of follow-up in routine clinical practice.

Study Limitations

This study has several strengths. It was designed as a prospective cohort study with systematic follow-up at a predefined six-month interval. Papilledema severity was evaluated using the standardized Frisén grading scale rather than a simple binary classification. Furthermore, funduscopic examinations were performed by an ophthalmologist with expertise in neuro-ophthalmology, and both eyes were assessed separately. This approach enabled a more detailed evaluation of papilledema severity and its longitudinal course.

Several limitations should also be acknowledged. First, this was a single-center study with a relatively small sample size, which may have limited the statistical power to detect moderate associations in subgroup analyses. The limited sample size also precluded multivariable analysis; therefore, the observed associations should be interpreted as exploratory rather than as evidence of independent effects. Second, the proportion of hemorrhagic lesions in our cohort was lower than that reported in larger multicenter cohorts such as the ISCVT (14). This difference may partly reflect selection bias, as severely affected patients with extensive hemorrhagic lesions may not have been able to undergo detailed ophthalmological evaluation at baseline. In addition, visual field outcomes were not systematically available and therefore could not be incorporated into the analysis, despite their clinical relevance in patients with papilledema. Information regarding intracranial pressure–lowering therapies during follow-up was also not systematically collected. Consequently, the potential influence of treatment-related factors on papilledema persistence could not be reliably evaluated. Although some treatment-related differences were observed between groups, treatment allocation was not standardized and the sample size was insufficient to determine independent treatment effects. Furthermore, follow-up MRI data were not available for all patients, which may have introduced selection bias into the

analysis of recanalization and its association with papilledema persistence. Finally, intracranial pressure was not directly measured during follow-up; therefore, papilledema was used as a noninvasive clinical marker of intracranial hypertension.

CONCLUSION

In conclusion, papilledema is a common manifestation of CVST and may persist in a substantial proportion of patients during follow-up. The prevalence of baseline high-grade papilledema (Frisén grades 3–4) was higher among patients with persistent papilledema. Furthermore, complete recanalization at six months was observed more frequently in patients without persistent papilledema. In contrast, parenchymal lesions and focal neurological manifestations were not significantly associated with the persistence of papilledema. These findings underscore the importance of comprehensive neuro-ophthalmological evaluation at the time of diagnosis and continued follow-up thereafter, particularly in patients presenting with high-grade papilledema.

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RESEARCH ARTICLE

Association of Biochemical Indices with Skeletal Involvement in Primary Hyperparathyroidism

Primer Hiperparatiroidizmde Biyokimyasal İndekslerin İskelet Tutulumu ile İlişkisi

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ABSTRACT

Objective: Primary hyperparathyroidism (PHPT) is frequently associated with osteoporosis and cortical bone loss. This study aimed to investigate associations of biochemical parameters, adenoma size, the parathyroid function index (PFI), and the Wisconsin index (WIN) with osteoporosis and cortical skeletal involvement in patients with PHPT.

Materials and Methods: This retrospective study included 269 patients with PHPT. Participants were grouped by osteoporosis status. Demographic, biochemical, and densitometric data, along with PFI and WIN, were assessed. Among patients with osteoporosis, associations between distal one-third radius T-scores and biochemical parameters, composite indices, and adenoma size were examined. ROC analysis evaluated the ability of alkaline phosphatase (ALP), PTH, PFI, and WIN to distinguish osteoporosis.

Results: Osteoporosis was identified in 124 patients (46.1%). Patients with osteoporosis were older than those without osteoporosis ($p<0.001$). ALP levels were higher ($p<0.001$), whereas PTH levels showed a borderline increase ($p=0.050$). Distal one-third radius T-scores were inversely associated with serum calcium (Ca), PTH, ALP, PFI, and WIN (all $p\leq0.005$). The receiver operating characteristic (ROC) analysis showed that ALP had modest discriminative performance for osteoporosis [area under the curve (AUC)=0.674, $p<0.001$]. In contrast, PTH, PFI, and WIN showed no meaningful discriminative ability.

Conclusion: Osteoporosis was common in PHPT and associated with older age, higher ALP levels, and borderline-high PTH concentrations. PFI and WIN were associated with cortical bone loss but had limited utility for identifying osteoporosis, whereas ALP showed the highest, albeit modest, discriminatory performance among the evaluated parameters.

Keywords: Alkaline phosphatase, osteoporosis, parathyroid function index, primary hyperparathyroidism, Wisconsin index

ÖZET

Amaç: Primer hiperparatiroidizm (PHPT), sıklıkla osteoporoz ve kortikal kemik kaybı ile ilişkilidir. Bu çalışmada, PHPT'li hastalarda biyokimyasal parametreler, adenom boyutu, paratiroid fonksiyon indeksi (PFI) ve Wisconsin indeksi (WIN) ile osteoporoz ve kortikal iskelet tutulumu arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif çalışmaya primer hiperparatiroidizm (PHPT) tanısı alan 269 hasta dahil edildi. Hastalar osteoporoz varlığına göre gruplandırıldı. Demografik, biyokimyasal ve dansitometrik veriler ile paratiroid fonksiyon indeksi (PFI) ve Wisconsin indeksi (WIN) değerlendirildi. Osteoporozu olan hastalarda distal üçte bir radius T-skorları ile biyokimyasal parametreler, kompozit indeksler ve adenom boyutu arasındaki ilişkiler incelendi. Alkalen fosfataz (ALP), parathormon (PTH), PFI ve WIN'in osteoporozu ayırt etme performansı ROC analizi ile değerlendirildi.

Bulgular: Osteoporoz 124 hastada (%46,1) saptandı. Osteoporozu olan hastalar, osteoporozu olmayanlara göre daha ileri yaşta idi ($p<0,001$). ALP düzeyleri osteoporoz grubunda anlamlı olarak daha yüksek bulunurken ($p<0,001$), PTH düzeyleri sınırda anlamlı bir artış gösterdi ($p = 0,050$). Distal üçte bir radius T-skorları ile serum kalsiyum (Ca), PTH, ALP, PFI ve WIN değerleri arasında anlamlı negatif korelasyonlar saptandı (tümü için $p\leq0,005$). Alıcı çalışma karakteristiği (ROC) analizinde, ALP'nin osteoporozu ayırt etme performansının orta düzeyde olduğu görüldü [eğri altındaki alan (AUC)=0,674; $p<0,001$]. Buna karşın, PTH, PFI ve WIN'in osteoporozu ayırt etmede anlamlı bir ayırt edici güce sahip olmadığı belirlendi.

Sonuç: PHPT'li hastalarda osteoporoz sık görülmekte olup ileri yaş, yüksek ALP düzeyleri ve sınırda yüksek PTH konsantrasyonlarıyla ilişkilidir. PFI ve WIN kortikal kemik kaybı ile ilişkili bulunmasına karşın, osteoporozun belirlenmesindeki ayırt edici değerleri sınırlıdır. Buna karşılık, ALP değerlendirilen parametreler arasında en yüksek ayırt edici performansı göstermiş olmakla birlikte, bu performans yalnızca sınırlı düzeydedir.

Anahtar Kelimeler: Alkalen fosfataz, osteoporoz, paratiroid fonksiyon indeksi, primer hiperparatiroidizm, Wisconsin indeksi

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INTRODUCTION

Parathyroid hormone (PTH) plays a central role in maintaining calcium (Ca) and phosphate balance. Under normal conditions, PTH secretion is regulated by Ca-sensing receptors (CaSRs) on parathyroid cells, which respond to fluctuations in circulating ionized Ca levels. In PHPT, this regulation is disrupted, leading to excessive PTH secretion despite hypercalcemia (1). Persistently elevated PTH levels promote bone resorption, stimulate renal 1α-hydroxylase activity to increase production of active vitamin D, and enhance intestinal Ca absorption. Moreover, increased renal tubular Ca reabsorption further contributes to elevated serum Ca concentrations (2). PHPT predominantly occurs in older individuals, particularly postmenopausal women, with epidemiological studies reporting a prevalence of approximately 0.84% in the general population (3). The disorder most commonly results from a hyperfunctioning parathyroid adenoma arising from monoclonal expansion of parathyroid cells and is frequently associated with decreased CaSR expression within parathyroid tissue (4). Skeletal involvement is a major clinical manifestation of PHPT. Although cortical bone loss is considered the hallmark skeletal feature of the disease, alterations in trabecular bone microarchitecture have also been documented (5). Consequently, bone deterioration in PHPT is not restricted to cortical-rich regions such as the distal one-third radius but may also affect trabecular sites, including the lumbar spine (5,6). Previous studies have reported osteoporosis and osteopenia in approximately 48.4% and 39.9% of patients with PHPT, respectively (7). Osteoporosis is characterized by impaired bone strength resulting from reduced bone mass and deterioration in bone quality, ultimately increasing fracture susceptibility. The clinical burden of osteoporosis extends beyond low bone mineral density because osteoporotic fractures are associated with substantial disability, healthcare utilization, and mortality. Worldwide estimates indicate that nearly nine million osteoporotic fractures occur annually, including fractures of the hip, forearm, and vertebrae (8). Among these fracture types, hip and vertebral fractures are associated with particularly adverse clinical outcomes and increased mortality risk (9).

Dual-energy X-ray absorptiometry (DXA) is the standard method for measuring bone mineral density and diagnosing osteoporosis. In PHPT, the distal one-third of the radius warrants particular attention because cortical bone deterioration is often more pronounced at this site than at the lumbar spine or hip (10,11). Although reduced BMD and osteoporosis are well-recognized manifestations of PHPT, the relationship between skeletal involvement and biochemical parameters remains incompletely understood. Serum Ca and PTH concentrations are considered indicators of biochemical disease severity; however, their associations with bone loss have yielded inconsistent results across previous studies (7). Similarly, 24-hour urinary Ca excretion (24-h urine Ca), a marker of hypercalciuria, has been associated with lower BMD, although its relationship to cortical bone loss remains unclear. Other biochemical markers of bone metabolism, including serum 25-hydroxyvitamin D [25(OH)D] and alkaline phosphatase (ALP), may also influence skeletal health; however, there is still no clear consensus regarding their relationship to osteoporosis in patients with PHPT (7,12). Furthermore, studies specifically evaluating the relationship between biochemical parameters and cortical bone loss at skeletal sites, such as the distal one-third of the radius, remain limited.

Recently, composite biochemical indices such as the parathyroid function index (PFI) and Wisconsin index (WIN), derived from routine biochemical parameters, have been proposed as practical markers of disease activity and severity in PHPT (13). However, data on their association with osteoporosis and cortical skeletal involvement remain scarce. Therefore, the present study aimed to investigate the association of serum Ca, P, PTH, 25(OH)D, ALP, 24-h urine Ca, PFI, WIN, and adenoma size with osteoporosis in patients with PHPT. Additionally, we aimed to evaluate the relationship between these parameters and distal one-third radius T-scores, which serve as indicators of cortical skeletal involvement.

MATERIALS AND METHODS

This retrospective study was conducted at a tertiary endocrine center and included patients with PHPT evaluated from July 2022 to March 2026. Eligible patients were identified using the institutional electronic database, and those with complete demographic, biochemical, imaging, and densitometric records were enrolled. Clinical, biochemical, and imaging variables were extracted from medical records, including corrected serum Ca (mg/dL), P (mg/dL), PTH (pg/mL), 25(OH)D (ng/mL), ALP (U/L), 24-h urine Ca (mg/day), DXA findings, and ultrasonographic adenoma diameter (mm). Bone mineral density was assessed using dual-energy X-ray absorptiometry (DXA). All measurements were performed on the same DXA scanner (STRATOS, Diagnostic Medical Systems [DMS], Montpellier, France) throughout the study period. Routine quality control and calibration procedures were performed consistently in accordance with the manufacturer's recommendations and institutional quality assurance protocols. Bone status was interpreted according to the International Society for Clinical Densitometry (ISCD) recommendations (10). Osteoporosis was defined as a T-score ≤−2.5 at any major skeletal site in postmenopausal women and in men aged ≥50 years. In premenopausal women and in men aged <50 years, Z-scores were used for diagnostic classification. Participants with a Z-score ≤−2.0 were classified as having bone mineral density below the expected range for age. They were included in the osteoporosis group for this study. Comparisons of biochemical parameters were performed between patients with and without osteoporosis. Correlation analyses were performed using distal one-third radius T-scores as continuous variables.

The PFI and WIN were calculated using the following formulas: PFI = [corrected serum Ca (mmol/L) × PTH (pmol/L)] / serum phosphorus (mmol/L), and WIN = corrected serum Ca (mmol/L) × PTH (pg/mL) (13). For PFI calculation, corrected serum Ca and P were expressed in mmol/L, and PTH in pmol/L. For WIN calculation, corrected serum Ca was expressed in

mmol/L and PTH in pg/mL.

The study was approved by the KTO Karatay University Non-Drug and Non-Medical Device Research Ethics Committee (meeting number: 08; meeting date: April 30, 2026; decision number: 2026/031). Because the study was retrospective, only anonymized data from existing patient records were analyzed.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous data were presented as mean ± standard deviation or as median (25th–75th percentile), depending on their distribution. Categorical variables were expressed as frequencies and percentages. Between-group comparisons were performed using Student's t-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Relationships between distal one-third radius T-scores and clinical or biochemical variables, including adenoma size, were examined using Pearson's or Spearman's correlation analysis, as appropriate. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of biochemical markers and composite indices for osteoporosis. The area under the curve (AUC), 95% confidence intervals (CI), sensitivity, specificity, and optimal cutoff values were calculated. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 269 patients with PHPT were included in the study, of whom 124 had osteoporosis and 145 did not. Patients in the osteoporosis group were significantly older than those without osteoporosis (60.18 ± 9.45 vs. 52.58 ± 9.33 years, p<0.001). The proportion of female patients was comparable between the two groups, with more than 80% in each group (83.9% vs. 84.1%, p=0.953). Among the female participants, seven in the osteoporosis group and twenty in the non-osteoporosis group were premenopausal; all remaining women were postmenopausal. The prevalence of nephrolithiasis was similar between patients with and without osteoporosis. Renal stones were identified in 19 of 124 patients (15.3%) in the osteoporosis group and in 22 of 145 patients (15.2%) in the non-osteoporosis group (p=0.973). Likewise, adenoma size did not differ significantly between the groups. The median adenoma diameter was 13 mm (10–19 mm) in patients with osteoporosis and 12 mm (9.25–16 mm) in those without osteoporosis (p=0.163). Detailed biochemical and densitometric characteristics of the study cohort are presented in Table 1.

Biochemical comparisons showed similar corrected serum Ca levels between the osteoporosis and non-osteoporosis groups (10.58 ± 0.66 vs. 10.50 ± 0.66 mg/dL, p=0.665). Serum P levels were also comparable between groups [2.70 (2.30–3.10) vs. 2.70 (2.50–3.12) mg/dL, p=0.522]. In contrast, creatinine (Cr) levels were significantly lower in patients with osteoporosis [0.63 (0.56–0.74) vs. 0.71 (0.62–0.78) mg/dL, p=0.004]. Patients with osteoporosis had significantly higher ALP levels than those without osteoporosis [113.50 (87.50–151.25) vs. 94.50

Table 1. Comparison of demographic, biochemical, and densitometric characteristics between PHPT patients with and without osteoporosis.

	Osteoporosis n =124	Non-osteoporosis n = 145	p
Age (years)	60.18 ± 9.45	52.58 ± 9.33	**<0.001**
Sex, n (%)			0.953
Female	104 (83.90%)	122 (84.10%)	
Male	20 (16.10%)	23 (15.90%)	
Nephrolithiasis, n (%)			0.973
Present	19 (15.30%)	22 (15.20%)	
Absent	105 (84.70%)	123 (84.80%)	
Adenoma diameter, mm	13 (10–19)	12 (9.25–16)	0.163
Ca, mg/dL	10.58 ± 0.66	10.50 ± 0.66	0.665
P, mg/dL	2.70 (2.30–3.10)	2.70 (2.50–3.12)	0.522
Cr, mg/dL	0.63 (0.56–0.74)	0.71 (0.62–0.78)	**0.004**
ALP, U/L	113.50 (87.50–151.25)	94.50 (76–108.50)	**<0.001**
PTH, pg/mL	125 (92–191.50)	112 (85.75–147.75)	0.050
25(OH)D, ng/mL	15.65 (10.00–22.63)	17.70 (11.85–22.28)	0.236
24-h urine Ca, mg/day	355.50 ± 145.98	339.50 ± 172.20	0.204
PFI	39.76 (26.26–66.28)	35.87 (24.51–53.35)	0.150
WIN	328.50 (230.60–519)	294.30 (217.20–397.20)	0.081
Lumbar spine T-score	-3.00 (-3.43 to -2.48)	-1.20 (-1.93 to -0.50)	**<0.001**
Femoral neck T-score	-1.61 ± 0.68	-0.61 ± 0.76	**<0.001**
One-third radius T-score	-2.90 (-3.63 to -2.30)	-0.85 (-1.50 to 0.10)	**<0.001**

Values are presented as mean ± standard deviation or median (25th–75th percentile), unless otherwise indicated. Comparisons between groups were performed using the independent-samples t-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. **Statistical significance was accepted as p < 0.05.** ALP: Alkaline phosphatase, Ca: Calcium, Cr: Creatinine, DXA: Dual-energy X-ray absorptiometry, mm: Millimeter, PFI: Parathyroid function index, P: Phosphorus, PTH: Parathyroid hormone, 25(OH)D: 25-hydroxyvitamin D, WIN: Wisconsin index.

(76–108.50) U/L, p<0.001]. PTH levels were also higher in the osteoporosis group, although the difference was borderline significant [125 (92–191.50) vs. 112 (85.75–147.75) pg/mL, p=0.050].

Serum 25(OH)D levels and 24-h urinary Ca excretion were comparable between the groups. The median 25(OH)D level was 15.65 ng/mL (10.00–22.63) in patients with osteoporosis and 17.70 ng/mL (11.85–22.28) in those without osteoporosis (p=0.236). Similarly, mean 24-h urinary Ca excretion was 355.50 ± 145.98 mg/day in the osteoporosis group and 339.50 ± 172.20 mg/day in the non-osteoporosis group (p = 0.204). The PFI and WIN values were higher in patients with osteoporosis; however, these differences were not statistically significant. The median PFI was 39.76 (26.26–66.28) in the osteoporosis group and 35.87 (24.51–53.35) in the non-osteoporosis group (p=0.150). Similarly, WIN values were 328.50 (230.60–519) and 294.30 (217.20–397.20) in the osteoporosis and non-osteoporosis groups, respectively (p=0.081). Bone mineral density parameters were significantly lower in patients with osteoporosis. Lumbar spine T-scores were −3.00 (−3.43 to −2.48) in the osteoporosis group and −1.20 (−1.93 to −0.50) in the non-osteoporosis group (p<0.001). Femoral neck T-scores were also significantly lower in patients with osteoporosis (−1.61 ± 0.68 vs. −0.61 ± 0.76, p<0.001). Likewise, one-third radius T-scores were significantly lower in the osteoporosis group [−2.90 (−3.63 to −2.30) vs. −0.85 (−1.50 to 0.10), p<0.001].

Correlation analysis among patients with osteoporosis showed significant negative correlations between one-third radius T-scores and several biochemical parameters, as presented in Table 2. One-third radius T-scores were negatively correlated with serum Ca levels (r=−0.253, p=0.005), PTH (r=−0.293, p=0.001), ALP (r=−0.279, p=0.002), PFI (r=−0.283, p=0.002), and WIN values (r=−0.306, p=0.001).

ROC curve analyses of biochemical parameters for discriminating osteoporosis in patients with PHPT are shown in Figure 1. As shown in Figure 1A, ALP demonstrated modest discriminatory performance for osteoporosis, with an AUC of 0.674 (95% CI: 0.607–0.741, p<0.001), whereas PTH showed no significant discriminatory ability (AUC=0.566, 95% CI: 0.495–0.637, p=0.069). In Figure 1B, neither PFI nor WIN demonstrated meaningful discriminatory ability for osteoporosis. The AUC values were 0.513 (95% CI: 0.442–0.584, p=0.716) for PFI and 0.519 (95% CI: 0.448–0.590, p=0.603) for WIN.

Table 2. Correlations of one-third radius T-scores with clinical and biochemical parameters in PHPT patients with osteoporosis

Variable	Correlation coefficient (r)	p value
Cr	−0.121	0.184
Ca	−0.253	**0.005**
P	0.061	0.513
25(OH)D	0.156	0.089
PTH	−0.293	**0.001**
ALP	−0.279	**0.002**
PFI	−0.283	**0.002**
WIN	−0.306	**0.001**
Adenoma diameter	−0.102	0.266

Values are presented as Pearson's or Spearman's correlation coefficients, as appropriate. Statistical significance was considered at p < 0.05, and statistically significant p-values are shown in bold. ALP: Alkaline phosphatase, Ca: Calcium, Cr: Creatinine, P: Phosphorus, PFI: Parathyroid function index, PTH: Parathyroid hormone, 25(OH)D: 25-hydroxyvitamin D, WIN: Wisconsin index.

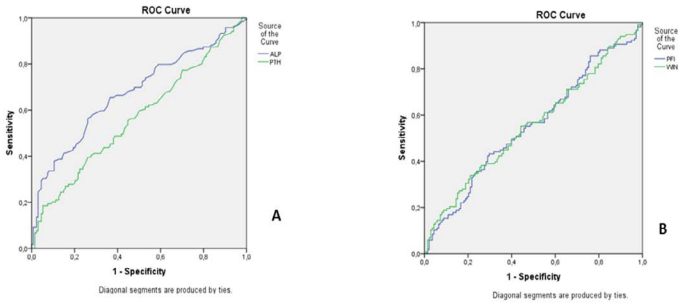

Figure 1. ROC curve analysis of biochemical parameters for discriminating osteoporosis in patients with PHPT
(A) ALP and PTH
ALP: AUC=0.674 (95% CI: 0.607-0.741), p<0.001
PTH: AUC=0.566 (95% CI: 0.495-0.637), p=0.069
(B) PFI and WIN
PFI: AUC=0.513 (95% CI: 0.442-0.584), p=0.716
WIN: AUC=0.519 (95% CI: 0.448-0.590), p=0.603

DISCUSSION

Previous studies have reported osteoporosis and osteopenia prevalence in patients with PHPT at approximately 48.4% and 39.9%, respectively (7). Consistent with the literature, osteoporosis was detected in 46.1% of patients with PHPT in the present study. PHPT is characterized by reduced bone mineral density and predominantly affects cortical bone; however, trabecular skeletal sites may also be adversely affected (5,7). In our study, patients with osteoporosis had significantly lower T-scores at the lumbar spine, femoral neck, and distal one-third radius, indicating involvement of both trabecular and cortical bone compartments. Although cortical bone involvement is considered the classic skeletal manifestation of PHPT, trabecular bone loss may also occur, particularly in patients with more severe or prolonged disease activity (5,6). Similar findings were reported by Kocabaş et al., who demonstrated that patients with lower baseline bone mineral density exhibited more pronounced skeletal involvement and evaluated skeletal recovery following parathyroidectomy in patients with PHPT (14). These findings further support the clinical importance of comprehensive skeletal assessment, including both trabecular and cortical skeletal sites, in patients with PHPT.

Furthermore, patients with osteoporosis exhibited significantly higher ALP levels and borderline higher PTH

levels than those without osteoporosis. Previous studies have demonstrated that elevated PTH levels in PHPT are associated with increased bone turnover and reduced bone mineral density, particularly at cortical skeletal sites. Bone turnover markers, including ALP, have been reported to correlate with disease severity and skeletal involvement in PHPT (15,16). In agreement with previous reports, patients with osteoporosis in our study had higher ALP levels and borderline higher PTH levels than those without osteoporosis. Moreover, ROC curve analysis showed that ALP had modest but statistically significant ability to discriminate osteoporosis in patients with PHPT (AUC=0.674), whereas PTH did not demonstrate significant discriminatory performance. However, the observed AUC indicates only modest discriminatory accuracy. Therefore, although ALP may serve as a useful adjunctive marker of skeletal involvement in PHPT, it should not be considered a reliable standalone predictor of osteoporosis and should be interpreted alongside clinical, biochemical, and densitometric findings.

Age is an established risk factor for skeletal deterioration, and the significantly older age of patients with osteoporosis in our cohort supports its contribution to bone involvement in PHPT (7). Vitamin D deficiency has been proposed to exacerbate the skeletal effects of PHPT by increasing PTH secretion and accelerating bone remodeling. Walker et al. demonstrated that lower 25(OH)D levels were associated with higher circulating PTH concentrations and greater deterioration of bone microarchitecture, suggesting a protective role of vitamin D in preserving skeletal health (17). Nevertheless, the association between serum 25(OH)D concentrations and osteoporosis in PHPT remains uncertain. Inoue et al. reported inverse relationships between 25(OH)D levels and markers of disease severity, including serum Ca and PTH, although these associations did not reach statistical significance (18). Similarly, our findings showed comparable 25(OH)D levels in patients with and without osteoporosis. Collectively, these observations indicate that vitamin D status alone may not be a major determinant of osteoporosis in PHPT. In contrast, age and disease-related biochemical alterations appear to have a greater impact on skeletal involvement.

Another finding of our study was significantly lower serum Cr levels in patients with osteoporosis. Previous studies have suggested that lower serum Cr concentrations may reflect reduced muscle mass, which has been associated with lower bone mineral density and an increased risk of osteoporosis, particularly in older individuals (19). The close relationship between muscle and bone health has led to the concept of the bone–muscle unit, in which reduced muscle mass may contribute to skeletal fragility and bone loss. In addition to biochemical parameters, several disease-related characteristics have been investigated as potential determinants of skeletal involvement in PHPT. Among these, adenoma size has been proposed as a potential indicator of disease severity, as larger adenomas are generally associated with higher serum Ca and PTH concentrations and a greater biochemical disease burden (20). Recently, Gezer et al. demonstrated a significant negative correlation between parathyroid adenoma volume and distal one-third radius bone mineral density, suggesting that larger adenomas may be associated with more pronounced cortical bone loss in patients with PHPT (21). In contrast, adenoma diameter did not differ significantly between patients with and without osteoporosis in our cohort. These findings suggest that adenoma size alone may not adequately reflect the extent of skeletal involvement or the risk of osteoporosis in PHPT.

The parathyroid function index (PFI) was originally developed as a biochemical tool to improve differentiation of PHPT from secondary hyperparathyroidism, particularly in patients with vitamin D deficiency and normocalcemic presentations. Guo et al. proposed the PFI formula based on the characteristic biochemical profile of PHPT, which typically includes elevated serum Ca and PTH levels and reduced serum P concentrations. In their study, PFI demonstrated high diagnostic sensitivity and specificity for distinguishing PHPT from vitamin D deficiency–related secondary hyperparathyroidism (22). Similarly, subsequent studies have suggested that PFI may serve as a simple and inexpensive diagnostic marker for identifying PHPT and differentiating it from other causes of elevated PTH levels (23). Therefore, PFI has primarily been studied as a diagnostic index of parathyroid functional activity rather than as a direct marker of skeletal involvement or the severity of osteoporosis. More recently, the potential role of PFI in predicting PHPT-related complications has attracted increasing interest. Baser et al. reported that a PFI of 36.43 predicted nephrolithiasis with 86% sensitivity and 68% specificity, suggesting that this index may reflect disease severity and complication risk; however, PFI was not identified as an independent predictor in multivariable analysis (13). In our cohort, although PFI values were numerically higher in patients with osteoporosis than in those without osteoporosis, the difference did not reach statistical significance. Nevertheless, within the osteoporosis group, PFI showed a significant negative correlation with one-third radius T-scores, indicating that higher PFI values are associated with more severe cortical bone loss. However, despite this correlation, PFI showed no meaningful discriminatory ability to identify osteoporosis in ROC analysis (AUC = 0.513, 95% CI: 0.442–0.584, $p = 0.716$). These findings suggest that PFI primarily reflects parathyroid functional activity and disease burden rather than osteoporosis risk. These findings are consistent with recent evidence indicating that PHPT is associated with systemic inflammatory and metabolic alterations that improve after parathyroidectomy, further supporting the concept that PHPT is a multisystem disorder and that biochemical markers may reflect overall disease burden beyond skeletal manifestations (24).

The Wisconsin Index (WIN), calculated as the product of serum Ca and PTH concentrations, was introduced by Mazeh et al. as a practical biochemical indicator of PHPT severity (20). Their findings showed that higher WIN values were linked to greater adenoma weight and increased biochemical disease activity, suggesting that WIN may reflect overall disease burden. Subsequent studies have examined WIN's utility in predicting

PHPT-related complications, particularly osteoporosis and nephrolithiasis. In a multicenter cross-sectional study, Baser et al. found a significant association between WIN and osteoporosis and proposed a cutoff of 283.29, which showed favorable diagnostic performance (13). In contrast, WIN values did not differ significantly between patients with and without osteoporosis in the present study. However, among individuals with osteoporosis, WIN showed a modest but significant inverse correlation with distal one-third radius T-scores (r=−0.306, p=0.001). This suggests that higher WIN values are associated with greater cortical bone loss. Given that the distal one-third radius consists predominantly of cortical bone and is particularly susceptible to the catabolic effects of excess PTH, this finding may have clinical relevance. Nevertheless, ROC analysis showed no meaningful discriminatory ability of WIN for identifying osteoporosis (AUC=0.519, 95% CI: 0.448–0.590, p=0.603). Therefore, although WIN may reflect certain aspects of skeletal involvement in PHPT, our results do not support its use as a reliable standalone marker for osteoporosis prediction.

Study Limitations

This study has several limitations. The retrospective, single-center design may reduce the external validity of the findings. In addition, most participants were women, reflecting the epidemiology of PHPT but potentially limiting extrapolation to male patients. Advanced techniques for evaluating bone quality, including high-resolution peripheral quantitative computed tomography and trabecular bone score analysis, were unavailable. Bone turnover markers other than ALP were not assessed. Furthermore, the observational design precludes causal inference regarding the relationship between biochemical variables and skeletal involvement. Nevertheless, the relatively large cohort and the concurrent assessment of conventional biochemical markers with PFI and WIN strengthen the study findings.

CONCLUSION

Osteoporosis was identified in 46.1% of patients with PHPT and was associated with older age, higher ALP levels, and borderline-higher PTH concentrations. Distal one-third radius T-scores showed significant negative correlations with serum Ca, PTH, ALP, PFI, and WIN, highlighting the close relationship between biochemical disease activity and cortical skeletal involvement. Among the evaluated parameters, ALP showed only modest discriminatory performance for osteoporosis, whereas PFI and WIN were associated with cortical bone loss but had no meaningful ability to identify osteoporosis.

DECLARATIONS

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OPEN

RESEARCH ARTICLE

Pan-Immune-Inflammation Value Is Independently Associated With Vascular Burden in Patients Undergoing Carotid Artery Stenting

Karotis Arter Stentleme Uygulanan Hastalarda Pan-İmmün-İnflamasyon Değerinin Vasküler Yük ile Bağımsız İlişkisi

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ABSTRACT

Objective: The pan-immune-inflammation value (PIV) is a composite inflammatory biomarker investigated in cardiovascular diseases. This study evaluated the association between PIV and vascular comorbidity burden in patients undergoing carotid artery stenting (CAS).

Materials and Methods: This retrospective study included 221 patients who underwent CAS between 2010 and 2025. PIV was calculated from peripheral blood cells. Vascular burden comprised hypertension, diabetes mellitus, hyperlipidemia, smoking, coronary artery disease, and previous cerebrovascular events. Patients were categorized into low (0–2) and high (3–5) burden groups. Associations were assessed using correlation and regression analyses, and discrimination by ROC analysis.

Results: PIV was higher in patients with high vascular burden (428.9 [287.1–701.9] vs. 287.1 [202.1–452.5], p=0.001) and correlated positively with vascular burden (rho=0.317, p<0.001). Each 100-unit increase in PIV was independently associated with high vascular burden (OR=1.152; 95% CI: 1.058–1.255; p=0.001). In adjusted ordinal regression, PIV was associated with higher vascular burden (OR=1.116; 95% CI: 1.062–1.174; p<0.001). ROC analysis yielded an AUC of 0.651 (95% CI: 0.577–0.725).

Conclusion: Higher PIV was independently associated with greater vascular comorbidity burden in patients undergoing CAS. However, its modest discriminatory performance limits its use as a standalone risk-stratification tool.

Keywords: Pan-immune-inflammation value, carotid artery stenting, vascular burden, inflammation, atherosclerosis

ÖZET

Amaç: Pan-immün-inflamasyon değeri (PIV), kardiyovasküler hastalıklarda araştırılan bileşik bir inflamatuvar biyobelirteçtir. Bu çalışmada, karotis arter stentleme (KAS) uygulanan hastalarda PIV ile vasküler komorbidite yükü arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntemler: Retrospektif çalışmaya 2010–2025 yılları arasında KAS uygulanan 221 hasta dahil edildi. PIV periferik kan hücrelerinden hesaplandı. Vasküler yük skoru; hipertansiyon, diabetes mellitus, hiperlipidemi, sigara, koroner arter hastalığı ve geçirilmiş serebrovasküler olaydan oluşan altı bileşenle belirlendi. Hastalar düşük (0–2) ve yüksek (3–5) yük gruplarına ayrıldı. İlişkiler korelasyon ve regresyon analizleriyle, ayırt edici performans ROC analiziyle değerlendirildi.

Bulgular: PIV, yüksek vasküler yük grubunda daha yüksekti (428,9 [287,1–701,9] vs. 287,1 [202,1–452,5], p=0,001). PIV ile vasküler yük arasında pozitif korelasyon vardı (rho=0,317, p<0,001). Her 100 birimlik PIV artışı, yüksek vasküler yük ile bağımsız ilişkiliydi (OR=1,152; %95 GA: 1,058–1,255; p=0,001). Düzeltilmiş ordinal regresyonda PIV, daha yüksek vasküler yük ile ilişkiliydi (OR=1,116; %95 GA: 1,062–1,174; p<0,001). ROC analizinde AUC 0,651 (%95 GA: 0,577–0,725) bulundu.

Sonuç: Yüksek PIV, KAS hastalarında daha yüksek vasküler komorbidite yükü ile bağımsız ilişkilidir. Ancak sınırlı ayırt edici performansı nedeniyle PIV tek başına risk sınıflandırma aracı olarak kullanılmamalıdır.

Anahtar Kelimeler: Pan-immün-inflamasyon değeri, karotis arter stentleme, vasküler yük, inflamasyon, ateroskleroz

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INTRODUCTION

Carotid artery stenosis remains an important cause of ischemic stroke and contributes substantially to global cerebrovascular morbidity and mortality despite advances in preventive strategies and revascularization techniques (1,2). Carotid artery stenting (CAS) has emerged as an effective alternative to carotid endarterectomy in selected patients; however, residual vascular risk and recurrent ischemic events continue to represent important clinical challenges, particularly among patients with multiple cardiovascular comorbidities (3–5). Patients undergoing CAS frequently have multiple cardiovascular risk factors and established atherosclerotic comorbidities, reflecting a broader burden of systemic vascular disease that may not be fully captured by the severity of the carotid lesion alone (4–6). Atherosclerosis is increasingly recognized as a chronic inflammatory and immune-mediated vascular disease characterized by endothelial dysfunction, lipid accumulation, oxidative stress, leukocyte recruitment, and platelet activation (7–10). Persistent vascular inflammation contributes to plaque progression, destabilization, and thromboembolic complications through complex interactions involving endothelial cells, monocytes, neutrophils, inflammatory cytokines, and activated platelets (8–11). In addition, residual inflammatory risk has emerged as a major determinant of recurrent cardiovascular and cerebrovascular events despite optimal lipid-lowering therapy (9,12). Recent evidence suggests that persistent inflammation within the vascular microenvironment plays an important role in carotid plaque vulnerability and the pathogenesis of ischemic stroke (10,13).

Platelets are central mediators of thromboinflammation and actively contribute to vascular inflammation, endothelial dysfunction, and atherosclerotic plaque progression (14,15). Beyond their traditional role in thrombosis and hemostasis, activated platelets modulate leukocyte recruitment, cytokine signaling, and immune activation within the vascular microenvironment (11,15). Experimental and translational studies have demonstrated that platelet-mediated inflammatory pathways contribute to atherosclerotic progression and vascular injury (15,16). In recent years, inflammation-based hematologic biomarkers derived from routinely measured blood parameters have attracted increasing interest as practical tools for cardiovascular and cerebrovascular risk assessment (17–19). These include the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the systemic immune-inflammation index (SII), and the pan-immune-inflammation value (PIV), all of which integrate different circulating immune and hematologic cell populations. Compared with conventional single-parameter inflammatory markers, these composite indices may provide a broader representation of systemic inflammatory and thromboinflammatory activity.

Recent evidence suggests that inflammatory and platelet-related biomarkers are associated with carotid plaque vulnerability and clinical outcomes in patients with carotid artery disease (10,13). In patients undergoing CAS, Keskin et al. demonstrated that SII was independently associated with adverse outcomes (20). Similarly, imaging studies have highlighted the close relationship between inflammatory activity and imaging features of carotid plaque vulnerability (13). Platelet-related biomarkers have also been associated with clinical characteristics and vascular events in patients with atherosclerotic carotid artery stenosis (10,16). More recently, composite nutritional and immune-inflammatory indices have also been investigated as readily available markers of cardiovascular disease burden and risk in other clinical populations, including patients with heart failure with preserved ejection fraction and those undergoing mitral balloon valvuloplasty (21,22). These findings suggest that systemic inflammatory indices may reflect broader cardiovascular disease burden. Most previous studies of patients undergoing CAS have primarily focused on procedural outcomes, cardiovascular or cerebrovascular events, or disease-specific prognostic endpoints, whereas the association between PIV and cumulative vascular comorbidity burden has not been sufficiently characterized. Importantly, the vascular burden score used in the present study reflects the accumulation of major cardiovascular risk factors and established vascular comorbidities rather than anatomical carotid disease burden or stenosis severity. Therefore, the present study aimed to investigate the association between PIV and cumulative vascular comorbidity burden in patients undergoing CAS. We hypothesized that higher PIV levels would be associated with greater cumulative vascular comorbidity burden.

MATERIALS AND METHODS

Design and Participants

This retrospective observational study included 221 consecutive patients who underwent CAS at a tertiary cardiovascular center from 2010 to 2025. The aim of this study was to evaluate the association between systemic inflammatory burden and cumulative vascular comorbidity burden in patients with carotid artery stenosis who underwent CAS. Because follow-up data were not consistently available, the analysis was restricted to baseline demographic, clinical, and laboratory parameters. Patients were eligible if they had undergone CAS for carotid artery stenosis and had the baseline demographic, clinical, and laboratory data required for the present analysis. Patients lacking sufficient baseline data to calculate either PIV or the vascular burden score were excluded. To assess cumulative vascular comorbidity burden, a vascular burden score was constructed based on the presence of major atherosclerotic risk factors and vascular comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, smoking, a history of coronary artery disease, and prior cerebrovascular events. Each variable was assigned 1 point when present, yielding a theoretical score ranging from 0 to 6. In the present cohort, the observed scores ranged from 0 to 5 because no patient had all six components.

Patients were stratified into two groups according to their vascular burden score: low vascular burden (0–2) and high

vascular burden (3–5). This investigator-defined categorization was used to distinguish patients with fewer vascular risk factors and comorbidities from those with multiple concurrent vascular risk factors and established vascular comorbidities. The cutoff was not externally validated and should therefore not be interpreted as an established clinical threshold.

Data Collection

Demographic characteristics (age and sex), cardiovascular risk factors (smoking status, hypertension, diabetes mellitus, and hyperlipidemia), a history of coronary artery disease, and prior cerebrovascular events were retrieved from electronic medical records. Baseline laboratory parameters, including complete blood count, fasting glucose, glycated hemoglobin (HbA1c), renal function tests, and lipid profile, were obtained from blood samples collected before the CAS procedure.

PIV was calculated using peripheral blood cell counts according to the following formula:

PIV = (neutrophil count × platelet count × monocyte count) / lymphocyte count

PIV is considered a composite marker integrating circulating neutrophil, platelet, monocyte, and lymphocyte counts and has been investigated as a surrogate of systemic immune-inflammatory activity.

For regression analyses, PIV values were normalized by dividing by 100 (PIV100) to improve model interpretability.

The variables constituting the vascular burden score were considered components of the outcome and were therefore not entered as separate covariates in the multivariable regression models.

Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Akdeniz University (Approval No: TBAEK-510, Date: June 4, 2026). The requirement for informed consent was waived due to the retrospective nature of the study.

Statistical Analysis

Continuous variables were summarized as either mean ± standard deviation or median with interquartile range, depending on their distributions. Categorical variables were reported as counts and percentages. Comparisons between groups were conducted using the independent-samples t-test or Mann–Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables when appropriate.

The association between PIV and the vascular burden score was evaluated using Spearman rank correlation analysis. Multivariable binary logistic regression analysis was performed to assess the independent association between PIV and high vascular burden. The model incorporated age, sex, and PIV100, and results were presented as odds ratios with corresponding 95% confidence intervals. Age and sex were included as basic demographic covariates, while PIV was the primary variable of interest. The individual components of the vascular burden score were not included in the model because they were used to define the dependent variable.

As a sensitivity analysis, the vascular burden score was also analyzed as an ordinal variable using ordinal logistic regression. The model was adjusted for age, sex, GFR, and PIV. The proportional odds assumption was assessed using the test of parallel lines. Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminative ability of PIV in identifying high vascular burden. The optimal cutoff point was determined using the Youden index, and the area under the curve, along with sensitivity and specificity, was reported. A two-sided p value <0.05 was considered indicative of statistical significance. All analyses were carried out using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 221 patients who underwent carotid artery stenting were included in the study. According to the vascular burden score classification, 131 patients (59.3%) were categorized as having low vascular burden (score 0–2), whereas 90 patients (40.7%) were classified as having high vascular burden (score 3–5). Baseline demographic, clinical, laboratory, and echocardiographic characteristics according to vascular burden groups are summarized in Table 1. There were no significant differences between groups regarding age or sex distribution. The prevalence of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, and prior cerebrovascular events was higher in the high vascular burden group; these variables were components of the vascular burden score and therefore these differences were inherent in the score definition rather than independent findings. Smoking prevalence did not differ significantly between the groups (p = 0.145). Patients with high vascular burden had significantly higher fasting glucose and HbA1c levels (both p < 0.001) and a significantly lower ejection fraction (p = 0.003). Among hematological parameters, platelet count was significantly lower in patients with high vascular burden (254,717 ± 71,006 vs. 229,166 ± 56,602 cells/μL, p = 0.003). Neutrophil, lymphocyte, and monocyte counts did not differ significantly between the low- and high vascular burden groups (p = 0.317, p = 0.973, and p = 0.679, respectively). Despite the lower platelet count, PIV was significantly higher in patients with high vascular burden than in those with low vascular burden (median [IQR]: 428.9 [287.1–701.9] vs. 287.1 [202.1–452.5], p = 0.001) (Table 1).

Spearman correlation analysis demonstrated a positive but modest correlation between PIV and the vascular burden score (Spearman's rho = 0.317, p <0.001) (Table 2). In multivariable logistic regression analysis including age, sex, and PIV100, PIV100 remained independently associated with high vascular burden (OR: 1.152 per 100-unit increase, 95% CI: 1.058–1.255, p = 0.001), whereas age and sex were not independently associated with high vascular burden after adjustment (Table 3). In a sensitivity analysis using the vascular burden score as an ordinal variable, PIV remained independently associated with higher vascular burden. After adjustment for age, sex, and GFR, each 100-unit increase in PIV was associated with 11.6%

Table 1. Baseline demographic, clinical, laboratory, and echocardiographic characteristics according to vascular burden groups

Variable	Low vascular burden (0–2) (n=131)	High vascular burden (3–5) (n=90)	p-value
Age, years	69.4 ± 10.5	68.9 ± 9.5	0.719
Male sex, n (%)	101 (77.1)	73 (81.1)	0.474
Diabetes mellitus, n (%)	12 (9.2)	60 (66.7)	<0.001
Hypertension, n (%)	65 (49.6)	78 (86.7)	<0.001
Hyperlipidemia, n (%)	11 (8.4)	53 (58.9)	<0.001
Smoking, n (%)	28 (21.4)	27 (30.0)	0.145
A history of coronary artery disease, n (%)	12 (9.2)	29 (32.2)	<0.001
A history of cerebrovascular event, n (%)	68 (51.9)	65 (72.2)	0.002
GFR, mL/min/1.73m²	77 ± 20	75 ± 19	0.666
WBC, cells/μL	8135 ± 2285	8475 ± 2611	0.307
Neutrophil count, cells/μL†	5,200 (3,800–6,700)	4,800 (4,000–5,800)	0.317
Lymphocyte count, cells/μL†	2,000 (1,500–2,600)	2,100 (1,500–2,600)	0.973
Monocyte count, cells/μL†	600 (500–800)	600 (500–750)	0.679
Hemoglobin, g/dL	13.21 ± 1.69	13.31 ± 1.59	0.665
Platelet count, cells/μL	254,717 ± 71,006	229,166 ± 56,602	0.003
LDL cholesterol, mg/dL	117.08 ± 36.97	124.74 ± 38.61	0.138
HDL cholesterol, mg/dL	42.34 ± 9.14	40.82 ± 8.69	0.212
Total cholesterol, mg/dL	190.9 ± 42.8	200.2 ± 49.7	0.152
Triglycerides, mg/dL†	143 (108–191)	166 (118–238)	0.568
Creatinine, mg/dL	1.03 ± 0.30	1.10 ± 0.82	0.436
Sodium, mmol/L	137 ± 11	138 ± 3.2	0.484
Potassium, mmol/L	4.44 ± 0.4	4.51 ± 0.5	0.241
Glucose, mg/dL†	98 (90–122)	136 (108–175)	<0.001
HbA1c, %	6.14 ± 0.89	8.14 ± 2.04	<0.001
AST, U/L	22.5 ± 10.9	22.2 ± 9.3	0.863
ALT, U/L	19.4 ± 12.4	19.7 ± 12.0	0.835
Ejection fraction, %	61.9 ± 6.9	58.5 ± 9.2	0.003
PIV†	287.1 (202.1–452.5)	428.9 (287.1–701.9)	0.001

Values are presented as mean ± standard deviation (SD), median (interquartile range [IQR]), or number (percentage), as appropriate. Continuous variables were compared using the independent-samples t-test or Mann–Whitney U test according to data distribution, and categorical variables were compared using the chi-square test. †Variables with non-normal distribution are presented as median (IQR). Abbreviations: PIV, Pan-Immune-Inflammation Value; GFR, glomerular filtration rate; WBC, white blood cell count; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2. Correlation between Pan-Immune-Inflammation Value (PIV) and the vascular burden score

Variable	Spearman rho	p
PIV vs vascular burden score	0.317	<0.001

Spearman rank correlation analysis was used to evaluate the association between PIV and the vascular burden score. PIV: Pan-Immune-Inflammation Value.

Table 3. Multivariable logistic regression analysis identifying independent predictors of high vascular burden

Variable	OR	95% CI	p
Male sex	0.929	0.464–1.858	0.834
Age	0.997	0.970–1.025	0.855
PIV100	1.152	1.058–1.255	0.001

Multivariable logistic regression model adjusted for age, sex, and PIV100. PIV100 represents the Pan-Immune-Inflammation Value per 100-unit increase. OR, odds ratio; CI, confidence interval.

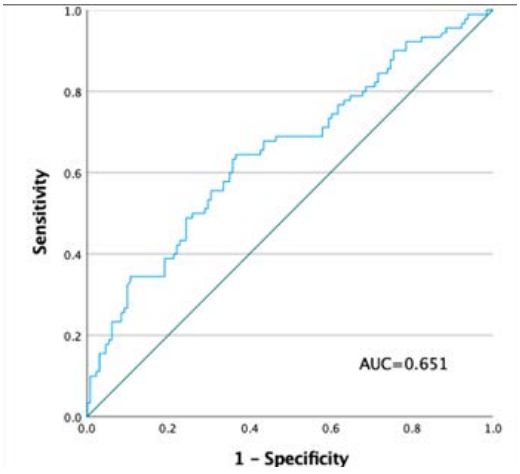

Figure 1. Receiver operating characteristic (ROC) curve of PIV for predicting high vascular burden.
The area under the curve (AUC) was 0.651 (95% CI: 0.577–0.725; p <0.001). The optimal cutoff value was 334, with 64% sensitivity and 60% specificity.

Table 4. Receiver operating characteristic (ROC) curve analysis of PIV for identifying high vascular burden

Parameter	Value
AUC	0.651
95% CI	0.577–0.725
p-value	<0.001
Optimal cutoff value	334
Sensitivity	64%
Specificity	60%

ROC curve analysis was performed to evaluate the discriminatory ability of PIV for identifying patients with high vascular burden. The optimal cutoff value was determined using the Youden index. AUC, area under the curve; CI, confidence interval.

higher odds of being in a higher vascular burden category (OR, 1.116; 95% CI, 1.062–1.174; p<0.001). The proportional odds assumption was not violated (test of parallel lines, p=0.181).

ROC curve analysis demonstrated modest discriminatory performance of PIV for identifying patients with high vascular burden (AUC = 0.651, 95% CI: 0.577–0.725, p <0.001). A PIV cutoff value of approximately 334 yielded a sensitivity of 64% and a specificity of 60% (Table 4, Figure 1).

DISCUSSION

In the present study, we found that higher PIV was independently associated with greater cumulative vascular comorbidity burden in patients undergoing CAS. Patients with higher vascular burden scores had significantly higher PIV levels, while ROC analysis showed only modest discriminatory performance. These findings suggest that PIV may reflect systemic inflammatory activity in patients with a greater accumulation of vascular risk factors and established vascular comorbidities. However, the observational design does not establish causality or prognostic utility. Atherosclerosis is increasingly recognized as a chronic inflammatory and immune-mediated disease characterized by endothelial dysfunction, lipid accumulation, leukocyte recruitment, platelet activation, and complex interactions between innate and adaptive immune responses. Persistent inflammation contributes to plaque progression, destabilization, and thromboembolic complications and represents an important component of residual cardiovascular risk. These mechanisms provide a biological rationale for investigating routinely available inflammatory biomarkers as potential indicators of systemic vascular disease burden (6–9,23).

Inflammatory activation is particularly relevant in patients undergoing CAS. Previous studies have demonstrated associations between inflammatory markers and peri-procedural embolization, stroke, restenosis, and adverse outcomes after carotid interventions. Aronow et al. demonstrated that leukocyte count independently predicted microembolic Doppler signals during carotid stenting, suggesting a relationship between systemic inflammatory activation and procedural embolization (24). Similarly, Gröschel et al. reported that preprocedural C-reactive protein levels were associated with stroke and death in patients undergoing carotid stenting (25). Wasser et al. further demonstrated an association between inflammatory markers and in-stent restenosis after CAS (26). Together, these findings indicate that systemic inflammatory activity is relevant to both the procedural and longer-term manifestations of carotid atherosclerotic disease.

Recent research has increasingly focused on composite inflammatory indices derived from routinely available hematological parameters. Such indices may capture the interaction between innate immune activation, platelet-mediated thrombosis, and lymphocyte-related immune regulation more comprehensively than individual inflammatory cell counts. PIV integrates neutrophil, platelet, monocyte, and lymphocyte counts into a single index and therefore theoretically captures several components of the systemic thromboinflammatory response simultaneously. The increasing use of composite immune-inflammatory biomarkers across cardiovascular diseases further supports their potential relevance for characterizing systemic vascular inflammation (17–19). Current evidence regarding composite immune-inflammatory biomarkers in cardiovascular disease is rapidly expanding. Previous studies have demonstrated associations between systemic immune-inflammatory indices and adverse cardiovascular outcomes in patients with cardiovascular disease. In the specific setting of carotid artery stenting, Morikawa et al. demonstrated that the systemic immune-inflammation index was associated with prognosis after CAS, further supporting the relevance of systemic inflammatory status in this population (27). The clinical relevance of composite immune-inflammatory indices has also been explored beyond carotid artery disease. Recent studies have evaluated nutritional and immune-inflammatory indices in patients with heart failure with preserved ejection fraction and those undergoing mitral balloon valvuloplasty, demonstrating their potential association with cardiovascular disease characteristics and outcomes (21,22). Although these studies evaluated different populations and inflammatory indices rather than PIV specifically, they provide additional evidence that readily available composite inflammatory markers may reflect the broader systemic burden of cardiovascular disease.

Our findings extend this concept to patients undergoing CAS by examining the relationship between PIV and cumulative vascular comorbidity burden rather than procedural outcomes or anatomical carotid disease severity. The vascular burden score used in the present study comprised six components: hypertension, diabetes mellitus, hyperlipidemia, smoking, a history of coronary artery disease, and previous cerebrovascular events, with one point assigned for each component. Thus, the score should be interpreted as an investigator-defined measure of the accumulation of major vascular risk factors and established vascular comorbidities, rather than as an anatomical measure of carotid stenosis, plaque burden, or total vascular lesion extent. Patients with higher scores had significantly higher PIV values, supporting an association between systemic inflammatory activity and the accumulation

of vascular comorbidities. Importantly, the higher prevalence of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, and previous cerebrovascular events in the high-burden group should not be interpreted as independent findings, because these variables were themselves components of the vascular burden score. Their greater frequency in the high-score group was therefore expected by definition. Instead, the more relevant findings were the differences in variables that were not directly incorporated into the score, particularly fasting glucose, HbA1c, ejection fraction, platelet count, and PIV.

PIV remained independently associated with high vascular burden after adjustment for age and sex. Each 100-unit increase in PIV was associated with approximately 15% higher odds of belonging to the high vascular burden group. Importantly, this association remained consistent when the vascular burden score was analyzed across its full ordinal range rather than dichotomized. In the ordinal logistic regression model, each 100-unit increase in PIV was associated with 11.6% higher odds of being in a higher vascular burden category (OR, 1.116; 95% CI, 1.062–1.174; $p<0.001$), after adjustment for age, sex, and GFR. The proportional odds assumption was not rejected (test of parallel lines, $p=0.181$), supporting the validity of the ordinal model. These findings provide additional support for the robustness of the association between PIV and cumulative vascular comorbidity burden. The absence of an independent association between age and vascular burden should be interpreted cautiously, particularly given the cross-sectional design and relatively limited sample size, and should not be interpreted as evidence that inflammatory activity reflects vascular aging more accurately than chronological age. The correlation between PIV and the vascular burden score was positive but modest (Spearman's rho = 0.317), indicating that the association between PIV and cumulative vascular comorbidity burden was relatively limited. Furthermore, the absence of adjustment for all potential inflammatory and clinical confounders means that residual confounding cannot be excluded. Therefore, the present findings support an independent statistical association between PIV and cumulative vascular comorbidity burden but do not establish PIV as a causal determinant or validated clinical predictor.

The ROC analysis further emphasizes the need for a cautious interpretation. PIV demonstrated an AUC of 0.651, with a sensitivity of 64% and specificity of 60% at a cutoff of approximately 334. These values indicate only modest discriminatory ability and are insufficient to support the use of PIV as a standalone diagnostic or risk-stratification tool. Rather, PIV may be considered a complementary inflammatory marker that could potentially provide additional information when interpreted together with established clinical risk factors and vascular imaging findings. Whether PIV provides incremental predictive value beyond conventional clinical and imaging variables remains unknown and requires prospective validation. The significantly lower platelet count observed in the high vascular burden group despite higher PIV values deserves consideration. PIV is a composite index determined by the combined values of neutrophil, platelet, monocyte, and lymphocyte counts rather than by platelet count alone. In the present study, neutrophil, lymphocyte, and monocyte counts did not differ significantly between the low- and high vascular burden groups ($p=0.317$, $p=0.973$, and $p=0.679$, respectively). Therefore, the higher PIV observed in the high-burden group cannot be attributed to a significant difference in any single PIV component based on these univariate comparisons. Rather, the finding reflects the combined contribution of the four cellular parameters to the composite PIV. Nevertheless, because PIV is a multiplicative index, the relative contribution of each individual component to the observed between-group difference cannot be determined from these analyses alone.

Diabetes mellitus was more prevalent in patients with high vascular burden, who also had significantly higher fasting glucose and HbA1c levels. Diabetes contributes to accelerated atherosclerosis through chronic low-grade inflammation, endothelial dysfunction, oxidative stress, and platelet activation (28,29). However, because diabetes was one of the six components of the vascular burden score, its higher prevalence in the high-burden group was inherent in the score construction rather than an independent finding. The observed metabolic differences nevertheless provide biological context for the association between systemic inflammatory activity and cumulative vascular comorbidity burden. Another important consideration is the potential influence of recent cerebrovascular events on PIV. Because the study was retrospective, the exact interval between a previous cerebrovascular event and blood sampling could not be consistently standardized. Consequently, acute or subacute inflammatory responses related to a recent cerebrovascular event may have contributed to PIV values in some patients. This issue is particularly relevant because previous cerebrovascular events were also incorporated into the vascular burden score. Therefore, the association between PIV and the composite score may partly reflect inflammation associated with recent vascular events rather than solely chronic systemic inflammatory burden. The present study has several strengths. First, to our knowledge, few studies have specifically examined the association between PIV and cumulative vascular comorbidity burden in patients undergoing CAS. Second, PIV is derived from routinely available complete blood count parameters and therefore does not require specialized or costly laboratory testing. Third, the study explicitly distinguishes cumulative vascular comorbidity burden from anatomical carotid disease burden, thereby addressing a clinically relevant aspect of systemic atherosclerotic disease that may not be captured by stenosis severity alone.

Study Limitations

Several limitations should be acknowledged. First, the retrospective, single-center design and relatively modest sample size limit causal inference, precision of estimates, and generalizability. Second, the vascular burden score was investigator-defined and has not been externally validated; therefore, it should be considered a descriptive measure of cumulative vascular comorbidity burden rather than a

validated risk score. Third, the absence of longitudinal follow-up precluded assessment of the prognostic value of PIV for subsequent clinical events. Fourth, detailed information on symptomatic status, carotid stenosis characteristics, plaque morphology, and background medical treatment was not consistently available. Finally, potential confounding factors, including active infection, chronic inflammatory conditions, and medications affecting inflammatory or hematological parameters, could not be comprehensively assessed, and advanced inflammatory biomarkers such as high-sensitivity C-reactive protein and interleukin-6 were not routinely available.

Future prospective multicenter studies with larger samples, standardized blood sampling, detailed carotid imaging, and longitudinal clinical follow-up are warranted to determine whether PIV provides incremental prognostic or risk-stratification value beyond conventional clinical and imaging variables.

CONCLUSION

In patients undergoing carotid artery stenting, higher PIV was independently associated with greater cumulative vascular comorbidity burden. However, its modest discriminatory performance does not support its use as a standalone risk-stratification or prognostic tool. PIV may provide complementary information regarding systemic immune-inflammatory activity in this population. Further prospective studies are needed to establish its clinical utility.

DECLARATIONS

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RESEARCH ARTICLE

HPV Testing and Vaccination Knowledge and Uptake Among Final-Year Medical Students in Central Anatolia: A Cross-Sectional Study

Orta Anadolu'daki Son Sınıf Tıp Öğrencileri Arasında HPV Testi ve Aşısı Hakkında Bilgi Düzeyi ve Uygulanma Durumu: Kesitsel Bir Çalışma

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ABSTRACT

Objective: This study aimed to evaluate knowledge of human papillomavirus (HPV), HPV testing, and HPV vaccination among final-year medical students in Central Anatolia and to determine HPV vaccination uptake.

Materials and Methods: We conducted this cross-sectional descriptive study between March and June 2025. After ethics committee approval, we distributed an online questionnaire to intern doctors from eight medical faculties in Konya, Ankara, Kayseri, Aksaray, and Karaman in the Central Anatolia Region. A total of 384 interns who voluntarily participated and completed the questionnaire were included in the study. Data were collected using an online survey comprising sociodemographic characteristics and the 33-item Turkish-validated Human Papillomavirus Knowledge Scale (HPV-KS). Statistical analyses were performed using SPSS version 31, and group comparisons were conducted using the Mann–Whitney U test. A p value of <0.05 was considered statistically significant.

Results: Among the 384 intern doctors included in the study, only 2.1% had received the HPV vaccine. The mean HPV knowledge score was 24.64±3.92. Among the subdomains, general HPV knowledge was highest, whereas knowledge regarding the protective effects of HPV vaccines was lowest. Notable gaps were identified in knowledge related to HPV testing and vaccination. No significant associations were observed between sociodemographic or behavioural characteristics and HPV knowledge levels (p>0.05).

Conclusion: Final-year medical students demonstrated significant deficiencies in HPV-related knowledge and very low vaccination uptake. These findings suggest that current medical education may be insufficient in terms of preventive medicine. Strengthening HPV-related education may improve future patient counselling and contribute to increasing vaccination rates.

Keywords: Human Papillomavirus (HPV), HPV vaccination, medical students, HPV knowledge

ÖZET

Amaç: Bu çalışmanın amacı, Orta Anadolu'daki son sınıf tıp öğrencilerinde insan papillomavirüsü (HPV), HPV testi ve HPV aşısına ilişkin bilgi düzeyini değerlendirmek ve HPV aşılanma durumunu belirlemektir.

Gereç ve Yöntemler: Bu kesitsel ve tanımlayıcı çalışma, Mart–Haziran 2025 tarihleri arasında Orta Anadolu'daki çeşitli tıp fakültelerinde öğrenim gören intörn doktorlar arasında gerçekleştirildi. Gönüllü olarak katılan ve çevrimiçi anketi eksiksiz dolduran 384 intörn çalışmaya dahil edildi. Veriler, sosyodemografik özellikleri içeren çevrimiçi anket formu ve Türkçe geçerlilik-güvenilirliği yapılmış 33 maddelik HPV Bilgi Ölçeği (HPV-KS) kullanılarak toplandı. İstatistiksel analizler SPSS 31 programı ile yapıldı ve gruplar arası karşılaştırmalarda Mann–Whitney U testi kullanıldı. p<0,05 anlamlı kabul edildi.

Bulgular: Çalışmaya katılan 384 intörn doktorun yalnızca %2,1'inin HPV aşısı olduğu saptandı. Ortalama HPV bilgi puanı 24,64±3,92 idi. Alt boyutlar incelendiğinde, genel HPV bilgi düzeyinin en yüksek, HPV aşısının koruyuculuğuna ilişkin bilginin ise en düşük olduğu görüldü. HPV testi ve aşıya yönelik bilgi alanlarında önemli eksiklikler dikkat çekti. Sosyodemografik ve davranışsal özellikler ile HPV bilgi düzeyi arasında anlamlı bir ilişki saptanmadı (p>0,05).

Sonuç: Son sınıf tıp öğrencilerinde HPV ile ilişkili bilgi düzeyinde önemli eksiklikler ve oldukça düşük aşılanma oranı bulunmaktadır. Bu bulgular, mevcut tıp eğitiminin koruyucu hekimlik açısından yetersiz olabileceğini düşündürmektedir. HPV eğitiminin güçlendirilmesi, gelecekte hasta danışmanlığı ve aşılanma oranlarının artırılmasına katkı sağlayabilir.

Anahtar Kelimeler: İnsan Papillomavirüsü (HPV), HPV aşısı, tıp öğrencileri, HPV bilgi düzeyi

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INTRODUCTION

Human papillomavirus (HPV) infection is among the most prevalent sexually transmitted diseases worldwide and plays a major role in the development of multiple malignancies. It is estimated that HPV-related cancers constitute approximately 4–5% of the global cancer burden (1,2). The presence of HPV DNA in nearly all cervical cancer cases highlights its fundamental etiological role in this disease. Beyond cervical cancer, HPV has also been implicated in the pathogenesis of several other malignancies, including anal, oropharyngeal, vulvar, vaginal, and penile cancers (3,4). To date, more than 200 HPV genotypes have been identified, of which approximately 14 are considered high-risk due to their oncogenic potential. Among these, HPV types 16 and 18 account for nearly 70% of cervical cancer cases (2,5). The majority of HPV infections remain asymptomatic, facilitating unintentional transmission among individuals. This underscores the importance of improving public awareness regarding HPV infection, including its modes of transmission as well as available preventive and screening strategies. In this context, strengthening educational initiatives, vaccination programs, and screening efforts is essential for reducing the burden of cervical cancer and other HPV-related malignancies (6,7).

Intern doctors, as senior medical students, play a critical role in improving HPV awareness, as they will soon engage directly with the population in primary healthcare settings after graduation. This study therefore sought to evaluate the adequacy of HPV- and HPV vaccination–related educational content within medical school curricula and to objectively assess intern doctors' knowledge levels on these topics. The findings of this research may help inform curriculum revisions, support the development of targeted educational interventions, and strengthen vaccination and screening strategies during the early stages of medical practice.

MATERIALS AND METHODS

Design and Participants:

This cross-sectional descriptive study was designed between March and June 2025. During the study preparation phase, the study protocol was developed, the questionnaire was prepared, and communication was established with participating medical faculties. Following approval from the KTO Karatay University Faculty of Medicine Non-Drug and Non-Medical Device Research Ethics Committee (Approval No: 2025/019; 12 June 2025), the online questionnaire was distributed, and data collection was conducted thereafter. Participants were recruited from eight medical faculties located in Konya, Ankara, Kayseri, Aksaray, and Karaman, including both public and foundation universities in the Central Anatolia Region. The questionnaire was disseminated through institutional and student communication networks. Participation was voluntary, convenience sampling was used, and only fully completed questionnaires were included in the final analysis.

The Human Papillomavirus Knowledge Scale (HPV-KS) was utilised to assess participants' knowledge levels regarding human papillomavirus (HPV), HPV testing, and HPV vaccination. The scale was originally developed by Waller et al. in 2013, and its Turkish validity and reliability study was conducted by Demir Bozkurt and Özdemir in 2023. The instrument consists of 33 items, each scored as "1" for correct responses, while incorrect or "I do not know" responses are scored as "0", yielding a total possible score ranging from 0 to 33, with higher scores indicating greater knowledge regarding HPV (Supplementary File S2).

The scale comprises four subdomains:

General knowledge about HPV (AÖ1), knowledge related to HPV testing (AÖ2), knowledge of existing types of HPV vaccines (AÖ3), and awareness of the protective properties of HPV vaccines (AÖ4). The questionnaire was prepared electronically using Google Forms and distributed online. In addition to the HPV Knowledge Scale, the survey included questions on sociodemographic and behavioural characteristics, including age, gender, marital status, type of university attended (public or private), smoking status, sexual activity status, and history of HPV vaccination.

The inclusion criteria were being an actively practising intern doctor and providing complete responses to all questionnaire items. Questionnaires that were partially completed or contained inconsistent responses were excluded from the analysis. Participation was entirely voluntary. To minimise potential social desirability and reporting bias, the survey was administered anonymously and without collecting any personally identifiable information. The target sample size was determined based on the estimated number of accessible intern doctors in the participating universities during the data collection period, and all eligible students who could be reached were invited to take part in the study.

Ethical Approval:

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the KTO Karatay University Faculty of Medicine Non-Drug and Non-Medical Device Research Ethics Committee (Approval No: 2025/019; 12 June 2025) before participant recruitment and data collection commenced. Electronic informed consent was obtained from all participants before they completed the questionnaire. Data were collected anonymously without requesting any personally identifiable information, and the confidentiality of all participants was strictly maintained.

Statistical analysis:

Statistical analyses were performed using IBM SPSS Statistics version 31 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean, standard deviation, median, quartiles, and minimum–maximum values for quantitative variables, and as frequencies and percentages for categorical variables. The distribution of quantitative variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. As the majority of scale and subscale scores did not show a normal distribution, comparisons between two independent groups were conducted using the Mann–Whitney U test. All HPV Knowledge Scale total and subscale scores were analysed as continuous variables and were not categorised into predefined

groups.Because only fully completed questionnaires were included in the analysis, no missing data were present for the variables used in the statistical analyses.

Box-and-whisker plots were used to visually present the distribution of total and subscale scores of the HPV Knowledge Scale across categories of selected categorical variables. No subgroup, interaction, or sensitivity analyses were performed. A two-sided p value of <0.05 was considered statistically significant, and all statistical tests were interpreted with a 95% confidence interval. The internal consistency of the HPV Knowledge Scale in the current study sample was assessed using Cronbach's alpha coefficient. Correct responses were scored as 1, whereas incorrect and "I do not know" responses were scored as 0, in accordance with the scoring procedure of the scale.

RESULTS

The sociodemographic characteristics of the 384 intern doctors included in the study are presented in Table 1. Of the participants, 56.3% were female and 43.8% were male. The majority of the participants were single (97.4%), while only 2.6% were married. Regarding the type of university attended, 88.5% were studying at public universities and 11.5% at private (foundation) universities. When HPV vaccination status was evaluated, it was determined that only 2.1% of the intern doctors had received at least one dose of the HPV vaccine, whereas 97.9% reported not having been vaccinated. Regarding smoking habits, 16.1% of the participants reported current smoking, while 83.9% stated that they were non-smokers. Evaluation of sexual activity revealed that 5.7% of the participants reported being sexually active, while 94.3% reported not having an active sexual life (Table 1).

The HPV Knowledge Scale (HPV-KS) total score reflects the overall level of knowledge regarding HPV. The first subdimension of the scale (AO1) evaluates general knowledge about HPV, the second subdimension (AO2) assesses knowledge related to HPV testing, the third subdimension (AO3) measures awareness of currently available HPV vaccines, and the fourth subdimension (AO4) evaluates knowledge regarding the protective properties of HPV vaccines. The scale comprises 16 items in AO1, 6 items in AO2, 5 items in AO3, and 6 items in AO4. The mean total HPV knowledge score was 24.640 ± 3.922 (range: 6–32). The mean AO1 score was 12.599 ± 1.572 (range: 6–15), while the mean AO2 score was 4.333 ± 1.339 (range: 0–6). The mean AO3 score was 4.338 ± 0.957 (range: 0–5), and the mean AO4 score was 3.369 ± 1.319 (range: 0–6). The presence of minimum scores of zero in AO2, AO3, and AO4 indicates that some participants reported no correct responses in the domains of HPV testing and HPV vaccination. The mean scores of the HPV testing- and vaccine-related subdimensions (AO2, AO3, and AO4) were similar, suggesting comparable levels of awareness across these domains. Among all subdimensions, general HPV knowledge (AO1) showed the highest mean score, whereas knowledge related to the protective properties of HPV vaccines (AO4) showed the lowest mean score. Overall, these findings indicate that while general awareness of HPV was relatively adequate, important gaps remain in knowledge related to screening and vaccination (Table 2).

Because only fully completed questionnaires were included in the analyses, no missing data were present for the main outcome variables. Comparisons of total and subscale HPV Knowledge Scale scores according to sociodemographic and behavioural characteristics are summarised in Table 3. There were no statistically significant differences between male and female participants in either the total score or any of the subscale scores (all $p > 0.05$). Similarly, marital status was not associated with HPV knowledge levels, and no significant differences were observed between single and married participants across the total or subscale scores (all $p > 0.05$). The comparison between students attending public and private universities likewise revealed no significant differences in the total or subscale scores of the HPV Knowledge Scale

Table 1. Sociodemographic Characteristics of the Study Participants

Variable	Category	n (%)
Gender	Male	168 (43.8)
	Female	216 (56.3)
Marital Status	Single	374 (97.4)
	Married	10 (2.6)
Type of University	Public	340 (88.5)
	Private	44 (11.5)
HPV Vaccination	Yes	8 (2.1)
Status	No	376 (97.9)
Smoking	Yes	62 (16.1)
Status	No	322 (83.9)
Sexual Activity	Yes	22 (5.7)
	No	362 (94.3)
Total		84 (100.0)

Table 2. Distribution of Responses According to Subdomains of the HPV Knowledge Scale

Subdomains of HPV-KS (n:384)	Min-Max	Mean±SD
What do you know about HPV?	6-15	12.59±1.57
What do you know about HPV testing?	0-6	4.33±1.34
What do you know about the types of available HPV vaccines?	0-5	4.34±0.96
What do you know about the protective properties of HPV vaccines?	0-6	3.37±1.32
Total Score	6-32	24.64±3.92

Min: Minimum, Max: Maximum, SD: Standard Deviation

Table 3. Comparison of HPV Knowledge Scale Total and Subscale Scores According to Sociodemographic Variables

Variables	Categories	First Subdimension Median (Q1-Q3) Mean±SD	Second Subdimension Median (Q1-Q3) Mean±SD	Third Subdimension Median (Q1-Q3) Mean±SD	Fourth Subdimension Median (Q1-Q3) Mean±SD	Total Score Median (Q1-Q3) Mean±SD
Gender						
	Male	13(12-14)	4(4-5)	5(4-5)	3(2-4)	25(23-27)
		12.66±1.55	4.40±1.28	4.44±0.76	3.17±1.35	24.69±3.62
	Female	13(12-14)	5(3-5)	5(4-5)	4(3-4)	25(23-27)
		12.55±1.59	4.27±1.38	4.26±1.07	3.52±1.28	24.60±4.16
	p-value	0.413	0.626	0.492	0.112	0.883
Marital Status						
	Single	13(12-14)	4(4-5)	5(4-5)	4(3-4)	25(23-27)
		12.62±1.57	4.31±1.34	4.34±0.96	3.36±1.31	24.63±3.94
	Married	13(10.50-13)	5(4.50-6)	4(4-5)	4(2-5)	26(22-28)
		12.00±1.41	5.20±0.84	4.40±0.55	3.60±1.82	25.20±3.35
	p-value	0.337	0.125	0.738	0.724	0.746
University Type						
	Public	13(12-14)	4(4-5)	5(4-5)	3(3-4)	25(23-27)
		12.59±1.57	4.28±1.33	4.35±0.98	3.36±1.30	24.58±3.88
	Private	13(12-14)	5(4-6)	4(4-5)	4(2-4.25)	25.50(23.75-28.25)
		12.64±1.62	4.68±1.39	4.27±0.77	3.45±1.47	25.04±4.31
	p-value	0.669	0.090	0.336	0.629	0.395
HPV Vaccination Status						
	Vaccinated	12.50 (11.25-14.50)	4(3.25-5.50)	5(5-5)	2.50(2-3.75)	23(23-28.25)
		12.75±1.71	4.25±1.26	5.00±0.00	2.75±0.96	24.75±3.50
	Not Vaccinated	13(12-14)	4(4-5)	5(4-5)	4(3-4)	25(23-27)
		12.59±1.57	4.34±1.34	4.32±0.96	3.38±1.32	24.64±3.94
	p-value	0.955	0.712	0.094	0.230	0.677
Smoking Status						
	Yes	13(12-14)	4(3-5)	5(4-5)	3(2-4)	25(22-27)
		12.52±1.98	4.03±1.52	4.09±1.39	3.06±1.44	23.71±4.98
	No	13(12-14)	5(4-5)	5(4-5)	4(3-4)	25(23-27)
		12.61±1.48	4.39±1.29	4.38±0.84	3.43±1.29	24.82±3.67
	p-value	0.803	0.250	0.489	0.268	0.442
Sexual Activity	Yes	13(11-13)	5(3-6)	4(4-5)	4(2-4)	25(21-28)
		12.18±1.33	4.45±1.37	4.18±0.75	3.36±1.36	24.18±3.28
	No	13(12-14)	4(4-5)	5(4-5)	4(3-4)	25(23-27)
		12.62±1.59	4.33±1.34	4.34±0.97	3.37±1.32	24.66±3.96
	p-value	0.282	0.780	0.244	0.881	0.479

Q1: 1st quartile, Median: 2nd quartile, Q3: 3rd quartile, SD: Standard Deviation

(all $p > 0.05$). HPV vaccination status was not associated with knowledge levels, as vaccinated and unvaccinated participants demonstrated comparable scores in the overall scale and in each subdimension (all $p > 0.05$). In addition, no statistically significant differences in HPV knowledge were observed between smokers and non-smokers, or between participants who reported being sexually active and those who were not (all $p > 0.05$). When the distribution of HPV knowledge scale total and subscale scores according to sociodemographic variables was examined, it was observed that there were generally similar distribution structures among the groups, the median values ??were close to each other, and the observed differences were at a limited level (Figure 1.).

All HPV Knowledge Scale total and subscale scores were analysed as continuous variables and were not categorised into predefined groups. No additional subgroup or sensitivity analyses were performed. The HPV Knowledge Scale demonstrated acceptable internal consistency in the current sample, with a Cronbach's alpha coefficient of 0.768.

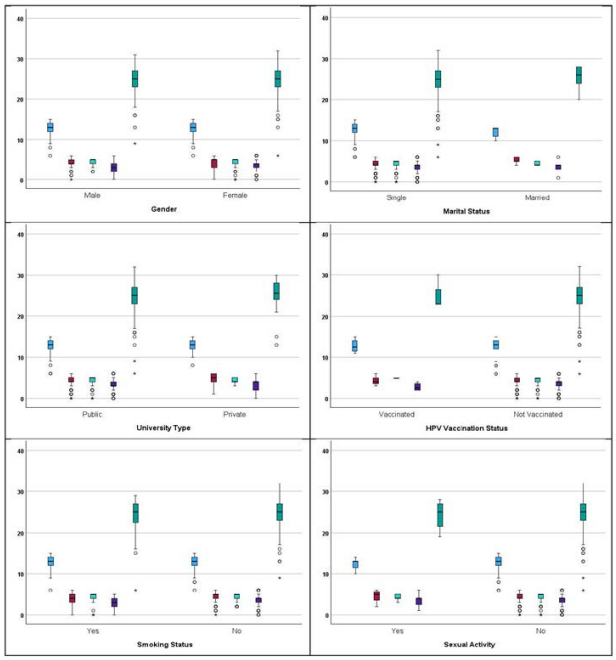

Figure 1. Boxplots of HPV Knowledge Scale Total and Subscale Scores According to Sociodemographic Variables

DISCUSSION

The findings of this cross-sectional study conducted among final-year medical students in Central Anatolia revealed notable deficiencies in HPV-related knowledge, particularly in the domains of testing and vaccination, together with a remarkably low rate of vaccine uptake. Collectively, these results indicate that current medical training may not adequately convert HPV-related theoretical information into practical knowledge and preventive behaviours at the early stages of clinical practice. In the present study, HPV knowledge scores were comparable across all examined variables, including gender, marital status, university type, vaccination status, smoking, and sexual activity, suggesting a consistently low baseline level of knowledge that cannot be attributed to sociodemographic or behavioural differences. Similar findings have been reported in studies conducted in Saudi Arabia, where medical students demonstrated limited HPV-related knowledge and low vaccination uptake, as well as in China, where higher knowledge levels were associated with a greater likelihood of recommending HPV vaccination (9,10). Likewise, studies from Türkiye have highlighted insufficient HPV awareness and notable vaccine hesitancy among medical trainees (1). Although research from the United States indicates a relatively better understanding of HPV's oncogenic role, important gaps persist in knowledge related to vaccination schedules and screening practices. In line with these observations, our results showed that the lowest mean scores were observed in the subdomains of HPV testing, vaccine types, and the protective effects of vaccination, pointing to deficiencies in prevention-oriented competencies that are critical for effective patient counselling and public health promotion (12,13).

The exceptionally low vaccination rate in our cohort (2.1%) is particularly noteworthy. Given the World Health Organization's recognition of HPV vaccination as an important component of cervical cancer prevention and the prevention of other HPV-associated malignancies, this low uptake among future physicians warrants attention (1). The lower level of knowledge regarding HPV vaccination and its protective effects compared with general HPV knowledge may be related to both educational and healthcare system factors. Although medical students receive information about HPV and its association with cervical cancer during undergraduate training, opportunities for practical exposure to HPV vaccination, including vaccine indications, schedules, and counselling, may be more limited. In addition, HPV vaccination was not routinely included in the national immunization program in Türkiye during the study period, which may have further limited students' exposure to vaccination practices in routine clinical settings (14). Greater emphasis on the practical aspects of HPV vaccination in undergraduate medical education may therefore help address these specific knowledge gaps. The absence of gender-based differences in knowledge in our sample contrasts with some previous studies reporting higher knowledge levels among women; differences in curricular exposure, clinical training environments, and public health engagement may partly explain these discrepancies (15).

Policy implications: National medical curricula should incorporate competency-based HPV education modules that explicitly address screening algorithms, vaccine indications and schedules, and structured approaches to counselling vaccine-hesitant individuals. In parallel, collaboration between the Ministries of Health and Education to facilitate on-campus access to HPV vaccination for medical students such as free vaccination programmes and reminder systems may help position future physicians as early adopters and credible advocates for HPV prevention.

Study Limitations

Several limitations of this study should be acknowledged. First, participation was voluntary and data were collected through an online survey, which may have introduced selection bias and limited the representativeness of the study population. Second, HPV-related knowledge, vaccination status and personal behaviours were self-reported and may therefore be affected by recall bias and social desirability bias, despite the anonymous design of the questionnaire. In addition, the cross-sectional nature of the study precludes any causal interpretation of the observed associations between individual characteristics and knowledge levels. Finally, although the sample size was relatively large, the study was confined to intern doctors in the Central Anatolia Region, and unmeasured institutional or curricular differences between medical schools may have influenced the findings.

CONCLUSION

Final-year medical students demonstrated substantial deficiencies in HPV testing and vaccination knowledge and an extremely low level of vaccine uptake. These findings indicate that current curricula are not adequately equipping future physicians with prevention-focused competencies. Enhancing the content, scope, and practical application of HPV education-particularly screening pathways, vaccine indications and schedules, and communication strategies to address hesitancy-may strengthen students' personal preventive behaviours, improve counselling efficacy, and ultimately contribute to reducing the national burden of HPV-related disease.

DECLARATIONS

Conflict of Interest: *The authors declare no competing interests.*

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