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The Evolving Regulatory Landscape of Artificial Intelligence in Healthcare: Balancing Innovation, Regulation, and the Human Factor

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Keywords: Artificial intelligence, privacy, legislation

Artificial intelligence (AI) is reshaping healthcare, from diagnostic imaging to predictive analytics and personalised medicine (1). Its potential to improve outcomes, reduce administrative burden, and transform clinical practice is immense. Yet, as algorithms begin to influence life-and-death decisions, society faces a pressing question: how can we regulate AI responsibly without stifling innovation or eroding trust? The answer lies not in choosing between progress and protection, but in creating laws that are both technically informed and firmly grounded in humanity. Regulation is essential, but it must recognise technical constraints, support innovation where appropriate, and, above all, protect patients.

Unlike AI used in purely commercial or logistical settings, healthcare AI operates in an environment where errors can be devastating. Many advanced models function as so-called "black boxes", offering results without a clear explanation of how they were reached. When a system misdiagnoses a tumour or fails to flag an allergy, the legal question of who is responsible, the developer, clinician, or institution, becomes murky. This lack of transparency complicates accountability and poses a real challenge for both law and ethics. Such incidents are not theoretical abstractions. Real-world examples have already revealed racial and socio-economic bias in commercial algorithms that allocate healthcare resources. In some cases, systems offered less care to equally sick patients from under-represented groups, exposing how bias in training data can amplify inequality (2). AI may also cause false diagnosis or treatment. In a recent example in the United Kingdom a patient was sent a letter for a diabetic eye screening despite not being diagnosed due to AI-driven operations (3). For the individual patient misdiagnosed or misinformed, even psychological distress from a false or delayed diagnosis is a tangible form of harm.

Existing legal frameworks were not designed with such complexity in mind. Traditional doctrines of negligence and product liability assume human agency and direct causation, yet AI blurs both. A radiologist who misses a lesion might face malpractice proceedings, but what if the fault lies in the algorithm's flawed training data or insufficient validation? Existing regimes rarely address this nuance. The challenge is not merely to patch old laws but to reinterpret them and, when they fall short, rethink accountability for a world in which human and machine decisions are intertwined. The solution cannot be a rigid regulatory code but rather a flexible, adaptive framework capable of evolving with technological change.

Recent regulatory efforts such as the European Union's Artificial Intelligence Act (4), despite critics arguing otherwise, signal movement in this direction. The Act's risk-based approach, which categorises AI systems by their potential impact on safety and fundamental rights classifies certain medical AI use cases as "high risk", demanding stricter oversight, such as risk management, human supervision, and post-market monitoring. Yet this is only one facet. The AI Act, for instance, is rooted largely in product safety law, focusing on the AI system as a marketable item rather than on how it is used over time in clinical contexts (5). Real-world deployment often diverges from testing conditions; algorithms

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may drift, and datasets may age. Regulation must therefore extend beyond static oversight, ensuring that safety and fairness persist long after an AI tool leaves the laboratory.

Overregulation, however, carries its own risks. Excessive procedural hurdles or inflexible rules can discourage innovation, preventing potentially life-saving tools from reaching patients. Healthcare AI develops rapidly, and laws that take years to adapt may already be obsolete by the time they are implemented. The challenge, then, is to create governance mechanisms that are responsive but not reckless, frameworks that encourage experimentation under supervision, with strong auditing and feedback loops rather than static compliance checklists. Regulatory sandboxes exemplify this approach by allowing iterative learning between developers and regulators, helping both sides refine their understanding of safe innovation. Indeed, AI Act contains specific provisions on regulatory sandboxes while the United Kingdom has "AI Airlock" sandbox allows innovators to test medical AI tools in controlled conditions, balancing safety with experimentation (6).

Data governance remains another area of tension. Health data is the raw material of AI in health. Regulations such as the General Data Protection Regulation (7) and Health Insurance Portability and Accountability Act (8) impose strict rules on collection, storage, and processing, rightly protecting individuals' privacy and autonomy. Yet AI systems thrive on large and diverse datasets, and overly restrictive access rules can hamper model accuracy, limit representativeness, and inadvertently perpetuate bias. The challenge is not to weaken privacy protections but to enable ethical innovation within them. Privacy-preserving technologies, such as federated learning and differential privacy, can allow insights to be drawn from distributed data without compromising individual identities. Regulatory models should encourage such approaches, demonstrating that privacy and progress need not be opposing forces (9).

Even with sophisticated legal instruments, the success of AI regulation depends on something less technical but more fundamental: understanding. Regulations only work if the people they are designed to protect can comprehend them. For most patients, and indeed for many clinicians, the mechanisms of AI and the meaning of data disclosures are opaque. Patients are often unaware that an algorithm contributed to their diagnosis or treatment, and even when they are informed, the language used is frequently impenetrable. If individuals cannot understand their rights, the limitations of AI tools, or how to challenge an adverse outcome, then the protections offered by law remain largely theoretical. True transparency is not achieved by publishing complex technical documents but by ensuring that information is conveyed in accessible, human terms. Clinicians need clear guidance on how to explain AI's role in care, and patients deserve communication that respects both their intelligence and their anxiety. There are studies demonstrating that communicating AI error rates to patients may also decrease perceived liability (10).

Ultimately, regulation is not only a technical exercise. AI in healthcare must be governed by principles that place human welfare, dignity, and comprehension at the centre. Innovation is vital, and it drives progress and can save lives. However, in the health domain it should not take precedence over safety or psychological well-being. Every regulation, every ethical guideline, must begin with the patient, not the algorithm. The measure of effective governance is not how many rules are written but how well those rules are understood and trusted by those they aim to protect.

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The Use of Artificial Intelligence by the Administration in Health Services and the Resulting Liability in Turkish Law

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INTRODUCTION

In recent years, artificial intelligence (AI) has initiated a transformation in the delivery of health services. Utilizing AI alongside traditional methods is a requirement of the principle of adapting public services to modern needs (1). AI has extended from imaging analysis to early and accurate diagnosis, from personalized treatments to drug development, and from home healthcare to hospital management. It has influenced the organization and operation of healthcare institutions and ensured effective use of limited resources (2).

The status of health services is explicitly provided under Article 56 of the Turkish Constitution, which mandates the State to ensure that everyone lives in physical and mental health and to establish and operate the necessary organizational structure. Thus, the integration and regulation of AI in health services also fall under the responsibility of the State.

The purpose of this article is to discuss the legal basis, limits, and potential liabilities of the administration's use of AI in the delivery of healthcare services under Turkish law. The use of AI in health services may conflict with the traditional concept of public service and raises new questions of liability.

I. The Use of AI in Health Services

AI is defined as "software that can generate outputs such as content, predictions, recommendations, or decisions for human-defined objectives, influencing the environment with which it interacts" (3). According to the Council of Europe's 2018 declaration, AI systems "demonstrate intelligent behavior by analyzing their environment and taking action to achieve specific goals, functioning with a certain degree of autonomy" (4). Thus, AI—like a human—has the ability to make decisions independently based on available data (5).

AI offers opportunities that go beyond assisting physicians in organizing, diagnosing, or treating patients; it allows for direct diagnosis or treatment without human medical personnel.

A. The Legal Framework of AI Use in Health Services

Turkish legislation does not currently contain explicit provisions on whether or to what extent AI may be used in healthcare. According to Article 1 of the Law No. 1219 on the Practice of Medicine and Medical Sciences, only graduates of medical faculties are authorized to diagnose and treat patients. Therefore, the delegation of such functions entirely to AI is not legally permissible (6). AI may serve only as a decision-support tool to assist or complement the physician's judgment (7).

Constitutionally, Article 128 provides that essential and permanent duties of the State must be performed by public officials. Therefore, in health services, AI can be used only when the final authority remains with the physician (8). For non-clinical tasks—such as data management, administration, or organization—there is no restriction on the use of AI.

However, the use of AI must also comply with the principle of legality: every administrative act and public service must have a legal basis (9). Thus, AI integration into public healthcare must rest on a statutory foundation.

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B. The Classification of AI Use in Health Services

A key legal issue concerns whether AI used to assist in diagnosis or treatment can be classified as a medical device. A "medical device" refers to any instrument, apparatus, software, or accessory used for medical purposes whose principal intended effect is not achieved through pharmacological, immunological, or metabolic means (10).

To qualify as a medical device, a product must aim at diagnosis, prevention, monitoring, prediction, prognosis, treatment, control, or alleviation of disease or injury, or the modification of an anatomical structure or physiological process (11).

Although software is included in the definition, Turkish law lacks explicit provisions regarding software as a medical device. However, Turkish regulations are largely harmonized with the European Union (EU) Medical Device Regulation (2017/745) (12), and thus the EU Medical Software Guide serves as a reference.

According to the EU Guide, software qualifies as a medical device if it performs data processing (not merely storage or transmission), provides outputs, and contributes directly to improving health.

Therefore, AI software that operates autonomously and assists in diagnosis or treatment based on data analysis qualifies as a medical device (6). Conversely, AI used only for recordkeeping or data transfer does not.

If AI is classified as a medical device, it falls under the Medical Device Regulation, subject to limitations and obligations on market placement, operation, and manufacturer or importer liability.

II. Administrative Liability for AI Use in Health Services

Due to its complex algorithmic nature, AI can yield unpredictable results, which may not be fully explained by traditional administrative law principles. For instance, if an AI-based diagnostic tool produces incorrect results causing harm to a patient, it is unclear whether liability rests with the administration, the physician, or the software developer.

Under Articles 40, 125, and 129 of the Constitution, administrative liability arises in two forms: fault-based (service fault) and strict (no-fault) liability.

A. Fault-Based (Service Fault) Liability

A service fault occurs when there is a defect, irregularity, or failure in the establishment, organization, or functioning of a public service. In healthcare, such faults can arise in several AI-related scenarios (13).

If a physician uses an unapproved AI tool—one that lacks Ministry of Health authorization or medical device licensing—any resulting harm constitutes a breach of medical standards, and the administration is liable for the physician's conduct.

If the AI system is medically approved but harm results from the physician's misinterpretation of AI-generated data (14), the administration compensates the damage but may seek recourse against the negligent physician (15).

Failure to review or verify AI outputs before acting on them also constitutes a service fault. For example, if a doctor applies AI-generated radiological findings without validation, administrative liability arises.

Because AI systems must be regularly updated with new data to maintain accuracy, the failure of the administration to ensure timely updates constitutes another form of service fault (1).

B. Strict (No-Fault) Liability

Strict liability is based on the principle that damages arising from risky public activities should be borne by society as a whole. It relies on two doctrines: risk liability and equitable distribution of sacrifice.

Under the risk principle, the administration must compensate for damage caused by dangerous tools or activities—even without fault—if such risks are inherent in public service (16).

AI use in healthcare can be considered a hazardous and unpredictable activity (17). AI systems may produce erroneous outcomes if not properly updated, lack sensitivity to complex data, or fail to respond to unexpected events as quickly as humans (18). Therefore, the mere use of AI entails risk (19).

If an AI algorithm, during its self-learning process, produces unforeseen outcomes, or malfunctions due to external data errors, the administration bears strict liability for resulting harm.

When AI systems are developed by private entities, the contractor or software provider may also be liable (20). The administration may compensate the victim and subsequently seek recourse from the developer (21).

CONCLUSION

The use of AI in health services reshapes both the delivery of public healthcare and the scope of administrative liability in Turkish law. Although current legislation lacks explicit regulation, AI can only be used under physician supervision as a decision-support tool; otherwise, it would breach constitutional and legal limits.

Administrative liability should be assessed within the dual framework of fault-based and strict liability, ensuring that AI-based healthcare applications remain safe, transparent, and auditable, as required by the principle of legal security.

Footnotes

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Association of Pre-operative Hematological, Inflammatory Markers, and Myoma Characteristics with Post-operative Erythrocyte Suspension Requirement Following Myomectomy: A Retrospective Observational Study

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ABSTRACT

Objective: To evaluate the association of pre-operative hematologic and inflammatory markers, fibroid burden, surgical factors, and surgeon experience with post-operative erythrocyte suspension (ES) transfusion risk in patients undergoing laparotomic (LM) and laparoscopic myomectomy (LSM).

Methods: This retrospective case-control study included patients undergoing LM or LSM. Baseline demographics, clinical characteristics, pre- and post-operative hematologic and inflammatory parameters, and surgical data were analyzed. Multivariate logistic regression identified independent predictors of ES transfusion. Receiver operating characteristic curves established the pre-operative hemoglobin cut-off values that predict transfusion risk.

Results: Transfusion groups had longer operation times, larger and heavier fibroids, and lower pre-operative hemoglobin in both LM and LSM cohorts. Myoma count and surgeon experience were independent predictors of transfusion only in the LM group, [odds ratio (OR) =1.128 and OR =0.916, respectively]. No inflammatory markers, including systemic immune-inflammation index, significantly predicted transfusion. Pre-operative hemoglobin cut-off of 11.75 g/dL predicted transfusion with moderate accuracy in both LM [area under the curve (AUC) =0.633] and LSM (AUC =0.639) groups. Surgeon experience reduced transfusion risk in LM, but not in LSM.

Conclusion: Fibroid burden, operation time, and surgeon experience significantly influence transfusion risk in myomectomy, especially in open surgery. A pre-operative hemoglobin level of 11.75 g/dL serves as a useful threshold for anemia management to minimize transfusion needs. Incorporating these clinical factors into perioperative planning may improve patient safety and reduce transfusion-related complications. Further prospective studies are needed to refine prediction models.

Keywords: Inflammatory markers, laparoscopy, laparotomy, myomectomy, siri, surgeon experience, transfusion risk

INTRODUCTION

Background

Uterine fibroids (leiomyomas) are the most common benign tumors among women of reproductive age, often presenting with heavy menstrual bleeding, pelvic pain, and infertility. Myomectomy the surgical removal of fibroids, is performed to relieve these symptoms while preserving the uterus, particularly in women desiring future fertility. By age 50, uterine fibroids have been reported in up to 70% of White women and 80% of Black women (1). Although hysterectomy remains the most frequently performed surgery for symptomatic fibroids, myomectomy is increasingly favored in younger women to maintain reproductive potential. However, compared to hysterectomy, myomectomy is associated with greater intraoperative blood loss due to uterine anatomic disruption and tumor-related neovascularization.

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Myoma size, location, and number significantly influence bleeding risk and thus transfusion rates. In a tertiary center, open (abdominal) myomectomy transfusion rates ranged from 4.7% to 6.4%, whereas laparoscopic myomectomy (LSM) transfusion rates were approximately 2.2% (2). Intraoperative transfusions not only increase morbidity but also impact recovery and resource utilization. Average blood loss in large multiple fibroids can approach 800 mL (2).

Recent research indicates that various platelet indices (PIs), including platelet count (PLT); plateletcrit (PCT); mean platelet volume (MPV); platelet-large cell ratio (P-LCR); platelet distribution width (PDW); and alongside the neutrophil-to-lymphocyte ratio (NLR), an indirect indicator of inflammation; as well as the systemic immune-inflammation index (SII) [SII = platelets × neutrophils (NEU)/lymphocytes] and the systemic inflammatory response index (SIRI) (SIRI = monocytes × NEUs/lymphocytes), undergo notable alterations in different clinical conditions. Elevated SII levels have been linked to unfavorable prognoses in cancer patients and in other diseases, such as ischemic stroke, where a high SII correlates with increased mortality and the likelihood of hemorrhagic transformation (2,3). These observations point to a potential role for SII in predicting outcomes during acute bleeding events, although additional studies are required to validate its diagnostic precision and determine appropriate cut-off values (4). Several publications have also investigated the prognostic utility of these biomarkers in predicting bleeding risk, including contexts like gastrointestinal hemorrhage and the need for platelet transfusions after cardiopulmonary bypass surgery (5,6). Given the considerable variability in surgical bleeding during myomectomy and the clinical impact of transfusion decisions, identifying reliable pre-operative predictors of erythrocyte suspension (ES) transfusion need is clinically important. Akay et al. (7) recently reported that SII may be a significant marker for predicting postpartum hemorrhage risk, underscoring the potential utility of this biomarker in hemorrhagic conditions. Therefore, assessing pre-operative SII and SIRI values could facilitate individualized risk stratification and optimize resource allocation in gynecologic surgery.

Objectives

This study aimed to examine the relationship between myoma characteristics, pre-operative hemogram parameters, PIs, and the need for post-operative ES transfusion in patients undergoing myomectomy. By analyzing these routinely collected laboratory parameters alongside demographic and pathological data, we sought to determine their potential utility as predictors of transfusion requirements in this surgical population.

METHODS

Study Design

This retrospective observational cohort study was conducted to assess the relationship between pre-operative hemogram and PIs and the post-operative requirement for ES transfusion in patients undergoing myomectomy.

Setting and Participants

The study was carried out in the Department of Gynecology and Obstetrics a tertiary care center between 01.04.2020 and 01.04.2024. Medical records of all women aged 20-60 years who underwent open [laparotomic (LM)] or LSM for symptomatic uterine fibroids during this period were reviewed. To eliminate potential confounding influences on PIs, patients with any additional conditions such as diabetes mellitus, malignancies other than sarcoma, autoimmune diseases, or known bleeding disorders were excluded. Other exclusion criteria included pre-operative anemia [defined as hemoglobin (Hb) <10 g/dL], pre-operative or intraoperative ES transfusion, conversion to hysterectomy during the procedure, or missing laboratory or surgical data. The selection process of study participants is summarized in Figure 1.

Ethical Considerations

The Institutional Review Board of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital approved this retrospective study (approval no: KAEK/12.06.2024.27, date: 26.06.2024). Given the retrospective design, the requirement for informed consent was waived. The study adhered to the principles outlined in the Declaration of Helsinki.

Variables

The primary outcome of the study was the requirement for post-operative ES transfusion, defined as the administration of one or more units of ES within the first 48 hours following surgery.

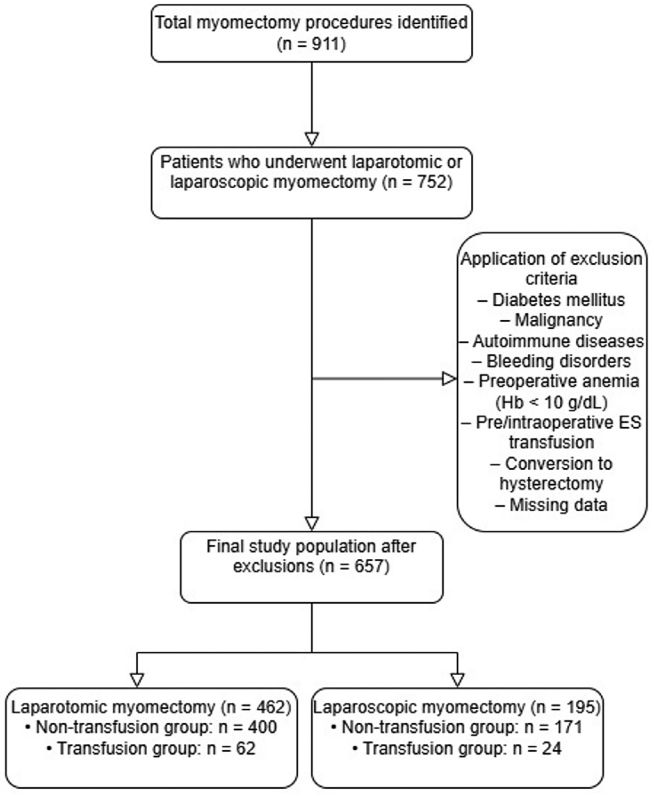

Figure 1. Flow diagram of participants
Hb: Hemoglobin, ES: Erythrocyte suspension

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Independent variables included laboratory parameters such as pre-operative and post-operative (6-hour) complete blood count values. These encompassed PLT; PCT; MPV; PDW; and P-LCR. The inflammatory markers, NLR, platelet-to-lymphocyte ratio (PLR), SIRI, and SII, were also calculated, along with Hb and hematocrit (HCT) levels.

Potential confounding variables considered were age, body mass index (BMI), surgeon experience (in years), surgical approach (laparoscopic vs. open), fibroid characteristics (size, number, and location), operative time, and estimated intraoperative blood loss.

Bias

To minimize selection bias, all consecutive eligible patients during the study period were included. Observer bias was mitigated by blinding the data analyst to transfusion outcomes until completion of statistical modeling.

Study Size

Based on the pilot study by Mohr et al. (6), an effect size of 0.997 was assumed. With an alpha level of 0.05 and a statistical power of 80%, the minimum required sample size was calculated to be 34 patients in total, with at least 17 patients in each group.

Quantitative Variables

Continuous variables were analyzed without transformation. Patients were grouped according to post-operative ES transfusion status (transfusion vs. no transfusion). The relationship between laboratory parameters and transfusion need was evaluated using univariate and multivariate methods.

Statistical Analysis

Statistical analyses were conducted using SPSS version 27.0. Descriptive statistics were used to summarize the data. Continuous variables were reported as mean ± standard deviation or as median with interquartile range (25^{th}-75^{th} percentiles), depending on the distribution. Categorical variables were presented as frequencies and percentages. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. For data with a normal distribution, comparisons between two groups were made using the Student's t-test. For non-normally distributed data, the Mann-Whitney U test was applied for two-group comparisons. Categorical variables were analyzed using either the chi-square test or Fisher's exact test, as appropriate. To determine the optimal cut-off values of pre-operative parameters for predicting the need for ES transfusion, receiver operating characteristic curve analysis was performed, and the area under the curve (AUC) was used to evaluate diagnostic accuracy. Multivariate logistic regression was conducted to identify independent predictors of ES transfusion, with results expressed as odds ratios (OR) and 95% confidence intervals (CI).

RESULTS

Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics, including age, BMI, and comorbidities, were comparable between transfusion and non-transfusion groups in both surgical approaches.

Age, BMI Obstetric History and Previous Abdominal Surgery

Age and BMI did not differ significantly between transfusion and non-transfusion groups in either cohort. In the LM group, mean age was 38.89 vs. 39.12 years (p=0.777), and BMI was 26.74 vs. 26.59 kg/m² (p=0.803). In the LSM group, age was: 38.25 vs. 34.80 years (p=0.468), and BMI was: 26.32 vs. 24.76 kg/m² (p=0.135) (Table 1).

Gravidity was significantly different in the LM group [2.00 (0.00-3.00) vs. 1.00 (0.00-2.00), p=0.033]. No significant differences in gravidity, parity, or previous abdominal surgery history were observed in the LSM group. Type of delivery was similar across all subgroups (Table 1).

Myoma Characteristics

In the LM group, myoma pathology differed significantly between the transfusion and non-transfusion groups (p=0.003), with higher leiomyoma prevalence in the non-transfusion group. No significant differences were found in myoma pathology between subgroups in the LSM group (p=0.982) (Table 1).

Surgical and Laboratory Characteristics

Table 2 summarizes the surgical, pathological, and laboratory characteristics of the study population, highlighting significant differences between transfusion and non-transfusion groups across both LM and LSM cohorts.

In the LM cohort, myoma pathology differed significantly between transfusion groups (p=0.003), with a higher prevalence of leiomyoma in the non-transfusion group. No such difference was observed in the LSM group (p=0.982).

Operation time was significantly longer in transfusion groups in both LM (132.21 vs. 95.77 minutes, p<0.001) and LSM (196.33 vs. 152.89 minutes, p=0.004) cohorts. In LM, more myomas were removed in the transfusion group (2.00 vs. 1.00, p=0.021), although this difference was not observed in LSM (p=0.633). The maximum myoma diameter was larger in transfused patients, in both LM (10.00 vs. 8.00 cm, p<0.001) and LSM (11.50 vs. 10.00 cm, p=0.012). Similarly, myoma weight was significantly higher in transfusion groups; 226.0 vs. 164.8 g in LM (p=0.008) and 167.4 vs. 125.5 g in LSM (p=0.015).

Surgeon experience was lower in the LM transfusion group (4.00 vs. 5.00 years, p=0.044), but no significant difference was found in LSM (p=0.261).

Pre-operative Hb levels were significantly lower in transfusion groups for both LM (11.36 vs. 11.98 g/dL, p=0.002) and LSM (11.47 vs. 12.08 g/dL, p=0.023). Post-operative Hb and HCT values declined in all groups, with a significantly greater drop among those who received transfusions (p<0.001).

White blood cell counts increased post-operatively across all groups (p<0.001), consistent with an inflammatory response, but there were no significant differences between transfusion and non-transfusion groups (p>0.05). Pre-operative PLTs were similar

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Table 1. Demographic and clinical characteristics of participants by transfusion status

Operation			Laparotomic myomectomy			Laparoscopic myomectomy		
			Non-transfusion group (n=400)	Transfusion group (n=62)	p-value	Non-transfusion group (n=171)	Transfusion group (n=24)	p-value
Age[a] (years)			38.89±5.81	39.12±5.64	p=0.777	38.25±6.55	34.80±8.46	p=0.468
BMI[a] (kg/m^2)			26.74±4.54	26.59±4.55	p=0.803	26.32±4.92	24.76±3.70	p=0.135
Previous abdominal surgery[c] (n)			136 (34.1%)	16 (26.2%)	p=0.224	66 (38.8%)	6 (25.0%)	p=0.189
Gravidity[b] (n)			2.00 (0.00-3.00)	1.00 (0.00-2.00)	**p=0.033**	1.00 (0.00-3.00)	2.00 (1.00-3.00)	p=0.493
Parity[b] (n)			1.00 (0.00-2.00)	1.00 (0.00-2.00)	p=0.078	1.00 (0.00-2.00)	2.00 (0.00-3.00)	p=0.181
Type of delivery[c] n (%)		Nulliparous	157 (39.3%)	30 (48.4%)	p=0.243	70 (40.9%)	7 (29.2%)	p=0.274
		VD	128 (32.0%)	20 (32.3%)		57 (33.3%)	12 (50.0%)	
		CS	115 (28.8%)	12 (19.4%)		44 (25.7%)	5 (20.8%)	
Myoma pathology[c] n (%)	*Leiomyoma*		200 (50.0%)	24 (38.7%)	**p=0.003**	89 (52.0%)	12 (50.0%)	p=0.982
	Degenerated leiomyoma		173 (43.3%)	29 (46.8%)		70 (40.9%)	11 (45.8%)	
	Cellular leiomyoma		15 (3.8%)	3 (4.8%)		8 (4.7%)	1 (4.2%)	
	Adenomyoma		4 (1.0%)	2 (3.2%)		-	-	
	Bizarre leiomyoma		5 (1.3%)	1 (1.6%)		1 (0.6%)	0 (0.0%)	
	Mitotically active leiomyoma		1 (0.3%)	0 (0.0%)		1 (0.6%)	0 (0.0%)	
	Fumarate hydratase deficiency		0 (0.0%)	1 (1.6%)		2 (1.2%)	0 (0.0%)	
	STUMP		2 (0.5%)	0 (0.0%)		-	-	
	Malignancy		0 (0.0%)	2 (3.2%)		-	-	

[a]: Normal distribution, mean ± standard deviation, [b]: Non-normal distribution, median (25-75%), [c]: Categorical data, number (%), BMI: Body mass index, VD: Vaginal delivery, CS: Cesarean section, STUMP: Smooth muscle tumor of uncertain malignant potential

between groups. However, post-operative PLTs were lower in the LM transfusion group (233.5 vs. 250×10^9/L, p=0.023) but not significantly different in LSM (p=0.096).

Pre-operative PIs and inflammatory markers [PDW, NEU, basophil (BAS), PCT, P-LCR, NLR, PLR, SII] showed no significant differences between transfusion groups in either cohort. Post-operatively, only PCT was significantly lower in the LM transfusion group (p=0.029); however, no significant differences were noted in the LSM cohort (p=0.169).

Intra-group Changes

Significant intra-group changes from pre-operative to post-operative periods were observed for most hematologic and inflammatory parameters (p<0.001). These changes indicate a robust inflammatory and hematologic response to myomectomy regardless of transfusion status. The median number of ES transfusion units was significantly higher in the transfusion groups in both LM and LSM [2.00 (1.00-2.00) units, p<0.001].

Multivariate binary logistic regression analysis results are shown in Table 3. For patients who underwent LM myomectomy, myoma count [regression coefficient (B)=0.120, OR=1.128, 95% CI: 1.045-1.217, p=0.002)] and surgeon experience (B=-0.088, OR=0.916, 95% CI: 0.851-0.986, p=0.020) were significant predictors. Age (B=0.006, OR=1.006, 95% CI: 0.949-1.066, p=0.848), BMI (B=-0.032, OR=0.968, 95% CI: 0.898-1.044, p=0.401), and pre-operative SIRI (B=-0.321, OR=0.725, 95% CI: 0.423-1.244, p=0.243) were not significant.

In the LSM group, none of the variables was statistically significant: age (B=0.022, OR=1.023, 95% CI: 0.929-1.126, p=0.649), BMI (B=-0.152, OR=0.859, 95% CI: 0.729-1.012, p=0.070), myoma count (B=-0.066, OR=0.936, 95% CI: 0.269-3.261, p=0.918), surgeon experience (B=-0.138, OR=0.871, 95% CI: 0.751-1.012, p=0.071), and pre-operative SIRI (B=0.018, OR=1.018, 95% CI: 0.854-1.213, p=0.843).

The pre-operative Hb cut-off values for predicting post-operative ES transfusion are presented in Table 4 and Figure 2. In the LM myomectomy group, the AUC was 0.633 (95% CI: 0.559-0.707, p=0.001), with a cut-off value of 11.75 g/dL, sensitivity of 58.1%, and specificity of 57.8%. In the LSM group, the AUC was 0.639 (95% CI: 0.512-0.767, p=0.027), with a cut-off value of 11.75 g/dL, sensitivity of 58.3%, and specificity of 60.8%.

DISCUSSION

Inflammation is a key factor in the development of bleeding disorders, especially during sepsis. The systemic inflammatory

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Table 2. Comparison of surgical and perioperative data based on ES transfusion status

Operation	Laparotomic myomectomy			Laparoscopic myomectomy		
	Non-transfusion group (n=400)	Transfusion group (n=62)	p-value	Non-transfusion group (n=171)	Transfusion group (n=24)	p-value
Operation duration[a] (min)	95.77±39.69	132.21±48.65	**p<0.001**	152.89±65.16	196.33±87.31	**p=0.004**
Myoma count[b] (n)	1.00 (1.00-3.00)	2.00 (1.00-5.00)	**p=0.021**	1.00 (1.00-1.00)	1.00 (1.00-1.00)	p=0.633
Maximum myoma diameter[b] (cm)	8.0 (7.0-10.0)	10.0 (9.5-11.0)	**p<0.001**	10.0 (8.0-12.0)	11.5 (11.5-15.0)	**p=0.012**
Myoma weight[b] (gr)	164.8 (83.7-267.8	226.0 (166.7-313.8)	**p=0.008**	125.5 (58.6-204.0)	167.4 (156.9-190.4)	**p=0.015**
Surgeon experience[b] (years)	5.00 (3.00-10.00)	4.00 (2.00-9.00)	**p=0.044**	6.00 (3.00-10.00)	4.00 (2.00-10.00)	p=0.261
ES transfusion unit[b] (n)	0.00 (0.00-0.00)	2.00 (1.00-2.00)	**p<0.001**	0.00 (0.00-0.00)	2.00 (1.00-2.00)	**p<0.001**
Hb differance[b] (g/dL)	1.25 (0.60-1.90)	2.10 (1.40-2.80)	**p<0.001**	1.00 (0.50-1.60)	2.50 (1.60-3.70)	**p<0.001**
Hb[a] (g/dL)						
Pre-operative	11.98±1.48	11.36±1.53	**p=0.002**	12.08±1.19	11.47±1.36	**p=0.023**
Post-operative	10.73±1.29	9.20±1.25	**p<0.001**	10.99±1.24	8.47±1.42	**p=0.023**
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
HCT[a] (%)						
Pre-operative	36.99±3.79	35.59±3.89	**p=0.089**	36.97±3.14	35.89±3.70	p=0.126
Post-operative	32.76±3.39	28.51±3.32	**p<0.001**	33.34±3.96	26.30±4.38	**p<0.001**
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
WBC[b] (109/L)						
Pre-operative	7.30 (6.17-8.66)	7.16 (5.47-8.23)	p=0.089	7.51 (6.39-8.86)	7.67 (6.41-8.71)	p=0.978
Post-operative	13.44 (11.21-15.77)	13.61 (11.52-15.49)	p=0.736	13.99 (11.89-16.66)	12.58 (11.71-16.08)	p=0.342
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
PLT[b] (10^9/L)						
Pre-operative	299.00 (251.00-344.50)	296.00 (236.00-332.00)	p=0.270	284.00 (234.00-323.00)	284.50 (240.50-352.50)	p=0.415
Post-operative	250.00 (211.00-297.50)	233.50 (189.00-270.00)	p=0.023	234.00 (192.00-280.00)	212.50 (157.50-265.50)	p=0.096
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
LYM[b] (10^9/L)						
Pre-operative	2.10 (1.69-2.67)	1.96 (1.60-2.49)	p=0.083	2.17 (1.79-2.77)	1.89 (1.60-2.38)	p=0.057
Post-operative	0.97 (0.68-1.40)	0.78 (0.61-1.10)	p=0.007	0.81 (0.62-1.20)	0.56 (0.47-0.97)	**p=0.030**
p-value	p<0.001	p<0.001		p<0.001	p<0.001	
MON[b] (10^9/L)						
Pre-operative	0.52 (0.42-0.64)	0.48 (0.37-0.58)	p=0.035	0.51 (0.43-0.65)	0.56 (0.42-0.67)	p=0.7487
Post-operative	0.65 (0.49-0.82)	0.64 (0.48-0.87)	p=0.780	0.65 (0.44-0.83)	0.70 (0.56-0.79)	p=0.510
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p=0.145**	
MPV[b] (fL)						
Pre-operative	10.50 (10.01-11.10)	11.01 (10.06-11.50)	p=0.067	10.50 (10.02-11.10)	10.70 (10.03-11.10)	p=0.668
Post-operative	10.40 (10.00-11.05)	10.75 (10.04-11.10)	p=0.240	10.10 (10.00-11.06)	10.55 (9.96-11.20)	p=0.624
p-value	**p<0.001**	**p=0.009**		**p<0.001**	**p=0.145**	

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Table 2. Continued

Operation	Laparotomic myomectomy			Laparoscopic myomectomy		
	Non-transfusion group (n=400)	Transfusion group (n=62)	p-value	Non-transfusion group (n=171)	Transfusion group (n=24)	p-value
PDW[b] (10^9/L)						
Pre-operative	12.10 (11.05-14.00)	13.05 (11.09-14.90)	p=0.116	12.09 (11.05-14.04)	13.10 (11.55-14.04)	p=0.178
Post-operative	12.03 (11.00-13.10)	12.20 (11.40-13.30)	p=0.159	12.03 (10.70-13.60)	12.34 (10.19-14.04)	p=0.687
p-value	**p<0.001**	**p=0.041**		**p<0.001**	**p=0.032**	
NEU[b] (10^9/L)						
Pre-operative	4.42 (3.59-5.37)	4.33 (3.26-5.05)	p=0.202	4.44 (3.75-5.59)	5.01 (3.65-5.50)	p=0.561
Post-operative	11.79 (9.53-14.03)	12.03 (10.31-13.77)	p=0.912	12.31 (10.33-15.10)	11.63 (10.80-14.13)	p=0.633
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
BAS[b] (10^9/L)						
Pre-operative	0.03 (0.02-0.04)	0.02 (0.01-0.04)	p=0.003	0.03 (0.02-0.04)	0.03 (0.02-0.03)	p=0.780
Post-operative	0.02 (0.01-0.02)	0.01 (0.01-0.02)	p=0.017	0.01 (0.01-0.02)	0.01 (0.01-0.02)	P=0.352
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
PCT[b] (%)						
Pre-operative	0.32 (0.28-0.36)	0.33 (0.28-0.37)	p=0.704	0.30 (0.26-0.35)	0.31 (0.27-0.38)	p=0.102
Post-operative	0.27 (0.23-0.31)	0.26 (0.21-0.29)	p=0.220	0.25 (0.22-0.29)	0.24 (0.18-0.28)	p=0.096
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
P-LCR[b]						
Pre-operative	30.20 (25.50-36.20)	32.35 (26.20-36.90)	p=0.158	30.80 (25.70-36.60)	31.90 (26.55-37.20)	p=0.190
Post-operative	29.20 (25.30-35.20)	31.55 (25.30-36.70)	p=0.624	29.80 (25.00-35.30)	33.50 (24.95-36.20)	p=0.386
p-value	**p=0.001**	**p=0.036**		**p=0.007**	**p=0.513**	
NLR[b]						
Pre-operative	2.07 (1.61-2.69)	1.96 (1.60-2.42)	p=0.444	2.05 (1.59-2.57)	2.61 (1.64-3.17)	**p=0.044**
Post-operative	12.31 (7.58-18.49)	14.42 (9.27-21.54)	p=0.097	14.90 (9.49-22.27)	19.91 (11.20-29.28)	**p=0.048**
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
PLR[b]						
Pre-operative	136.59 (108.33-181.91)	143.49 (114.45-182.63)	p=0.593	124.34 (104.37-158.16)	152.81 (125.57-196.69)	p=0.190
Post-operative	250.10 (169.32-375.00)	269.77 (204.82-375.95)	p=0.011	291.35 (195.08-406.25)	298.62 (221.83-514.17)	p=0.224
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
SII[b]						
Pre-operative	596.11 (457.20-842.12)	572.22 (444.79-734.77)	p=0.220	573.40 (423.67-770.13)	777.39 (495.43-1260.68)	p=0.339
Post-operative	2976.81 (1688.15-4853.92)	3220.41 (2151.56-4789.23)	p=0.037	3560.20 (2274.61-5236.63)	3226.46 (2557.44-5977.21)	p=0.444
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	
SIRI[b]						
Pre-operative	1.08 (0.82-1.48)	0.95 (0.70-1.33)	p=0.113	1.04 (0.78-1.43)	1.30 (0.90-1.89)	**p=0.007**
Post-operative	7.17 (4.48-11.51)	9.72 (5.86-14.31)	p=0.140	8.59 (5.06-14.15)	10.85 (7.71-16.12)	p=0.060
p-value	**p<0.001**	**p<0.001**		**p<0.001**	**p<0.001**	

[a]: Normal distribution, mean ± standard deviation, [b]: Non-normal distribution, median (25-75%), ES: Erythrocyte suspension, Hb: Hemoglobin, HCT: Hematocrit, WBC: White blood cell count, PLT: Platelet count, LYM: Lymphocyte, MON: Monocyte, NEU: Neutrophil, BAS: Basophil, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, P-LCR: Platelet-large cell ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index

response triggered by sepsis closely interacts with coagulation pathways, potentially resulting in disseminated intravascular coagulation (DIC). DIC is characterized by extensive fibrin buildup and impaired fibrinolysis. Inflammatory agents, including cytokines and chemokines, stimulate tissue factor expression on monocytes and endothelial cells, which promotes thrombin production and concurrently inhibits natural anticoagulant systems like protein C and antithrombin (8). This imbalance causes microvascular clotting and tissue ischemia, leading to organ dysfunction. Furthermore, increased levels of inflammatory markers such as interleukins and tumor necrosis factor-α are associated with the severity of DIC, highlighting the importance of inflammation in diagnosing and predicting outcomes in sepsis-related coagulopathy (9). Although bleeding disorders in sepsis have been extensively studied, emerging evidence emphasizes the critical interaction between inflammation and coagulation in driving disease progression and contributing to morbidity and mortality.

The SII, introduced by Huang et al. (10) in 2019, represents the involvement of platelets, NEUs, and lymphocytes in inflammation, with the first two promoting inflammation and lymphocytes regulating immune responses. Elevated SII values have been linked to poor prognosis in cancer patients and other conditions such as ischemic stroke, where they predict mortality and hemorrhagic transformation (3,11). These observations imply that SII might also serve as a prognostic marker in acute bleeding events, though additional studies are needed to confirm its diagnostic accuracy and define cut-off points (4).

Moreover, the absence of significant differences in SII values across American Society of Anesthesiologists groups (p=0.821) indicates similar inflammatory states among risk categories, supporting cohort uniformity. Nevertheless, further investigation is required to clarify the influence of inflammation on transfusion outcomes, as chronic inflammatory conditions may affect anemia severity and transfusion responses (12).

This study's strengths include its matched case-control design, which reduces selection bias, and its use of routinely available blood markers to predict transfusion needs, thereby enhancing clinical applicability. Additionally, focusing on a clearly defined patient group improves relevance to comparable surgical populations. Importantly, this is the first study to evaluate PIs, inflammatory markers, and SII as predictors of ES transfusion in patients undergoing myomectomy.

Key Findings

Comparison with Existing Literature

Recent studies suggest systemic inflammation plays a role in fibroid pathogenesis and growth. In a retrospective case-control study of 357 patients, Çınar et al. (13) stratified cases by fibroid diameter (≤5 cm vs. >5 cm) and found that larger fibroids were associated with altered clinical parameters. In our cohort, larger and more numerous fibroids increased transfusion needs. In the LM group, transfused patients had more fibroids (median 2.0 vs. 1.0; p=0.021), but no difference was seen in LSM (p=0.633). Maximum fibroid diameter and weight were higher in transfused patients in both the LM (10.0 vs. 8.0 cm, 226.0 vs. 164.8 g) and the LSM (11.5 vs. 10.0 cm, 548.8 vs. 125.5 g) groups (all p<0.05). These results align with Çınar et al. (13) indicating fibroid size and burden increases the risk of bleeding and transfusion. The fibroid count

Table 3. Multivariate binary logistic regression analysis for predicting post-operative ES transfusion need

Variable	B	OR	95% CI	p-value
Laparotomic myomectomy				
Age (years)	0.006	1.006	0.949-1.066	p=0.848
BMI (kg/m²)	-0.032	0.968	0.898-1.044	p=0.401
Myoma count	0.120	1.128	1.045-1.217	p=0.002
Surgeon experience (years)	-0.088	0.916	0.851-0.986	p=0.020
SIRI pre-operative	-0.321	0.725	0.423-1.244	p=0.243
Laparoscopic myomectomy				
Age (years)	0.022	1.023	0.929-1.126	p=0.649
BMI (kg/m²)	-0.152	0.859	0.729-1.012	p=0.070
Myoma count	-0.066	0.936	0.269-3.261	p=0.918
Surgeon experience (years)	-0.138	0871	0.751-1.012	p=0.071
SIRI pre-operative	0.018	1.018	0.854-1.213	p=0.843

B: Regression coefficient, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, ES: Erythrocyte suspension, SIRI: Systemic inflammatory response index

Table 4. Hb cut-off values for predicting post-operative ES transfusion

Parameters	AUC (95% CI)	Cut-off (youden index)	Sensitivity (%)	Specificity (%)	p-value
Laparotomic pre-operative Hb	0.633 (0.559-0.707)	11.75	58.1	57.8	p=0.001
Laparoscopic pre-operative Hb	0.639 (0.512-0.767)	11.75	58.3	60.8	p=0.027

AUC: Area under the curve, CI: Confidence interval, ES: Erythrocyte suspension, Hb: Hemoglobin

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difference in LM may reflect surgical preference for laparotomy with higher fibroid burden, not an inherent risk of the approach.

Platelet Indices and Inflammatory Markers

Several studies have examined PIs and inflammatory markers in gynecologic and other tumors. For instance, clinicians have observed that low PCT and elevated PDW (≥23%) independently predict increased risk of postpartum hemorrhage (14). In patients with gynecologic malignancies, elevated PLT and PCT, along with decreased MPV, have been reported (6). Papillary thyroid carcinoma patients exhibit significantly higher PCT and lower PDW (15). In endometriosis, PCT increases while MPV and PDW decrease (5). Advanced breast cancer is associated with changes in platelet-related indices, with low PCT portending better survival outcomes (16). PCT has also been proposed as a sensitive biomarker for Crohn's disease activity (17).

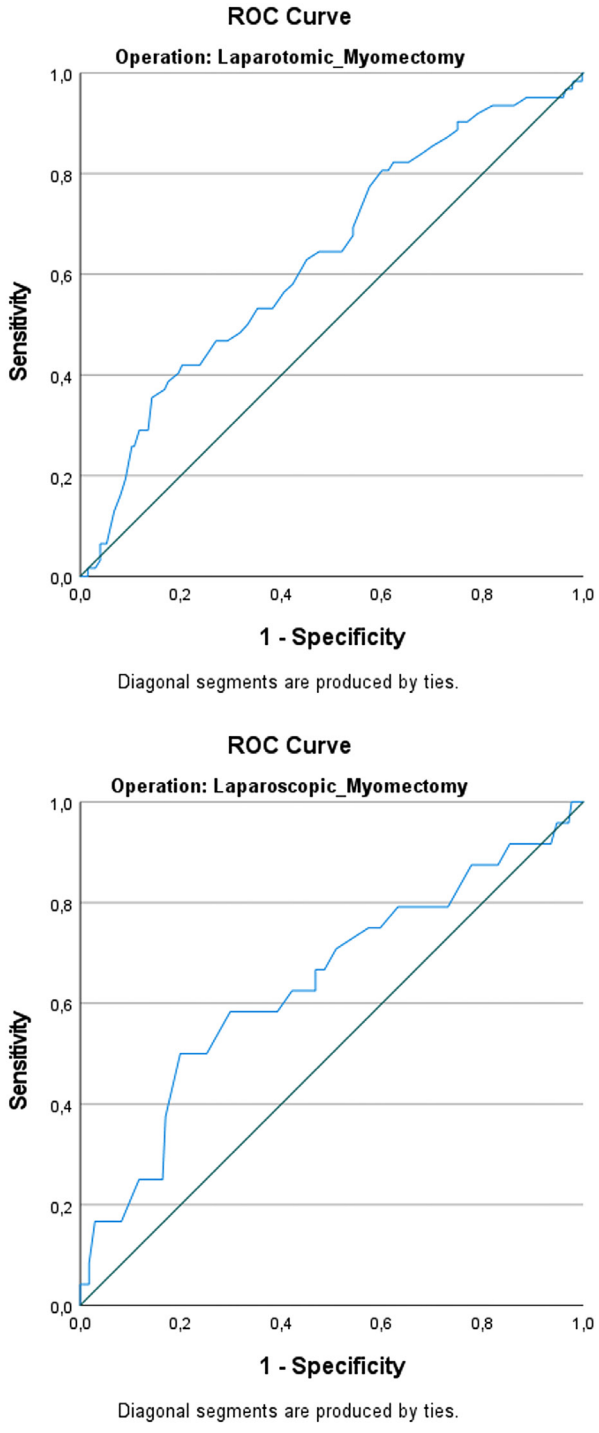

Figure 2. ROC curve of hemoglobin (Hb) cut-off values for predicting post-operative erythrocyte suspension (ES) transfusion in laparotomic and laparoscopic myomectomy
ROC: Receiver operating characteristic

Regarding perioperative settings, Mohr et al. (6) reported that low MPV (<7.7 fL) and low PCT (<0.01) are significant cut-off values for predicting platelet transfusion after cardiopulmonary bypass. van Dijk et al. (15) found that PLT and indices serve as risk factors for postpartum hemorrhage (7). Elevated NLR, as an indirect marker of inflammation, has been associated with gastrointestinal bleeding in children with Henoch-Schonlein purpura (5). In uterine leiomyomas, chronic inflammation plays a pivotal role in pathogenesis, and NLR has been proposed to differentiate myomas from sarcomas or endometriosis (18,19).

Çaltekin et al. (20) retrospectively evaluated 102 patients with uterine leiomyomas and found that compared to those with smaller fibroids (≤5 cm), patients with larger fibroids (>5 cm) exhibited a significant increase in NLR and a decrease in lymphocyte/monocyte ratio, whereas PLR did not differ significantly between size groups. In our cohort, pre-operative PDW, NEU, BAS, PCT, P-LCR, NLR, PLR, and SII showed no significant difference between transfused and non-transfused patients (all p>0.05). Post-operatively, only PCT was lower in the transfused LM subgroup (p=0.029), with no differences in LSM (p=0.169). Thus, while fibroid size affects some inflammatory markers, pre-operative markers did not predict transfusion need, though, post-operative PCT reduction may indicate platelet depletion from bleeding.

Comparison of Surgical Approaches for Myomectomy

When comparing LM and LSM in terms of transfusion risk, our findings highlight notable differences that align with and expand upon existing knowledge. In both surgical approaches, longer operative times were significantly associated with increased transfusion rates, with LM transfused patients averaging 132.2±48.7 minutes compared to 95.8±39.7 minutes in non-transfused cases (p<0.001); LSM transfused patients demonstrated even longer durations, 196.3±87.3 minutes versus 152.9±65.2 minutes, respectively (p=0.004). These results are consistent with Hamilton et al. (21) who identified the operation time exceeding 197 minutes as a key intraoperative risk factor for transfusion during LSM. Hamilton's study, highlights pre-operative factors (race, bleeding disorders, HCT) and intraoperative variables (specimen weight, intramural myomas) in a risk stratification tool. Our study adds real operative time data to the LM and LSM groups, emphasizing surgical duration and the impact of complexity on transfusion needs. These findings emphasize the need for tailored surgical planning to reduce transfusion risks.

In our cohort, fibroid burden (number, size, weight) predicted transfusion only in LM patients, with transfused cases showing higher myoma count (2.0 vs. 1.0; p=0.021), diameter (10.0 vs. 8.0 cm; p<0.001), and weight (226.0 vs. 164.8 g; p=0.008). In LSM, only diameter and weight differed significantly, not myoma count (p=0.633). This aligns with Pundir et al. (22) who found increased bleeding and transfusion risks with larger uteri (≥20 weeks), ≥10 fibroids, and more extensive surgery, including repeat myomectomies. Their analysis further highlights increased complications and blood loss in repeat myomectomies, emphasizing fibroid burden and surgical complexity, as critical factors influencing perioperative transfusion risk. Together, these data underscore the importance of fibroid load assessment and surgical planning, particularly in open approaches, to mitigate bleeding risks and optimize patient safety.

Surgeon experience significantly affected transfusion risk in LM, with transfused patients operated on by less experienced surgeons (median 4.0 vs. 5.0 years, p=0.044); each additional year of surgeon experience reduced transfusion odds by 8.4% (OR= 0.916, p=0.020). Experience had no significant effect in LSM cases. This reflects LM's technical challenges, especially with multiple fibroids. A recent meta-analysis supports that LSM causes less blood loss and fewer complications than open surgery, despite the longer operative times due to a steeper learning curve and higher technical demands (23). Bipolar diathermy, vasopressin injection, and temporary uterine artery clipping reduce bleeding during laparoscopy. Odejinmi et al. (24) reported shorter operative times and less blood loss in laparoscopic hysterectomy versus myomectomy, underscoring the roles of patient selection and surgeon expertise. While laparoscopic methods reduce blood loss and complications, surgeon experience remains key, especially in open surgery. Larger fibroid size and weight increase bleeding risk in both approaches, but multiple fibroids and surgeon experience are especially critical in LSM (LM). LSM appears less affected by fibroid multiplicity, likely due to better visualization and hemostatic control (24).

Clinical Implications

Longer operative times and larger fibroid burden, particularly larger size, increase transfusion risk in LM, where surgical experience independently lowers this risk. In LSM, fibroid size remains a risk factor, but myoma count and surgeon experience do not.

A pre-operative Hb cut-off of 11.75 g/dL (LM AUC: 0.633; LSM AUC: 0.639) provides a useful threshold for anemia correction to reduce transfusions. Incorporating fibroid characteristics, surgical approach, and surgeon experience into risk models can improve perioperative care.

Study Limitations

This retrospective study evaluated the association between pre-operative hemogram parameters, PIs, and the need for post-operative ES transfusion in patients undergoing myomectomy. Lower pre-operative Hb levels, prolonged operative time, and greater estimated blood loss were independently associated with an increased likelihood of ES transfusion. In the open (LM) cohort, both myoma count and surgeon experience emerged as additional independent predictors.

Strengths of this study include a comprehensive analysis of hematologic and coagulation parameters in a large, consecutively sampled cohort, as well as blinded data review to minimize bias. However, limitations include its retrospective, single-center design, which restricts causal inference and generalizability, along with the absence of coagulation biomarkers such as fibrinogen and D-dimer that could enhance transfusion risk prediction

CONCLUSION

Our study highlights that the size and number of fibroids, alongside operative time and surgeon experience, are key determinants of transfusion risk in myomectomy patients. While larger fibroids increase bleeding risk across both LM and laparoscopic approaches, the cumulative effect of multiple fibroids and surgical expertise notably impacts outcomes in open surgery. Pre-operative Hb level serves as a practical threshold to guide anemia management and reduce transfusion needs. Incorporating these clinical factors into perioperative risk assessments can enhance surgical planning, minimize transfusion-related complications, and improve patient safety. Further prospective studies including additional biomarkers are warranted to refine prediction models and optimize care.

Ethics

Ethics Committee Approval: The Institutional Review Board of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital approved this retrospective study (approval no: KAEK/12.06.2024.27, date: 26.06.2024).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Footnotes

Author Contributions: Surgical and Medical Practices - C.T., G.G.; Concept - C.T., E.D., E.T., B.T., O.M.G., G.G.; Design - C.T., E.D., E.T., B.T., O.M.G.; Data Collection and/or Processing - E.D., B.T., O.M.G.; Analysis and/or Interpretation - C.T., E.T., G.G.; Writing - C.T., E.D., E.T., B.T., O.M.G., G.G.

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Comparison of the Knowledge Levels of Turkish and Syrian Individuals Living in Türkiye Regarding Hearing and Balance

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ABSTRACT

Objective: Our study aimed to identify the knowledge levels related to hearing and balance of Syrian and Turkish nationals and address any deficiencies through planned training.

Methods: Our study is prospective descriptive research. The study was carried out in a public area. The study was conducted with two groups of Turkish and Syrian nationals. Participants were first given the "Hearing and Balance Knowledge Level Questionnaire", followed by a 30-minute structured training using brochures related to the topics in the questionnaire. After this training, they were administered the questionnaire again.

Results: In the first stage, the questionnaire scores of Turkish nationals were significantly higher than the Syrians ($p<0.05$), and after the training, no significant difference was found ($p=0.985$). Before the training, there was no statistical difference within the groups according to gender and working status of the participants ($p>0.05$). Before training, median questionnaire scores increased with education level, but only the bachelor's level showed a significant difference in scores. A moderate positive correlation between education level and pre-training scores was observed in Syrians ($p<0.05$), but not Turks. Both groups showed a low yet significant positive correlation between income and pre-training questionnaire scores ($p<0.05$). After the training, there was no statistically significant difference between the two groups based on education level, except middle and high school degrees, and monthly income. The question with the lowest rate of correct answers in both groups was the 20th question, which was about tinnitus.

Conclusion: In Samsun city of Türkiye, a knowledge gap regarding audiology, audiologists, hearing/balance loss, tinnitus, hearing aids, cochlear implants, and vertigo was identified in both groups, particularly among Syrian nationals, and educational interventions can address this gap.

Keywords: Balance, balance awareness, hearing, hearing awareness, Syrian national, Turkish national

INTRODUCTION

Health is an important concept for individuals and society; it is a type of service that should be prioritized (1). Healthcare, on the other hand, refers to a set of services provided by health institutions and professionals for the protection, improvement, treatment, and rehabilitation of public health (2). The healthcare infrastructure aiming to provide the best service in countries includes well-trained service providers, access to reliable and up-to-date scientific information, and well-developed facilities (3). However, significant events such as wars push countries into large-scale problems, disrupt all services, particularly healthcare, and lead to the forced migration of individuals living in these countries. One of these countries is Syria today. With the outbreak of the civil war in Syria in March 2011, the country's healthcare infrastructure collapsed; 50% of state hospitals became unusable, and half of the healthcare workforce left the country (4). Millions of people have been displaced within the country, and a large portion has been forced to leave their homeland. As of July 25, 2024, it is known that there are a total of 3,105,539 individuals under temporary protection in Türkiye who have come from Syria of these individuals, 73.9% are women and children (5).

Türkiye is a large country with a vast area, a growing economy, and a population of more than 85 million. According to the United Nations population projections, in 2023, Türkiye ranked

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18th in population size among 194 countries (6). On the other hand, Türkiye hosts the largest refugee population in the world, with Syrians having the highest population density among these refugees (7). The official language of Türkiye is Turkish (8).

One of the main reasons refugees in different countries do not benefit effectively and easily from healthcare services is the "language" barrier (limitations in expressing the complaint and understanding the other part), but a lack of knowledge about the healthcare facilities and infrastructure in the host countries can also prevent these individuals from accessing healthcare. By identifying knowledge levels in specific areas and addressing deficiencies, significant contributions can be made to the health of these individuals and the society they live in. Moreover, the conscious and accurate demand for healthcare services by individuals of different nationalities can allow the host countries to assess the performance of their healthcare systems and structure health reforms for refugees. In this context, the current study aims to determine the knowledge levels of Syrian nationals living in Samsun regarding hearing and balance health/diseases, and compare them with Turkish nationals. Another aim of the study is to evaluate the knowledge levels of both groups after the training. This study also aims to raise awareness on the subject.

METHODS

Our study is prospective and descriptive. For the present study, ethical approval was obtained from the Clinical Research Ethics Committee at Samsun Ondokuz Mayıs University (decision no: OMÜ KAEK 2023/14, date: 24.06.2024), and permission was also granted by the Atakum Municipality in Samsun, where the study was conducted. Research was carried out in accordance with the Declaration of Helsinki.

A stand was set-up between 03:00 and 07:00 p.m. for 1 week in a children's playground in a region with a high density of Syrian individuals. The individuals who visited this stand constituted the study's target audience. The study was conducted with two groups, one consisting of Turkish nationals and the other of Syrian nationals. Syrian nationals over 18 who have lived in Türkiye for two years, learned Turkish (no objective measurement was used to measure the individuals' Turkish proficiency; they were evaluated based on their ability to speak, understand, and maintain communication spontaneously during a 5-10 minute conversation), and volunteered to participate in the study were included. Turkish nationals over 18 who agreed to participate in the study were informed about the purpose of the study and signed an informed consent form. Individuals who did not wish to participate, those who were illiterate, those who could not communicate in Turkish, those who had previously received any training related to hearing and balance, individuals from different nationalities (e.g., Iran, Iraq), individuals with a history of ear surgery, and those with complaints of balance and hearing loss were excluded from the study. To raise public awareness, demos of ears, hearing aids, and cochlear implants were also displayed on the table in the stand. Those who did not agree to participate but visited the stand for information were allowed to examine the demos, and the researchers answered their questions.

The study's sample size was calculated as at least 88 participants, 44 in each group, with 95% power and 0.05 margin of error using the G*Power 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) package. Over one week, 1,000 people visited the stand, and 200 volunteers (100 Syrian, 100 Turkish nationals) were given questionnaires and asked to complete them. Individuals who agreed to participate were asked to complete a socio-demographic data collection form. Then, the "Hearing and Balance Knowledge Level Questionnaire", consisting of 27 items, was created by the researchers based on a literature review and expert opinions, and was applied to measure the participants' knowledge levels on hearing and balance issues. Then, a 30-minute structured training was provided with printed or electronic posters and brochures (which could also be accessed via smartphone QR codes) related to the topic. The training also covered any areas or questions the participants did not know or had incomplete knowledge of in the questionnaire. Finally, the participants' knowledge levels were re-assessed using the "Hearing and Balance Knowledge Level Questionnaire".

The questionnaire was designed to be answered with "yes", "no" or "I do not know". In the Hearing and Balance Knowledge Level Questionnaire, the first two items are related to audiology; items 3-8 and 17 are about hearing loss; items 9-11 are about newborn hearing screening; items 12-14 are about hearing aids; items 15-16 and 18-19 are about cochlear implants; items 20-22 are about tinnitus (ringing in the ears); item 23 is about noise; and items 24-27 are related to dizziness and balance.

For each item correctly answered in the questionnaire, one point was given, while incorrect answers or those marked as "I do not know" were given zero points. The total score was calculated. The questionnaire has a possible score range from zero to a maximum of twenty-seven points. An increase in the score obtained from the questionnaire indicates that the level of knowledge has increased. Correct answers to the Hearing and Balance Knowledge Level Questionnaire are shown in Table 1.

Statistical Analysis

IBM SPSS 22.0 software was used for data analysis. Frequency and percentage values were provided for qualitative variables. The quantitative variables were not normally distributed; therefore, these variables were presented as the median and interquartile range (25th-75th percentiles). Group differences were assessed using the Mann-Whitney U test; intra-group differences were assessed using the Wilcoxon rank test, and correlations were analyzed using Spearman's rank correlation coefficient. The internal consistency of the questionnaire items was examined using the Cronbach's alpha coefficient. A statistical significance level of $p<0.05$ was considered in the evaluations.

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RESULTS

The mean age of the Turkish nationals participating in our study was 35.78±11.62 years (minimum: 18, maximum: 70), and for the Syrian nationals, it was 34.11±12.30 years (minimum: 18, maximum: 65). No significant difference was found between the groups (p>0.05). Two hundred people, 100 in each group, participated in the study. Fifty-one female participants (51.0%) and forty-nine male Turkish participants (49%), and fifty female (50%) and fifty male (50%) Syrian participants were included in the study, with no significant difference between the groups in terms of gender (p>0.05). The average duration of stay for Syrian nationals in Türkiye was 7.64±3.20 years. The socio-demographic information of the participants is shown in Table 2.

When the internal consistency of all the items in the Hearing and Balance Knowledge Level Questionnaire created by the researchers was examined, the Cronbach's alpha coefficient was found to be 0.897, indicating high consistency among the questionnaire items. The participants' responses to the 27-item Hearing and Balance Knowledge Level Questionnaire before and after training are shown in Table 3. The question that Turkish nationals answered correctly the most was question 9, related to newborn hearing screening, while the question that Syrian nationals answered correctly the most was question 6, which states that hearing loss may worsen over time, if not intervened. The question with the lowest percentage of correct answers in both groups was question 20, related to tinnitus.

The median pre-training questionnaire scores of Turkish nationality participants were 16.00 (14.00-21.00), and the median post-training questionnaire scores were 25.00 (25.00-26.00). The median pre-training questionnaire scores of Syrian nationality

Table 1. Hearing and Balance Knowledge Level Questionnaire and correct answers

Queationnaire items	Responses		
	Yes	No	I do not know
1. Audiology is a branch of science that deals only with hearing		X	
2. Audiologists only perform hearing tests		X	
3. There are different types of hearing loss	X		
4. There are degrees of hearing loss	X		
5. Hearing can sometimes be regained after a hearing loss has occurred	X		
6. If left untreated, some hearing loss may worsen over time	X		
7. The ear is an organ responsible only for hearing		X	
8. Early diagnosis and treatment are of no benefit in hearing loss		X	
9. Every newborn baby needs to have a hearing test (ABR)	X		
10. Newborn hearing screening test will hurt my baby		X	
11. Some diseases experienced by the mother during pregnancy (measles, etc.) negatively affect the baby's hearing	X		
12. A hearing aid amplifies sounds so a person with hearing loss can hear more	X		
13. Hearing aids can be purchased without a prescription in Türkiye		X	
14. Hearing aids vary depending on the degree of hearing loss	X		
15. Cochlear implants are devices popularly known as bionic ears	X		
16. A cochlear implant (bionic ear) is surgically attached to the inner ear	X		
17. Hearing loss in children affects language and speech development	X		
18. Patients with cochlear implants (bionic ear) can hear as well as those with normal hearing	X		
19. Children with severe hearing loss should receive cochlear implants early	X		
20. There is a difference between tinnitus and ear-ringing		X	
21. Tinnitus is a disease		X	
22. One of the most common causes of tinnitus is noise exposure	X		
23. Listening to music using headphones for a long time and at high volume does not hurt hearing		X	
24. Loss of balance, vertigo, or dizziness is caused only by problems in the inner ear		X	
25. Some medications have adverse effects on hearing and balance	X		
26. Some of the diseases that cause vertigo can be treated	X		
27. Some individuals with vertigo benefit from balance exercises	X		

ABR: Auditory brainstem response

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participants were 16.00 (11.25-18.00), and the median post-training questionnaire was 25.00 (25.00-26.00). Although the questionnaire median values of Turkish and Syrian individuals were the same before the training, it was observed that there was a statistical significant difference between the groups ($p<0.05$). The distribution of questionnaire median values after training was compared between the groups using the Mann-Whitney U test, and no significant difference was found ($p=0.985$) (Figure 1).

The questionnaire median values of Turkish and Syrian nationals, based on education level and monthly income, are shown in Table 4. Before training, although there was no statistically significant difference between education levels in both groups, except for the bachelor group, it was determined that median values increased as education levels increased. There was no statistically significant difference between the questionnaire median values, except for participants with a monthly income of 30,001 Turkish lira and above. In the study, the post-training median values of the questionnaire, according to monthly income and education level (excluding middle and high school levels), were similar in both groups.

Before the training, the correlation and comparison of the Hearing and Balance Knowledge Level Questionnaire median values within groups were examined according to demographic variables such as gender, active employment status, education level, and monthly income. Although the median values of the pre-training questionnaire according to gender were not statistically significant ($p>0.05$), in both groups for male and female participants, women's scores were higher than men's in both groups. The pre-training questionnaire median values were similar between working and non-working participants in both groups ($p>0.05$). No correlation was found between education level and pre-training questionnaire median values in Turkish participants. However, a moderate positive correlation was observed between education level and pre-training questionnaire scores in Syrian participants ($p<0.05$). Both groups found a low but statistically significant positive correlation between monthly income and pre-training questionnaire scores ($p<0.05$). The within-group correlations and comparisons of pre-training questionnaire median values based on gender, employment status, education level, and monthly income are presented in Table 5.

Table 2. Socio-demographic information of participants

Variables		Participants of Turkish nationality n (%)	Participants of Syrian nationality n (%)
Gender	Female	51 (51%)	50 (50%)
	Male	49 (49%)	50 (50%)
Educational status	Primary school	2 (2%)	1 (1%)
	Middle school	5 (5%)	7 (7%)
	High school	19 (19%)	26 (26%)
	Associate degree	11 (11%)	15 (15%)
	Bachelor degree	57 (57%)	46 (46%)
	Postgraduate	6 (6%)	5 (5%)
Profession	Student	19 (19%)	32 (32%)
	Civil servant	16 (16%)	4 (4%)
	Teacher	18 (18%)	16 (16%)
	Self-employment	27 (27%)	27 (27%)
	Doctor	1 (1%)	3 (3%)
	Retired	4 (4%)	6 (6%)
	Housewife	14 (14%)	10 (10%)
	Dentist	1 (1%)	2 (2%)
Active working status	Working	50 (50%)	34 (34%)
	Not working	50 (50%)	66 (66%)
Monthly income	0-10,000 TL	6 (6%)	28 (28%)
	10,001-20,000 TL	20 (20%)	27 (27%)
	20,001-30,000 TL	20 (20%)	22 (22%)
	30,001 TL and above	54 (54%)	23 (23%)

N: Number, %: Percentage, TL: Turkish lira

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Table 3. Distribution of participants' responses to the Hearing and Balance Knowledge Level Questionnaire before and after training

Questionnaire items	Pre-training				Post-training			
	Participants of Turkish nationality (n=100)		Participants of Syrian nationality (n=100)		Participants of Turkish nationality (n=100)		Participants of Syrian nationality (n=100)	
	Correct answer (n%)	Wrong answer (n%)	Correct answer (n%)	Wrong answer (n%)	Correct answer (n%)	Wrong answer (n%)	Correct answer (n%)	Wrong answer (n%)
1. Audiology is a branch of science that deals only with hearing	29 (29%)	71 (71%)	27 (27%)	73 (73%)	99 (99%)	1 (1%)	99 (99%)	1 (1%)
2. Audiologists only perform hearing tests	44 (44%)	56 (56%)	34 (34%)	66 (66%)	99 (99%)	1 (1%)	99 (99%)	1 (1%)
3. There are different types of hearing loss	84 (84%)	16 (16%)	87 (87%)	13 (13%)	100 (100%)	0 (0%)	100 (100%)	0 (0%)
4. There are degrees of hearing loss	90 (90%)	10 (10%)	90 (90%)	10 (10%)	100 (100%)	0 (0%)	100 (100%)	0 (0%)
5. Hearing can sometimes be regained after a hearing loss has occurred	61 (61%)	39 (39%)	45 (45%)	55 (55%)	95 (95%)	5 (5%)	99 (99%)	1 (1%)
6. If left untreated, some hearing loss may worsen over time	90 (90%)	10 (10%)	92 (92%)	8 (8%)	99 (99%)	1 (1%)	100 (100%)	0 (0%)
7. The ear is an organ responsible only for hearing	59 (59%)	41 (41%)	59 (59%)	41 (41%)	99 (99%)	1 (1%)	99 (99%)	1 (1%)
8. Early diagnosis and treatment are of no benefit in hearing loss	81 (81%)	19 (19%)	75 (75%)	25 (25%)	99 (99%)	1 (1%)	100 (100%)	0 (0%)
9. Every newborn baby needs to have a hearing test (ABR)	92 (92%)	8 (8%)	74 (74%)	26 (26%)	94 (94%)	6 (6%)	98 (98%)	2 (2%)
10. Newborn hearing screening test will hurt my baby	81 (81%)	19 (19%)	72 (72%)	28 (28%)	99 (99%)	1 (1%)	97 (97%)	3 (3%)
11. Some diseases experienced by the mother during pregnancy (measles, etc.) negatively affect the baby's hearing	63 (63%)	37 (37%)	40 (40%)	60 (60%)	96 (96%)	4 (4%)	94 (94%)	6 (6%)
12. A hearing aid amplifies sounds so a person with hearing loss can hear more	81 (81%)	19 (19%)	67 (67%)	33 (33%)	100 (100%)	0 (0%)	100 (100%)	0 (0%)
13. Hearing aids can be purchased without a prescription in Türkiye	51 (51%)	49 (49%)	33 (33%)	67 (67%)	58 (58%)	42 (42%)	63 (63%)	37 (37%)
14. Hearing aids vary depending on the degree of hearing loss	82 (82%)	18 (18%)	70 (70%)	30 (30%)	98 (98%)	2 (2%)	100 (100%)	0 (0%)
15. Cochlear implants are devices popularly known as bionic ears	44 (44%)	56 (56%)	32 (32%)	68 (68%)	96 (96%)	4 (4%)	97 (97%)	3 (3%)
16. A cochlear implant (bionic ear) is surgically attached to the inner ear	43 (43%)	57 (57%)	25 (25%)	75 (75%)	93 (93%)	7 (7%)	95 (95%)	5 (5%)
17. Hearing loss in children affects language and speech development	85 (85%)	15 (15%)	68 (68%)	32 (32%)	97 (97%)	3 (3%)	97 (97%)	3 (3%)
18. Patients with cochlear implants (bionic ear) can hear as well as those with normal hearing	40 (40%)	60 (60%)	14 (14%)	86 (86%)	79 (79%)	21 (21%)	90 (90%)	10 (10%)
19. Children with severe hearing loss should receive cochlear implants early	49 (49%)	51 (51%)	28 (28%)	72 (72%)	91 (91%)	9 (9%)	95 (95%)	5 (5%)
20. There is a difference between tinnitus and ear-ringing	22 (22%)	78 (78%)	13 (13%)	87 (87%)	97 (97%)	3 (3%)	92 (92%)	8 (8%)
21. Tinnitus is a disease	31 (31%)	69 (69%)	26 (26%)	74 (74%)	94 (94%)	6 (6%)	93 (93%)	7 (7%)
22. One of the most common causes of tinnitus is noise exposure	49 (49%)	51 (51%)	55 (55%)	45 (45%)	98 (98%)	2 (2%)	92 (92%)	8 (8%)

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Table 3. Continued

Questionnaire items	Pre-training				Post-training			
	Participants of Turkish nationality (n=100)		Participants of Syrian nationality (n=100)		Participants of Turkish nationality (n=100)		Participants of Syrian nationality (n=100)	
	Correct answer (n%)	Wrong answer (n%)	Correct answer (n%)	Wrong answer (n%)	Correct answer (n%)	Wrong answer (n%)	Correct answer (n%)	Wrong answer (n%)
23. Listening to music using headphones for a long time and at high volume does not hurt hearing	79 (79%)	21 (21%)	48 (48%)	52 (52%)	100 (100%)	0 (0%)	93 (93%)	7 (7%)
24. Loss of balance, vertigo, or dizziness is caused only by problems in the inner ear	47 (47%)	53 (53%)	27 (27%)	73 (73%)	81 (81%)	19 (19%)	64 (64%)	36 (36%)
25. Some medications have adverse effects on hearing and balance	76 (76%)	24 (24%)	59 (59%)	41 (41%)	99 (99%)	1 (1%)	93 (93%)	7 (7%)
26. Some of the diseases that cause vertigo can be treated	70 (70%)	30 (30%)	62 (62%)	38 (38%)	100 (100%)	0 (0%)	97 (97%)	3 (3%)
27. Some individuals with vertigo benefit from balance exercises	69 (69%)	31 (31%)	56 (56%)	44 (44%)	97 (97%)	3 (3%)	98 (98%)	2 (2%)

N: Number, %: Percentage, ABR: Auditory brainstem response

Table 4. Median values of questionnaire before and after training based on socio-demographic variables in the groups

Variables	Pre-training		p-value	Post-training		p-value
	Questionnaire median values of Turkish nationalities participants median (25th and 75th quartiles)	Questionnaire median values of Syrian nationalities participants median (25th and 75th quartiles)		Questionnaire median values of Turkish nationalities participants median (25th and 75th quartiles)	Questionnaire median values of Syrian nationalities participants median (25th and 75th quartiles)	
Education status						
Primary school	14.00 (14.00-14.00)	6.00 (6.00-6.00)	-	24.50 [24.00- (-)]	20.00 (20.00-20.00)	-
Middle school	16.00 (12.00-20.00)	16.00 (10.75-17.25)	0.612	25.00 (25.00-26.00)	20.00 (20.00-20.00)	**0.003***
High school	16.00 (12.00-18.00)	16.00 (13.00-18.00)	0.459	25.00 (24.00-26.00)	25.50 (25.00-26.00)	**0.037***
Associate degree	16.00 (14.50-22.50)	16.00 (13.00-18.00)	0.470	25.00 (24.00-26.00)	25.00 (25.00-26.00)	1.000
Bachelor degree	18.00 (14.00-22.00)	15.00 (15.00-16.00)	**0.002***	25.00 (25.00-27.00)	25.00 (25.00-26.00)	0.694
Postgraduate	20.00 (16.50-23.00)	19.00 (13.50-22.00)	0.548	25.00 (24.00-26.00)	26.00 (25.00-27.00)	0.247
Monthly income						
0-10,000 TL	12.00 (7.50-16.25)	13.00 (7.25-16.00)	0.912	25.00 (24.00-26.00)	25.00 (24.00-26.00)	0.912
10,001-20,000 TL	16.00 (14.25-20.75)	17.00 (12.00-18.00)	0.294	25.00 (23.25-26.00)	25.00 (25.00-26.00)	0.557
20,001-30,000 TL	16.00 (13.25-18.75)	15.50 (11.75-18.25)	0.433	25.00 (24.25-26.00)	25.00 (25.00-26.25)	0.358
30,001 TL and above	18.50 (15.00-22.00)	16.00 (13.00-18.00)	**0.038***	25.00 (25.00-27.00)	25.00 (25.00-26.00)	0.865

*: $p<0.05$

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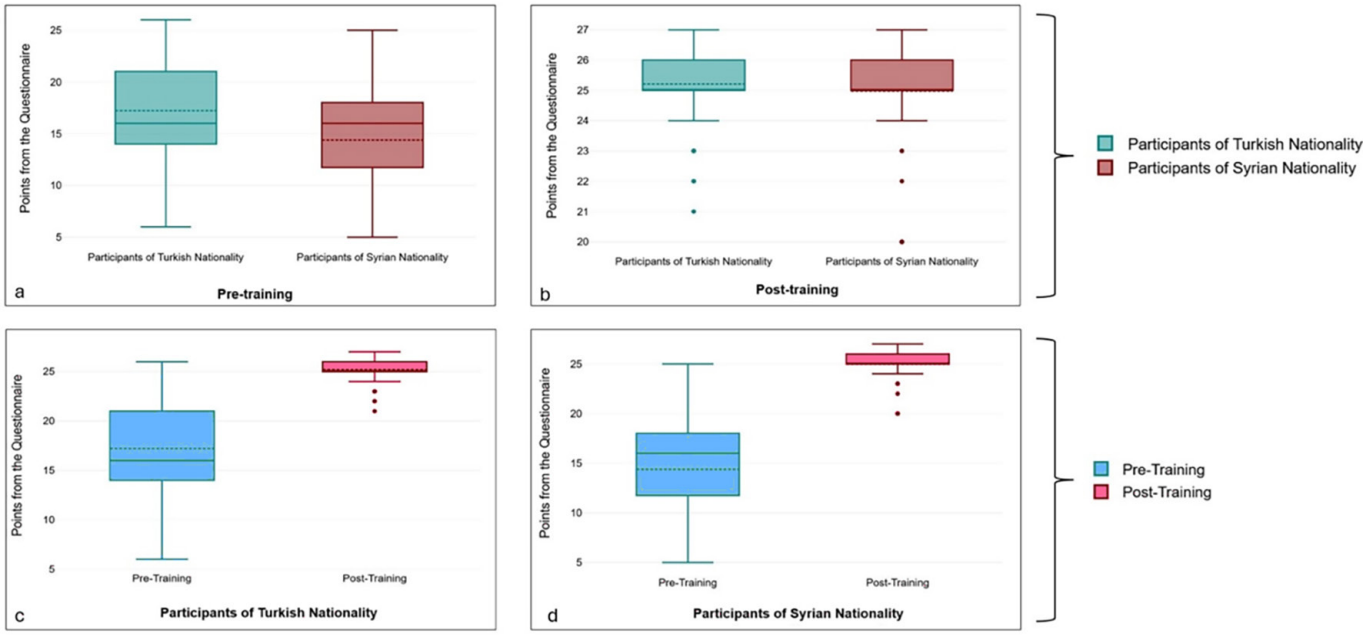

Figure 1. Distribution of questionnaire median values between groups (a,b) and within groups (c,d) before and after training. (a) Intergroup comparison of pre-training questionnaire median values, (b) intergroup comparison of post-training questionnaire median values, (c) intragroup comparison of pre-training and post-training questionnaire median values of Turkish nationality participants, (d) intragroup comparison of pre-training and post-training questionnaire median values of Syrian nationality participants

Table 5. Compare and correlation of hearing and balance knowledge level questionnaire scores within groups based on demographic variables before training

	Participants of Turkish nationality median (25th and 75th quartiles)	Participants of Syrian nationality median (25th and 75th quartiles)
Gender		
Female	17.00 (14.00-22.00)	16.00 (11.00-18.00)
Male	16.00 (14.00-20.00)	15.50 (12.00-17.00)
p-value	0.509	0.594
Active working status		
Working	18.00 (14.00-22.00)	15.00 (10.75-17.00)
Not working	16.00 (14.00-20.00)	16.00 (12.00-18.00)
p-value	0.098	0.286
Educational status	r=0.164, p=0.104	**r=0.333, p<0.001***
Monthly income	**r=0.251, p=0.012***	**r=0.286, p=0.004***

*: p<0.05

DISCUSSION

Access to essential services such as education and healthcare has been disrupted due to the war in Syria. Reasons like the destruction of schools and families fleeing their homes due to security concerns have led to a scientific gap that needs to be addressed. This study aimed to assess the levels of knowledge in audiology of Turkish nationals living in Türkiye and Syrian nationals who migrated due to difficulties in their country, specifically in audiology. In our study, for this purpose, the participants' knowledge levels regarding hearing and balance in two groups were assessed, and it was aimed to address any potential gaps through the planned training, which was then discussed with the literature.

According to the initial data obtained from our study, it was found that Syrian participants scored significantly lower than Turkish participants in terms of the accuracy of the questionnaire items. Specifically, for item 9 of the questionnaire, which states, "Every newborn should undergo a hearing test (Automated - auditory brainstem response)", 74% of Syrian participants answered correctly, while 92% of Turkish participants provided a much higher rate of correct responses. Although the same screening protocols are applied to refugees giving birth in Türkiye, according to these data, it is observed that the knowledge level of Syrian nationals regarding newborn hearing screening is more limited. The newborn hearing screening program (NHSP) in Türkiye was started in 2004 and is currently actively carried out in 81 provinces. According to the 2022 data from the General Directorate of Public Health, 95.8% of newborns in Türkiye undergo screening every year for hearing (9). The NHSP implemented in Türkiye is the responsibility of the Health Ministry, and the Joint Committee on Infant Hearing principles have been adopted in the program (10). In this regard, great importance is given to the hearing screening program in our country. Care is taken to inform families who have a new baby before the baby is discharged. In addition, hearing screenings are routinely performed for babies before they leave the hospital. Special care is taken to closely monitor babies who

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have not passed the screening in case of potential hearing loss (11). An important factor contributing to the higher scores of Turkish participants on this item is the effective healthcare policies related to the hearing screening programs implemented in Türkiye.

When examining the questionnaire scores, Turkish and Syrian participants scored the lowest on item 20, about tinnitus, indicating a lack of shared knowledge. Overall, when looking at the average questionnaire scores, Turkish participants answered 17 out of 27 questions correctly (62%), while Syrian participants answered 14 correctly (51%). Based on these results, it can be concluded that awareness and knowledge regarding hearing and balance is not at the desired level in both groups. While hearing and balance disorders are quite common, they are often less well-known compared to other health issues they are generally not life-threatening. To increase awareness of hearing and balance loss, associations, various organizations and hearing professionals in Türkiye and around the world periodically conduct studies. The common conclusion of all these studies is a general lack of knowledge regarding hearing and hearing health issues (12-17). A study by Tuz et al. (13) conducted for World Hearing Awareness Day on March 3rd, concluded that educational efforts on hearing health are essential. Joubert et al. (18) in their study evaluating the public's awareness of Audiology profession, hearing, hearing losses, and hearing health, stated that there is a lack of awareness about audiologists and the services they offer. In Türkiye, while newborn and first-grade children's hearing screening programs are effectively implemented, a routine hearing screening program for adults and older persons does not exist. Furthermore, balance screening is not conducted in any age group. In summary, there is no routine screening program for hearing and balance health, and this lack concerns all age groups in our country (except newborns and first-grade children). On the other hand, the department of audiology, whose main area of interest is all kinds of hearing screening programs, hearing and balance health/diseases, has started as an undergraduate education in Türkiye since 2011 (19). Currently, audiologists continue to be trained in 25 universities in Türkiye (20). However, the employment of graduated audiologists in institutions affiliated with the Ministry of Health and other ministries is insufficient (21). We believe that the shortage of appointed audiologists and the insufficient level of related audiological activities affect all individuals living within Türkiye's borders, contributing to the lack of awareness regarding hearing and balance health/issues.

Syrian individuals have suffered significant losses in education, as well as in other areas, due to the ongoing war in their country for more than a decade. Considering the conditions in the region, many individuals have faced a lack of knowledge regarding hearing and balance issues, and treatment options. The lower questionnaire scores of these individuals compared to Turkish participants can be attributed to their adaptation process in a new country and community after migrating, as well as the disruptions in their education due to their primary focus on meeting basic needs. Moreover, following the training, which we provided using various materials, the correct response rates for Turkish and Syrian participants regarding items 9 and 20 increased. Overall, the percentage of correct answers given by both groups significantly improved, reaching an increase of approximately 25 percentage points (92%) for each group. We believe that the training we provided, particularly related to hearing and balance functions, will contribute to early diagnosis/intervention, rehabilitation, and preventive services for potential diseases or hearing and balance loss.

In a study conducted by Crandell et al. (22) with young adults, where knowledge and attitudes regarding hearing loss were assessed in terms of racial differences, similar results were found regarding knowledge levels across races, in contrast to the findings of our study. However, the researchers emphasized the need for comparisons based on socio-demographic characteristics such as gender, age, or income. According to our study data, especially before the training, the rate of correct answers given to the questionnaire was higher among women than among men, among both Turkish and Syrian participants. In other words, gender appears to be an important parameter affecting questionnaire scores. Similarly, in a study conducted by Di Berardino et al. (17) using a questionnaire to assess ear and hearing health, it was reported that women provided better answers to the questions and that societal awareness of hearing loss in infants was high. In a study conducted at Hacettepe University, the "Mothers' Views on Hearing Loss in Infants" questionnaire was translated into Arabic and administered to Syrian mothers. The results showed they had good knowledge about hearing loss and risk factors in infants and demonstrated a positive attitude towards early detection and intervention (23). Similarly, in a study measuring public awareness of ear health and hearing loss, it was reported that women provided a higher percentage of correct answers to the questions compared to men (24). Women's tendency to take more responsibility for the care of family members and health issues may have contributed to the higher questionnaire scores.

In the initial period before providing training, employment status did not have any effect on the scores of the questionnaire we used. However, as expected, level of education and monthly income affected the scores, with higher education levels (for Syrian nationals) and income levels (in both groups) leading to higher questionnaire scores. After the training, the questionnaire scores of both groups were similar in terms of education level (except middle and high school) and monthly income.

Although we set the condition that participants in our study had not previously received any training on hearing and balance, our data collection form did not inquire about the presence of diseases in the family, related to the specified areas. It should be noted that if individuals in the family have hearing and balance loss-related diseases, participants may have higher awareness and knowledge levels, which could affect the questionnaire scores. Moreover, when reviewing the literature, it can be seen that the questions used in the "Ear and Hearing Care Programme" manual prepared by the World Health Organization have been culturally adapted and used in various studies. In these studies,

broader topics such as hearing loss and its correct management in infants, ear cleaning, treatment and care, the effects of excessive exposure to loud noise and sound, and ear symptoms that lead to diagnostic delays have been investigated (17,24-26). In our study, however, we focused on more specific topics such as audiology, audiologists, newborn hearing screening, hearing aids, cochlear implants, tinnitus (ringing in the ears), dizziness, and balance. We also provided compensatory training in case of knowledge gaps and evaluated the contribution of this training.

Study Limitations

The limitation of our study is that we collected data from a single point in 1 week. Data collection from different locations (such as hospitals and universities) and over more extended periods may be useful for subsequent studies. Another limitation of our study is that we did not analyze questionnaire content or construct validity. In subsequent research, it would be beneficial to assess construct or content validity.

CONCLUSION

Based on the findings of our study, a knowledge gap regarding audiology, audiologists, hearing/balance loss, tinnitus, hearing aids, cochlear implants, and vertigo was identified in both groups, particularly among Syrian nationals, and can be addressed through educational interventions.

By determining the knowledge levels on selected health-related topics and addressing the gaps, significant contributions can be made to the health of all individuals living in the country. It can make positive contributions, especially in terms of protecting against diseases or consciously determining individual needs in case of illness and requesting the needs from health institutions. The conscious and informed demand for healthcare services by individuals of different nationalities living in Türkiye could allow the host country to review its healthcare system, evaluate its performance, and structure health reforms for refugees. Therefore, it is essential for academics, physicians, and especially audiologists working in ear nose and throat and audiology departments to play an important role in expanding informational activities on hearing and balance health and loss at the national level.

Our study was conducted on a relatively small population. Future research could benefit from including individuals from different regions within the country to determine regional differences.

Ethics

Ethics Committee Approval: For the present study, ethical approval was obtained from the Clinical Research Ethics Committee at Samsun Ondokuz Mayıs University (decision no: OMÜ KAEK 2023/14, date: 24.06.2024).

Informed Consent: Our study is prospective and descriptive. Turkish nationals over 18 who agreed to participate in the study were informed about the purpose of the study and signed an informed consent form.

Footnotes

Author Contributions: Surgical and Medical Practices - H.T.D.; Concept - H.T.D., A.K.; Design - H.T.D., A.K.; Data Collection and/or Processing - H.T.D., H.H., M.H., T.H.; Analysis and/or Interpretation - H.T.D., M.H.; Literature Search - H.T.D., A.K., H.H., M.H., T.H.; Writing - H.T.D., A.K.

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Anatomical and Histological Characterization of the SOOF: Redefining Midface Support

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ABSTRACT

Objective: The suborbicularis oculi fat (SOOF) is a distinct fibro-adipose tissue with critical functional and aesthetic roles in the midface. Despite its clinical relevance, the precise anatomical and histological characteristics of this condition remain underdefined. This study aims to delineate the structural organization and tissue composition of the SOOF, with a focus on its relationship with the orbicularis oculi muscle (OOM) and the superficial muscular aponeurotic system (SMAS).

Methods: Tissue samples from the lateral infraorbital region, including skin, SMAS, OOM, and SOOF, were harvested post-mortem from ten body donors without prior head or neck interventions. Samples were fixed in 4.5% formaldehyde, sectioned, and stained using hematoxylin and eosin and masson's trichrome. Histological analyses focused on collagen organization, muscle integration, and vascularization.

Results: SOOF was identified as a multilayered, vascularized tissue located beneath the OOM and connected to the SMAS through fibrous septa. Masson's Trichrome staining revealed dense, well-aligned collagen bundles and interspersed muscle fibers, forming a complex ligamentous structure. These findings suggest a dynamic interface between connective and contractile elements, supporting both the structural and functional integrity of the lower eyelid and midface region.

Conclusion: The SOOF is not a passive fat pad but a myofibrous unit integrated with adjacent anatomical structures. Its anatomical continuity with the SMAS and OOM underscores its importance in facial dynamics, aging, and surgical intervention. A deeper understanding of SOOF morphology enables more precise, functionally informed approaches to midfacial rejuvenation and reconstructive surgery.

Keywords: Suborbicularis oculi fat (SOOF), superficial musculoaponeurotic system (SMAS), orbicularis oculi muscle (OOM), facial anatomy, midface rejuvenation

INTRODUCTION

Suborbicularis oculi fat (SOOF) is a distinct adipose structure located beneath the orbicularis oculi muscle (OOM) residing supraperiosteally in the inferolateral region of the orbit. It is positioned above the zygomatic arch and below the lateral half of the infraorbital rim, extending from +15 degrees medially to -87 degrees laterally relative to the caudal vertical mid-pupillary line. This fat pad plays a significant role in facial aesthetics and function, contributing to the contour and volume of the midface and lower eyelid region (1).

Previous studies emphasized the anatomical continuity between the SOOF, superficial muscular aponeurotic system (SMAS), and OOM, which plays a key role in facial surgeries. The SMAS, a fibrous, three-dimensional meshwork, provides structural support to the facial skin and muscles, including the OOM (2).

Historically, the term "SOOF" was coined in reference to lower eyelid blepharoplasty procedures, where the fat pad was often resected to prevent contour defects (3). Despite its clinical relevance, the SOOF has not been formally included in anatomical terminologies such as Nomina Anatomica, leading to ongoing debates regarding its exact anatomical boundaries and morphological characteristics (1,4). A clear understanding of SOOF anatomy is crucial because it significantly affects the success of surgeries that treat midfacial aging and conditions, such as lower eyelid ectropion and facial palsy (5). Given the variability in orbital defects and the lack of consensus in their classification,

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reconstructive approaches often rely on the surgeon's experience (6). The reconstruction of orbital defects presents a complex challenge, demanding a nuanced approach that considers anatomical layers, defect size, and location to achieve predictable, stable, and functionally sound results (7). The classification systems, although valuable, often fail to comprehensively address the status of the orbital floor and zygoma, which are critical for midface function and cosmesis (8). The primary goal of eyelid reconstruction is to establish a stable eyelid margin that ensures proper dimensions and tension in both open and closed states, and to achieve eyelid symmetry without any rough or uneven internal surfaces, while optimizing aesthetics (9).

Facial aging is strongly influenced by changes in fat compartments, especially the position and morphology of the SOOF (10). Given the close anatomical and functional relationship between the SOOF and its surrounding structures, understanding its role in facial dynamics is essential for improving surgical interventions aimed at rejuvenating the periorbital and midfacial regions (11).

METHODS

Ethical approval was obtained from the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (number: 2025/7-7/23, date: 27.03.2025). This study strictly adhered to the principles outlined in the Declaration of Helsinki, ensuring the highest standards of research integrity and ethical conduct. Given that our study utilizes cadaveric specimens, obtaining a consent form is not necessary, allowing us to focus entirely on the research objectives without legal constraints.

Whole-graft tissue blocks of the skin, SMAS, OOM, and SOOF from the lateral infraorbital region were collected post-mortem from ten body donors, and fixed in 4.5% formaldehyde. The donor sites showed no visible scars or tissue damage, and the medical history revealed no surgical intervention or radiation of the head and neck area. SOOF was localized macroscopically using the method described by Hwang et al. (12), in which tissue blocks were removed.

Histological Analysis

Following fixation in 4.5% formaldehyde, tissue blocks measuring 1×2×1 cm^3 were processed for paraffin embedding. Serial sections were obtained in the vertical plane at a thickness of 5 µm, and every tenth section was collected for histological evaluation. Masson's trichrome staining was applied to the selected sections. Photomicrographs were captured using a Zeiss Axiocam camera attachment at × 5 and × 40 objective magnifications. The sections were examined under a Zeiss Scope A1 microscope (Germany), and additional micrographs were acquired. All micrographs were edited and assembled using Adobe Photoshop 2024 (Adobe Inc., San Jose, California, United States).

In developing this work, the authors harnessed the capabilities of OpenAI's ChatGPT, Jenni, and Grammarly to create insightful summaries of relevant research articles. These artificial intelligence (AI)-generated summaries were rigorously evaluated against manually crafted summaries by field experts, ensuring accuracy and relevance. Upon validating their quality, these summaries were seamlessly integrated into the literature review section of the manuscript. The authors carefully reviewed and refined the content, assuming full responsibility for the integrity of the publication. The strategic use of these AI tools significantly enhanced the efficiency of the literature review process and greatly enriched the depth and breadth of the research insights collected.

Statistical Analysis

This qualitative study offers a compelling exploration of the histological characteristics of specific tissue samples obtained from cadavers, grounded in carefully formulated hypotheses-driven observations. Given its qualitative focus, the study does not rely on quantitative measurements or comparisons; instead, it provides an in-depth evaluation of the morphological and histological structures observed within the tissue samples. Consequently, conventional parametric or non-parametric statistical analyses are not applicable in this context. The results are articulated descriptively, drawing on the expertise of anatomists and histologists, and are thoughtfully interpreted with respect to the existing body of literature. This approach not only enhances the validity of the findings but also enriches the overall understanding of the tissue characteristics studied.

RESULTS

Hematoxylin and Eosin (H and E) Staining

At low magnification (x5), full-thickness skin sections, including the epidermis, dermis, and subcutaneous tissue, were examined. The SOOF region was identified by its anatomical location beneath the OOM, appearing as a deep fat pad. In this area, collagenous septa were noted as dense, eosinophilic bundles extending from the dermis into the submuscular adipose tissue. These fibrous septa displayed a stratified architecture and functioned as anchoring structures between the deep dermis and the underlying fat compartments. The fibrous septa extended to the upper layers of the OOM and divided the fat into lobules that contained muscle fibers. These septa reached the surface of the OOM, forming the fibro-muscular septa of the infraorbital SMAS, thus establishing a direct anatomical connection between the SOOF and the SMAS (Figure 1). Unlike the fibrous structures within the SMAS, the septa of the SOOF exhibited a smoother surface and aligned parallel to the fibers of the OOM.

Additionally, vascular structures, including small to medium-sized blood vessels, were observed interspersed among the collagen fibers and adjacent to muscle fascicles. Muscle bundles beneath the collagenous framework displayed a striated morphology, with peripheral nuclei indicative of skeletal muscle tissue. The SOOF ligament complex demonstrated a well-organized, fibrous composition, maintaining continuity with the surrounding muscular and vascular elements.

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Masson's Trichrome Staining

Masson's Trichrome staining effectively highlighted the connective tissue elements. The collagen fibers within the SOOF ligament complex stained prominently blue, allowing clear differentiation from the surrounding muscular (red) and vascular components (Figure 2). These collagen bundles extended vertically and obliquely beneath the OOM, suggesting their supportive role in maintaining facial soft tissue integrity. The fibrous structures were organized in a multilayered configuration, with several fibers converging at the interface between muscle and fat. Vascular channels, filled with erythrocytes, were frequently detected between the collagen bundles, confirming the vascularized nature of the SOOF region.

At higher magnification (x40), Masson's Trichrome staining (Figure 2) provided a detailed visualization of the ultrastructural organization within the SOOF ligaments. Collagen fibers were stained blue, showing a dense and orderly fibrillar structure. Notably, muscle fibers were observed interspersed among these collagen structures (Figure 3). This coexistence of muscle and collagen fibers underscores the complex myofibrous nature of the SOOF ligament. The proximity and partial integration of muscle fibers within the collagen matrix suggest an interactive structure between connective and contractile tissues, which may contribute to the structural stability and functional mobility of the SOOF. The collective staining characteristics and microanatomical arrangement of the SOOF ligaments support their classification as specialized, vascularized, collagenous structures with embedded muscle elements. These components serve a dual role, providing positional support and mechanical coordination for the lower eyelid and midface region.

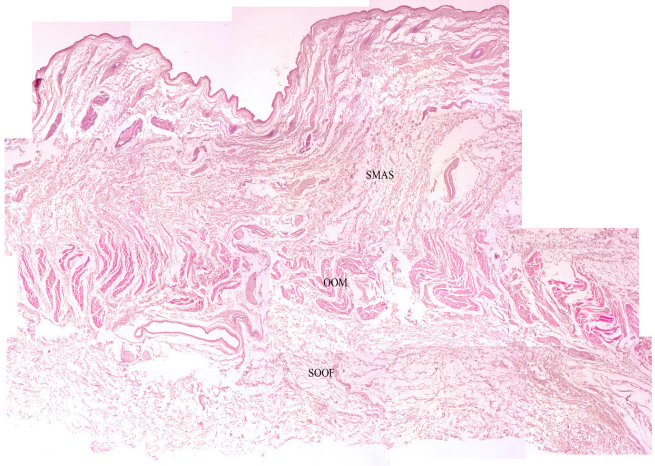

Figure 1. Hematoxylin and eosin stained micrograph of the connection between SOOF, OOM and SMAS (Composed by stitching images taken at x50 magnifications)

SOOF: Suborbicularis oculi fat, OOM: Orbicularis oculi muscle, SMAS: Superficial muscular aponeurotic system

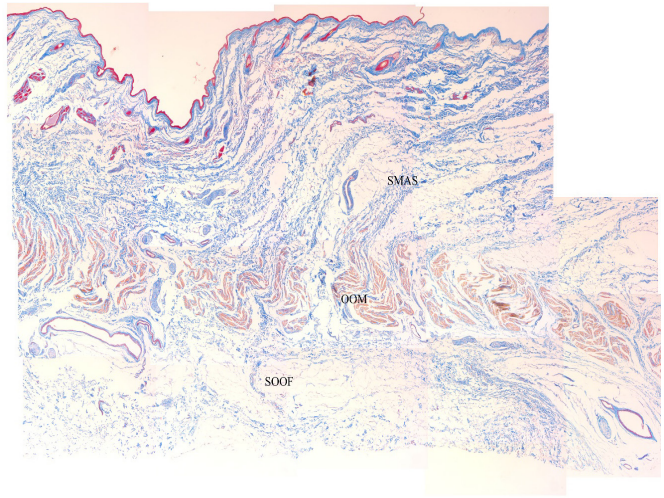

Figure 2. Masson's Trichrome-stained section illustrating the anatomical relationship between the SMAS, OOM and the SOOF. Collagenous structures are stained blue, highlighting dense fibrous septa extending from the dermis into the submuscular adipose tissue. These septa pass through and around the OOM, dividing the SOOF into lobular compartments. (Composed by stitching images taken at x50 magnifications)

SOOF: Suborbicularis oculi fat, OOM: Orbicularis oculi muscle, SMAS: Superficial muscular aponeurotic system

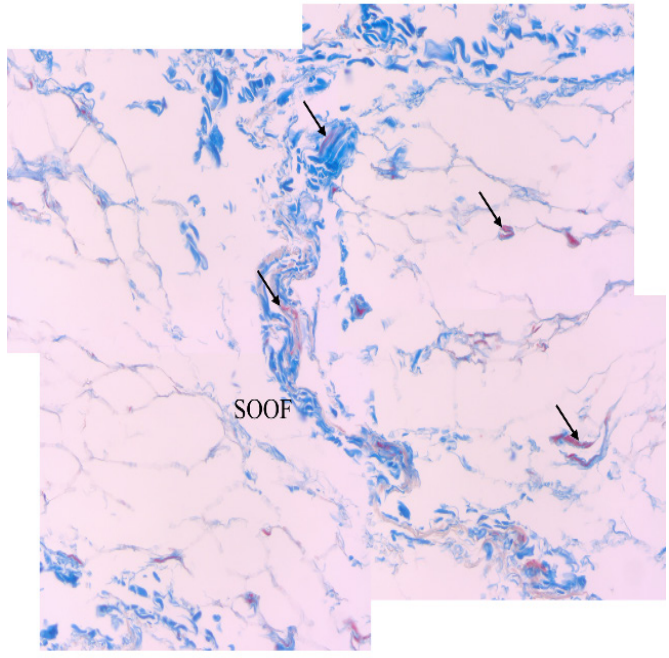

Figure 3. Representative histologic section of the SOOF region stained with Masson's Trichrome. Collagen fibers appear intensely blue within the SOOF ligament and forming multilayered bundles adjacent to the suborbicular fat pads. (SOOF: Suborbicularis oculi fat; arrow, muscle fiber) (Composed by stitching images taken at x400 magnifications)

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DISCUSSION

SOOF is located between the OOM and the infraorbital SMAS. This anatomical arrangement creates a three-dimensional fibrous network that encircles adipose structures, allowing SOOF to act as a cushion that reduces friction during OOM movements. When the OOM contracts, the movement is transmitted through the SMAS to the skin, while SOOF is simultaneously displaced. Histological studies reveal that SOOF comprises a mixture of fibrous and adipose tissues, distinguishing it from the more homogenous orbital fat. The fibrous component consists of interconnected chambers filled with adipocytes, supporting earlier findings on three-dimensional tissue formations (1,13).

Research by Rohrich et al. (14), demonstrated that methylene blue injected into the sub-OOM plane spreads throughout the SOOF, indicating its division into medial and lateral anatomical regions. The fibrous structure surrounding the adipose tissue can be more clearly visualized using 3D reconstruction techniques, especially when methylene blue is injected before imaging (14).

The histomorphological similarities between SOOF and SMAS suggest these structures may function as cohesive units. However, the absence of muscle fibers within SOOF indicates functional differences between these tissues. For example, removing SOOF may lead to poor long-term outcomes because the lack of continuous muscle contraction after excision hinders the muscle's functional role, potentially resulting in ptosis. Additionally, procedures that lift SOOF, particularly when combined with lateral tarsal strip techniques, have effectively treated conditions such as congenital and Bell's palsy, lower eyelid retraction, and midface sagging. In contrast, malar fat repositioning and facelift surgeries may yield short-term successful results but lack long-term stability. This instability may be attributed to the thinner, atrophic cheek tissues in patients with congenital facial paralysis, which makes them more malleable after surgical intervention (15-17).

Structural findings indicate that SOOF forms a fibro-adipose cushion along the inferolateral orbital border, connecting to the OOM through fibrous septa. These findings support that SOOF and SMAS share similar functional properties, underscoring the need for more region-specific and tailored facial rejuvenation procedures (1,18). Age-related fat redistribution, such as the loss of deep cheek fat and accumulation of fat in the lower jaw, necessitates a versatile treatment approach that combines liposuction and fat transfer techniques. This approach aligns with the understanding that different fat compartments may lose or gain volume in various ways over time, explaining the need for distinct procedures for the same individual (19).

The location and dynamic nature of SOOF offer valuable insights for periorbital rejuvenation in a region that presents surgical challenges. SOOF augmentation has emerged as an effective method to smooth the orbital-cheek junction and restore volume. Fat transfer or SOOF injections are widely used to address volume loss in this area (20). However, having precise anatomical knowledge is essential for the accurate placement of these injections. For example, placing fillers subperiostally is often anatomically inaccurate, as fat compartments cannot be accessed directly in this way. The position of the tear trough and the extent of lid retraction are essential elements to consider during lower lid blepharoplasty. Conservative and surgical methods have been developed to rejuvenate the periorbital region, but few effectively treat the lower eyelid's medial third (21). Subdermal laminar implantation of a collagen-elastin matrix offers a novel approach to enhance facial contours and skin quality in the infraorbital and upper midface regions, as demonstrated by clinical and histological results. These results suggest that collagen matrices can serve as an auxiliary tool in both aesthetic and reconstructive surgical procedures (22). Restoring a youthful appearance frequently requires a multifaceted approach, addressing concerns such as radial lip lines, reduced bony support in the maxilla and mandible, and the descent of adipose tissue that contributes to the formation of jowls (23). Minimally invasive techniques, including liposuction, laser therapy, platysmotomy, and the use of filaments, have gained popularity for correcting age-related changes in the face and neck, highlighting the need, for objective visualization of the affected anatomical structures to ensure their effectiveness and prevent complications (24).

Understanding the structural and functional characteristics of SOOF facilitates a deeper comprehension of how mimetic muscle contractions impact the lower face. These insights enable a more comprehensive evaluation of the roles of various tissues in facial aging, particularly the interplay between deep and superficial fat compartments. These findings support the use of individualized approaches tailored to each patient's facial morphology and aging pattern.

Study Limitations

The cadavers used for training purposes presented challenges with obtaining sufficient tissue samples as defined in the methods section. Repeated thawing and refreezing during various anatomy courses sometimes compromised the fixation process, leading to tissue artifacts that affected histological measurements.

As a result, we opted not to perform quantitative assessments and instead, provided a detailed description of the tissue characteristics, highlighting our commitment to delivering meaningful insights despite these limitations.

CONCLUSION

This study highlights the SOOF as a structurally complex, fibro-adipose and vascularized unit with direct anatomical continuity to the OOM and the SMAS. Unlike passive fat pads, SOOF is a structurally integrated zone that combines connective and muscle tissue, supporting the midface and lower eyelid. These findings highlight the importance of preserving or targeting the SOOF in facial rejuvenation. Anatomically precise, compartment-specific techniques are preferable to generalized lifting, as they ensure stable and aesthetically successful outcomes.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Hamidiye Scientific Research Ethics Committee (number: 2025/7-7/23, date: 27.03.2025).

Informed Consent: Given that our study utilizes cadaveric specimens, obtaining a consent form is not necessary, allowing us to focus entirely on the research objectives without legal constraints.

Footnotes

Author Contributions: Surgical and Medical Practices - B.Z.K., B.K., F.T.K.; Concept - B.Z.K., B.K., F.T.K.; Design - B.Z.K., B.K., F.T.K.; Data Collection and/or Processing - B.Z.K., B.K., F.O., F.T.K.; Analysis and/or Interpretation - B.Z.K., B.K., F.O., F.T.K.; Literature Search - B.Z.K., B.K., F.O., F.T.K.; Writing - B.Z.K., B.K.

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

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Comparison of the Effects of Asymmetrical Directionality and Narrow Directionality on Speech Perception in Noise in Hearing Aids

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ABSTRACT

Objective: The speech perception performance of hearing aid users decreases in the presence of noise. The most effective way to improve speech intelligibility in noise is to use directional microphones close to the sound source. This study aims to investigate the effect of asymmetric directionality, a microphone directionality mode, on speech intelligibility in difficult listening conditions, while maintaining environmental awareness through a mechanism acting like the human ear.

Methods: The study included 32 participants aged 20-50 years with bilateral flat moderate-to-moderately severe sensorineural hearing loss. At the time of assessment, participants used hearing aids bilaterally, with the fitting performed using the Real Ear Measurement method. Speech performance in noise across various microphone directional modes was evaluated using the Turkish Matrix test.

Results: According to the obtained data, a significant signal-to-noise ratio (SNR) increase was found for all microphone directionality modes when comparing the adaptive procedure in quiet and noisy conditions ($p<0.01$). A significant correlation was also found between the adaptive noise and non-adaptive procedures in terms of performance gain ($p<0.01$). In the asymmetric directionality mode, a statistically significant higher performance was observed compared to the omnidirectional mode ($p<0.05$).

Conclusion: Our study has revealed that the narrow and asymmetric directionality modes of the microphone improve speech performance by enhancing the SNR in noisy environments. We also concluded that asymmetric directional microphones proved more advantageous than the omnidirectional mode.

Keywords: Hearing aid, adaptive directionality, narrow directionality, asymmetric directionality, speech intelligibility

INTRODUCTION

One of the greatest challenges for hearing aid users is speech perception in the presence of background noise. This is partly because listeners with sensorineural hearing loss require a better signal-to-noise ratio (SNR) than people with normal hearing in order to understand the same information (1). Near-source directional microphones, which detect sounds from multiplefocus on sounds from specific directions within the auditory field, are the most effective way to improve speech intelligibility in noisy environments. These microphones enhance signals from the front and attenuate those from the side or rear, thereby improving SNR.

Binaural directional hearing aids operate in directional or omnidirectional modes, configured symmetrically and asymmetrically as needed. Hearing aids are designed to automatically switch between these modes in order to optimise speech intelligibility. This automatic switching provides the localisation and sound quality benefits of omnidirectional microphones without compromising speech intelligibility (2).

The narrow directionality of hearing aids enables users to focus on speech coming from directly in front of them by reducing distracting noise from behind and to the sides. Unlike hearing aids with narrow directionality, asymmetric directionality technologies improve speech intelligibility by making use of the benefits of directional microphones while maintaining users' environmental awareness. In this technology, the microphone of one hearing aid is omnidirectional, while the microphone of the other hearing aid is directional (3).

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While studies have shown the positive effects of directional microphones on speech intelligibility, debate continues as to whether hearing aid users benefit from directional microphones in noisy environments. When determining directional algorithms, other factors such as environmental awareness and localization ability should also be considered in addition to speech intelligibility (4).

The most recent test battery used to evaluate speech intelligibility in noise is the Turkish Matrix test (TURMatriks). This test has both adaptive and non-adaptive procedures and uses five-word sentences consisting of a subject, number, adjective, object, and verb as the target stimulus. Background noise is obtained by superimposing the target stimuli 30 times. The noise level is fixed at an intensity level of 65 dB and the test starts with an SNR of 0 dB. In the adaptive procedure, the noise level is automatically adjusted by the software depending on the participant's response (5). This method determines the lowest SNR at which the 50% speech perception threshold is obtained in noise. In the non-adaptive procedure, the intensity level is fixed and speech discrimination performance is evaluated in the presence of background noise.

Speech-in-noise tests should be used to assess the effectiveness of hearing aids for people with hearing loss. These tests more accurately reflect the acoustic environments encountered in everyday life and the factors affecting communication abilities. Additionally, these tests can evaluate microphone directionality technologies, which enhance speech perception by amplifying the signal while reducing background noise.

The aim of our study is to identify the microphone directionality mode that provides the highest level of speech intelligibility in challenging listening environments involving negative factors, such as background noise. This will allow us to program hearing aids most appropriately depending on the auditory scene, thereby increasing patient satisfaction.

METHODS

Participants

The study included 32 participants with bilateral moderate or moderately severe sensorineural hearing loss and no history of hearing aid use. There are no mental disorders present in the participants. To prevent the possible effects of the duration of hearing loss, the study included patients diagnosed within the last year. Eighteen of the participants were female, and 14 were male; the mean age of the participants was 40.41 (±9.92) years (Table 1). Subgroups were formed by applying the three-directionality mode to all participants in sequence.

The power analysis based on microphone directionality yielded an effect size of 4.57 and 85% power at a 95% confidence interval and a significance level of 0.005, with n=32 participants.

Procedure

All participants in the study underwent an otoscopic examination first. If a plug that would prevent the REM procedure was present, the external ear canal was cleaned using curette removal or aspiration techniques.

Participants with pathology that could cause conductive hearing loss were excluded from the study. Following this, the participants underwent an audiological assessment consisting of impedance measurement, pure tone audiometry (125-8000 Hz), and speech audiometry. Hearing aid trials were then carried out on participants with bilateral moderate to moderately severe sensorineural hearing loss.

In our study, we evaluated the performance of different microphone directionality modes on a single brand of hearing aid, so that different hearing aid parameterswould not affect performance. We used the Beltone Trust 17 Receiver in Ear model hearing aid, which has an asymmetric directional microphone mode. For bilateral programming, the hearing aids were fitted with three different microphone directionality modes. All other hearing aid features, except for the microphone directionality modes, were disabled. Fitting was performed using the REM procedure. Gain adjustments for each microphone mode were recorded in the device memory during fitting.

Speech-in-noise tests are widely accepted as more representative of real-life listening conditions, and tools such as the TURMatriks, are more effective for assessing listeners' hearing when they are exposed to sentences containing an average of seven to eight syllables in everyday life, rather than to isolated words in a quiet environment. Given these advantages, the TURMatriks was administered to participants using the AuricalAud clinical audiometer (GN Otometrics; Taastrup, Denmark) and Oldenburg Measurement Applications software, after fitting in order to assess their ability to understand speech in noisy environments.

The test stimulus and background noise were presented through two loudspeakers. The loudspeaker through which the test stimuli were presented was positioned at an azimuth of 90°. The loudspeaker through which the background noise was presented was positioned at an azimuth of 270°. Both loudspeakers were placed 1 m from the subject (Figure 1).

Both adaptive and non-adaptive procedures were used in the TURMatriks. The adaptive procedure applied to the participants was performed in both quiet, and in listening conditions in the presence of noise. The non-adaptive procedure was performed under listening conditions of 0 dB SNR and +10 dB SNR. The protocol used to administer the test is shown in Table 2.

Statistical Analysis

The results of the TURMatriks were compared for all three microphone directionality modes. The Shapiro-Wilk test was used to assess the distribution of the data. The independent Samples t-test was used to compare normally distributed data between two groups. The Mann-Whitney U test was used to compare non-normally distributed data between two groups. Spearman's correlation analysis was used to analyze the relationship between numerical variables. Descriptive statistics for normally distributed

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Table 1. Demographical and audiological findings of participants

		Median	IQR	Mean ± sd.	
Age		20	44.5	40.41±9.92	
Gender	Female n (%)	18 (56.25%)			
	Male n (%)	14 (43.75%)			
Test ear		Air-conduction PTA (dB)	Bone-conduction PTA (dB)	SRT (dB)	SDS (%)
		Mean ± sd.	**Mean ± sd.**	**Mean ± sd.**	**Mean ± sd.**
Right		52.78±6	48.16±5.90	48.28±6.91	80.34±7.91
Left		53.81±5.32	48.53±5.21	49.63±6.76	80.69±7.49

IQR: Interquartile range, PTA: Pure-tone average, sd.: Standard deviation, SRT: Speech reception threshold, SDS: Speech Discrimination scores

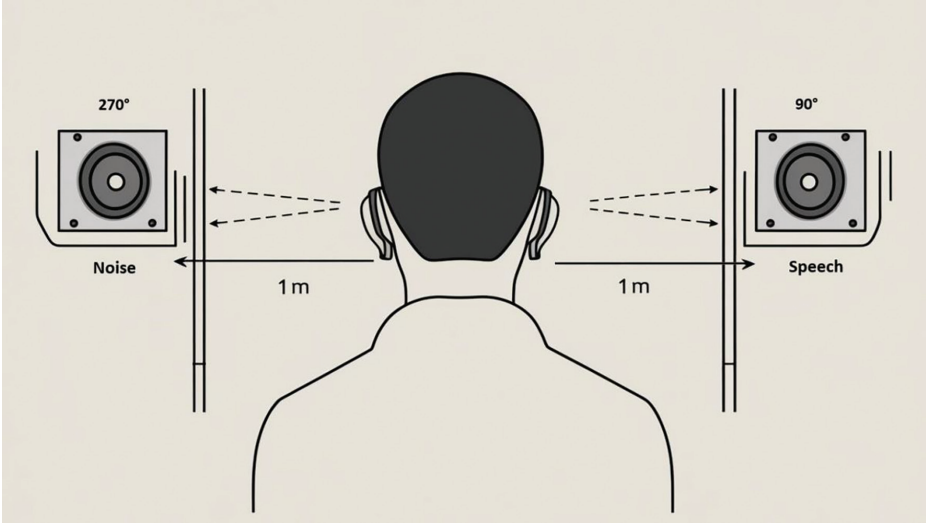

Figure 1. Patient and speaker positions in the Turkish Matrix test

Table 2. Presentation of Turkish Matrix test procedures applied to subjects, microphone directionality modes, and test sequence

Test sequence	Microphone directionality mode	Adaptive procedure	Non-adaptive procedure
1	Omnidirectional	Quiet	
2	Directional	Quiet	
3	Asymmetric directional	Quiet	
4	Omnidirectional	Noise	
5	Directional	Noise	
6	Asymmetric directional	Noise	
7	Omnidirectional		+10 dB SNR
8	Directional		+10 dB SNR
9	Asymmetric directional		+10 dB SNR
10	Omnidirectional		0 dB SNR
11	Directional		0 dB SNR
12	Asymmetric directional		0 dB SNR

SNR: Signal-to-noise ratio

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numerical data were expressed as the mean ± standard deviation, while descriptive statistics for non-normally distributed data, they were expressed as the median (interquartile range). All statistical analyses were performed and reported using IBM SPSS Statistics 22.0 at a significance level of p=0.05.

Ethical Statement

Our study was conducted at İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Audiometry. (Ethical Committee No: 59491012-300-154161). This study protocol was reviewed and approved by the Clinical Research Ethics Committee of Cerrahpaşa Faculty of Medicine (approval number: 186586, date: 05.12.2019). All participants in this clinical evaluation received verbal and written information. Written informed consent was obtained from all individuals before the start of the evaluation.

RESULTS

Table 1 shows the participants' pure-tone audiometry results, including air and bone conduction thresholds, as well as the pure-tone average (PTA). The PTA is calculated by taking the four-frequency average (500, 1000, 2000, and 4000 Hz). It also shows the results of the speech reception threshold (SRT) test. All results are shown in dB. The results of the Speech Discrimination scores (SDS) test are shown as a percentage of performance in Table 1. Additionally, the age and gender distributions of the participants are also provided in Table 1.

Figure 2 shows the results of applying the Adaptive Quiet and Adaptive Noise procedures, in three different modes of the same hearing aid. A statistically significant difference was observed between the procedures applied for all three microphone directionality modes (p<0.001). It was concluded that the values obtained using the Adaptive Quiet procedure were significantly lower than those obtained using the Adaptive Noise procedure in all three microphone directionality modes. Consequently, it can be seen that the 50% SRT increases and performance deteriorates in a noisy environment.

The Non-Adaptive Matrix +10 dB SNR and Non-Adaptive Matrix 0 dB SNR procedures were applied to three modes of the same hearing aid. When the results were compared, a statistically significant difference was found between the two procedures in the omnidirectional and asymmetric directional microphone modes (p=0.008 and p=0.037, respectively; Figure 3).

However, when the results obtained in directional mode were compared, no statistically significant difference was found between the tests (p=0.079) (Figure 3). Speech intelligibility decreased and performance deteriorated significantly at 0 dB SNR for the Non-Adaptive Matrix procedure in both the omnidirectional and asymmetric directional microphone modes (Figure 3).

The results of the Spearman correlation analysis examining the relationship between the results obtained using the Adaptive Matrix Noise procedure and the Non-Adaptive Matrix 0 dB SNR and +10 dB SNR procedures, in three different microphone directivity modes, are summarised in Table 3.

The relationship between SNR (dB) values obtained in the adaptive noise procedure test and SDS (%) values obtained in the non-adaptive procedure at 0 and +10 dB SNR was examined in the omnidirectional, directional, and asymmetric directional modes of the hearing aid. A significant negative correlation was found for all three modes of microphone directionality (p<0.001) (Table 3). Applying the adaptive noise procedure to participants in each of the three directional modes separately resulted in significant improvements in speech performance compared to the non-adaptive procedure at a lower SNR compared to +10 dB SNR. Significant improvements in speech performance were observed in the non-adaptive procedure, 0 dB SNR tests (Table 3).

The results evaluating the difference between the paired values obtained in the different microphone directionality modes are summarised in Table 4 for each subtest. It was concluded that there was no statistically significant difference between the groups for all four subtests in omnidirectional and directional microphone modes (p>0.05).

When the results of the four subtests of the TURMatrix test were compared for omnidirectional microphone configuration directional microphone modes, a statistically significant difference was observed in the results of the 0 dB SNR tests for the adaptive quiet, adaptive noise, and non-adaptive procedures (p=0.040, p=0.021 and p=0.042, respectively). The statistical analysis of these comparisons is shown in Table 4. According to these results, the Adaptive Quiet Procedure test showed that the intensity level required for a 50% SRT was significantly higher with the omnidirectional mode than with the asymmetric directional mode (p=0.04). The Adaptive Noise Procedure test results showed that the SNR for a 50% SRT in noise was significantly higher with the omnidirectional mode than with the asymmetric directional mode (p=0.021). The non-adaptive procedure 0 dB SNR test showed that speech intelligibility was significantly lower with the omnidirectional mode than with the asymmetric directional mode (p=0.042). However, the non-adaptive procedure +10 dB SNR test did not reveal a statistically significant difference between the two modes (p=0.134) (Table 4).

When the results of the four subtests of the directional and asymmetrical directional microphone modes were compared with those of the TURMatriks test, and the Adaptive-Quiet, Adaptive-Noise, Non-Adaptive +10 dB SNR, and Non-Adaptive 0 dB SNR procedures, no statistically significant differences were found (p>0.05). The statistical analysis of the comparisons made is shown in Table 4.

DISCUSSION

Directional microphones in hearing aids are designed to transmit sounds from the front while attenuating those from other directions (5). These characteristics mean that directional microphones play an important role in speech perception in noisy environments by preserving interaural cues due to their directional sensitivity. They can increase the SNR by up to 6 dB (6). They can improve localization and, consequently, speech

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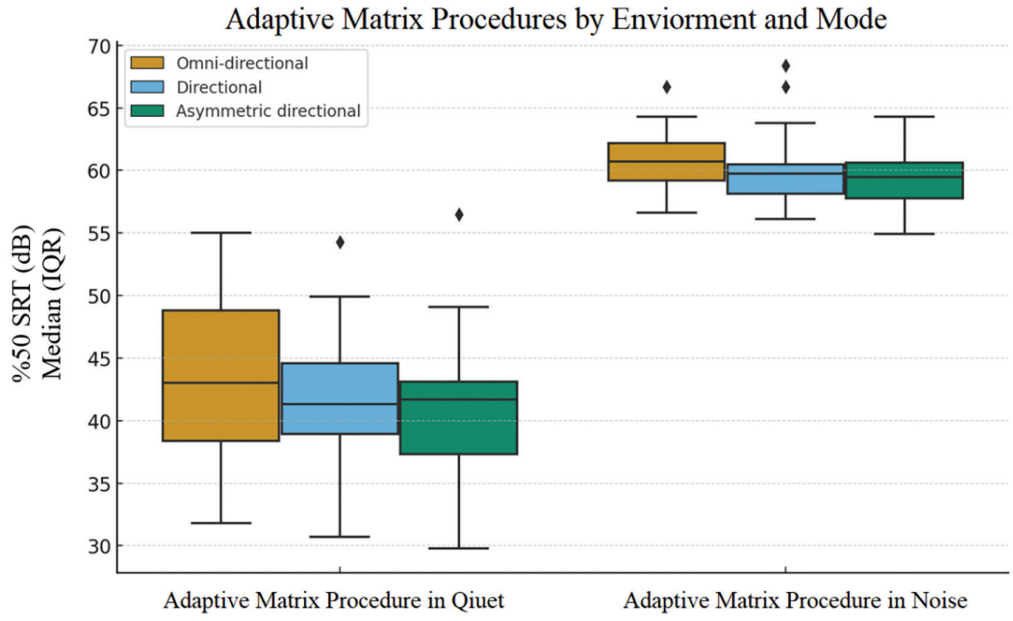

Figure 2. Comparison of sound pressure levels in dB at which 50% SRT is achieved in different microphone directionality modes, Adaptive-Silent and Adaptive-Noise procedures. Data are reported as median (IQR)

SRT: Speech reception threshold, IQR: Interquartile range

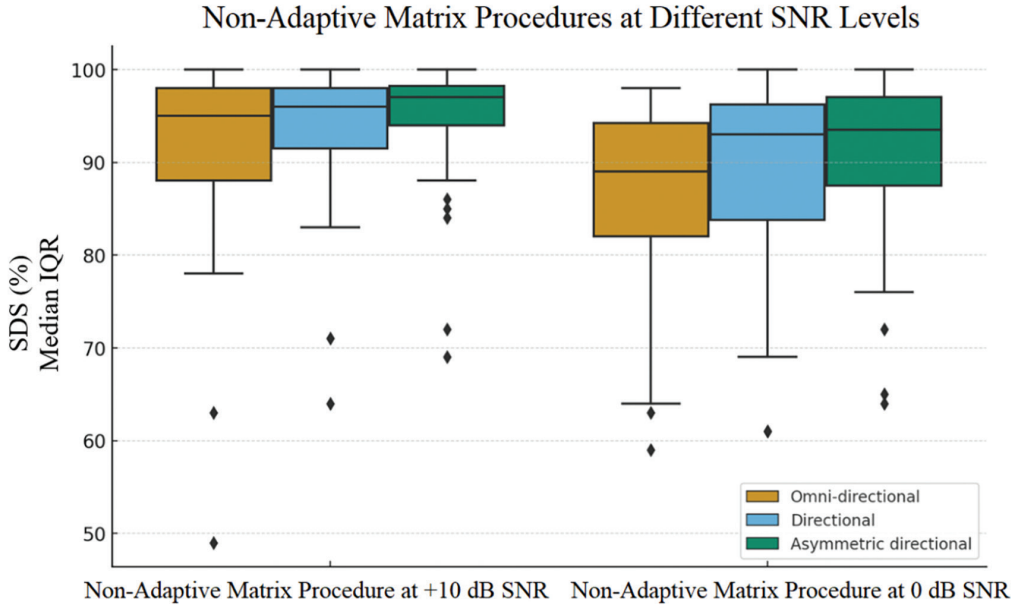

Figure 3. Comparison of Speech Discrimination scores (SDS) values obtained in Non-Adaptive Matrix Procedure +10 dB SNR and Non-Adaptive Matrix Procedure 0 dB SNR tests for different microphone directionality modes, expressed as a percentage. Data are reported as median (IQR)

IQR: Interquartile range, SNR: Signal-to-noise ratio

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Table 3. Evaluation of the correlation of SNR (dB) value negativity obtained in the adaptive-noise procedure test with the high SDS (%) performance obtained in the non-adaptive procedure +10 dB SNR and 0 dB SNR procedures in different microphone directivity modes

			Non-adaptive procedure +10 dB SNR	**Non-adaptive procedure 0 dB SNR**
Omnidirectional	Adaptive-noise procedure	r	-0.646	-0.700
		p	p<0.001	p<0.001
			Non-adaptive procedure +10 dB SNR	**Non-adaptive procedure 0 dB SNR**
Directional	Adaptive-noise procedure	r	-0.646	-0.710
		p	p<0.001	p<0.001
			Non-adaptive procedure +10 dB SNR	**Non-adaptive procedure 0 dB SNR**
Asymmetric directional	Adaptive-noise procedure	r	-0.595	-0.764
		p	p<0.001	p<0.001

SNR: Signal-to-noise ratio, SDS: Speech Discrimination scores

Table 4. Comparison of the findings from the Turkish Matrix test subtests between omnidirectional, directional, and asymmetric directional microphone modes

	Omni-directional	**Directional**	**p[a,b]-value**
Adaptive-quiet procedure-SRT (dB)	43.74±6.3	41.78±5.1	0.181[a]
Adaptive-noise procedure -SNR (dB)	-4.30 (3.53)	-5.30 (2.33)	0.058[b]
Non-adaptive procedure +10 dB SNR-SDS (%)	95 (10)	96 (7.50)	0.571[b]
Non-adaptive procedure 0 dB SNR-SDS (%)	89 (16.50)	93 (12)	0.129[b]
	Omni-directional	**Asymmetric directional**	**p[a,b]-value**
Adaptive-quiet procedure-SRT (dB)	43.74±6.3	40.63±5.45	**0.040[a]**
Adaptive-noise procedure -SNR (dB)	-4.30 (3.53)	-5.40 (3.03)	**0.021[a]**
Non-adaptive procedure +10 dB SNR-SDS (%)	95 (10)	97 (4.75)	0.134[b]
Non-adaptive procedure 0 dB SNR-SDS (%)	89 (14.75)	93.50 (10.50)	**0.042[b]**
	Directional	**Asymmetric directional**	**p[a,b]-value**
Adaptive-quiet procedure-SRT (dB)	41.78±5.17	40.63±5.45	0.392[a]
Adaptive-noise procedure -SNR (dB)	-5.30 (2.33)	-5.40 (3.03)	0.610[b]
Non-adaptive procedure +10 dB SNR-SDS (%)	96 (7.50)	97 (4.75)	0.318[b]
Non-adaptive procedure 0 dB SNR-SDS (%)	93 (12)	93.50 (10.50)	0.623[b]

p[a]: The p-value for the independent samples t-test. p[b]: The p-value for the Mann-Whitney U test. *Data are reported as mean ± standard deviation and median (IQR).
SRT: Speech reception threshold, SDS: Speech discrimination score, SNR: Signal-to-noise ratio, IQR: Interquartile range

recognition, particularly when speech and noise originate from different directions (7).

Geetha et al. (8) concluded that people with mild to moderate hearing loss benefit from hearing aids with wireless technology in terms of speech perception and localisation in noise. When directional microphones in hearing aids with wireless synchronisation were compared with those without, it was found that wireless synchronisation improves hearing in noise. In our study, speech performance was better with the asymmetric directional mode in hearing aids that use wireless synchronisation technology and constantly analyzes the acoustic environment, than with omnidirectional microphones (p<0.05) (Table 4). Our results support the study by Geetha et al. (8).

Härkönen et al. (9) reported that despite achieving good scores on the Finnish Speaking test in quiet environments, cochlear implant users experienced significant difficulties in everyday listening conditions. Dietz et al. (10) argued that, although good SRT scores were obtained using the use of monosyllabic isolated words, listening problems persisted in everyday life, and that the Adaptive Quiet Procedure test would provide a more realistic assessment than speech tests using isolated words. This study compared the values obtained in the Adaptive Quiet Procedure and Adaptive Noise Procedure tests to investigate the effects of quiet and noisy environments on the speech understanding of hearing aid users. However, for all three microphone directionality modes of the hearing aids, the SRT level providing a 50% SRT was

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significantly higher, statistically ($p<0.05$) when the Matrix test was used in noise compared to the Adaptive Quiet Procedure (Figure 2). Considering that everyday life consists of noisy listening conditions and that a decrease in speech perception performance is detected in the presence of noise, it is necessary to include tests for listening in noise when assessing hearing aid users. When conducting these tests, it is also important to establish evaluation procedures that include different microphone modes to determine which mode gives each individual the best results.

Slugocki et al. (11) investigated the electrophysiological representation of speech stimuli using directional microphones and noise reduction technologies. The study used cortical (P1-N1-P2 complex) and subcortical evoked potentials. It observed statistically significant improvements in cortical potential components when directional microphones and noise reduction technologies were used. However, no such changes were found in subcortical potential components (11). In our study, no statistically significant differences were observed between adaptive and non-adaptive procedures of the TURMatriks, or between directional and omnidirectional microphones ($p>0.05$) (Table 4). These studies recommend evaluating speech performance and microphone directionality modes in noise more thoroughly, by investigating different parameters using electrophysiological and behavioral methods.

Browning et al. (12) investigated the effect of microphone directionality on critical SNR in noisy environments. Although both omnidirectional and directional microphones were used, a statistically significant improvement in SNR values was observed with directional microphones in the presence of noise compared to omnidirectional microphones (12). In our study, no statistically significant improvement in critical SNR values was observed when omnidirectional and directional microphones were compared ($p>0.05$), (Table 4). In their studies, Browning et al. (12) worked with a pediatric group and always delivered the target stimulus from a front loudspeaker at a 0° or 300° azimuth. In our study, however, the adult group was included. In addition, the acoustic stimulus was delivered from a loudspeaker located at a 90° azimuth (Figure 1). It is therefore assumed that the reasons for the different results in the two studies are factors such as the Factors such as age distribution of the study group, stimulus presentation angle, and hearing aid use experience are presumed to contribute to the different results observed in the two studies.

Ricketts and Picou (13) investigated the impact of microphone directionality modes on the ability to understand speech in the presence of background noise, which included children aged 11-17 in their study. As the participants were of school age, the researchers simulated a classroom environment to evaluate their speech comprehension skills in the presence of background noise. The evaluations were conducted using omnidirectional and directional microphone modes within the framework of symmetric directionality, as well, and another mode of asymmetric directionality as well. The target stimulus for the different directionality modes was delivered by front (0°) and rear (180°) loudspeakers. In the test condition where speech stimuli were presented from the front loudspeaker, the directional microphone mode performed better than the asymmetric and omnidirectional modes, with participants performing similarly to their normal-hearing peers (13). While lower performance was observed with directional microphones in our study ($p=0.181$, $p=0.058$, $p=0.571$, $p=0.129$; Table 4), whereas, higher performance was observed with asymmetric directionality thancompared to omnidirectional microphones ($p=0.040$, $p=0.021$, $p=0.134$, $p=0.042$; Table 4). A review of related studies shows that directional microphones are advantageous for speech stimuli coming from the front speaker; our study obtained similar results to those in the literature (14-16).

In the same study, Ricketts and Picou (13) included a test condition in which the target stimulus was presented from the rear speaker (180°) and the noise from the front speaker (0°). They found that the benefits of directional microphones were lost in the front loudspeaker test condition when the target stimulus was presented from the rear loudspeaker. In another study, Keidser et al. (17), conducted experiments with azimuths of 90 and 270 and found no significant difference between omnidirectional and directional modes. However, Van den Bogaert et al. (18) showed that the directional mode performed worse than the omnidirectional mode under the same conditions. Based on these findings, azimuths of 0° and 180° are ideal for directional microphones. However, these azimuths do not accurately reflect real-world listening conditions. Therefore, to better reflect the challenging listening conditions encountered in daily life, our study was designed with stimuli using listening conditions at 90 and 270 azimuths.

These findings emphasised the importance of switching appropriately between microphone directionality modes, particularly in environments such as classrooms where the source of the target stimulus is constantly changing. It was thought that using the asymmetric directionality mode could reduce the decrease inmitigate the decline in performance. However, it has been argued that maximum speech perception performance cannot be achieved with the asymmetric directionality mode compared with bilateral directional microphones (13). In our study, however, a target speech stimulus was presented by a 90° azimuthally positioned loudspeaker, which reduced the advantages of directional microphones and created challenging listening conditions. In light of our results, no significant difference was observed in performance between directional microphones, omnidirectional microphones, and asymmetric directional microphones in light of our results. Our study, while supporting the work of Rickett and Picou (13), found statistically significant improvements ($p<0.05$, Table 4) in the asymmetric directional mode compared to the omnidirectional mode. This suggests that asymmetric directionality offers an advantage under challenging listening conditions.

In their study of 30 cochlear implant users aged between 20 and 66 years, Polat et al. (19) found a correlation between the Non-Adaptive Quiet procedure and the Adaptive Quiet procedure.

However, they did not investigate the correlation in the presence of noise in both procedures (18). In our study, we investigated the correlations between the adaptive noise procedure and the Non-Adaptive +10 dB SNR, and Non-Adaptive 0 dB SNR subtests for all three microphone directionality modes. A statistically significant correlation was found between the Adaptive-Noise and non-adaptive procedure tests ($p<0.001$) (Table 3). Notably, the Adaptive-Noise procedure of the TURMatriks more accurately simulates everyday life with background noise. This procedure determines the critical SNR value, i.e., the most challenging listening condition at which the 50% SRT is achieved in the presence of noise. In the adaptive noise procedure, a more negative obtained SNR value was characterized by an increase in speech performance. Our study found a significant correlation between values obtained in the adaptive noise procedure and those in the non-adaptive +10 dB SNR ($p<0.001$), as well as the non-adaptive 0 dB SNR ($p<0.001$) tests. These are subtests that examine speech intelligibility at constant SNR values (Table 3). From this perspective, as the critical SNR improved in the presence of noise, an increase in speech intelligibility performance was observed at a fixed SNR in the presence of noise.

Study Limitations

Although subjective verification methods such as International Outcome Inventory for Hearing Aids (19), Abbreviated Profile of Hearing Aid Benefit (20), Speech, Spatial and Qualities of Hearing Scale (21) and Satisfaction with Amplification in Daily Life (22) were not used in our study, they are useful tools for assessing patient satisfaction and amplification success. It is believed that non-adaptive procedure tests that function as SDS in noise are also useful for evaluating hearing aids. Within the limitations of the study, increasing the number of subjects and comparing subjects with different types and degrees of hearing loss would allow more consistent differences between parameters to be identifiedus to identify more consistent differences between parameters. More detailed results on the effect of asymmetric directionality on hearing ability are expected to be obtained by presenting the speech stimulus from different speaker angles and by evaluating experienced hearing aid users.

CONCLUSION

The literature contains a limited number of studies on asymmetric directionality. This mode needs to be investigated in detail to better understand its effect on speech discrimination in noise and the role of the binaural squelch effect, especially in difficult listening conditions where directional microphones largely lose their advantage. Based on clinical findings, our study suggests that the asymmetric directionality mode is successful and better simulates the human hearing system compared to traditional methods. Achieving high speech intelligibility performance in this mode, while maintaining environmental awareness, indicates that further development and clinical validation of this mode are encouraged compared to directional and omnidirectional microphone modes. In crowded environments such as classrooms and meeting rooms, where the presence and location of sound and noise sources change daily, the effectiveness of directional microphones decreases, as they are more successful with frontal sounds. Conversely, asymmetric directionality, with its ability to rapidly adapt to changing listening conditions, is advantageous in such environments. This study mayserve as a valuable reference for future research in areas such as microphone directionality and listening skills in noisy environments.

Ethics

Ethics Committee Approval: Our study was conducted at İstanbul University-Cerrahpaşa, Cerrahpaşa of Medicine, Department of audiometry. (Ethical Committee No: 59491012-300-154161). This study protocol was reviewed and approved by the Clinical Research Ethics Committee of Cerrahpaşa Faculty of Medicine (approval number: 186586, date: 05.12.2019).

Informed Consent: All participants in this clinical evaluation received verbal and written information. Written informed consent was obtained from all individuals before the start of the evaluation.

Footnotes

Author Contributions: Surgical and Medical Practices - G.Y., E.K.; Concept - G.Y., E.K.; Design - G.Y., E.K.; Data Collection and/or Processing - G.Y.; Analysis and/or Interpretation - G.Y., E.K.; Literature Search - G.Y.; Writing - G.Y., E.K.

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

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Frequency of Hypermobility in Patients with Ulnar Entrapment Neuropathy

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ABSTRACT

Objective: To evaluate the association between generalized joint hypermobility (GJH) and electrodiagnostically confirmed ulnar neuropathy at the elbow (UNE), and to examine relationships between hypermobility measures and electrophysiological severity.

Methods: In a cross-sectional study at a tertiary center, 96 adults were enrolled: 48 UNE patients (confirmed by standardized nerve conduction studies) and 48 age/sex-matched controls. Hypermobility was assessed with age-specific Beighton thresholds, following the 2017 framework. GJH status incorporated the five-part questionnaire when borderline. Primary electrophysiological outcomes were distal motor latency (DML) and across-elbow/below-elbow motor conduction velocity (AE-BE MCV). Group comparisons used t-test/χ^2; associations used Spearman correlation (two-tailed α=0.05).

Results: Hypermobility indices were higher in UNE versus controls: Beighton score 3.4±2.1 vs. 2.0±1.5 (p=0.021) and GJH prevalence 68.8% vs 16.7% (p<0.001). Among UNE patients, age correlated with worse electrophysiology (DML: r=0.33, p=0.027; AE-BE MCV: r=-0.30, p=0.034). Higher Beighton scores are related to longer DML (r=0.28, p=0.041) and lower AE-BE MCV (r=-0.27, p=0.041). Longer symptom duration showed similar patterns (DML: r=0.34, p=0.023; AE-BE MCV: r=-0.32, p=0.028). Body mass index was not associated with the measured outcome (p>0.05). The presence of GJH correlated with higher DML (r=0.22, p=0.040) and lower AE-BE MCV (r=-0.24, p=0.036).

Conclusion: GJH is more prevalent in UNE and is linked to electrophysiological evidence of segmental conduction impairment at the elbow. Recognizing hypermobility may help stratify risk and expedite early evaluation and tailored prevention.

Keywords: Electromyography, ulnar nerve entrapment, joint instability, joint hypermobility, peripheral nerve injuries, numbness

INTRODUCTION

Ulnar neuropathy at the elbow (UNE) is the second most common entrapment neuropathy after carpal tunnel syndrome and represents a significant cause of upper extremity disability (1). Clinically, UNE presents with numbness, paresthesia, muscle weakness, and functional impairment in the forearm and hand, leading to a substantial reduction in quality of life and work productivity (2,3). Epidemiological data suggest that the prevalence of UNE can be as high as 5.9% in the general population, and increases further among those exposed to repetitive elbow movements in occupational settings (4). The resulting work disability and increased healthcare expenditures highlight UNE not only as a clinical problem but also as a significant socioeconomic burden one study reported that half of UNE patients received wage replacement for more than six months, with average direct and indirect costs totaling around USD 35,000 per case (5).

The pathophysiology of UNE involves several mechanisms, including compression within the cubital tunnel, traction during repetitive flexion-extension, and dynamic instability of the ulnar nerve. Known risk factors include prolonged elbow flexion, external compression, and elbow trauma (6,7). However, UNE does not develop in all individuals exposed to these factors, suggesting the contribution of intrinsic host-related susceptibility in addition to mechanical stress (8).

One such intrinsic factor is generalized joint hypermobility (GJH), characterized by increased connective tissue laxity and excessive joint range of motion (9). The prevalence of GJH varies depending on age, sex, and ethnicity, but rates as high as 10% have been reported in young adults (10,11). Women and younger

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individuals are disproportionately affected; in one recent adult cohort, the prevalence of GJH was 48.2% in females versus 20.4% in males (12).

Beyond musculoskeletal symptoms, GJH is linked to joint instability—including recurrent subluxations, ligamentous alterations, and soft tissue injuries—that can impose increased mechanical stress on peripheral nerves (13). In the elbow joint, laxity of the supporting connective tissues may predispose the ulnar nerve to subluxation or luxation during flexion, thereby amplifying friction and traction forces that facilitate UNE development (14). Recent studies lend support to this hypothesis. Dynamic ultrasonography has demonstrated a higher frequency of ulnar nerve instability during elbow flexion in hypermobile individuals (15). Similarly, surgical series have reported greater intraoperative mobility of the ulnar nerve in patients with joint hypermobility (16).

Nevertheless, the available literature remains limited. Most studies are small in scale, use heterogeneous definitions of hypermobility, and frequently lack electrodiagnostic (EDX) confirmation (17,18). Given that EDX studies are considered the gold standard for UNE diagnosis, this represents an important methodological gap (19). Current guidelines recommend standardized conduction protocols—including short-segment "inching" stimulation across the elbow—as well as defined thresholds for conduction velocity and amplitude changes, which provide high sensitivity for early diagnosis and accurate severity grading (15,18).

Against this background, the relationship between GJH and UNE warrants systematic investigation using contemporary diagnostic standards. Therefore, the present study aimed to evaluate the association between GJH and by EDX confirmed UNE in adults. We hypothesized that GJH may represent an independent host susceptibility factor, associated with UNE beyond the effects of age and sex.

METHODS

Study Design and Ethics

This cross-sectional observational study was conducted at the department of physical medicine and rehabilitation, a tertiary care university hospital, between April 2017 and November 2017. The study protocol was approved by the Başkent University Institutional Ethics Committee (decision no: 16/05, project no: KA15/382, date: 12.01.2016). All procedures adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Participants

Patients referred to the electroneuromyography laboratory with a preliminary clinical diagnosis of UNE were screened consecutively. Inclusion criteria were: (1) age between 18 to 65 years, (2) the presence of typical clinical symptoms (paresthesia in ulnar digits, nocturnal worsening of symptoms, weakness in intrinsic hand muscles), and (3) confirmation of UNE by both clinical and electrophysiological criteria. Exclusion criteria were (1) occupational risk factors with high repetitive elbow strain, (2) systemic diseases associated with neuropathy (e.g., diabetes mellitus, hypothyroidism, rheumatoid arthritis, crystal arthropathy), (3) history of elbow fracture, trauma, or surgery, (4) coexisting cervical radiculopathy, brachial plexopathy, or generalized polyneuropathy, (5) inability to complete standardized evaluations. Eligible patients were assigned to group 1 (UNE group) while age- and sex-matched healthy volunteers without neurological or rheumatological disease comprised group 2 (control group). Demographic and clinical data recorded included age, sex, body mass index (BMI), hand dominance, occupation, medical history, symptom duration, and symptom characteristics. Neurological examination included manual muscle testing of intrinsic hand muscles, sensory examination of the upper limb, and evaluation of Tinel's sign at the elbow (Figure 1).

Hypermobility Assessment

GJH was operationalized in line with the 2017 International Classification framework for hypermobility spectrum disorders and hypermobile Ehlers-Danlos syndrome (hEDS) (20). We did not attempt to diagnose hEDS; the exposure of interest was GJH as defined by age-specific Beighton thresholds. The Beighton examination (0-9) was performed bilaterally following a standardized script and without warm-up or stretching; borderline elbow/knee hyperextension was verified with a goniometer. Cut-offs were ≥5 for adults aged 18-50 years and ≥4 for those >50 years. In accordance with the 2017 framework, participants scoring one point below the relevant cut-off (i.e., Beighton= 4 for ages 18-50; Beighton= 3 for >50) completed the five-item historical hypermobility questionnaire (5PQ); therefore, a 5PQ score ≥2 was considered evidence of historical hypermobility and such individuals were classified as GJH-positive (20-22). All joint laxity assessments were performed independently by blinded physiatrists (masked to case/control status and EDX results).

Electrophysiological Examination

Electrophysiological examinations were done bilaterally, including the following techniques: (1) sensory orthodromic nerve conduction studies of the median and ulnar nerve were registered at the wrist stimulating the third and fifth digits, respectively; (2) median motor nerve conduction study was registered at the abductor pollicis brevis muscle stimulating the wrist and antecubital fossa; (3) ulnar motor nerve conduction study was registered at the abductor digiti minimi muscle stimulating the wrist, below elbow, and above elbow; (4) short segment technique at the elbow for ulnar nerve (stimulating 6 points separated by 2 cm segments from 4 cm distal to 6 cm proximal to the medial epicondyle). During electrophysiological examinations, subjects were lying in the supine position, and their elbows were flexed at 90° for an ulnar nerve conduction study. American Association of Neuromuscular and Electrodiagnostic Medicine criteria were used for the diagnosis of cubital tunnel syndrome (23,24).

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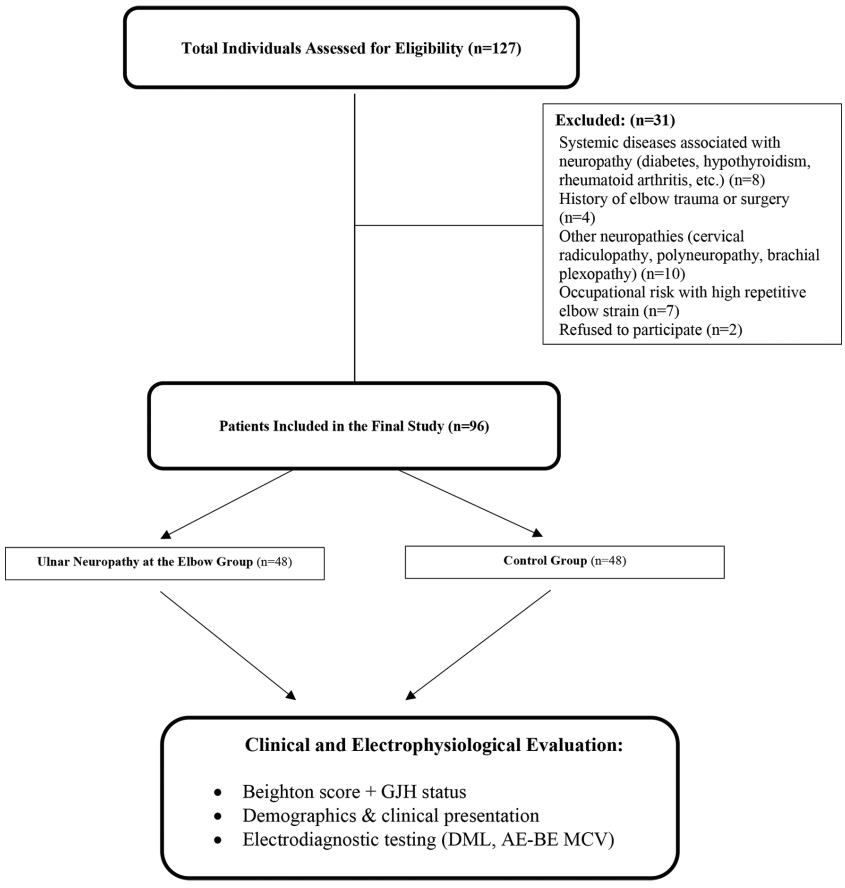

Figure 1. Flow chart of the study
GJH: Generalized joint hypermobility, DML: Distal motor latency, AE-BE MCV: Across-elbow motor conduction velocity

If any of the following findings were found in the study, the results were accepted as ulnar nerve entrapment at the elbow: an absolute nerve conduction velocity above elbow-to-below elbow of <50 m/sec, an above elbow-to-below elbow conduction velocity >10 m/sec slower or a 20% slowing compared with the below elbow-to-wrist segment, a decrease in compound muscle action potential peak amplitude from below elbow-to-above elbow of >20%, a significant change in compound muscle action potential configuration between the above and below elbow sites.

In addition to the above-mentioned techniques, ulnar nerve entrapment at the elbow was considered if any latency exceeded 0.7 msec in the short segment study technique. All electrophysiological examinations were done by an experienced physiatrist, using a Nihon Kohden® electrophysiological device.

Statistical Analysis

All statistical analyses were performed using SPSS statistics version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Normality of continuous data was assessed using the Kolmogorov-Smirnov test and inspection of histograms. Between-group comparisons of continuous variables (e.g., Beighton score, age, BMI) were performed with the independent-samples Student's t-test for normally distributed data. Categorical variables (e.g., sex distribution, prevalence of GJH) were compared using the chi-square test (χ^2) or Fisher's exact test when appropriate. Electrophysiological parameters, including distal motor latency (DML) and across-elbow/below-elbow motor conduction velocity (AE-BE MCV), were analyzed as continuous outcomes. Associations between clinical variables (age, Beighton score, symptom duration, BMI, and GJH status) and electrophysiological parameters were examined using the Spearman rank correlation test, as data were not normally distributed. Two-tailed p-values <0.05 were considered statistically significant.

RESULTS

A total of 96 adults were enrolled (48 with by EDX confirmed UNE and 48 controls); in total, 192 ulnar nerves underwent conduction studies. Baseline characteristics were comparable between groups: age 44.0±14.4 vs 45.7±9.7 years (p=0.502), female sex 32/48 (66.7%) vs 33/48 (68.8%) (p=0.830), and right-hand dominance 46/48 (95.8%) vs 47/48 (97.9%) (p=0.564). Within the UNE cohort, involvement was 54.2% left (26/48), 16.7% right (8/48), and 29.2% bilateral (14/48); the mean symptom duration was 157.6±18.8 months. The most frequent presenting symptom

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was numbness in digits IV and V (29/48), followed by hand pain (9/48), nocturnal numbness (5/48), weakness (3/48), and multiple symptoms (2/48) (Table 1).

Hypermobility indices were higher in UNE: Beighton score 3.4±2.1 vs 2.0±1.5 (p=0.021), and GJH prevalence (2017 framework) 68.8% (33/48) vs 16.7% (8/48) (p<0.001) (Table 2).

Age was positively correlated with DML (r=0.33, p=0.027) and negatively correlated with AE-BE MCV (r=-0.30, p=0.034). Beighton score showed a positive correlation with DML (r=0.28, p=0.041) and a negative correlation with AE-BE MCV (r=-0.27, p=0.041). Symptom duration was positively correlated with DML (r=0.34, p=0.023) and negatively with AE-BE MCV (r=-0.32, p=0.028). No significant correlation was found between BMI and electrophysiological parameters (DML: r=0.08, p=0.492; AE-BE MCV: r=-0.12, p=0.287). The presence of GJH (GJH, 2017 framework) was positively correlated with DML (r=0.22, p=0.040) and negatively correlated with AE-BE MCV (r=-0.24, p=0.036) (Table 3).

Table 1. Baseline characteristics of participants and clinical presentation in the UNE patients

Parameters	UNE (n=48)	Control (n=48)	p-value
Age (year) (mean ± SD)	44±14.4	45.7±9.7	0.502
Gender (%)			
Female	32 (66.7%)	33 (68.8%)	
Male	16 (33.3%)	15 (31.2%)	0.830
BMI (kg/m²) (mean ± SD)	24.2±3.3	23.5±3.7	0.336
Dominant hand (%)			
Right-handed	46 (95.8%)	47 (97.9%)	
Left-handed	2 (4.1%)	1 (2.1%)	0.564
Involvement side, n (%)			
Left	26 (54.2%)	-	
Right	8 (16.7%)	-	
Bilateral	14 (29.2%)	-	
Symptom duration (months) (mean ± SD)	157.6±18.8	-	
Presenting symptom, n (%)			
Numbness in digits IV-V	29 (60.4%)	-	
Hand pain	9 (18.8%)	-	
Nocturnal numbness	5 (10.4%)	-	
Weakness	3 (6.3%)	-	
Multiple symptoms	2 (4.2%)	-	

Values are **mean ± SD** for continuous variables and **n (%)** for categorical variables
UNE: Ulnar neuropathy at the elbow, BMI: Body mass index, SD: Standard deviation

Table 2. Comparison of hypermobility indices between UNE and control groups

Outcomes	UNE (n=48)	Controls (n=48)	p-value
Beighton score (mean ± SD)	3.4±2.1	2.0±1.5	**0.021***
GJH (2017 framework), n (%)			
Presence	68.75% (n=33)	16.6% (n=8)	**<0.001****
Absence	31.25 % (n=15)	83.4% (n=40)	

Values are **mean ± SD** for continuous variables and **n (%)** for categorical variables
*: Student's t-test, p<0.05 considered statistically significant, **: Chi-square test,
UNE: Ulnar neuropathy at the elbow, GJH: Generalized joint hypermobility, SD: Standard deviation

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Table 3. Correlation of clinical variables with electrophysiological parameters in UNE patients

Predictor	DML r (rho)	DML (p-value)	AE-BE MCV r (rho)	AE-BE MCV (p-value)
Age (years)	**0.33**	**0.027**	**-0.30**	**0.034**
Beighton score (0-9)	**0.28**	**0.041**	**-0.27**	**0.041**
Symptom duration (months)	**0.34**	**0.023**	**-0.32**	**0.028**
BMI (kg/m²)	0.08	0.492	-0.12	0.287
GJH (2017 framework)	**0.22**	**0.040**	**-0.24**	**0.036**

Spearman rank correlation coefficients (r) and corresponding two-tailed p-values are shown separately. Bold indicates statistically significant correlations ($p<0.05$) Negative r: Indicates inverse association, DML: Distal motor latency, AE-BE MCV: Across-elbow/below-elbow, motor conduction velocity BMI: Body mass index, GJH: Generalized joint hypermobility

DISCUSSION

Our study indicates that GJH is considerably more common in patients with by EDX confirmed UNE than in matched controls. Higher Beighton scores and GJH status on its own align with a less favorable electrophysiological profile, which is reflected by longer DML and slower across-elbow conduction velocity. These patterns mirror the effects of older age and longer symptom duration, whereas BMI shows no meaningful association with nerve conduction. Taken together, the data support a model in which intrinsic connective-tissue properties, rather than general body habitus, influence segmental conduction in UNE, consistent with contemporary views that host factors help shape entrapment neuropathies beyond external mechanical load alone (8,25).

In line with these findings, recent ultrasound studies demonstrate that elbow flexion alters the shape of the cubital tunnel, increases ulnar nerve movement, and can lead to temporary subluxation or dislocation, even in otherwise healthy individuals (15,26,27). This provides a clear structural basis on which connective tissue properties may influence vulnerability to UNE.

From a mechanistic standpoint, ligamentous and retinacular laxity likely amplifies flexion-induced narrowing of the cubital tunnel and raises intra-tunnel pressure, increasing ulnar-nerve excursion, contact stress, and shear, changes that culminate in focal demyelination, resulting in the distal latency/velocity pattern we observed (28).

In parallel, contemporary reviews integrating ultrasound, clinical, and electrophysiological data describe how positional narrowing, intermittent compression, and perineural microvascular instability can converge to impair conduction in cubital tunnel syndrome (25). Importantly, dynamic instability on imaging correlates with greater electrophysiological severity, reinforcing that laxity is not merely an anatomic variant but a physiologically relevant risk state (29).

Epidemiologically, GJH is reported in approximately 2-57% of the general population, with prevalence influenced by age, sex, and ethnicity; making its marked enrichment in our EDX-confirmed UNE cohort unlikely to be coincidental (30).

Comparable associations between joint laxity and conduction impairment have been reported in other entrapment neuropathies, such as wrist neuropathies in hEDS, and our EDX-confirmed UNE findings echo this cross-site pattern by translating anatomical susceptibility into measurable electrophysiological change (31).

Clinically, recognizing hypermobility as a modifier of UNE risk highlights the value of routine Beighton screening, which can help identify patients who may benefit from early stabilization strategies and tailored follow-up (25,32). Collectively, these mechanistic and epidemiologic signals support treating GJH as a true disease modifier rather than a coincidental comorbidity.

This study's key strength is that it links a clear host phenotype to objective nerve physiology in an EDX-confirmed UNE cohort. It shows the effect across two independent markers: prolonged DML, and reduced across-elbow conduction velocity. A matched-control design, prespecified adjustment for age, sex, symptom duration, and BMI, and signal stability in sensitivity analyses collectively support strong internal validity.

Study Limitations

This study has several limitations that should be acknowledged. First, its single-center design may restrict the generalizability of the findings to broader populations. Second, the cross-sectional nature of the study precludes any inference of causal relationships between GJH and the development of UNE. Third, although the sample size was sufficient to detect significant associations, it remained relatively modest, which may have limited the statistical power to identify subtler effects. Finally, advanced imaging modalities such as dynamic ultrasound or MRI, were not incorporated to complement the electrophysiological assessments, which could have provided additional insights into structural mechanisms underlying nerve instability.

CONCLUSION

GJH appears to be a significant host-related susceptibility factor for UNE, with potential implications for clinical assessment and management. Recognition of hypermobility in patients presenting with ulnar-distribution symptoms may support earlier EDX evaluation and guide targeted preventive and rehabilitative strategies, such as ergonomic counseling and stabilization-focused physiotherapy. Future multicenter prospective studies integrating electrophysiology and imaging are warranted to

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confirm causality, clarify underlying mechanisms, and evaluate whether tailored interventions can reduce risk in hypermobile individuals.

Ethics

Ethics Committee Approval: The study protocol was approved by the Başkent University Institutional Ethics Committee (decision no: 16/05, project no: KA15/382, date: 12.01.2016).

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

Footnotes

Author Contributions: Surgical and Medical Practices - Ö.F.B.; Concept - Ö.F.B., P.Ö.Ç., D.O.; Design - Ö.F.B., P.Ö.Ç., E.E.Ö.E., D.O.; Data Collection and/or Processing - Ö.F.B., P.Ö.Ç., E.E.Ö.E., D.O.; Analysis and/or Interpretation - Ö.F.B., P.Ö.Ç.; Literature Search - Ö.F.B., P.Ö.Ç., E.E.Ö.E., D.O.; Writing - Ö.F.B., P.Ö.Ç.

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

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Prediction of Hepatitis C Virus Viremia and Determination of Signal-to-cut-off Value Using Roche Elecsys Anti-HCV Screening Test

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ABSTRACT

Objective: For the diagnosis of hepatitis C virus (HCV), the detection of HCV antibodies by serological tests is primarily performed using enzyme immunoassays and chemiluminescence-based methods, and positive results are confirmed by HCV ribonucleic acid (RNA) testing. This study aimed to evaluate the performance of the anti-HCV test and to determine the optimal signal-to-cut-off (S/CO) ratio for predicting viremia.

Methods: Anti-HCV levels in serum samples were analyzed using the electrochemiluminescent immunoassay method, while HCV RNA was detected in plasma samples using real-time polymerase chain reaction.

Results: A total of 1,010 anti-HCV-reactive patients (474 males, 536 females) were included. The median age was 52 years for males and 62 years for females ($p<0.001$). HCV RNA positivity was detected in 16.6% (168/1,1010) of the patients. The median anti-HCV S/CO value was 48.70 in HCV-RNA-positive individuals and 37.65 in HCV-RNA-negative individuals ($p<0.001$). All patients with an S/CO ratio <1.25 were HCV RNA negative, whereas those with an S/CO ratio >293 were HCV RNA positive. Receiver operating characteristic analysis yielded an area under the curve (AUC) of 0.59 (95% confidence interval: 0.55-0.82), with an optimal S/CO of 8.23 yielding 95.2% sensitivity and 36% specificity.

Conclusion: The optimal S/CO value yielding the highest sum of sensitivity and specificity was determined to be 8.23. Although an S/CO of 8.23 showed promise for detecting viremia in our cohort, the relatively low AUC of 0.59 suggests that its utility may be limited and that it should be interpreted cautiously, particularly in low-prevalence populations.

Keywords: Hepatitis C virus, immunoassay, polymerase chain reaction, ROC curve, sensitivity

INTRODUCTION

Hepatitis C virus (HCV) belongs to the *Flaviviridae* family and has a positive-sense, single-stranded ribonucleic acid (RNA) genome (1). This virus, transmitted primarily through parenteral routes, is common among hemodialysis patients and intravenous drug users (2). HCV infection is recognized as an important cause of liver-related health problems worldwide (3,4). According to the World Health Organization data, the Eastern Mediterranean and Europe report the highest HCV infection rates, at 2.3% and 1.5%, respectively. In other regions, the frequency of HCV infection is estimated to range between 0.5% and 1% (5). In Türkiye, a study conducted in 2012 reported that the prevalence of anti-HCV was between 0.5% and 1% (6).

HCV diagnosis typically commences with detection of antibodies using enzyme immunoassay (EIA) (7). HCV antibody reactivity is assessed by the signal-to-cut-off (S/CO) ratio, calculated as the optical density of the test sample divided by the cut-off value (8). While these tests exhibit high sensitivity and specificity, false-positive results are frequently encountered in populations where anti-HCV prevalence is below 10% (9,10). To confirm the presence of an active infection, HCV RNA testing is recommended for individuals with a positive anti-HCV antibody result (9). However, a positive anti-HCV test does not always indicate an active infection; it may reflect ongoing viremia, a previously resolved infection, or a false-positive result (4).

False-positive results may occur, especially in cases with low-titer HCV antibody reactivity. These results pose diagnostic challenges for low-risk groups, immunocompromised individuals, and populations without liver disease. Reported false-positive rates range from 15% to 60% among healthcare workers, blood donors, individuals with sexually transmitted infections, and those with healthy immune systems (11,12).

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Anti-HCV antibodies are typically detected in viremic patients and in individuals with resolved infections (7). The critical role of anti-HCV antibody S/CO in predicting viremia has been reported in the literature (6). Researchers have investigated estimates of viremia produced by various commercial immunoassay kits. S/CO cut-offs reported for predicting viremia across these kits include: Abbott HCV EIA 2.0 (≥3.8), Ortho HCV version 3.0 EIA (≥3.8), Vitros anti-HCV (≥8), AxSYM anti-HCV (≥10.0), Architect anti-HCV (≥5.0), and Advia Centaur HCV (≥11.0). All these cut-offs demonstrate a positive predictive value (PPV) of ≥95% (13). High anti-HCV S/CO values are associated with HCV RNA positivity, suggesting that the S/CO value can be a predictor of viremia. Therefore, determining the optimum S/CO values for diagnosing HCV infection remains important (2,5,13).

This study aims to determine the optimal S/CO ratio of a commercial immunoassay kit for predicting true antibody positivity and HCV RNA viremia among anti-HCV-reactive patients.

METHODS

Ethical approval for this study was obtained from the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-BADEK-2024-806, date: 28.08.2024). The study was conducted in accordance with the Declaration of Helsinki.

Retrospective analysis was conducted on results from patients whose serum samples processed by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Hospital Microbiology Virology Laboratory showed anti-HCV reactivity between October 2022 and January 2024 and for whom concurrent HCV RNA testing was performed. During this period, all individuals who presented to our hospital with a reactive Roche Elecsys anti-HCV screening test result were included in the study.

The primary inclusion criteria were patients identified as positive or reactive by the Roche Elecsys anti-HCV screening test who had undergone an HCV RNA polymerase chain reaction test within the same timeframe as the anti-HCV reactivity detection (preferably within 30 days).

During the study period, patients with missing HCV RNA results, those with results obtained outside the study period, or those who underwent more than one anti-HCV or HCV RNA test were excluded to ensure uniformity in data evaluation. However, since HCV RNA testing was not universally performed for all anti-HCV-reactive patients, a degree of selection bias may have affected the observed viremic rate.

Due to the retrospective nature of our study, it was not possible to systematically access detailed clinical information such as patients' immunosuppressive status, prior HCV treatment history, or chronic comorbidities, nor to comprehensively evaluate the potential effects of these factors on anti-HCV antibody levels. This was acknowledged as a fundamental limitation of the study and was taken into account when interpreting the results.

Anti-HCV testing in serum samples was performed using the electrochemiluminescence immunoassay method on a Cobas® 8000 analyzer with the Elecsys anti-HCV kit (both from Roche Diagnostics GmbH, Germany). This test kit uses recombinant antigens derived from the structural core protein and the non-structural NS3 and NS4 proteins encoded by the HCV genome. According to the Elecsys anti-HCV test criteria, samples with a cut-off index below 0.9 were considered non-reactive, those between 0.9 and 1.0 were considered borderline, and those with values of 1.0 or higher were considered reactive. All samples with borderline results were reanalyzed in accordance with the manufacturer's instructions. The study group consisted of patients who were anti-HCV reactive and had HCV RNA test results available.

HCV RNA detection was carried out using the Roche Cobas® 8800 system, which integrates both viral RNA isolation and amplification processes. RNA extraction and quantitative assessment of HCV RNA were performed using the RNA Isolation Kit and the HCV Quantitative Nucleic Acid Test Kit (Roche Diagnostics GmbH, Germany).

Patient results were retrospectively analyzed using the laboratory information management system.

Statistical Analysis

Data analysis was conducted using SPSS version 25 (SPSS Inc., Chicago, IL, USA). The normality of variable distributions was assessed by both visual inspection and the Kolmogorov-Smirnov test. To compare median values between two groups, the Mann-Whitney U test was applied, whereas the Kruskal-Wallis test was employed for comparisons across multiple age categories. The association between categorical variables was examined using the Pearson's chi-square test.

The HCV RNA test was considered the reference (gold standard) method, and the effectiveness of the anti-HCV test in detecting viremia was assessed by receiver operating characteristic (ROC) curve analysis. Key cut-off values were identified using ROC analysis, and the sensitivity, specificity, PPV, and negative predictive value (NPV) were calculated accordingly, along with their 95% confidence intervals (CI). No outlier exclusion or data transformation was applied to S/CO values prior to ROC analysis; all analyses used raw S/CO values. Statistical significance was defined as $p<0.05$.

RESULTS

A total of 1,010 patients with anti-HCV reactivity [474 males (46.9%) and 536 females (53.1%)] were included in the study. The median age was 52 years (range: 2-92 years) for male patients and 62 years (range: 2-101 years) for female patients; this difference was statistically significant ($p<0.001$). The median anti-HCV S/CO values were 47.1 for males and 35.5 for females ($p=0.01$).

HCV RNA positivity was observed in 16.6% (168/1,010) of anti-HCV-reactive patients. The median ages of HCV RNA-positive male and

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female patients were 36 and 62 years, respectively (p=0.002). The median anti-HCV S/CO values were 67.17 (range, 1.25-379) in HCV RNA-positive individuals and 37.65 (range, 1.25-293) in HCV RNA-negative individuals; this difference was statistically significant (p<0.001; Table 1). All 49 patients with an anti-HCV S/CO ratio <1.25, including those with low S/CO values above the reactive cut-off (≥1.0), were HCV RNA negative, whereas all 9 patients with an S/CO ratio >293 were HCV RNA positive.

The lowest HCV RNA positivity rate (2.4%) was observed in the group with S/CO values between 1 and 4, whereas the highest positivity rate (23.8%) was observed in the group with S/CO values ≥15 (p<0.001) (Table 2). According to the ROC analysis, the sensitivity, specificity, PPV, and NPV at an S/CO threshold of 8.23 were 95.2%, 36%, 22.9%, and 97.4%, respectively (Table 3). The area under the curve (AUC) was 0.59 (95% CI: 0.55-0.82); this was statistically significant (p<0.001).

The ROC curve illustrating the predictive performance of the anti-HCV screening test for HCV viremia is presented in Figure 1.

Table 1. Basic features of patients according to HCV RNA levels

	All patients (n=1010)	Viremia group (n=168)	Non-viremia group (n=842)	p-value†
Male, n (%)	474 (46.9)	93 (55.4)	381 (45.2)	0.017
Female, n (%)	536 (53.1)	75 (44.6)	461 (54.8)	
Age*, year	58	46.5	59	0.007
Age range	2-101	11-97	2-101	
Anti-HCV S/CO* (S/CO§ range)	48.70 (1.01-379)	67.17 (1.25-379)	37.65 (1.01-293)	<0.001

*: Median, §: S/CO: Signal-to-cut-off, †: Pearson's chi-square (comparison by gender), Mann-Withney U test (comparison by age and anti-HCV S/CO values), HCV: Hepatitis C virus, RNA: Ribonucleic acid

Table 2. HCV RNA positivity dispersion of anti-HCV reactive patients

HCV RNA				
Anti-HCV S/CO*	**Positive, n (%)**	**Negative, n (%)**	**All, n (%)**	**p-value†**
1-4	6 (2.4)	242 (97.6)	248 (100)	
5-9	7 (7.3)	89 (92.7)	96 (100)	
10-14	2 (8.7)	21 (91.3)	23 (100)	<0.001
≥15	153 (23.8)	490 (76.2)	643 (100)	
≥1 (All reactive results)	168 (16.6)	842 (83.4)	1010 (100)	

*: S/CO: Signal-to-cut-off value, †: Pearson's chi-square, HCV: Hepatitis C virus, RNA: Ribonucleic acid

Table 3. The performance of anti-HCV ECLIA test for prediction of HCV viremia

Parameters	Anti-HCV S/CO ratios and test performances, (%)				
S/CO	1.24	7.54	8.23	15.01	100.10
Sensitivity (%)	100	95.2	95.2	91.1	82.7
Specificity (%)	4.5	35.2	36.0	41.8	26.7
PPV (%)	17.3	22.7	22.9	23.8	18.4
NPV (%)	100	97.4	97.4	95.9	88.6

S/CO: Signal-to-cut-off, PPV: Positive predictive value, NPV: Negative predictive value, ECLIA: Electrochemiluminescence immunoassay, HCV: Hepatitis C virus

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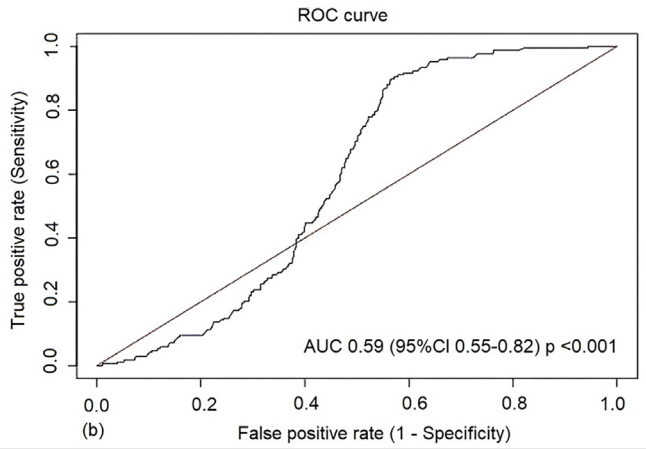

Figure 1. Diagnostic performance of the anti-HCV screening test
AUC: Area under the curve, ROC: Receiver operating characteristic, HCV: Hepatitis C virus

DISCUSSION

The accuracy of EIA tests in diagnosing HCV has improved markedly since anti-HCV screening was first introduced in 1989. Although these tests are reported to have an accuracy exceeding 99%, false-positive rates remain high in low-prevalence populations (13). Several factors can contribute to false-positive anti-HCV results, including elevated gamma globulin levels (e.g., individuals of African descent, patients with multiple myeloma, or individuals with rheumatoid factor), liver diseases, autoimmune disorders, viral infections such as human immunodeficiency virus or hepatitis B virus, previous vaccinations, prolonged serum storage, and temperature fluctuations (14).

In 2003, the CDC proposed a diagnostic algorithm that included the S/CO ratio, nucleic acid amplification test (NAAT), and recombinant immunoblot assay (RIBA). However, in 2013, RIBA was removed from the algorithm, and only NAAT was retained as a confirmatory method. As a result, distinguishing between false-positive anti-HCV results and past infections became more challenging (15). Anti-HCV reactivity may indicate viremia, a past infection, or a false-positive result (4). False-positive results not only complicate diagnosis but also lead to unnecessary additional testing and patient anxiety, underscoring the importance of improved predictive cut-offs (8,14,16).

In this study, no viremia was detected in patients with anti-HCV S/CO ≤1.24, while HCV RNA positivity was found in 23.8% of those with S/CO ≥15. Production of anti-HCV antibodies results from antigenic stimulation due to viral replication, and higher anti-HCV antibody levels are often correlated with increased viral stimulation (17). The optimal S/CO cut-off was determined to be 8.23, yielding 95.2% sensitivity and 36% specificity. However, the ROC AUC was only 0.59, indicating limited diagnostic performance. This high sensitivity underscores the test's potential clinical value, especially for early detection of HCV infection in large-scale screening programs and resource-limited settings. Furthermore, it may reduce the need for more costly HCV RNA testing.

Although this cut-off is comparable to values reported in regional studies, its relatively low AUC limits general applicability. Therefore, our findings should be interpreted as context-specific data, reflecting the characteristics of our study population and the Elecsys testing platform, rather than as a universally applicable diagnostic cut-off. Regional variations are evident in the literature, potentially reflecting differences in population characteristics, genotype distribution, disease prevalence, and healthcare settings. For instance, Huang et al. (18) in Taiwan (low prevalence, predominantly genotype 1b) reported no HCV RNA detection in patients with S/CO ≤10; for values >10, sensitivity and specificity were both 81%. In Korea, Seo et al. (4) in a study with high screening coverage and mixed genotype distribution, reported 94.4% sensitivity and 97.3% specificity for an S/CO of 10.9. Tiwari et al. (19) in India (higher prevalence and genotype 3 predominance), found 95% sensitivity and 92% specificity for an S/CO ≥6. Moretti et al. (20) conducted a study in Italy and recommended cut-offs of 10.3 for 95% PPV and 3.0 for NPV. In Türkiye, Gülseren et al. (21) in Balıkesir reported anti-HCV cut-offs of 8.9 and 5.0 that were highly predictive of viremia. Similarly, Şanlıdağ et al. (22) in Manisa observed a strong correlation between anti-HCV levels (S/CO) and HCV RNA. Furthermore, Fidan et al. (23) in Ankara reported a 56.2% RNA positivity among patients with S/CO values greater than 10; no viremia was detected in any patient with S/CO values below 3.0.

Recent studies have proposed different S/CO cut-offs, varying by test system and patient demographics. In a study conducted in İstanbul, Türkiye, Sarıkaya et al. (24) determined a cut-off of 10.86 for Elecsys, with 96.1% sensitivity and 61.2% specificity. Although this is higher than the cut-off in our study, it still provides strong predictive value. Kang et al. (25) conducted a study in Korea and reported an AUC of 0.970, sensitivity of 99.7%, and specificity of 87.5% at S/CO=8; they identified S/CO=5 as a cut-off or ruling out false positives. Our value of 8.23 aligns with these findings. Nevertheless, the lower AUC in our study indicates limited discriminatory power and highlights the importance of interpreting S/CO values in relation to local population dynamics, testing protocols, and prevalence settings. Given the variability observed, each laboratory should consider establishing its own decision limits tailored to the population it serves and the test platform it uses.

Dabanlıoğlu et al. (26) reported a sensitivity of 72% and a specificity of 88% at an S/CO cut-off of 15.4. Such a high cut-off may help reduce false positives and lower costs. As shown in Table 4, the distribution of S/CO values and corresponding HCV RNA positivity rates in our cohort further illustrates this relationship, highlighting the trade-off between sensitivity, specificity, and cost-effectiveness when selecting an optimal cut-off (4,18,19,21,22,24-26).

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Table 4. Comparison of S/CO values, sensitivity, and specificity of different immunoassay methods in predicting HCV viremia

Country	S/CO value	Sen. (%)	Spe. (%)	Assay	Manufacturer	Format	Ref.
Korea	10.9	94.4	97.3	Architect	Abbott Lab.	CLIA	(4)
Taiwan	10.0	81.0	81.0	AxSYM HCV 3.0	Abbott Lab.	MEIA	(18)
India	6.0	95.0	92.0	Vitros®	Ortho-clinical Diag.	CLIA	(19)
Korea	8.0	99.7	87.5	Architect	Abbott Lab.	CLIA	(25)
Türkiye	8.9	93.0	91.0	Architect	Abbott Lab.	CLIA	(21)
Türkiye	5.0	95.6	52.7	Architect LiaisonXL Murex	Abbott Lab. DiaSorin	CLIA CLIA	(22)
Türkiye	10.86	96.1	61.2	Elecsys	Roche Diag.	ECLIA	(24)
Türkiye	15.4	72.0	88.0	Architect	Abbott Lab.	CLIA	(26)
Türkiye*	8.23	95.2	36.0	Elecsys	Roche Diag.	ECLIA	-

*: This study, S/CO: Signal-to-cut-off, HCV: Hepatitis C virus, Sen.: Sensitivity, Spe.: Specificity, Ref: Reference, Diag.: Diagnostics, Lab: Laboratories, MEIA: Microparticle enzyme immunoassay, CLIA: Chemiluminescent immunoassay, ECLIA: Electrochemiluminescence immunoassay

Although the predictive power of S/CO values for viremia is well-supported, their use should not rely solely on a cut-off-based interpretation. Our results emphasize that specificity and diagnostic performance vary significantly based on test kit, population, and epidemiological context (24-27). Recent evidence also highlights the importance of accounting for false-positive rates and performance differences across platforms when making clinical decisions (24-27). Therefore, when constructing diagnostic algorithms based on S/CO, factors such as platform compatibility and false-positive risk must be considered.

Kang et al. (25) reported false-positive rates up to 45% in low-prevalence settings. Dabanlıoğlu et al. (26) reported a false-positive rate of 13.9%. Both studies support the incorporation of S/CO values into diagnostic workflows. Cho et al. (27) reported that Elecsys had an AUC of only 0.432 and performed worse than the Atellica and Alinity systems. These findings, along with those by Sarıkaya et al. (24), Kang et al. (25), and Dabanlıoğlu et al. (26), indicate that laboratories should establish system-specific cut-off values based on local data.

Sarıkaya et al. (24) reported S/CO values in patients with HCV genotype 1b; however, their study did not specifically examine the association between genotype and S/CO. Nonetheless, S/CO values remain potential virological markers for patient risk stratification, with low values (<3-5) indicating a low likelihood of viremia (14,24-28). Further research is needed to determine its independence from genotype.

Study Limitations

Several limitations of this study should be acknowledged. Because it was designed as a retrospective epidemiological study, it was not possible to assess whether the patients had received treatment. Additionally, only patients with both anti-HCV reactivity and concurrent HCV RNA results were included. This inclusion criterion may have introduced selection bias, as patients who underwent HCV RNA testing could represent a subgroup with higher clinical suspicion of active infection, different demographic characteristics or comorbidity profiles, or specific risk factors compared with all anti-HCV-reactive individuals. Consequently, the observed viremic rate in our sample may be overestimated relative to the general anti-HCV-reactive population. This limitation reduces the external validity (generalizability) of our findings and should be considered when interpreting the results and when comparing them with studies that include broader or unselected populations. The modest AUC value in our dataset may also stem from patient-related variables, such as advanced age and comorbidity burden, both of which can affect the immune response and reduce the predictive performance of antibody-based assays, such as Elecsys. These variables should be taken into account when comparing diagnostic accuracy across studies.

CONCLUSION

This study found that the diagnostic performance of anti-HCV S/CO values in detecting viremia was limited, as indicated by ROC analysis. These findings suggest that S/CO values alone are insufficient to reliably predict HCV viremia and should be interpreted in conjunction with confirmatory testing and population-specific characteristics.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-BADEK-2024-806, date: 28.08.2024).

Informed Consent: Retrospective study.

Footnotes

Author Contributions: Concept - A.B., M.F.K., G.K.; Design - A.B., M.F.K., G.K.; Data Collection and/or Processing - A.B., M.F.K.; Analysis and/or Interpretation - A.B., M.F.K.; Literature Search - A.B., M.F.K., G.K.; Writing - A.B., M.F.K., G.K.

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

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Dimethyl Fumarate's Potential in Methanol Toxicity: A Critical Perspective on Future Research Directions

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Keywords: Dimethyl fumarate, methanol toxicity, retinal protection, oxidative stress, neuroprotection

Dear Editor,

After reading the study by Akyuz Unsal et al. (1) investigating the effects of dimethyl fumarate (DMF) on methanol (MeOH) toxicity, we would like to address an important gap in this research area. As the authors noted, the effects of DMF on organ-level MeOH toxicity have not been previously investigated, particularly considering the significant retinal side effects.

MeOH poisoning causes oxidative stress and retinal ganglion cell damage through its formic acid metabolite. DMF's proven antioxidant and anti-inflammatory properties in multiple sclerosis and psoriasis treatment may provide protective effects against these toxic processes (2). Indeed, DMF activates the *Nrf2* pathway, increasing antioxidant gene expression while suppressing pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha (3).

Although the study results were unexpected, the demonstration of DMF's safety profile is valuable. However, its potential for retinal protection could not be fully evaluated. Literature reports show that DMF exhibits protective effects in age-related macular degeneration, uveitis, and light-induced photoreceptor loss (4). These findings suggest DMF's therapeutic potential against MeOH's retinal toxicity.

The study's limitations, particularly the failure to establish a toxicity model, may have masked DMF's true effects. Future studies should include specific ophthalmological evaluations such as optical coherence tomography, electroretinography, and retinal ganglion cell counting. Additionally, testing different DMF doses and administration timing would be critical for determining optimal protective protocols.

Given the limited treatment options for MeOH poisoning, investigating multi-target agents like DMF is of great importance. Particularly, DMF's dual action of reducing oxidative stress and suppressing inflammation offers an ideal protective profile against MeOH's bidirectional toxic mechanisms (5).

This investigation represents a valuable foundation for exploring DMF's therapeutic potential in MeOH toxicity, despite methodological challenges encountered. Future research employing more sophisticated toxicity models and comprehensive retinal assessments could provide crucial insights that may ultimately translate into clinical therapeutic strategies for this life-threatening condition (6).

Sincerely,

Footnotes

Author Contributions: Surgical and Medical Practices - M.Ö.; Concept - M.N.S.; Design - M.N.S.; Data Collection and/or Processing - M.Ö.; Analysis and/ or Interpretation - M.N.S.; Literature Search - M.N.S.; Writing - M.N.S.

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