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Awake Tracheal Intubation During the COVID-19 Pandemic: A Systematic Literature Review

COVID-19 Pandemisi Sırasında Uyanık Trakeal Entübasyon: Sistematik Literatür Derlemesi

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Abstract

Awake tracheal intubation (ATI) is a key strategy in managing anticipated difficult airways, particularly when maintaining spontaneous respiration and airway reflexes is critical. During the coronavirus disease-2019 (COVID-19) pandemic, concerns about aerosol generation shifted intubation practices toward methods prioritizing safety. However, published data on ATI in patients with suspected or confirmed COVID-19 remain scarce. This systematic review was conducted in accordance with the PRISMA 2020 guidelines. A comprehensive literature search was performed in PubMed (MEDLINE) and the Web of Science Core Collection from database inception to April 30, 2025. Studies involving adult patients (≥18 years) with confirmed or suspected COVID-19 infection who underwent ATI were included. Eligible study designs comprised case reports, case series, observational studies, and randomized or quasi-randomized trials. Simulation studies, animal studies, reviews, and non-clinical reports were excluded. Study selection and data extraction were independently performed by multiple reviewers, with disagreements resolved by consensus. Methodological quality was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports. Six studies met the inclusion criteria. All ATI procedures were performed using fiberoptic bronchoscopy; videolaryngoscopy was not reported in any case. Topical lidocaine anesthesia was used in most cases, while no patients received regional nerve blocks. Sedation was administered in most cases. Oxygen therapy was provided in the majority of patients, commonly via nasal cannula. Most procedures occurred in the operating room, although

Öz

Uyanık trakeal entübasyon (UTE), zor hava yolu öngörüldüğü durumların yönetiminde temel bir stratejidir. Özellikle spontan solunumun ve hava yolu reflekslerinin korunmasının kritik olduğu durumlarda kullanılmaktadır. Koronavirüs hastalığı-2019 (COVID-19) pandemisi sırasında aerosol oluşumu ile ilgili endişeler olması sebebiyle güvenliği ön planda tutan yöntemlerle entübasyon yapılmasına eğilim olmuştur. Bununla beraber, şüpheli veya doğrulanmış COVID-19 hastalarında UTE uygulamalarına ilişkin yayımlanmış veriler oldukça sınırlıdır. Bu sistematik derleme, PRISMA 2020 kılavuzu doğrultusunda yapılmıştır. PubMed (MEDLINE) ve Web of Science Core Collection veri tabanlarında, 30 Nisan 2025'e kadar yayımlanan çalışmalar kapsamlı bir şekilde taranmıştır. Doğrulanmış veya şüpheli COVID-19 enfeksiyonu olan ve UTE yapılan 18 yaş ve üzeri hastaları içeren çalışmalar dahil edilmiştir. Olgu sunumları, olgu serileri, gözlemsel çalışmalar ile randomize veya yarı randomize çalışmalar değerlendirmeye alınmıştır. Simülasyon çalışmaları, hayvan deneyleri, derlemeler ve klinik uygulama içermeyen yayınlar dışlanmıştır. Çalışmaların seçimi ve veri çıkarımı birden fazla araştırmacı tarafından bağımsız olarak yapılmış, görüş ayrılıkları uzlaşı yoluyla giderilmiştir. Metodolojik kalite değerlendirmesi, Joanna Briggs Institute Olgu Sunumları için Kritik Değerlendirme Kontrol Listesi kullanılarak yapılmıştır. Dahil edilme kriterlerini karşılayan toplam altı çalışma belirlenmiştir. Tüm UTE girişimleri fiberoptik bronkoskopi kullanılarak gerçekleştirilmiş olup, hiçbir olguda videolaringoskopi bildirilmemiştir. Çoğu olguda topikal lidokain ile lokal anestezi uygulanmış, ancak hiçbir hastada

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Abstract

one setting was unspecified. No major complications were reported. Despite the relevance of ATI in difficult airway management, its use during the COVID-19 pandemic appears underreported. The limited number of cases in the literature may not reflect rarity but rather hesitation in clinical practice or under documentation. Greater transparency and sharing of clinical experiences are essential to inform future practice, particularly under high-risk conditions like pandemics.

Keywords: Airway management, COVID-19, intratracheal intubation

Öz

bölgesel sinir bloğu kullanılmamıştır. Hastaların büyük kısmına sedasyon uygulanmıştır. Hastaların çoğuna oksijen desteği sağlanmış ve en sık nazal kanül kullanılmıştır. İşlemlerin büyük bölümü ameliyathanede gerçekleştirilmiş olup, bir çalışmada uygulama ortamı belirtilmemiştir. Hiçbir olguda majör komplikasyon bildirilmemiştir. UTE, zor hava yolu yönetiminde önemli bir yere sahip olmasına rağmen COVID-19 pandemisi sırasında kullanımına ilişkin literatür verileri sınırlıdır. Literatürdeki olgu sayısının azlığı, zor entübasyonun nadirliğinden çok klinik çekinceler veya raporlama azlığına bağlı olabilir. Özellikle pandemi gibi yüksek riskli durumlarda, klinik deneyimlerin daha şeffaf şekilde paylaşılması, gelecekteki uygulamalara rehberlik edebilmek açısından büyük önem taşımaktadır.

Anahtar kelimeler: COVID-19, hava yolu yönetimi, trakeal entübasyon

Introduction

A difficult airway is defined as a clinical scenario in which an anesthesia-trained clinician encounters, either expectedly or unexpectedly, difficulty or failure in performing airway management procedures such as face mask ventilation, laryngoscopy, supraglottic airway ventilation, tracheal intubation, extubation, or invasive airway access (1-3). Since maintaining adequate ventilation, oxygenation, and airway patency is vital, the initial consideration for patients with an anticipated difficult airway undergoing surgery is whether anesthesia should be provided under local infiltration, regional anesthesia, or general anesthesia. The second critical consideration is to assess the likelihood and potential clinical implications of difficulties during mask ventilation, supraglottic airway use, laryngoscopy, tracheal intubation, or surgical airway access (4-7).

Anticipating airway difficulty and preparing an appropriate airway management strategy in advance is widely recognized as safer and more effective than relying on emergency rescue interventions after complications arise (8,9). Over recent decades, technological advancements—including videolaryngoscopes, flexible bronchoscopes, and improved oxygenation techniques—have significantly mitigated many of the challenges associated with anatomically difficult airways (10-12). Providing a secure airway represents one of the most critical steps in perioperative care and poses a particular challenge in patients with coronavirus disease-2019 (COVID-19), in whom airway management is considered both high-risk and technically demanding (13,14). Difficult airway management remains a major concern for anesthesiologists (15), and the coexistence of COVID-19 infection with an anticipated difficult airway constituted a substantial clinical challenge during the pandemic. In the early stages of the COVID-19 pandemic, multiple recommendations and guidelines were rapidly developed to enhance the safety of tracheal intubation for both patients and healthcare providers (16-19).

These guidelines generally emphasized minimizing the number of personnel involved, using appropriate personal protective equipment (PPE), assigning the most experienced clinician to airway management, utilizing videolaryngoscopy (VLS) as the first-line device, and avoiding aerosol-generating procedures whenever feasible (20).

Awake tracheal intubation (ATI) enhances patient safety by maintaining spontaneous ventilation, airway patency, gas exchange, and protective airway reflexes throughout the procedure, and is therefore considered a preferred technique in the management of anticipated difficult airways (1,21-26). Fiberoptic bronchoscopy (FOB)-guided ATI has long been regarded as the gold standard in such cases (27,28). However, several COVID-19 specific airway management guidelines recommended avoiding ATI unless clearly indicated, primarily due to concerns regarding aerosol generation associated with coughing during the procedure (16,29,30).

In this systematic literature review, we aimed to evaluate reported clinical approaches to ATI in adult patients with suspected or confirmed COVID-19 infection and an anticipated difficult airway, with particular emphasis on procedural techniques, airway anesthesia, sedation strategies, and infection control measures.

Methods

Protocol and registration: This systematic literature review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (31). Formal protocol registration was not undertaken, as this study involved a systematic review of published literature only and did not include individual patient-level data.

Literature search: A comprehensive literature search was performed in PubMed (MEDLINE) and the Web of Science Core Collection from database inception to April 30, 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to difficult airway management, COVID-19, and ATI. The final search was rerun on April 30, 2025, immediately prior to manuscript submission to ensure inclusion of recently published articles.

For PubMed, the complete search strategy was as follows:

("Difficult Airway"[tiab] OR "difficult airway"[tiab]) AND ("COVID-19"[Mesh] OR "SARS-CoV-2"[tiab] OR "coronavirus"[Mesh]) AND ("Intubation, Intratracheal"[Mesh] OR "awake intubation"[tiab] OR "awake fibreoptic intubation"[tiab] OR "awake fiberoptic intubation"[tiab] OR "ATI"[tiab]).

Filters were applied to limit results to human studies, adult patients (≥18 years), and articles published in English. No additional date restrictions were applied.

For Web of Science Core Collection, the following search string was used: TS=("difficult airway") AND TS=("COVID-19" OR "SARS-CoV-2" OR "coronavirus") AND TS=("awake intubation" OR "awake fibreoptic intubation" OR "awake fiberoptic intubation" OR "ATI"). Results were limited to articles and early access publications written in English.

In addition, the reference lists of all eligible studies were manually screened to identify further relevant publications. When necessary, corresponding authors were contacted to obtain missing or unclear data. Articles for which no response was received were evaluated based on the available published data.

Eligibility criteria: We included studies reporting adult patients (≥18 years) with confirmed or suspected COVID-19 infection who underwent oral or nasal ATI for any indication. Given the novelty of the disease and the limited available evidence, we included case reports, case series, retrospective and prospective observational studies, as well as randomized or quasi-randomized trials. Simulation studies, animal studies, reviews, and articles not involving clinical ATI were excluded.

Study selection: All retrieved titles and abstracts were independently screened by four authors (Y-O, H-YA, G-A, and A-E). Reasons for exclusion were documented. Disagreements were resolved by discussion with two additional reviewers (K-E and Z-S), who made the final inclusion decision. Full texts of potentially eligible articles were subsequently reviewed.

Data extraction: Data extraction was independently performed by four reviewers and cross-checked for accuracy. Disagreements were resolved by consensus or consultation with a senior reviewer. Extracted data included study type, patient characteristics, airway assessment findings, intubation technique, sedation and topical anesthesia methods, oxygen supplementation, PPE use, procedural setting, and reported outcomes.

Quality and risk-of-bias assessment: Given that the included evidence consisted primarily of case reports and letters, methodological quality was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports (32). Each study was evaluated independently by two reviewers. Disagreements were resolved by consensus. The results of this appraisal are summarized in Table 1.

Results

The literature search identified a total of 421 records. After removal of duplicate records (n=19), 402 records were screened by title and abstract, of which 198 were excluded as irrelevant. Full-text assessment was subsequently performed for 204 articles. Of these, studies focusing on tracheostomy (n=5), non-awake difficult airway management procedures (n=38), awake pronning (n=149), awake extracorporeal membrane oxygenation (n=3) and non-English language publications (n=3) were excluded. Ultimately, only six studies met the inclusion criteria. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Ultimately, six studies met the inclusion criteria and were included in the qualitative synthesis. These comprised three case reports, one correspondence, and two letters to the editor. Study characteristics are summarized in Table 2. The reported endotracheal tube sizes were 6.5 mm in two cases, 7.0 mm in two cases, and 7.5 mm in one case; in one report, tube size was not specified. Two studies described

oral intubation, two reported nasal intubation, and in two cases the intubation route was not clearly stated. VLS was not used in any of the included cases; all intubations were performed using FOB. An Ambu® aScope™ was used in two cases, while a C-MAC fiberoptic intubation scope (Karl Storz®) was used in one case; the bronchoscope brand was not reported in the remaining studies.

All ATIs were performed in patients with anatomical airway challenges, including tumors obstructing the visual field or restricted mouth opening. Airway anesthesia was achieved using topical local anesthetics in all cases. Sedation was administered in all but one patient, in whom sedation status was not reported. When sedation was used, spontaneous ventilation was preserved. Oxygen supplementation was reported in most cases, although two studies did not specify the oxygen delivery method. All procedures were performed in the operating room under full PPE, and no immediate airway-related complications were reported.

Ahmad et al. (33) reported ATI in a patient with a base-of-tongue tumor and suspected COVID-19. The procedure was conducted in the operating room with the entire team wearing PPE. The patient received dual-agent sedation with propofol and remifentanil in addition to topical airway anesthesia. Intubation was successfully performed using a 6.5 mm endotracheal tube and an Ambu® aScope™ 4 BronchoSlim (Ambu, Copenhagen, Denmark). Ghaly et al. (34) described ATI in a patient undergoing cervical spine surgery for stenosis and C6-C7 disc herniation with spinal cord compression. Although PPE use was not explicitly stated, it was visible in the accompanying photograph. Sedation and topical anesthesia protocols were not fully detailed; however, the patient reportedly had no recall following topicalization. A protective barrier device was used. Nasotracheal intubation was performed with a 7.5 mm tube using a C-MAC fiberoptic scope (Karl Storz®, Tuttlingen, Germany). Rajan et al. (35) reported ATI in a patient with restricted mouth opening due to tongue carcinoma and suspected COVID-19 infection. The

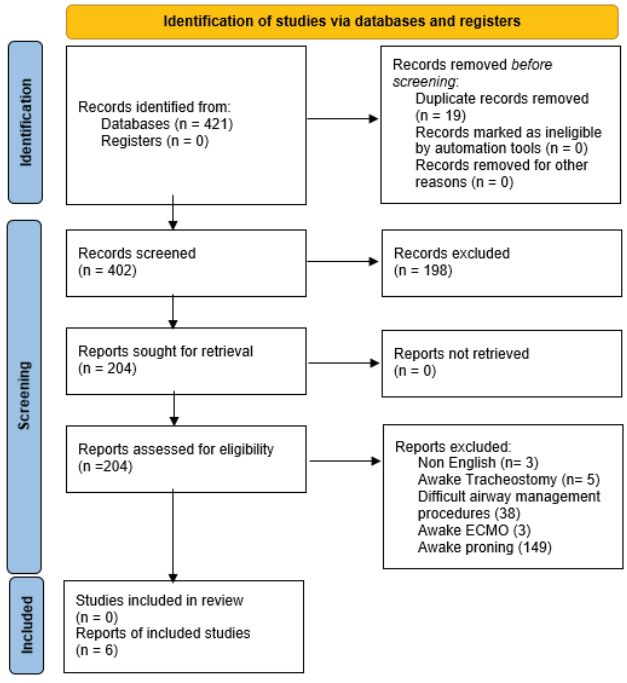

Figure 1. PRISMA 2020 flow diagram

ECMO: Extracorporeal membrane oxygenation, PRISMA: Preferred reporting items for systematic reviews and meta-analyses

Table 1. JBI critical appraisal checklist for case reports

JBI critical appraisal checklist for case reports	Phipps et al. (37)	Ahmad et al. (33)	Ip and Tham (36)	Ghaly et al. (34)	Rajan et al. (35)	Tone et al. (38)
Were patient's demographic characteristics clearly described?	No	Yes	No	Yes	Yes	Yes
Was the patient's history clearly described and presented as a timeline?	No	Yes	No	No	Yes	Yes
Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Were diagnostic tests or assessment methods and the results clearly described?	No	Yes	No	No	Yes	Yes
Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes	No	No	Yes	No
Was the post-intervention clinical condition clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Were adverse events (harms) or unanticipated events identified and described?	Yes	Yes	Yes	Unclear	Yes	Yes
Does the case report provide takeaway lessons?	Yes	Yes	Yes	Yes	Yes	Yes

Table 2. The characteristics of the included studies

Variables	Phipps et al. (37)	Ahmad et al. (33)	Ip and Tham (36)	Ghaly et al. (34)	Rajan et al. (35)	Tone et al. (38)
Article type	Correspondence	Case report	Letter to editor	Case report	Letter to editor	Letter to editor
COVID-19 PCR test result	Unknown	Unknown	Unknown	Unknown	Unknown	Positive
Indication for ATI	Maxillofacial surgery	Head and neck cancer	Head and neck cancer	Limited cervical-spine movement	Head and neck cancer	Abscess with airway compression
Antisialogogue	Glycopyrronium bromide	No	No	Unknown	Glycopyrronium bromide	No
Topicalisation	Lidocaine 4% atomiser device + lidocaine 10% spray + nasopharyngeal gazue packing coated with 4% lidocaine	Lidocaine 4% atomiser device + lidocaine 10% spray + nazopharyngeal gazue packing coated with 4% lidocaine	Lidocaine 4% atomiser device	Unknown	Lidocaine 2% nasal gel + lidocaine 10% spray	Lidocaine 4% with catheter
Oxygenation	Yes (4 L)	Yes (5 L)	Yes (2 L)	High flow	Unknown	Unknown
Sedation-analgesia (Y-N/agent)	Yes/remifentanyl	Yes/propofol + remifentanyl	Yes/remifentanyl	Unknown	No	Yes/unknown
Approach to ATI	Orotracheal	Nasotracheal	Unknown	Nasotracheal	Orotracheal	Unknown
FOB usage	Yes	Yes	Yes	Yes	Yes	Yes
Bronchoscope type	Ambu® aScope™ 4 Broncho size regular	Ambu® aScope™ 4 Broncho slim	Unknown	C-MAC fiber-optic scope (Karl Storz®, C-MAC)	Unknown	Unknown
ETT size ID (mm)	7	6.5	Unknown	7.5	7	unknown
Complications	No	No	No	Unknown	No	No
PPE	Yes	Yes	Unknown	Unknown	Yes	Yes
Barrier use	No	No	Yes	Yes	Yes	No
Operation room	Yes	Yes	Yes	Yes	Yes	Unknown
Number of patients	1	1	1	1	1	1

COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, ATI: Awake tracheal intubation, FOB: Fiberoptic bronchoscopy, PPE: personal protective equipment

procedure was performed in the operating room using topical anesthesia without sedation. Although PPE use was not explicitly described, it was visible in the published image. Nasotracheal intubation was successfully completed with a 7.0 mm tube using a fiberoptic bronchoscope. Ip and Tham (36), in a letter to the editor, described ATI in a patient with a tonsillar tumor. The procedure was conducted in the operating room with appropriate PPE. The patient received remifentanil sedation and topical anesthesia. The endotracheal tube size and route of intubation were not specified. Fiberoptic intubation was successfully achieved without reported complications. Phipps et al. (37), in a correspondence, described ATI in a patient undergoing emergency jaw surgery with suspected COVID-19 infection. The patient received remifentanil sedation and topical airway anesthesia. The procedure was performed in the operating room under full PPE. A 7.0 mm endotracheal tube was used, and intubation was completed using an Ambu® aScope™ 4 Broncho (regular size; Ambu, Ballerup, Denmark). Tone et al. (38) reported ATI in a patient with airway compression caused by a deep neck space abscess following tooth extraction and recent COVID-19 infection. The procedure was performed in the operating room with the entire team wearing PPE. Topical anesthesia was delivered using an epidural catheter advanced into the oropharynx. Preparations for emergency tracheostomy were described. The sedative agent, endotracheal tube size, and bronchoscope brand were not reported.

Bozych and Smith (39) described the case of a patient with Down syndrome (trisomy 21) and Ludwig's angina, diagnosed with COVID-19 pneumonia eight days prior. The patient was intubated due to respiratory distress in a hospital room. The authors did not specify the use of PPE, preoxygenation method, or bronchoscope brand. Topical anesthesia was administered via aerosolization, and ketamine was used for sedation. A video laryngoscope was employed during bronchoscope insertion, and intubation was completed with a 6.5 mm tube; consequently, the study was excluded from our review because of the use of VLS. Shamim et al. (40) described ATI in a COVID-19-positive patient with recurrent cancer and a Mallampati class IV airway. The entire team wore PPE during the procedure, which was performed in the operating room. To reduce gag reflex risk, no topicalization was performed. The patient was maintained under general anesthesia with propofol and sevoflurane while preserving spontaneous respiration. After two to three unsuccessful nasotracheal attempts, an orotracheal approach was adopted, and intubation was successfully completed with a 7.5 mm tube after approximately 20 minutes. The patient experienced two desaturation episodes; the bronchoscope brand was not specified. Because the procedure was performed under general anesthesia, this case was excluded from our review. Cai et al. (41) reported ATI in 12 COVID-19-positive ICU patients using a specially designed positive pressure protective hood. Sedation included midazolam, propofol, and morphine or fentanyl. Topical anesthesia was not mentioned. All intubations were uneventful. The article was excluded from our analysis because it was not written in English. Ontivero et al. (42) performed ATI in a patient with head and neck cancer undergoing surgery. The patient received oxygen via nasal cannula, dexmedetomidine sedation, and topical analgesia. Intubation was completed without complications. Similarly, Akavipat (43) reported a case involving a patient undergoing cervical spine fracture surgery, who was sedated with morphine and received topical lidocaine. Both case reports were excluded from our study due to their language.

When the case reports and letters to the editor were appraised using the JBI Critical Appraisal Checklist for Case Reports (Table 1), it was observed that, with the exception of two articles, all studies provided detailed demographic characteristics of the patients. Approximately half of the reports clearly described the patients' clinical status at presentation. All cases reported the current clinical condition and the indication for the procedure.

Assessment methods were described in roughly half of the articles, including airway evaluation parameters such as Mallampati classification, cervical range of motion, tongue characteristics, and the presence of symptoms such as dysphonia or stridor. In addition, some reports included radiological findings, such as computed tomography imaging, as part of the pre-procedural assessment.

Post-intervention clinical outcomes, specifically whether successful intubation was achieved, were reported in all studies. Adverse or unanticipated events were documented in all but one article, in which this domain was deemed unclear. Finally, all reports included key takeaway lessons or clinical implications derived from the cases.

Discussion

This systematic review demonstrates that published evidence regarding ATI in patients with suspected or confirmed COVID-19 and anticipated difficult airway is extremely limited and consists exclusively of low-level evidence, primarily case reports, letters to the editor, and

correspondence. As such, the observations presented herein are descriptive in nature and should be interpreted with caution, as they do not permit causal inference or formal comparisons between airway management strategies.

The primary objective of this review was to evaluate how ATI—indicated in approximately 1.06% of cases (27)—was implemented during the COVID-19 pandemic, given that the incidence of anticipated difficult airway ranges from 0.1% to 10.1% (44,45). This is particularly relevant because airway guidelines during the pandemic emphasized "safe, accurate, and fast" intubation (16). While ATI is an established airway management technique, the need to minimize aerosol generation during the pandemic led to a re-evaluation of its protocols and practices.

During this period, increasing patient cooperation, reducing the number of intubation attempts, and minimizing procedure duration became critical goals. Some studies suggested performing intubation and even extubation behind a protective plastic barrier to reduce aerosol spread (46,47). However, the use of plastic barriers declined over time due to the potential for increased contamination risk during their removal (48,49). Additionally, placing an awake patient under a plastic sheet may induce discomfort or trigger anxiety-related responses such as claustrophobia.

ATI comprises three fundamental components: Effective local anesthesia, adequate sedation, and accurate placement of the endotracheal tube. Coughing during intubation has been associated with increased transmission risk of SARS-CoV-2 to anesthesiologists, highlighting the importance of suppressing the cough reflex (50). Effective local anesthesia is therefore essential. Several COVID-19 guidelines advise against the use of atomized, sprayed, or nebulized local anesthetics (30,51-53). Alternatives such as local anesthetic gels, soaked swabs, or appropriate regional nerve blocks are recommended. The use of an endoscopic mask is another proposed method to reduce aerosol generation during ATI (53). In our review, topical anesthesia with lidocaine was used in most cases, and no patient received a nerve block. This preference may be attributed to the broader familiarity and ease of use of topical techniques compared to the expertise required for nerve blocks.

Sedation is another crucial factor in minimizing aerosolization. Guidelines generally support sedation to reduce patient anxiety and improve procedural tolerance (51). Although some researchers suggest that ATI can be performed safely without sedation (25,54,55), most agree that appropriate sedation enhances patient comfort and cooperation (56). Anxiety can activate sympathetic and parasympathetic responses, leading to elevated heart rate, hypertension, increased secretions, and heightened airway reflexes—all of which may hinder successful intubation (57). When administered at appropriate doses, sedation allows the patient to remain responsive to verbal commands while preserving airway reflexes, spontaneous breathing, and cardiovascular stability. Remifentanil and dexmedetomidine have been associated with high patient satisfaction in ATI (56), and single-agent use (rather than combination therapy) is generally considered safer (58). Propofol, although used, carries a higher risk of excessive sedation, coughing, and airway obstruction compared to remifentanil (59-62). Importantly, sedation should not be used as a substitute for insufficient airway anesthesia (63). In our analysis, sedation was used in all but one study, while in another, the use of sedation was not reported. No standardized sedation protocol was identified, suggesting that sedation strategies were based on patient-specific and clinical factors.

Importantly, variations in sedation techniques, topical anesthesia methods, and procedural settings across the included reports reflect individual clinical judgment rather than standardized protocols. These differences further limit the generalizability of the findings and underscore the exploratory nature of the available evidence.

FOB remains the gold standard for ATI in patients with anticipated difficult airway, especially when performed under sedation while preserving spontaneous respiration (1,64,65). However, proficiency with FOB requires significant training and frequent practice (23). VLS also offers excellent glottic visualization and enables successful intubation in difficult airway cases. Both FOB and VLS demonstrate comparable safety and success rates. Some guidelines even recommend VLS for ATI in COVID-19 patients, as it may allow faster intubation compared to FOB (66). VLS also accommodates the use of smaller-diameter endotracheal tubes (23). Despite this, all the studies included in our review utilized FOB. This may reflect clinicians' preference for the gold standard technique, particularly under the high-risk conditions of the pandemic. Although FOB was used in all included cases, this should not be interpreted as evidence of superiority over VLS. Rather, this finding likely reflects clinician preference, local expertise, and prevailing practice patterns during the early phases of the COVID-19 pandemic. According to COVID-19 airway guidelines, airway procedures should ideally be performed in isolated areas or negative pressure rooms (16,51,67-70).

An alternative is to convert a positive-pressure operating room into a negative-pressure environment (71). In most cases reviewed, ATI was conducted in the operating room; however, one case was performed outside the OR, and the setting was not specified in another. This setting is optimal for ATI, as it ensures access to skilled personnel, appropriate medications and equipment, and sufficient space (58).

Oxygen supplementation is essential during ATI. The reported incidence of desaturation during ATI with low-flow oxygen is 12-16%, whereas this drops to 0-1.5% when high-flow nasal oxygen is used (72-74). Most COVID-19 guidelines recommend preoxygenation with 100% oxygen via a tight-fitting face mask for five minutes prior to intubation (30,67-69). In our review, oxygen was generally administered via nasal cannula, although the flow rates varied between cases.

Finally, airway management should be performed by clinicians who are trained and experienced in the techniques they choose to use, especially under pandemic conditions (16). Procedures that generate aerosols should be avoided or minimized (19,69). The number of healthcare providers involved during such procedures should be kept to a minimum, and standard infection control precautions (e.g., hand hygiene and proper PPE) must be followed rigorously (19). According to the World Health Organization, the minimum PPE for airway management includes masks, eye protection, gowns, and gloves (75). Notably, approximately 39% of COVID-19 patients may require more than one airway intervention (76). Clinicians should therefore anticipate that ATI may be more challenging in this population, and that prolonged procedures, failed intubation, or the need for emergency surgical airways may occur more frequently.

Given the absence of controlled studies and the small number of reported cases, the conclusions drawn from this review should be regarded as hypothesis-generating rather than practice-directing. Future prospective studies and standardized reporting of awake intubation practices in high-risk infectious settings are needed to better inform clinical guidelines.

Conclusion

The COVID-19 pandemic markedly heightened awareness of both patient and provider safety during airway management. In this context, the principle of primum te ipsum protege ("protect yourself first") became as relevant as the longstanding maxim primum non-nocere ("first, do no harm").

This systematic review highlights the profound scarcity of published data on ATI in patients with suspected or confirmed COVID-19 infection and anticipated difficult airway. Given the low level of available evidence, conclusions should be regarded as hypothesis-generating rather than practice-changing.

The limited number of reported cases raises an inevitable question: Were such patients truly rare, or were their stories simply never written? It is conceivable that some of these patients—those with both suspected COVID-19 and anticipated difficult airways—never reached the point of publication due to clinical deterioration, resource limitations, or the inherent hesitation to perform aerosol-generating procedures under high-risk conditions. Ironically, it could be suggested that the presence of an anticipated difficult airway served as a form of passive protection—not biologically, but logistically—by prompting avoidance of intervention altogether. These silences in the literature may reflect not an absence of cases, but an absence of reporting.

We encourage clinicians to report and publish their experiences in this challenging clinical context. Transparent documentation of both successful and deferred airway management decisions may help inform future guidelines and preparedness for similar high-risk scenarios.

Footnotes

One of the authors of this article (K.E.) is a member of the Editorial Board of this journal. He was completely blinded to the peer review process of the article.

Authorship Contributions

Surgical and Medical Practices: Y.Ö., A.E., Concept: Y.Ö., A.E., Z.S., Design: Y.Ö., H.Y.A., K.E., Data Collection or Processing: H.Y.A., A.E., G.A., Analysis or Interpretation: H.Y.A., A.E., G.A., Literature Search: Y.Ö., G.A., Writing: Y.Ö., H.Y.A.

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ORIGINAL RESEARCH

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Impact of Blood Product Administration in Cardiovascular Surgery Patients: Center Experience

Kardiyovasküler Cerrahi Hastalarında Kan Ürünü Transfüzyonunun Etkisi: Merkez Deneyimi

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Abstract

Objective: Blood transfusion is a frequent intervention in cardiovascular surgeries. However, the timing of transfusion—whether during surgery or postoperatively in the intensive care unit (ICU)—may have distinct implications for patient outcomes. This study investigates how the timing of blood product administration affects extubation time, ICU length of stay, postoperative drainage volume, cardiac and renal parameters, hemodynamic support requirements, and ICU rhythm disturbances.

Method: This retrospective cohort study included adult patients who underwent coronary artery bypass grafting or valve surgery. Patients were grouped based on whether they received blood products intraoperatively or during ICU follow-up. Statistical analyses included t-tests, chi-square tests, and descriptive comparisons.

Results: Intraoperative transfusions were associated with shorter extubation times but longer ICU stays and higher drainage volumes. In contrast, ICU transfusions correlated with delayed extubation, higher mortality, more frequent non-sinus rhythms, and increased need for hemodynamic support. These findings highlight a clear temporal distinction in risk profiles associated with transfusion timing.

Öz

Amaç: Kardiyovasküler cerrahilerde sık uygulanan kan transfüzyonlarının, uygulama zamanına göre [intraoperatif vs. yoğun bakım ünitesi (YBÜ)] klinik sonuçlar üzerindeki etkileri farklılık gösterebilir. Bu çalışmada, transfüzyon zamanlamasının ekstübasyon süresi, YBÜ'de kalış süresi, postoperatif drenaj hacmi, kardiyak ve renal parametreler, hemodinamik destek ihtiyacı ve YBÜ ritim değişiklikleri üzerindeki etkileri araştırılmıştır.

Yöntem: Bu retrospektif kohort çalışmaya, koroner arter bypass greftleme veya kalp kapağı cerrahisi geçiren erişkin hastalar dahil edildi. Hastalar intraoperatif veya YBÜ'de transfüzyon almalarına göre gruplandırıldı. İstatistiksel analizlerde t-testi, ki-kare testi ve betimleyici yöntemler kullanıldı.

Bulgular: İntraoperatif transfüzyonlar daha kısa ekstübasyon süreleriyle ilişkiliyken, YBÜ kalış süresi ve drenaj hacimleri daha yüksekti. YBÜ döneminde yapılan transfüzyonlar ise uzamış ekstübasyon süresi, daha yüksek mortalite, sık görülen ritim bozuklukları ve artmış inotrop ihtiyacı ile ilişkiliydi. Bulgular, transfüzyon zamanlamasının klinik risk profilini etkileyen önemli bir faktör olduğunu göstermektedir.

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Abstract

Conclusion: The timing of blood product administration significantly affects postoperative outcomes. Intraoperative transfusions may address acute surgical needs, while ICU transfusions appear to be markers of postoperative instability and poorer prognosis. Timing should be considered a key factor in transfusion decision-making.

Keywords: Blood transfusion (includes blood typing), cardiopulmonary bypass, heart valve surgery, intensive care

Öz

Sonuç: Kan ürünü transfüzyonunun zamanlaması, postoperatif sonuçlar üzerinde belirleyici bir rol oynamaktadır. İntraoperatif transfüzyonlar cerrahi kayıpların yönetiminde etkili olabilirken, YBÜ transfüzyonları daha ciddi postoperatif komplikasyonların göstergesi olabilir. Transfüzyon kararları verilirken zamanlama mutlaka göz önünde bulundurulmalıdır.

Anahtar kelimeler: Kalp kapağı cerrahisi, kan transfüzyonu (kan grubu tayini dahil), kardiyopulmoner bypass, yoğun bakım

Introduction

Cardiovascular surgeries are critical interventions that often require the administration of blood products. While advancements in surgical techniques and perioperative care have significantly improved patient outcomes, these procedures are still associated with substantial morbidity and mortality, particularly in the postoperative period. One of the crucial components of perioperative management in cardiovascular surgery is the use of blood products to address intraoperative and postoperative blood loss. However, the administration of blood products carries its own set of risks and complications, which can influence patient recovery and outcomes (1,2).

The necessity of blood product administration in the perioperative period has been associated with various adverse outcomes, including prolonged mechanical ventilation, extended intensive care unit (ICU) stays, and increased rates of infection (3). Specifically, in the context of cardiovascular surgery, blood product administration has been associated with increased postoperative complications and longer recovery times (4). The physiological stress induced by major surgeries, compounded by the immunomodulatory effects of blood products, can exacerbate these complications, making postoperative management particularly challenging. The primary aim of this study is to evaluate the impact of the timing of blood product administration on mortality in patients undergoing cardiovascular surgery. The secondary aims include assessing the association of intraoperative and postoperative transfusions with morbidity-related outcomes, such as extubation time, length of hospital stay, postoperative drainage volume, revision surgery rates, and need for inotropic support.

Materials and Methods

Study Design

This retrospective cohort study was conducted to evaluate the impact of timing of blood product administration during the intraoperative period versus the postoperative period in the ICU on clinical outcomes in patients who underwent cardiovascular surgery [coronary artery bypass grafting (CABG) and valve replacement surgeries]. Ethical approval for the study was obtained from the Institutional Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval number: 2023.09.94).

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Given the retrospective nature of the study, the need for informed consent was waived by the IRB. Patient confidentiality was maintained by anonymizing the data during the analysis.

Study Population

The study included adult patients aged 18 years or older who underwent elective or emergency CABG or valve replacement surgery between 2016 and 2022 and were subsequently admitted to the ICU. Patients were included only if complete medical records were available. Those with incomplete documentation, those who underwent surgical procedures other than cardiovascular surgery, and those with an aortic cross-clamp duration exceeding 120 minutes were excluded. Patients who did not require postoperative ICU follow-up were also excluded.

Grouping of Patients

Patients were classified according to the timing of transfusion. Those who received blood products during surgery were categorized as the intraoperative transfusion group, regardless of whether additional transfusions were subsequently required in the ICU. Patients who did not receive any intraoperative transfusions but required blood product administration during ICU follow-up were categorized as the postoperative (ICU) transfusion group. This classification ensured mutually exclusive groups and enabled clear evaluation of the impact of transfusion timing on clinical outcomes.

Data Collection

Data were retrieved retrospectively from electronic medical records. Data collected included demographic variables [age, sex, body mass index (BMI)], comorbidities (diabetes mellitus and hypertension), intraoperative data on inotropic support and transfusion, and postoperative outcomes, including extubation time, length of ICU stay, drainage volumes on postoperative days 0 and 1, and lactate levels at baseline and 24 hours.

Outcome Measures

The primary outcomes were time to extubation and length of ICU stay. Secondary outcomes included postoperative drainage volume (on days 0 and 1) and preoperative lactate levels. In addition to comparing patients who did or did not receive blood products, all outcome measures were analyzed separately for two key transfusion periods: Intraoperative and ICU. This allowed the evaluation of how transfusion timing influenced recovery profiles and clinical risks.

Transfusion Protocol

Transfusion decisions were individualized based on hemodynamic status, laboratory results, and clinical context. Transfusion was typically considered when hemoglobin fell below 7 g/dL in stable patients and below 8 g/dL in hemodynamically unstable patients. In this study, the term "blood product" encompassed erythrocyte suspension, fresh-frozen plasma (FFP), and platelet transfusion; however, all transfused patients received at least ES. These criteria were consistent with international transfusion guidelines, balancing the risks and benefits of blood product administration (5,6).

Extubation Criteria

Early extubation was encouraged to optimize recovery. Patients were considered ready for extubation if they demonstrated hemodynamic stability without significant arrhythmias or hypotension, adequate spontaneous breathing and gas exchange, neurologic responsiveness, sufficient muscle strength, and strong cough reflex. Extubation was performed using a stepwise weaning protocol once these conditions were met.

Inotropic Drug Initiation Protocol

Inotropic support was initiated in cases of hemodynamic instability following surgery. Indications included clinical and biochemical evidence of low cardiac output syndrome, including hypotension, oliguria, cool extremities, altered mental status, and elevated lactate levels. During surgery, inotropes such as dobutamine, norepinephrine, or epinephrine were administered when significant hemodynamic compromise persisted despite adequate fluid resuscitation. Initiation was guided by visual assessment of contractility after cross-clamp removal and supported by blood pressure monitoring and arterial blood gas analysis. A mean arterial pressure below 65 mmHg that was refractory to fluids also constituted an indication. Doses were titrated according to each patient's response to achieve adequate perfusion and prevent complications.

Agitation

In this study, agitation was defined as a Richmond agitation-sedation scale (RASS) score of +2 or higher. For intubated patients, agitation was identified by observable behaviors, including restlessness, frequent non-purposeful movements, attempts to remove the endotracheal tube or other invasive lines, and resistance to care. These behaviors, documented by ICU nurses or physicians, were used as criteria to classify patients as agitated. In cases where RASS scoring was not explicitly recorded, the clinical documentation of agitation-related interventions (e.g., physical restraints, additional sedation) was also considered indicative of agitation.

Results Interpretation

The results were interpreted to assess the association between administration of blood products and postoperative clinical outcomes. The analysis focused on identifying significant differences in extubation times, ICU length of stay, and postoperative drainage volumes between patients who received blood products and those who did not. Additionally, preoperative ejection fraction (EF), creatinine (Cr), blood urea nitrogen (BUN), the need for inotropic and vasopressor support after cross-clamping and while in the ICU, and electrocardiogram (ECG) rhythms in the ICU were analyzed to assess cardiac and renal function, hemodynamic stability, and cardiac complications. Lactate and hemoglobin levels were also analyzed to assess metabolic response and recovery. The comprehensive evaluation of these variables provided insights into the multifaceted impact of blood product administration on patient outcomes following cardiovascular surgery.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Parametric tests (independent samples t-test) were applied to normally distributed data, whereas non-

parametric tests (Mann-Whitney U test) were used for data not conforming to a normal distribution. Continuous variables were expressed as mean ± standard deviation or median (Q1, Q3) and compared using the independent-samples t-test or the Mann-Whitney U test, as appropriate. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

Results

A total of 500 patients were included in the study. During the intraoperative period, 163 patients required administration of blood products, of whom 98 received FFP and 17 received platelet suspension. The remaining 337 patients did not receive any blood products. In the intensive care unit, 385 patients required a transfusion: 242 received FFP, 65 received platelet suspension, and 115 did not receive any transfusion.

Table 1 presents the comparison of demographic characteristics between patients who did or did not receive transfusions during the intraoperative period and the ICU follow-up. A significantly higher proportion of female patients received intraoperative transfusions (p=0.005). Hypertension was more common in the intraoperative transfusion group (p=0.004); no significant difference was found between ICU groups. There were no significant differences in the prevalence of diabetes mellitus or COPD between the transfusion and non-transfusion groups. Patients who received transfusions were significantly older in both periods (p=0.000 for both), whereas BMI values were similar across all groups.

Table 2 presents a comparison of preoperative determinants and postoperative outcomes between patients who received intraoperative transfusions and those who did not. Patients in the transfusion group had significantly shorter extubation times (p<0.001) but experienced longer hospital stays (p<0.001). Postoperative drainage volumes were higher in the transfusion group on both day 0 and day 1 (p=0.028 and p=0.023, respectively). Although preoperative EF, glomerular filtration rate (GFR), BUN, creatinine, and lactate levels were similar between the groups, preoperative hemoglobin levels were significantly lower in the transfusion group (p<0.001).

Regarding clinical outcomes, the transfusion group had significantly higher rates of revision surgery (p<0.001), postoperative agitation (p=0.029), and requirement for both cross and ICU inotropic support (p<0.001 for both). No statistically significant differences were observed between the groups with respect to ICU rhythm (defined as any rhythm other than sinus rhythm) or in-hospital mortality (p=0.388 and p=0.427, respectively). These findings suggest that intraoperative transfusion is associated with a more complex postoperative course, including higher complication rates and prolonged recovery (Table 2).

Table 3 compares preoperative determinants and postoperative outcomes between patients who did or did not receive transfusions during ICU follow-up. Patients in the transfusion group had significantly longer extubation times (p<0.001), longer hospital stays (p<0.001), and notably higher drainage volumes on postoperative days 0 and 1 (p<0.001 for both). Preoperative hemoglobin levels were significantly lower, and preoperative EF was slightly reduced, in the transfusion group (p<0.001 and p=0.048, respectively). Additionally, preoperative BUN levels were higher in transfused patients (p=0.001), whereas no significant differences were observed in lactate, GFR, or Cr levels.

Table 1. Demographic variables of the patients

	No transfusion in intraoperative period (n=337)	Transfusion in intraoperative period (n=163)	p-value	No transfusion in ICU follow-up (n=115)	Transfusion in ICU follow-up (n=243)	p-value
Gender (female/male)	123/214	81/82	**0.005***	36/79	95/148	0.153**
HT	22	131	**0.004***	79	167	0.996**
DM	156	81	0.475**	52	113	0.820**
COPD	54	33	0.243**	22	65	0.600**
Age (years)	71.53±12.80	67.04±11.36	**0.000*****	66.95±13.25	73.41±11.81	**0.000*****
BMI	27.06±4.14	27.90±4.22	0.168***	27.36±4.52	26.99±3.95	0.618***

HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, *: Fisher's exact test was applied, ICU: Intensive care unit, **: Chi-square test was applied, ***: Independent Sample t-test was applied

Postoperatively, the need for revision surgery was markedly higher among patients who received ICU transfusions (p=0.001). These patients also exhibited a higher incidence of non-sinus rhythms (p=0.024). ICU, cross inotropic support, and agitation rates did not differ significantly between the groups. Notably, in-hospital mortality was significantly higher in the ICU transfusion group (p=0.035), indicating an association between ICU transfusion and adverse clinical outcomes (Table 3).

Table 2. Comparison of preoperative determinants and postoperative outcomes between intraoperative transfusion status

	No transfusion (n=337)	Transfusion (n=163)	p-value
Extubation (hours)	12 (8,17)	17 (10.5,22)	0.000*
Discharge day	2 (1,3)	2 (2,4)	0.000*
Drainage day 0 (mL)	400 (200,600)	450 (300,700)	0.028*
Drainage day 1 (mL)	150 (50,300)	200 (100,400)	0.023*
Preoperative EF (%)	53.25±10.01	52.07±10.15	0.224*
Lactate preanesthesia (mmol/L)	1.02±0.37	0.95±0.41	0.153*
Preoperative HB (g/dL)	12.77±1.99	11.88±2.07	0.000*
Preoperative GFR (mL/min/1.73 m²)	79.13±22.11	76.85±25.88	0.382*
Preoperative BUN (mg/dL)	21.74±9.81	21.70±16.26	0.971*
Preoperative Cr (mg/dL)	1.02±0.50	1.00±0.52	0.703*
Revision	26	35	0.000**
Agitation	9	11	0.029**
Cross inotropic support	169	125	0.000**
ICU inotropic support	145	103	0.000**
ICU rhythm****	69	64	0.388***
Non-survivors	26	16	0.427***

EF: Ejection fraction, HB: Hemoglobin, GFR: Glomerular filtration rate, BUN: Blood urea nitrogen, Cr: Creatinine, ICU: Intensive care unit, *: Independent Sample t-test was applied, **: Fisher's exact test was applied, ***: Chi-square test was applied, ****: Rhythm other than sinus rhythm

Table 3. Comparison of preoperative determinants and postoperative outcomes between transfusion status in intensive care unit follow-up

	No transfusion (n=115)	Transfusion (n=243)	p-value
Extubation (hours)	7.5 (5.2,9)	10 (6,14)	0.000*
Discharge day	1 (1,1)	1.25 (1,2)	0.000*
Drainage day 0 (mL)	200 (110,300)	262.5 (200,450)	0.000*
Drainage day 1 (mL)	50 (0,100)	100 (0,200)	0.000*
Preoperative EF (%)	54.64±9.08	52.40±10.35	0.048**
Lactate preanesthesia (mmol/L)	1.068±0.428	0.981±0.333	0.059**
Preoperative HB (g/dL)	13.39±2.01	12.18±1.92	0.000**
Preoperative GFR (mL/min/1.73 m²)	80.71±22.65	76.32±23.88	0.149**
Preoperative BUN (mg/dL)	19.27±8.78	23.19±9.73	0.001**
Preoperative Cr (mg/dL)	0.98±0.38	1.03±0.54	0.149**
Revision	1	26	0.001***
Agitation	3	6	1****
Cross inotropic support	54	126	0.387***
ICU inotropic support	50	107	0.921***
ICU rhythm****	27	86	0.024**
Non-survivors	4	24	0.035**

EF: Ejection fraction, HB: Hemoglobin, GFR: Glomerular filtration rate, BUN: Blood urea nitrogen, Cr: Creatinine, ICU: Intensive care unit, *: Mann-Whitney U test was applied, *Independent Sample t-test was applied, **: Fisher's exact test was applied, ***: Chi-square test was applied, ****Rhythm other than sinus rhythm

Discussion

This study demonstrates that the timing of administration of blood products—whether during surgery or in the ICU—significantly affects postoperative outcomes in patients undergoing cardiovascular surgery. Our findings revealed that intraoperative transfusions were associated with shorter time to extubation, suggesting a potential benefit in the immediate management of surgical blood loss. However, these transfusions also correlated with longer ICU stays, increased drainage volumes, and greater need for inotropic support, indicating a more complex postoperative course. In contrast, ICU transfusions were associated with higher mortality, delayed extubation, prolonged ICU stay, and more frequent cardiac rhythm disturbances, reflecting ongoing hemodynamic instability and possibly more severe postoperative complications. These findings underscore the importance of determining not only whether to transfuse but also when to transfuse, because the timing of transfusion may serve as a surrogate marker for surgical complexity and patient risk.

Results of our study indicate that patients who received blood products intraoperatively had significantly different outcomes compared with those who did not. Specifically, extubation time was significantly shorter in patients who received intraoperative blood products than in those who did not. Additionally, the length of ICU stay was notably longer in the transfusion group than in the no-transfusion group. These results align with previous studies indicating that administration of blood products is associated with prolonged ICU stays (7,8).

Intraoperative blood product administration is beneficial for stabilizing patients during acute surgical blood loss; however, it has also been associated with prolonged extubation times and extended ICU stays, suggesting a more complicated postoperative course (9-12). In our study, patients who received intraoperative transfusions demonstrated significantly longer ICU stays than non-transfused patients, despite having shorter initial extubation times. Horvath et al. (13) similarly reported a strong association between transfusion exposure and both delayed weaning from mechanical ventilation and increased ICU length of stay. Ghiani et al. (4) also emphasized that transfusions are common in patients requiring prolonged ventilation and are strongly linked to delayed recovery trajectories. One possible explanation for these findings lies in the immunomodulatory effects of transfusions, which may exacerbate systemic inflammation, contribute to postoperative complications, and thereby prolong recovery (14). Taken together, these results highlight the complex balance between the immediate benefits of intraoperative transfusion for hemodynamic stabilization and the longer-term risks associated with extended ICU care, underlining the importance of judicious transfusion practices and targeted perioperative optimization strategies for cardiovascular surgery patients.

Transfusion-related immunomodulation (TRIM), which is known to exacerbate inflammatory responses and increase the risk of complications such as infections and delayed wound healing, has been well documented (14). Understanding these mechanisms is crucial for developing interventions that can mitigate these adverse effects and improve recovery trajectories for patients undergoing major surgeries.

It is well established that preoperative anemia is associated with increased morbidity and mortality in surgical patients; and optimizing preoperative hemoglobin levels can reduce the need for transfusions and improve postoperative outcomes (15,16). Consistent with these studies, our findings emphasize the importance of identifying and correcting anemia before surgery to minimize the risk of blood product administration and associated complications.

Patients receiving intraoperative blood products had higher postoperative drainage volumes on both the day of surgery and the first postoperative day. This finding suggests that these patients may have undergone more invasive procedures or experienced greater surgical trauma, necessitating blood transfusions. Increased drainage volumes indicate greater postoperative fluid loss and can complicate recovery by increasing the risk of anemia and hypovolemia, which may further necessitate blood transfusions (1).

A systematic review explored the significance of blood lactate kinetics in critically ill patients. It found that lactate levels are markers of tissue perfusion and stress and that monitoring these levels can provide insights into patient recovery and the effects of interventions such as blood transfusions (17).

No significant differences were found in BMI between patients who received blood products and those who did not, indicating that BMI was not a determinant of blood product administration in our cohort. Additionally, the prevalence of comorbidities such as diabetes mellitus and hypertension did not differ significantly between the

groups. These findings highlight that the need for blood products is more strongly associated with the severity of the surgical procedure and intraoperative blood loss than with patient demographics or baseline health status. This supports the notion that surgical factors, rather than patient characteristics, primarily drive the need for transfusions.

Previous studies have shown that patients with lower cardiac function are more likely to require transfusions, possibly due to their reduced ability to tolerate intraoperative and postoperative blood loss (18-20). Consistent with these findings, our study demonstrated that preoperative EF was lower in the transfusion group than in the no-transfusion group.

Preoperative Cr levels did not differ significantly between the groups, indicating similar baseline renal function. However, preoperative BUN levels were significantly higher in the transfusion group compared to the no-transfusion group. This suggests that patients with higher BUN levels, potentially indicating preoperative renal stress or dysfunction, are more likely to require blood product administration. This finding is also consistent with the previous study (10).

The need for inotropic and vasopressor support post-cross-clamping was significantly greater in the transfusion group compared with the no-transfusion group. This indicates a greater need for hemodynamic support in patients receiving blood products, likely due to increased cardiovascular instability or more complex surgical interventions. Mufti et al. (9) reported similar findings in their study.

Mufti et al. (9) also demonstrated an association between blood transfusion and an increased risk of cardiac arrhythmias. Our findings are consistent with their study; in the transfusion group, we observed a higher prevalence of ECG abnormalities.

Study Limitations

This study is retrospective in nature, which inherently limits the ability to establish causality between blood product administration and clinical outcomes. While associations can be identified, the retrospective design precludes definitive conclusions about causal relationships. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings to other institutions or patient populations with differing practices or demographics. The reliance on electronic medical records and clinical documentation may introduce reporting or data-entry biases, potentially affecting the accuracy and completeness of the dataset. Furthermore, the study does not account for potential confounders such as surgeon experience, intraoperative management strategies, or variations in transfusion thresholds, all of which could influence patient outcomes. Lastly, the lack of detailed data on transfusion-related complications, such as TRIM or transfusion-associated circulatory overload, limits the ability to evaluate specific risks associated with blood product administration.

Conclusion

This study highlights the importance of timing in blood product administration for cardiovascular surgery patients. While intraoperative transfusions may aid in managing acute surgical blood loss and allow earlier extubation, ICU transfusions appear to reflect ongoing postoperative instability and are associated with worse outcomes, including higher mortality. These findings highlight the need for a timing-conscious, individualized approach to transfusion strategies. Future multicenter prospective studies are warranted to refine transfusion protocols and improve postoperative recovery and survival.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Institutional Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval number: 2023.09.94).

Informed Consent: Given the retrospective nature of the study, the need for informed consent was waived by the IRB.

Footnotes

In this study, Artificial General Intelligence (AGI) has been utilized to enhance the readability of the paper, ensuring that the findings and discussions are accessible and comprehensible to a wider audience.

Authorship Contributions

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

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

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ORIGINAL RESEARCH

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The Effect of Prenatal Screening Tests on Maternal Anxiety Levels

Prenatal Tarama Testlerinin Maternal Kaygı Düzeyine Etkisi

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Abstract

Objective: Pregnancy is a challenging period for women, both physically and psychologically. Prenatal screening tests that provide an estimate of the risk of a fetal anomaly may affect maternal anxiety levels. The study aimed to investigate the state and trait anxiety levels of women in the first trimester before examination, after examination, and after receiving the results of the risk estimation.

Method: Pregnant women who applied to the Department of Perinatology at Cerrahpaşa Medical Faculty, İstanbul University-Cerrahpaşa for the first-trimester examination between January 2010 and December 2015 were included in the study. Twin pregnancies and women with psychiatric disorders were excluded. The Spielberger state-trait anxiety inventory was administered to 317 women to assess their anxiety levels.

Results: The level of state anxiety was lowest after the first-trimester examination. Differences in state anxiety levels between periods were statistically significant.

Conclusion: After the first-trimester examination, state anxiety levels decreased. Viewing the fetus on the screen and being informed about its anatomy have a reassuring effect on the women.

Keywords: Anxiety, first trimester, pregnancy

Öz

Amaç: Gebelik, kadınlar için hem fiziksel hem de psikolojik olarak zorlayıcı bir süreçtir. Fetal anomali için risk tahmini veren prenatal tarama testlerinin anne adaylarının kaygı düzeylerine etkisi olabilir. Çalışmada birinci trimester muayene öncesi, muayene sonrası, risk tahminini öğrendikten sonra kadınların durumluk ve sürekli kaygı düzeylerinin incelenmesi amaçlanmıştır.

Yöntem: İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi Perinatoloji Bölümü'ne Ocak 2010 ile Aralık 2015 arasında birinci trimester muayenesi için başvuran gebe kadınlar çalışmaya dahil edilmiştir. İkiz gebelikler ve psikiyatrik hastalığı olan kadınlar hariç tutulmuştur. Spielberger durumluk ve sürekli kaygı envanteri 317 kadına kaygı düzeylerini değerlendirmek için uygulanmıştır.

Bulgular: Birinci trimester muayene sonrası durumluk kaygı düzeyinin en düşük olduğu bulunmuştur. Farklı dönemler arasında durumluk kaygı düzeyleri bulguları istatistiksel olarak anlamlıydı.

Sonuç: Birinci trimester muayene sonrası durumluk kaygı düzeyleri azalmıştır. Fetüsün ekranda görülmesi ve anatomisi hakkında bilgi alınması kadınlarda rahatlatıcı bir etkiye sahiptir.

Anahtar kelimeler: Birinci trimester, gebelik, kaygı

Introduction

Pregnancy, which causes both physical and psychological burdens, is a challenging period in a woman's life. Feelings of responsibility for the baby's well-being, being faced with many uncertainties during pregnancy, and worries about childbirth and motherhood may increase anxiety levels (1,2).

Prenatal screening tests that estimate fetal anomaly risk are routinely offered to pregnant women in many countries (3,4). First trimester screening test which is composed

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of a combination of biochemical markers together with ultrasonographic markers is one of the tests used for the anomaly risk estimation (5). In the case of a high-risk of fetal anomaly, diagnostic tests are recommended to improve diagnostic accuracy (5,6). The effect of the prenatal ultrasound (USG) examination on maternal anxiety was first investigated many years ago (7).

Several tests were provided to evaluate the level of maternal anxiety. Among the tests, the Spielberger state-trait anxiety inventory measures two distinct constructs—state and trait—each of which comprises 20 questions, with responses scored on a scale from 1 to 4. The total score ranges from 20 to 80. A higher score indicates a higher level of maternal anxiety (8-11).

The aim of the study is to evaluate maternal anxiety levels before the first-trimester screening examination, after the screening, and after receiving the risk-estimation results.

Materials and Methods

Between January 2010 and December 2015, pregnant women who applied to the Department of Perinatology of Cerrahpaşa Medical Faculty, İstanbul University for the first trimester examination were included in the study. Women with twin pregnancies and those with psychiatric disorders were excluded from the study. The research was approved by Ethics Committee of the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (date: 05/04/2017, number: 131570). The study was conducted in accordance with the Declaration of Helsinki.

First-trimester examination is carried out to assess the risk of trisomies. During the examination, the fetus is shown to the expectant mother, and information is provided about the anatomy of the fetus. The anxiety levels of the women were evaluated before and after the first-trimester examination, and after being informed of the risk-estimation result. In three distinct periods, the Spielberger State-Trait Anxiety Inventory, which consists of two parts (state and trait), each containing 20 questions scored from 1 to 4, was completed by the women. The total score ranges from 20 to 80; higher scores indicate greater anxiety (8-11). While state anxiety refers to feelings at a specific moment, trait anxiety describes how the patient generally feels (10,11).

Statistical Analysis

Statistical analyses were carried out using SPSS version 20. The Kolmogorov-Smirnov test was used to evaluate the homogeneity of parametric variables. Values are presented as mean ± standard deviation, minimum, and maximum. Paired-samples t-test, chi-square test, and Wilcoxon test were used as appropriate for comparisons. $P<0.05$ was considered statistically significant.

Results

After excluding two women with psychiatric disorders and 16 twin pregnancies, 317 pregnant women who applied to the Department of Perinatology, Cerrahpaşa Medical Faculty, İstanbul University, for a first-trimester examination between January 2010 and December 2015 participated in the study.

The mean age of the participants was 29.11±4.87 years (range 18-41), and 185 (58.4%) were nulliparous. Table 1 presents the general and obstetric characteristics of the pregnant women in the study.

The state anxiety level was highest in during state 3 (after learning the risk-estimation results) and lowest in state 2 (after the first-trimester examination) ($p<0.05$).

In terms of trait anxiety, the highest score was recorded before the first-trimester examination, while the lowest score was recorded after the risk estimation (Table 2).

A subgroup analysis was performed. Women were categorized based on parity (nulliparous and non-nulliparous) and age (<35 years and ≥35 years), and comparisons were made between the groups.

No statistically significant differences in anxiety levels were observed across age groups.

Table 1. General and obstetrical characteristics of pregnant women participated in the study

Age (min-max) (mean ± SD)	(18-41) 29.11±4.87
Parity (min-max) (mean ± SD)	(0-4) 0.57±0.80
Nulliparous (n/N, %)	185/317, 58.4%
Abortus (n/N, %)	54/317, 17%
Termination (n/N, %)	11/317, 3.5%
Comorbidity (n/N, %)	26/317, 8.2%

SD: Standard deviation

No statistically significant difference was observed in relation to parity; however, nulliparous women showed a higher level of state anxiety (Tables 3, 4).

Discussion

Pregnancy causes physical and emotional changes in expectant mothers. Taking responsibility for someone other than the mother's own life, fear of childbirth, uncertainty about motherhood and the future, and concern for the baby's well-being are responsible for these changes (1,2).

Over time, prenatal screening tests, now part of routine prenatal care in many countries, have been developed to estimate the risk of fetal anomalies, and these tests may affect the psychological state of expectant mothers (3,4).

In our study, the state and trait anxiety levels of pregnant women were evaluated at three time points: before the first-trimester screening examination, after the examination, and after learning the risk estimation result. It was found that pregnant women had the lowest level of state anxiety after the first-trimester examination. This finding is similar to Da Silva et al.'s (9) study in which 146 pregnant women and 150 non-pregnant women were investigated in terms of their anxiety levels. Da Silva et al. (9) found that anxiety levels in pregnant women improved after the USG examination, and that advanced maternal age had a protective effect against stress. However, in terms of maternal age, we did not find a statistically significant difference in anxiety levels (9). USG examination helps to visualize the fetus and to perceive it concretely. For this reason, it generates reassurance about fetal well-being and attachment to the fetus (12).

In another study, Kowalcek et al. (13) investigated the state and trait anxiety levels of 332 pregnant women before and after examinations with negative or positive prenatal findings. Prenatal examinations revealed positive findings in 37 patients. While trait anxiety levels before prenatal examination did not differ significantly between the group with a positive prenatal test result and the group with a

Table 2. Comparison of the state trait anxiety levels according to evaluation periods

	Mean ± SD	Mean ± SD	p
Trait 1 vs. Trait 2	48.58±5.73	48.28±5.72	0.206
Trait 2 vs. Trait 3	48.28±5.72	47.90±5.56	0.153
Trait 3 vs. Trait 1	47.90±5.56	48.58±5.73	0.019*
State 1 vs. State 2	42.57±6.8	41.93±6.15	0.029*
State 2 vs. State 3	41.93±6.15	43.40±6.41	<0.001*
State 3 vs. State 1	43.40±6.41	42.57±6.8	0.028*

*: P<0.05, SD: Standard deviation

Table 3. Comparison of the state and trait anxiety levels according to parity

	Nulliparous (185)	Non-nulliparous (132)	p
Trait 1	48.70±6.03	48.40±5.29	0.632
Trait 2	48.31±5.83	48.25±5.59	0.992
Trait 3	48.05±6.09	47.69±4.75	0.553
State 1	43.13±6.46	41.78±7.24	0.089
State 2	42.46±6.18	41.19±6.04	0.069
State 3	43.94±6.16	42.64±6.71	0.079

Table 4. Comparison of the state and trait anxiety levels of the pregnant women according to age

	Under the age of 35 (264)	Age of 35 years and above (53)	p
Trait 1	48.57±5.81	48.71±5.57	0.865
Trait 2	48.36±5.87	48.00±5.21	0.647
Trait 3	47.83±5.72	48.54±4.68	0.335
State 1	42.64±7.02	41.98±5.79	0.468
State 2	42.08±6.29	40.98±5.46	0.196
State 3	43.48±6.62	43.00±5.61	0.578

negative result, state anxiety levels of the pregnant women, even before the prenatal test, differed significantly. There was no statistically significant difference in the state anxiety levels of women with positive findings before and after the prenatal test. State anxiety levels were significantly reduced after a negative result when pre- and post-prenatal-test measurements were compared (13).Chueh et al.'s (11) study compared maternal anxiety levels, measured with the STAI before screening, 1 week after screening, at the 22nd week of gestation, and at the 6th week postpartum, between two groups: one with increased nuchal translucency thickness and positive screening results (n=172) and the other with normal nuchal translucency thickness and negative screening results (n=180). Women who screened positive had higher state anxiety one week after screening, but no differences in state or trait anxiety levels were detected between the groups at other time points. Therefore, increased anxiety in women with positive screening test results does not persist. Consequently, clinicians' concerns about maternal anxiety should not constitute a barrier to screening tests (11).

High-risk and low-risk patients at 18-22 weeks' gestation were included in Api et al.'s (14) study. The high-risk group consisted of patients over the age of 35, those with abnormal maternal serum screening and suspicious fetal anatomy. Patients without these risk factors who were referred only for exclusion of anomalies constituted the low-risk group. High- and low-risk pregnant women underwent a USG examination, and their anxiety levels were assessed. No significant differences in trait anxiety levels were found between the two groups, both before and after USG examination. However, state anxiety scores recorded before the genetic sonogram were significantly higher in both groups than those observed after the genetic sonogram (14). This finding is consistent with the results of our study, as the women's state anxiety levels were lower after the first-trimester examination than before the USG examination.

Simó et al. (2) compared the anxiety levels of pregnant women before and after USG scans across the three trimesters. Consistent with previous studies, USG reduced state anxiety levels in each trimester (2). In our study, state and trait anxiety levels were analyzed in the first trimester, and state anxiety decreased after the first-trimester examination.

Study Limitations

A strength of the study is that it was conducted in the perinatology clinic, where physicians provided information to patients. On the other hand, the fact that not all pregnant women were evaluated by a single physician constitutes a limitation of the study.

Conclusion

To date, numerous studies have shown that ultrasound examination provides reassurance to expectant mothers. Viewing the fetus on the screen and receiving information about fetal anatomical structures help reduce anxiety in pregnant women.

Ethics

Ethics Committee Approval: The research is approved by the Ethics Committee of the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (date: 05/04/2017, number: 131570).

Informed Consent: All participants provided informed consent.

Footnotes

Authorship Contributions

Concept: I.S., C.Ş., Design: I.S., C.Ş., Data Collection or Processing: I.S., C.Ş., Analysis or Interpretation: I.S., C.Ş., Literature Search: I.S., C.Ş., Writing: I.S., C.Ş.

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ORIGINAL RESEARCH

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Comparison of the Effects of Tocilizumab and High-dose Steroid Treatment on Treatment Response and Mortality in Hospitalized COVID-19 Pneumonia Patients with Cytokine Storm

Sitokin Fırtınası Gelişen Hastanede Yatan COVID-19 Pnömonisi Hastalarında Tosilizumab ile Yüksek Doz Steroid Tedavisinin Tedavi Yanıtı ve Mortaliteye Etkilerinin Karşılaştırılması

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Abstract

Objective: Cytokine storm associated with coronavirus disease-2019 (COVID-19) is a major contributor to COVID-19-related mortality. This study aimed to evaluate and compare the clinical and laboratory effects, as well as mortality outcomes, of high-dose steroid therapy versus tocilizumab treatment in patients experiencing this hyperinflammatory state.

Method: This retrospective, single-center cohort study analyzed the records of 200 patients who were hospitalized at University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital with COVID-19 pneumonia and diagnosed with a cytokine storm between February 1 and September 30, 2021. Eligibility criteria required that patients have been treated exclusively with tocilizumab or high-

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) ile ilişkili sitokin fırtınası sendromu, hastalıkla ilişkili mortalitenin önemli bir nedenidir. Bu çalışmada; sitokin fırtınası gelişen hastalarda; yüksek doz steroidler ile tosilizumabın klinik ve laboratuvar sonuçlar ile mortalite üzerindeki etkilerini karşılaştırmayı amaçladık.

Yöntem: Bu retrospektif, tek merkezli kohort çalışma 1 Şubat 2021 ile 30 Eylül 2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, Gazi Yaşargil Eğitim ve Araştırma Hastanesi'nde COVID-19 pnömonisi nedeniyle hastaneye yatırılan ve sitokin fırtınası tanısı konulan 200 hastanın verileri incelenerek gerçekleştirilmiştir. Çalışmaya dahil edilen hastaların sitokin fırtınası için yalnızca tosilizumab veya yalnızca yüksek doz metilprednizolon almış olması şartı aranmıştır. Her tedavi

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Abstract

dose methylprednisolone for cytokine storm management. Each treatment group included 100 patients. Demographic characteristics, existing chronic conditions, symptom duration, and clinical and laboratory parameters at admission (prior to treatment) and 72 hours after treatment were assessed. Mortality outcomes were also analyzed using appropriate statistical methods.

Results: Of the 200 patients evaluated, 116 (58%) were male and 84 (42%) were female, with a mean age of 63.3±13.9 years. Comorbidities were present in 63.5% of patients and were more common in the steroid group (p=0.005); hypertension was the most prevalent comorbidity (49.5%). The mean interval from symptom onset to treatment was 9.8±2.9 days and was significantly longer in the tocilizumab group (p=0.001). Both treatments showed similar effects on C-reactive protein, D-dimer, and temperature. Steroids were more effective at improving oxygen saturation and reducing ferritin levels, while tocilizumab resulted in a greater increase in lymphocyte count (p<0.001). Mortality rates did not differ significantly (p=0.767).

Conclusion: Based on our comparison of immunomodulatory therapies for cytokine storm in the context of COVID-19, high-dose steroid treatment appears more favorable than tocilizumab when comparable efficacy is expected, primarily because of its greater cost-effectiveness and wider accessibility.

Keywords: COVID-19, cytokine storm, pulse steroid, tocilizumab

Öz

grubunda toplam 100 hasta analiz edilmiştir. Demografik veriler, kronik komorbiditeler, semptomların süresi ve başvuru sırasındaki, ilaç uygulamasından önceki ve ilaç uygulamasından 72 saat sonraki klinik ve laboratuvar değerleri, istatistiksel analiz yöntemleri kullanılarak mortalite sonuçları ile birlikte değerlendirilmiştir.

Bulgular: Çalışmaya dahil edilen 200 hastanın 116'sı (%58) erkek, 84'ü (%42) kadındı ve ortalama yaşları 63,3±13,9 yıldı. Komorbid hastalık oranı %63,5 olup, steroid tedavisi alan grupta bu oran anlamlı şekilde daha yüksekti (p=0,005). En sık görülen eşlik eden hastalık hipertansiyondu (%49,5). Semptomların başlamasından tedaviye kadar geçen süre ortalama 9,8±2,9 gün olup, tosilizumab grubunda bu süre belirgin şekilde daha uzundu (p=0,001). Her iki grup da C-reaktif protein, D-dimer ve vücut sıcaklığı parametrelerinde benzer iyileşme gösterdi. Yüksek doz metilprednizolon tedavisi oksijen satürasyonunu artırmada ve ferritin düzeyini düşürmede daha etkili olurken, tosilizumab tedavisi lenfosit sayısını artırmada daha başarılı bulundu (p<0,001). Mortalite açısından ise gruplar arasında anlamlı fark izlenmedi (p=0,767).

Sonuç: COVID-19 ile ilişkili sitokin fırtınası için immünomodülatör tedavileri karşılaştıran çalışmamız, maliyet etkin ve kolay erişilebilir olan yüksek doz steroid tedavisinin tosilizumaba tercih edilebileceğini düşündürmektedir.

Anahtar kelimeler: COVID-19, sitokin fırtınası, tosilizumab, yüksek doz steroid

Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), was first recognized in late 2019 and has since evolved into a global pandemic. By 2023, hundreds of millions of confirmed cases and millions of deaths had been reported worldwide, highlighting its profound impact on public health. Despite a declining incidence in some regions, the disease continues to exhibit a variable course across populations and remains a major concern because of its high transmissibility, including transmission from asymptomatic individuals and via multiple routes. These features have posed substantial challenges to prevention and management strategies and have underscored the importance of timely diagnosis and effective treatment approaches (1).

COVID-19 pneumonia typically progresses through two clinically distinct stages. The initial phase is dominated by viral replication, leading to direct tissue injury. In the subsequent phase, immune activation occurs as infected host cells trigger the recruitment of T lymphocytes, monocytes, and neutrophils, resulting in heightened cytokine release. In severe COVID-19 cases, this immune overactivation is mediated by cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-1β, IL-6, IL-8, and IL-12. This exaggerated inflammatory process, termed a "cytokine storm", is characterized particularly by marked elevations of IL-6 and TNF-α in the systemic circulation (2).

As the clinical severity of COVID-19 increases, acute lung injury—which primarily affects the lungs, the principal target of the virus—can advance to acute respiratory distress syndrome (ARDS). The pathogenesis of ARDS is closely linked to cytokine storm activity, and ARDS remains the predominant cause of mortality in patients with COVID-19 (3). Autopsy studies from China have revealed that individuals who died of severe COVID-19 had markedly elevated levels of IL-1, IL-6, and TNF-α in tissue specimens (4).

Multiple studies involving patients with COVID-19 have repeatedly demonstrated notably elevated IL-6 levels (5,6). Prompt identification of cytokine storm and timely intervention have been linked to improved clinical outcomes in patients with COVID-19 (7).

While antiviral and monoclonal antibody-based treatments mainly act during the initial phase of the disease by suppressing viral replication, immunomodulatory

agents—such as glucocorticoids and tocilizumab—are used to control the cytokine-driven hyperinflammatory state. Glucocorticoids exert their immunomodulatory effects by downregulating the expression of inflammation-related genes, leading to reduced levels of cytokines such as IL-6, IL-1β, IL-17, IL-12, GM-CSF, and TNF. Additionally, they inhibit enzymes like cyclooxygenase-2, suppress prostaglandin biosynthesis, and decrease inducible nitric oxide synthase activity (8,9).

Management of cytokine storm aims to suppress pro-inflammatory mediators—especially IL-6—while promoting anti-inflammatory responses, including the activity of cytokines like IL-10 (10).

As clinical research on COVID-19 expanded and scientific findings increasingly demonstrated the benefits of glucocorticoid therapy, the World Health Organization endorsed their use in severe cases—especially in patients with ARDS, sepsis, or septic shock, and those needing mechanical ventilation or vasopressor support (11).

The RECOVERY Collaborative Group (12) trial, which enrolled more than 6.000 participants, demonstrated that administration of 6 mg of dexamethasone daily for 10 days provided clinical benefit to patients with severe COVID-19. The results demonstrated that this therapy led to notable clinical improvement in critically ill patients when compared with the control group. Nonetheless, the same study emphasized that glucocorticoids did not provide significant benefit for individuals who did not need respiratory support (12).

Tocilizumab, an IL-6 receptor–targeting monoclonal antibody, is widely employed in the treatment of rheumatoid arthritis and various rheumatic disorders. Given the pivotal role of IL-6 in the development of cytokine storm and the association between elevated IL-6 levels and increased mortality in severe COVID-19 cases, tocilizumab was considered a promising therapeutic option for such patients. Consequently, the US Food and Drug Administration approved its use in hospitalized patients with COVID-19 pneumonia complicated by cytokine storm (13).

Moreover, a retrospective analysis of approximately 1.400 hospitalized patients with COVID-19 pneumonia revealed that tocilizumab therapy led to a notable reduction in both mechanical ventilation requirements and mortality rates (14).

This study aimed to compare the impact of high-dose steroid treatment—recognized for its low cost and wide availability—with that of tocilizumab, which is comparatively more expensive and less accessible, in hospitalized patients with severe COVID-19 pneumonia complicated by cytokine storm. The evaluation focused on clinical progression, laboratory markers, oxygenation status, and mortality outcomes.

Materials and Methods

Design of the Study and Selection of Participants

The study retrospectively analyzed patients diagnosed with severe or critical COVID-19 pneumonia who were admitted to either the general wards or the intensive care unit (ICU) at University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital. The study period spanned from February to September 2021, focusing on cases complicated by cytokine storm. Only patients who underwent treatment with either tocilizumab or high-dose methylprednisolone—without any additional immunomodulatory drugs—were included. The study protocol was approved by the Institutional Review Board of University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (approval no: 154; date: August 10, 2022), and, given the retrospective design, the requirement for informed consent was waived.

Patient information was obtained retrospectively via the hospital's information management system. Patient characteristics, including age, sex, and chronic conditions present before hospitalization, were systematically recorded. The clinical progression of each patient was assessed from medical records, including the duration of symptoms before hospital admission, the time from symptom onset to the initiation of either tocilizumab or high-dose steroid treatment, the length of oxygen support prior to treatment, the type of hospital unit where the patient received care (ward or ICU), and the number of hospitalization days in each setting. Clinical and laboratory data collected included oxygen saturation, body temperature, C-reactive protein (CRP), lymphocyte count, D-dimer, ferritin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), measured at admission, before treatment, and 72 hours after treatment. The primary outcome of the study was all-cause in-hospital mortality, while secondary outcomes were clinical and laboratory changes assessed 72 hours after initiation of immunomodulatory therapy.

A retrospective analysis of laboratory data from hospitalized COVID-19 patients in the inpatient ward and the ICU

showed that daily evaluations included CRP, complete blood count, D-dimer, ferritin, ALT, AST, bilirubin, and arterial blood gas measurements. In addition, daily chest X-rays were performed. The diagnosis of cytokine storm was based on trends in these laboratory parameters over time, deterioration on chest imaging, and clinical decline.

The criteria used to define cytokine storm included the following:

• Persistent high-grade fever

• Markedly elevated and progressively rising CRP levels (at least 10 times the upper normal limit)

• Continuously increasing ferritin concentrations (exceeding 400 µg/L)

• Rising D-dimer values over time

• Onset of lymphopenia, neutrophilia, and thrombocytopenia

• Abnormal liver function indicators, including ALT, AST, and LDH.

Due to variability in individual patient presentations and fluctuations in laboratory results relative to standard reference ranges, the core diagnostic criteria in this study were defined as: daily increases in ferritin, D-dimer, CRP, ALT, and AST levels; lymphocyte depletion; persistent fever; decline in oxygen saturation; and clinical and radiological progression to ARDS. This diagnostic approach aligns with the COVID-19 guideline issued by the Ministry of Health of the Republic of Turkey, which specifically addresses anticytokine and anti-inflammatory treatment strategies and coagulopathy management.

The reference ranges for the laboratory parameters examined in this study were based on the hospital's laboratory standards:

• Lymphocyte count: 1000-4800/µL

• CRP: <5 mg/L

• Ferritin: 30-400 µg/L

• Reference range for D-dimer: 0-243 ng/L

• ALT normal range: 0-41 U/L

• AST normal range: 0-40 U/L.

Treatment Protocols

Patients were categorized into two treatment groups:

High-dose steroid group: Patients received intravenous methylprednisolone at a daily dose of 250 mg for three days, after which the treatment was tapered stepwise and definitively discontinued on day 25 (Figure 1).

Tocilizumab group: Patients received a fixed 400-mg dose of tocilizumab administered intravenously over 1 hour, followed by a second identical dose 12 hours later, for a total dose of 800 mg.

In this study, the terms pulse steroid therapy and high-dose steroid therapy were used interchangeably.

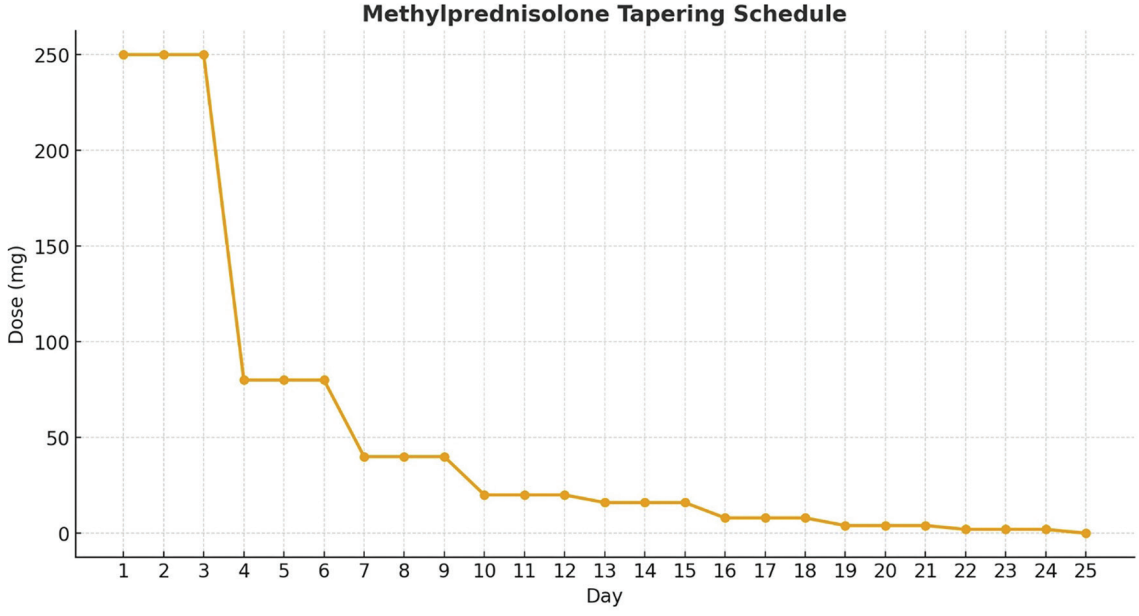

Figure 1. Methylprednisolone dose tapering schedule

Inclusion Criteria

• Individuals who were at least 18 years old at the time of diagnosis

• COVID-19 pneumonia cases complicated by cytokine storm, admitted either to the general inpatient service or the intensive care unit

• Patients identified as having severe or critical COVID-19, based on the classification criteria established by the National Institutes of Health

• Patients who received either tocilizumab or high-dose methylprednisolone for treatment.

Exclusion Criteria

• Patients younger than 18 years of age at the time of diagnosis

• Individuals identified as pregnant during hospital admission or the course of hospitalization

• Subjects with pre-existing diagnoses of solid organ malignancies or hematologic cancers

• Patients who refused treatment and did not provide informed consent for tocilizumab or high-dose methylprednisolone therapy.

Statistical Analysis

Statistical analysis was performed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as numbers (n) and percentages (%). Categorical comparisons were made using the chi-square test or Fisher's exact test where appropriate. The normality of distribution for continuous variables was assessed through the Kolmogorov-Smirnov test. For variables with a normal distribution, comparisons were made using the Student's t-test, whereas the Mann-Whitney U test was used for non-normally distributed variables. A p-value below 0.05 was considered statistically significant.

Results

Of the 200 patients evaluated in this study, 116 (58%) were male and 84 (42%) were female. In the tocilizumab group, 69 patients (69%) were male and 31 patients (31%) were female, whereas in the high-dose steroid group, 47 patients (47%) were male and 53 patients (53%) were female. The average age of all patients was 63.25±13.9 years. The mean age was 61.8±12.8 years in the tocilizumab group and 64.6±14.7 years in the steroid group.

Upon initial hospital admission, 124 patients (62%) were placed in the inpatient ward, while 76 patients (38%) were admitted directly to the ICU. Some patients who were first monitored in the inpatient ward required transfer to the ICU due to clinical worsening. Conversely, patients who completed their treatment in the ICU and showed signs of recovery were later managed in the inpatient ward until hospital discharge. A comprehensive overview of the patients' demographic data is provided in Table 1.

Compared with the tocilizumab group, the high-dose steroid group had a significantly shorter interval between symptom onset and treatment initiation (8.5±2.4 days vs. 11.1±2.9 days; p<0.05). Likewise, patients in the high-dose steroid group received oxygen therapy for a significantly shorter period prior to treatment initiation than those in the tocilizumab group (2.3±1.5 days vs. 3.5±2.8 days; p=0.006).

Table 1. Demographic details and admission-time clinical features of the cohort

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
Age (years)	63.25±13.9	61.8±12.8	64.6±14.7	0.09
Duration of symptoms prior to treatment initiation (days)	9.8±2.9	11.1±2.9	8.5±2.4	<0.001
Duration of oxygen support before treatment initiation (days)	2.9±2.3	3.5±2.8	2.3±1.5	0.006
Duration of symptoms before hospital admission (days)	6.4±2.4	6.6±2.6	6.1±2.2	0.156
Hospitalization unit (n, %)				0.08
- General ward	124 (62%)	56 (56%)	68 (68%)	
- Intensive care unit	76 (38%)	44 (44%)	32 (32%)	
Gender (n, %)				0.002
- Female	84 (42%)	31 (31%)	53 (53%)	
- Male	116 (58%)	69 (69%)	47 (47%)	

However, no statistically significant differences were found between the groups regarding age, duration of symptoms prior to hospital admission, or the initial site of hospitalization (inpatient ward versus ICU) (p>0.05) (Table 1).

When comorbidity status was assessed, 127 patients (63.5%) were found to have at least one chronic condition, whereas 73 patients (36.5%) had none. Comparison of the treatment groups showed that comorbidities occurred more frequently in the high-dose steroid group than in the tocilizumab group (p=0.005). Detailed information on the distribution of comorbidities for each group is provided in Table 2.

A comparative overview of the patients' clinical and laboratory findings at the time of admission for both groups is shown in Table 3.

Table 4 provides a comparative overview of clinical and laboratory measurements for the two treatment groups prior to commencement of therapy.

Table 5 compares the clinical and laboratory data of patients in both groups, measured at the 72nd hour after treatment administration.

Comparison of lengths of stay in inpatient and intensive care units revealed no statistically significant difference between the tocilizumab and pulse steroid groups (p>0.05).

Evaluation of patient groups regarding oxygen delivery methods revealed that nasal oxygen was more commonly used in the tocilizumab group, whereas the high-dose steroid group more frequently required oxygen via a reservoir mask (p<0.001) (Table 6).

Table 2. Evaluation of patients based on comorbidities

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
Comorbidity (n, %)	127 (63.5%)	54 (54%)	73 (73%)	0.005
- Absent	73 (36.5%)	46 (46%)	27 (27%)	
Hypertension (n, %)	99 (49.5%)	34 (34%)	65 (65%)	<0.001
- Absent	101 (50.5%)	66 (66%)	35 (35%)	
Chronic obstructive pulmonary disease (n, %)	15 (7.5%)	6 (6%)	9 (9%)	0.421
- Absent	185 (92.5%)	94 (94%)	91 (91%)	
Coronary artery disease (n, %)	42 (21%)	17 (17%)	25 (25%)	0.165
- Absent	158 (79%)	83 (83%)	75 (75%)	
Asthma (n, %)	9 (4.5%)	4 (4%)	5 (5%)	0.733
- Absent	191 (95.5%)	96 (96%)	95 (95%)	
Diabetes mellitus (n, %)	63 (31.5%)	24 (24%)	39 (39%)	0.022
- Absent	137 (68.5%)	76 (76%)	61 (61%)	
Chronic kidney disease (n, %)	18 (9%)	5 (5%)	13 (13%)	0.048
- Absent	182 (91%)	95 (95%)	87 (87%)	
Cerebrovascular disease (n, %)	2 (1%)	0	2 (2%)	0.155
- Absent	198 (99%)	100	98 (98%)	
Congestive heart failure (n, %)	12 (6%)	1 (1%)	11 (11%)	0.003
- Absent	188 (94%)	99 (99%)	89 (89%)	

Table 3. Initial clinical signs and laboratory values at hospital entry

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
SpO- (%)	88.6±6.45	87±7.9	90.2±3.9	0.002
Body temperature (°C)	36.5±0.86	36.9±1	36.1±0.3	<0.001
Lymphocyte count (/mm-)	988.5±604.9	1049.9±661.4	927.1±538.8	0.028
C-reactive protein (mg/L)	121.5±64.7	113.4±65.4	129.7±63.2	0.026
D-dimer (ng/mL)	1465.9±313.2	1113.7±3104.4	1818±3137	<0.001
Ferritin (ng/mL)	914.9±654.8	954.6±744	875.3±552.3	0.811
Alanine aminotransferase (U/L)	41.4±33.1	44.1±37.4	38.7±28.1	0.587
Aspartate aminotransferase (U/L)	54.3±33.5	58.8±90.1	49.8±32	0.973

As presented in Table 7, the statistical analysis showed no significant difference in mortality between the tocilizumab and pulse-steroid groups (p>0.05).

Discussion

A review of existing literature on immunomodulatory treatments in COVID-19 patients reveals that, although numerous studies address this topic, direct comparisons between high-dose steroid therapy and tocilizumab remain limited.

For instance, Kumar et al. (15) conducted a study similar in design to ours, involving 336 patients with severe COVID-19 in which they compared tocilizumab with pulse-steroid treatment. In their cohort, 72.9% were male and 27.1% were female, with a reported mean age of 57.4±13.6 years. Likewise, Mikulska et al. (16) evaluated 215 patients with COVID-19 pneumonia to compare the therapeutic efficacy of tocilizumab and steroids, reporting that 67.4% of participants were male and that the mean age was 67.9 years.

Table 4. Clinical and laboratory characteristics of patients before drug administration

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
SpO_2 (%)	86.2±6.8	82.9±7.2	89.4±4.5	<0.001
Body temperature (°C)	36.7±0.86	37.9±3.76	36.9±3.37	<0.001
Lymphocyte count (/mm³)	785.5±385.3	859.6±346.8	711.4±408.7	<0.001
C-reactive protein (mg/L)	149.8±66.6	149.4±73.7	150.1±59.1	0.464
D-dimer (ng/mL)	2949.9±475.5	2928.9±5269.4	2971±4205	0.114
Ferritin (ng/mL)	1249.4±731.3	1384.7±793.3	1114.06±639.3	0.005
Alanine aminotransferase (U/L)	47.8±38.6	51.9±45.7	43.6±29.4	0.397
Aspartate aminotransferase (U/L)	49.3±36.7	52.6±43.2	46.01±28.7	0.439

Table 5. Clinical parameters and lab results 72 hours post-treatment initiation

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
SpO_2 (%)	88.8±6.8	86.08±7.27	91.3±5.4	<0.001
Body temperature (°C)	36.1±0.35	36.1±0.32	36.09±0.38	0.188
Lymphocyte count (/mm³)	957.8±575.03	1136.1±584	786.9±513.03	<0.001
C-reactive protein (mg/L)	40.6±25.5	35.5±43.8	45.5±46.8	0.111
D-dimer (ng/mL)	3869.9±678.07	4694.3±8327.8	3079.5±4771	0.024
Ferritin (ng/mL)	1040.5±624.1	1210.1±661.6	877.8±541.05	<0.001
Alanine aminotransferase (U/L)	72.8±35.5	75.03±116	70.8±202	0.052
Aspartate aminotransferase (U/L)	71.5±33.2	77.7±150.5	65.6±292.1	<0.001

Table 6. Types of oxygen support administered to patients

Oxygen support type	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
Nasal oxygen	75 (37.5%)	51 (51%)	24 (24%)	<0.001
Reservoir mask	64 (32%)	15 (15%)	49 (49%)	
High-flow nasal cannula	6 (3%)	4 (4%)	2 (2%)	
Continuous positive airway pressure	41 (20.5%)	22 (22%)	19 (19%)	
Mechanical ventilation	14 (7%)	8 (8%)	6 (6%)	

Table 7. Comparison of mortality between groups

Mortality outcome	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
Present	70 (35%)	36 (36%)	34 (34%)	0.767
Absent	130 (65%)	64 (64%)	66 (66%)	

In our analysis, the average patient age was 63.25±13.9 years, with a gender distribution of 58% male and 42% female. Mikulska et al. (16) reported no statistically significant difference in age or sex distribution between treatment groups. In contrast, Kumar et al. (15) found a notably higher proportion of male patients in the tocilizumab arm (p=0.016), while age distribution remained statistically comparable between groups (p>0.05). A similar pattern was observed in our study: There was a significantly greater male predominance in the tocilizumab group (p=0.002), although no significant difference was detected with regard to age (p>0.05).

The findings of these studies indicate that both middle and older age groups are key risk factors linked to the progression of severe COVID-19, the onset of cytokine storm, and the need for immunomodulatory treatment. In Kumar et al.'s (15) research, diabetes mellitus emerged as the most prevalent comorbidity, while Mikulska et al. (16) reported hypertension as the leading chronic condition. Furthermore, in the latter study, 78.1% of patients were found to have at least one underlying disease (15,16).

In our cohort, 63.5% of the patients had at least one chronic condition, with hypertension being the most prevalent, affecting 49.5% of cases. When the comorbidity distribution was analyzed across groups, a significantly higher rate of chronic illnesses was observed in the pulse steroid group (p=0.005). Comparable studies have also identified chronic disease as a contributing factor to severe COVID-19 progression and an increased need for immunomodulatory intervention. Nevertheless, a meta-analysis indicated that the presence of comorbidities did not affect the therapeutic efficacy of either tocilizumab or steroids in managing cytokine storm (17).

In the study conducted by Kumar et al. (15), the duration of symptoms before hospital admission 5.53±4.69 days in the pulse steroid group and 5.04±2.55 days in the tocilizumab group, with no statistically significant difference between groups (p>0.05). Likewise, Mikulska et al. (16) reported the duration as 7.2±4.7 days for the pulse steroid group and 7.7±3.5 days for the tocilizumab group, with no statistically significant difference (p>0.05).

In our study, the mean duration of symptoms prior to hospital admission was 6.6±2.6 days in the pulse-steroid group and 6.1±2.2 days in the tocilizumab group, which aligns with the averages reported in previous studies. In line with the existing literature, the difference between the two groups was not statistically significant (p>0.05).

In our cohort, the average interval from symptom onset to the initiation of therapy was 9.8±2.9 days overall, with 11.1±2.9 days observed in the tocilizumab group and 8.5±2.4 days in the pulse steroid group. This observation is consistent with the literature, which notes that hyperinflammatory complications—such as admission to intensive care, cytokine storm, ARDS, the need for mechanical ventilation, and multi-organ dysfunction—typically emerge during the second week of illness (18).

In our study, oxygen saturation, body temperature, CRP, lymphocyte count, ferritin, D-dimer, ALT, and AST levels were evaluated at three time points: At hospital admission, immediately before treatment initiation, and 72 hours after drug administration. Comparison of measurements taken just prior to treatment with those at initial admission revealed an increase in CRP, D-dimer, and ferritin levels, along with elevated body temperature and reduced oxygen saturation and lymphocyte counts, findings that are consistent with the typical course of a cytokine storm.

Comparison of the two treatments' effects on clinical and laboratory markers at 72 hours post-administration showed that body temperature tended to decrease more in the tocilizumab group than in the pulse-steroid group, although the difference was not statistically significant. In contrast, the tocilizumab group showed a significantly greater increase in lymphocyte count (p<0.001). This finding aligns with the established immunosuppressive action of steroids, which are known to lower lymphocyte levels. Moreover, considering that IL-6 functions as an endogenous pyrogen, its inhibition is expected to reduce fever more effectively.

In addition, both treatment groups exhibited comparable reductions in CRP levels. However, ferritin—a key acute-phase reactant—demonstrated a more substantial decline in patients receiving pulse steroid therapy. Since D-dimer typically shows a slower downward trend, its levels continued to decrease in both groups even 72 hours after treatment.

It is widely recognized that mortality in COVID-19 correlates directly with the severity of ARDS. In patients with severe or critical disease, reported mortality rates vary substantially—from 12% up to 78%—depending on healthcare infrastructure and the circulating SARS-CoV-2 variant. Mortality rates generally range from 25% to 50%. Outcomes are often poorer in regions with limited medical resources, whereas lower mortality rates have been documented in areas with robust healthcare systems (18).

A wide range of pharmacological agents and therapeutic strategies has been investigated to reduce mortality among patients with COVID-19. In this context, numerous studies have assessed the impact of both tocilizumab and high-dose corticosteroids on mortality, particularly compared with standard treatment protocols.

A randomized controlled trial involving 66 non-intubated patients with severe COVID-19 compared high-dose methylprednisolone to standard treatment. The study reported a mortality rate of 5.9% in the methylprednisolone group versus 42.9% in the standard care group, indicating a statistically significant survival benefit in those receiving steroid therapy (19). Conversely, some other investigations have found no meaningful difference in mortality outcomes between corticosteroid-treated patients and those managed with standard care protocols (20).

Regarding the use of tocilizumab in COVID-19 treatment, Klopfenstein et al. (21) reported a mortality rate of 25% among patients receiving tocilizumab, significantly lower than the 48% observed in the standard care group (p=0.006). Furthermore, the study reported that patients treated with tocilizumab had lower rates of admission to intensive care units (21).

In comparative studies assessing the effectiveness of tocilizumab versus pulse steroid therapy, Kumar et al. (15) reported mortality rates of 36% in the tocilizumab group and 34% in the high-dose steroid group. The difference between the two treatments was not statistically significant (p>0.05) (15), indicating similar efficacy profiles.

Likewise, Mikulska et al. (16) reported mortality rates of 20.7% in the tocilizumab group, 20% in the pulse steroid group, and 12.5% in the group receiving both therapies. Their multivariate analysis, which accounted for key risk factors, showed no statistically significant differences in mortality outcomes among the three groups. The relatively lower mortality observed in this study compared to other reports may be attributed to the early initiation of immunomodulatory therapy—within three days of hospitalization—and the inclusion of only non-intubated patients (16).

In a study conducted in Turkey, Aslan et al. (22) divided ICU patients into three treatment arms: pulse steroid, tocilizumab, and combination therapy. Although no statistically significant differences in mortality was detected among the groups, the reported mortality rates remained high: 55% in the pulse steroids group, 60% in the tocilizumab group, and 50% in the combined treatment group (22).

Kılıç Erol et al. (23) evaluated 208 critically ill COVID-19 patients admitted to the ICU, of whom 114 received corticosteroids and 94 did not. In their analysis, overall mortality was higher among patients treated with steroids; however, after adjusting for independent predictors such as age, SOFA score, renal replacement therapy, and inotropic support, corticosteroid use was not identified as an independent determinant of mortality (23).

In contrast, our study of 200 patients with cytokine storm demonstrated that high-dose methylprednisolone and tocilizumab provided comparable efficacy, with no significant difference in mortality outcomes between the two treatment groups. These findings collectively suggest that, although crude analyses associated corticosteroid use with worse outcomes in severe COVID-19, after adjustment for confounding factors, corticosteroids did not independently increase mortality and may have represented a viable alternative to IL-6 blockade in the setting of cytokine storm.

In our study population, which consisted of patients with cytokine storm treated with either tocilizumab or pulse steroid therapy, the overall mortality rate was 35%. Specifically, mortality was 36% in the tocilizumab group and 34% in the pulse steroid group, and statistical analysis revealed no significant difference in mortality between the two treatment arms (p>0.05). These results were consistent with the findings reported by Kumar et al. (15).

Study Limitations

It is important to recognize certain limitations of this research. Most notably, the retrospective design, single-center cohort methodology, and limited sample size constrain the extent to which these results can be generalized. Another limitation was the lack of detailed documentation regarding additional treatments administered to patients beyond immunomodulatory agents.

Furthermore, the absence of measurements of cytokine levels, particularly IL-6, in laboratory evaluations posed a limitation. An additional limitation was the exclusion of patients who received combination therapy with tocilizumab and high-dose steroids for cytokine storm, which precluded direct comparison between monotherapy and combination therapy.

Furthermore, patients with severe and critical COVID-19 experiencing a cytokine storm who received only standard care were not included as a control group, meaning that the treatment groups were not compared with a

standard-care group, which represents an additional limitation of the study.

Finally, potential confounders such as circulating viral variants, vaccination rates, and temporal changes in clinical management during the study period (February-September 2021) could have influenced the outcomes and should be considered when interpreting the results.

Conclusion

Early identification of a cytokine storm and timely initiation of immunomodulatory therapy can lead to favorable treatment outcomes. Such treatment modalities are essential to control the excessive inflammatory response observed in COVID-19 patients with a cytokine storm. In our comparative analysis of high-dose methylprednisolone and tocilizumab, both agents demonstrated comparable efficacy in reducing inflammatory markers and showed similar mortality outcomes.

Based on our findings, high-dose methylprednisolone, due to its lower cost and accessibility, may serve as a viable alternative to tocilizumab in the treatment of COVID-19-related cytokine storm.

Ethics

Ethics Committee Approval: The Ethics Commission of University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital authorized the study and waived the necessity for informed consent (approval no: 154; date: August 10, 2022). The present study was conducted in accordance with the provisions of the Declaration of Helsinki (2013).

Informed Consent: Given the retrospective design, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.F.A., O.U., M.O., C.D., Concept: Ö.F.A., İ.S., O.U., S.K., Ş.K., Design: Ö.F.A., F.K., Ş.K., Data Collection or Processing: Ö.F.A., F.K., O.U., M.O., Ş.K., Analysis or Interpretation: Ö.F.A., İ.S., F.K., M.O., C.D., Literature Search: Ö.F.A., İ.S., O.U., S.K., Ş.K., C.D., Writing: Ö.F.A., C.D.

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ORIGINAL RESEARCH

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Clinical Outcomes Following Isolated Anterior Cruciate Ligament (ACL) Reconstruction Versus Combined ACL and Meniscus Surgery: A Comparative Study

Tek Başına Ön Çapraz Bağ (ACL) Rekonstrüksiyonu ile Kombine ACL ve Menisküs Ameliyatı Sonrası Klinik Sonuçlar: Karşılaştırmalı Bir Çalışma

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Abstract

Objective: In this retrospective study, we aimed to compare the clinical results of isolated anterior cruciate ligament (ACL) reconstruction and ACL reconstruction with meniscal repair or meniscal resection.

Method: The isolated ACL reconstruction group included 4 females and 25 males; the ACL reconstruction with meniscal repair group included 6 females and 21 males; and the ACL reconstruction with meniscectomy group included 4 females and 21 males. All patients underwent surgery using a transtibial, quadruple hamstring autograft, single-bundle, and single-tunnel endobutton technique. Meniscal tears were repaired using the all-inside technique. Demographic characteristics, preoperative and postoperative one-year functional scores (Lysholm, Tegner, Cincinnati, and International Knee Documentation Committee), preoperative and postoperative one-year anterior drawer test and Lachman test, injury-to-surgery intervals, meniscus tear type, and posterior tibial slope angles were compared across all groups.

Results: Fifty-six percent of the meniscus resection group underwent surgery after 12 months, and the likelihood of a meniscal tear pattern unsuitable for repair was increased. We found that postoperative functional outcomes were significantly higher in all three groups compared to preoperative outcomes, and early clinical outcomes were satisfactory in all three groups. The Tegner activity level score was significantly higher in the group that underwent meniscal repair

Öz

Amaç: Retrospektif olan bu çalışmamızda izole ön çapraz bağ (ÖÇB) rekonstrüksiyonu ve ÖÇB rekonstrüksiyonu ile birlikte menisküs tamiri veya menisküs rezeksiyonunun klinik sonuçlarını karşılaştırmak amaçlanmıştır.

Yöntem: İzole ÖÇB rekonstrüksiyonu grubunda 4 kadın ve 25 erkek, ÖÇB rekonstrüksiyonu ile birlikte menisküs tamiri yapılan grubunda 6 kadın ve 21 erkek, ÖÇB rekonstrüksiyon ile birlikte menisektomi yapılan grubunda 4'ü kadın 21'i erkek hasta dahil edildi. Tüm hastalarımız transtibial, dörtlü hamstring otogreft ile tek demet ve tek tünel endobutton yöntemiyle opere edildi. Menisküs yırtıkları ise tamamen içerde yöntemle onarıldı. Tüm grupların demografik özellikler, preop ve postop birinci yılda fonksiyonel skorlamaları (Lysholm, Tegner, Cincinnati ve Uluslararası Diz Dokümantasyon Komitesi), preop ve postop 1. yıl ön çekmece testi ve lachman testleri, yaralanma-operasyon arasında geçen süreleri, menisküsün yırtık tipi ve posterior tibial eğim açıları karşılaştırıldı.

Bulgular: Menisküs rezeksiyonu yapılan grubun %56'sı 12. aydan sonra ameliyat olup hastaların menisküs yırtıkların onarıma uygun olmayan bir menisküs yırtığı paternine karşılaşma olasılığı artmış olduğu görüldü. Her üç grubun post-op fonksiyonel sonuçları preop sonuçlarına göre anlamlı düzeyde yüksek ve her üç grubun erken dönemde klinik sonuçları tatmin edici seviyede saptadık. Tegner aktivite düzeyi skoru ÖÇB rekonstrüksiyon ile beraber menisküs

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Abstract

with anterior cruciate ligament reconstruction compared to the group that underwent meniscal resection.

Conclusion: In our study, patients who underwent meniscus repair had higher Tegner activity scores than those who underwent meniscectomy. Weight-bearing and movement restrictions were prescribed for patients with meniscus repair. These results demonstrate that weight-bearing and movement restrictions have no impact on clinical outcomes. Patients should be advised to attempt to return to sports or previous activities as quickly and safely as possible.

Keywords: ACL reconstruction, meniscus repair, meniscectomy

Öz

onarımı olan grupta menisküs rezeksiyonu yapılan grubuna göre anlamlı düzeyde yüksek saptadık.

Sonuç: Çalışmamızda menisküs tamiri yapılan hastalar menisketomi yapılanlara göre daha yüksek tegner aktivite skorlarına sahiptiler. Menisküs tamiri olan hastalarda yük verme ve hareket kısıtlaması verilmişti. Bu sonuçlara göre yük verme ve hareket kısıtlamasının klinik sonuçlarına etkisi olmadığını gösterdi. Hastaların en kısa sürede ve güvenli bir şekilde spora veya eski aktivitelerine dönmeye çabalamalarını tavsiye edilmelidir.

Anahtar kelimeler: Ön çapraz bağ rekonstrüksiyon, menisketomi, menisküs tamiri

Introduction

Anterior cruciate ligament (ACL) tears are commonly observed ligamentous lesions of the knee joint, a complex and dynamic structure composed of the tibiofemoral and patellofemoral articulations, often resulting from athletic activities. Female athletes, especially in games such as soccer and basketball, have higher injury rates than men (1). ACL is necessary for preserving the knee's static and dynamic stability. During sports activities, the knee is frequently injured through non-contact mechanisms including landing, abrupt deceleration, changes in direction and rotation while in valgus and extension (2). Among the other significant causes of ACL injuries are those resulting from high-energy events, such as falls from significant heights and motor vehicle accidents.

In a complete ACL tear, the patient hears a "pop" sound. Common symptoms are pain and swelling caused by intra-articular bleeding. This pain usually limits the mobility of the knee. Another common symptom is a feeling of emptiness in the knee. It can feel like the patient suddenly slips while walking or running fast, increasing the risk of falling. On the other hand, partial ACL ruptures may not lead to knee instability, allowing individuals to return to play after the injury (3). However, in highly active individuals or athletes, overall quality of life can be substantially impacted.

The ACL, which acts as the main stabilizer of the knee, can also lead to other intra-articular injuries when it ruptures. Meniscal lesions have been shown to be associated with 60% of cruciate ligament damage (4). In studies related to ACL reconstruction in the literature, low thigh muscle strength was observed in all graft types (5). Treatment of these two structures together is discussed in the literature with respect to clinical outcomes.

The study sought to compare clinical outcomes between isolated ACL-R and ACL-R combined with meniscal repair or meniscectomy.

Materials and Methods

This study was conducted after the approval received from the Tekirdağ Namık Kemal University Local Ethics Committee meeting dated 28.11.2023 (protocol number 2023.197.11.11.11) and patient consents were obtained.

From 01/01/2019 to 01/11/2022, hospital electronic records were reviewed for 110 patients who underwent ACL reconstruction, and 81 individuals meeting the appropriate criteria were included in this retrospective investigation. All surgeries were performed using the transtibial with a quadruple hamstring autograft and fixed with the single bundle, single-tunnel EndoButton method. The all-inside technique was employed for meniscal repair, and resections were classified as partial or total meniscectomy.

In our study, patients were categorized into three groups: isolated ACL-R, ACL-R combined with meniscal repair, and ACL-R with meniscectomy. Patients aged between 18-48 years who had undergone tendon reconstruction with quadruple hamstring tendon autograft and single-bundle, and single-tunnel EndoButton method at least one year ago; those who had undergone meniscal repair or meniscectomy with ACL-R; those who performed quadriceps strengthening exercises or attendance in physical therapy and rehabilitation in the first 3 months after surgery, those who did not have a sedentary lifestyle before the surgery, and those who were deemed suitable to resume sports in the sixth month of treatment were included.

Patients with a history of revision surgery due to ACL re-rupture; additional knee pathologies other than meniscal injuries, including lateral or medial collateral ligament injuries, MPFL injury, or chondral injury; or re-traumatization after surgery were excluded.

At the time of presentation, 24 patients reported knee pain, a subjective sensation of pressure, and swelling. After history taking, physical examination was performed and Lachman test, anterior drawer, posterior drawer and McMurray tests were noted. Two-way radiographs and magnetic resonance imaging of the knee were examined in detail. Rest, knee brace, cold application and non-steroidal anti-inflammatory drugs were recommended for patients with acute injury history. A preoperative rehabilitation program was applied with the aim of improving range of motion and enhancing the quadriceps strength. Patients were admitted to the clinic one day prior to the operation and preoperative preparations were started.

Lyshlom scoring, International Knee Documentation Committee (IKDC) scoring, Cincinnati scoring and Tegner activity scoring forms were analyzed preoperatively and at 1 year post-op, and post-op lachman test (-), (+), (++), (++), (++++) and anterior drawer tests (-), (+), (++), (++++) were analyzed at 1 year. Age, gender, height, weight, body mass index (BMI), follow-up time, preop lachman test (-), (+), (++), (+++), (++++), anterior drawer test (-), (+), (++), (++++), side of injury, mechanism of injury (sports/non-sports related, contact/non-contact injury) time from injury to operation, type of meniscal tear, and posterior tibial slope angles were investigated.

Using the posterior tibial cortex method introduced by Hewett et al. (6), the anatomical axis of the tibia was established. On a lateral knee radiograph, the posterior tibial slope was computed as the angle -90 formed between lines tangent to the posterior tibial cortex and the tibial plateau. Among the patients, 29 underwent isolated ACL reconstruction (4 females and 25 males), while 27 underwent ACL reconstruction with meniscal repair (6 females and 21 males). In the group that underwent meniscectomy with ACL reconstruction, there were 25 patients, 4 females and 21 males. The mean follow-up period was 17.8 months (mean age 31.8 years) in the isolated ACL R group, 20.5 months (mean age 28 years) in the ACL R+ meniscal repair group, and 22.5 months (mean age 31.4 years) in the ACL R+ meniscectomy group. The IKDC subjective knee form, a reliable and valid knee-specific tool assessing symptoms, function, and sports activity, is suitable for patients who had diverse knee conditions and allows for outcome comparisons between groups.

Statistical Analysis

Data were analyzed using SPSS (IBM SPSS Statistics 27), with results summarized through frequency tables and descriptive statistics. Non-parametric methods were applied for measurement values not following a normal distribution, with comparisons between two dependent groups conducted using the Wilcoxon test (Z-table value), comparisons among three or more independent groups using the Kruskal-Wallis H test (χ^2-table value), and associations between two qualitative variables assessed via Pearson's χ^2 cross tables.

Results

No statistically significant associations existed between the groups and variables including sex, side, type of anesthesia, sports involvement, and injury mechanism ($p>0.05$). These characteristics were consistent and comparable across the groups. However, significant differences in the time from injury to surgery were observed among the three groups ($\chi^2=20,029$; $p<0.001$).

It was determined that 21 (72.4%) in the isolated ACL R group and 17 (63.0%) in the ACL R+ meniscal repair group were 0-6 months, while 14 (56.0%) in the ACL R+ meniscectomy group were >12 months. It was determined that the time of injury was predominantly 0-6 months in those with isolated ACL R and ACL R+ meniscus repair, and predominantly >12 months in those with ACL + meniscectomy (Table 1).

The groups exhibited a statistically significant association with the type of meniscal tear ($\chi^2=11.577$; $p=0.041$). As a result of the post-hoc analysis to identify the source of the significant association, it was found that the association was due to the fact that no flap was performed in the ACL R+ meniscal repair group, whereas in the ACL R+ meniscectomy group, flaps were performed in 7 patients (28.0%) (Table 2).

No statistically significant differences in age (years), follow-up period, or BMI (kg/m²) were observed across the groups ($p>0.05$) (Table 3).

Preoperative and postoperative IKDC scores did not differ significantly across the groups ($p>0.05$) (Table 4, Graphic 1).

Patients in the isolated ACL R group exhibited a statistically significant difference in IKDC scores across the follow-up periods ($Z=-4.706$; $p<0.001$). Postoperative IKDC scores were significantly greater compared to preoperative scores.

IKDC scores differed significantly among patients in the ACL R+ meniscal repair group based on their treatment

processes (Z=-4.543; p<0.001). Postoperative IKDC was significantly greater compared to preoperative values.

When preoperative Tegner scores were examined by group, a statistically significant difference was observed (χ^2=9.749; p=0.008). Pairwise comparisons with Bonferroni correction were used to identify the groups responsible for this difference, revealing a significant difference between the isolated ACL R group and those with ACL R+ meniscal repair.

Table 1. Analysis of the association between study groups and qualitative characteristics

Variable	Isolated ACL R (n=29)		ACL R+ meniscal repair (n=27)		ACL R+ meniscectomy (n=25)		Statistical analysis* probability
	n	%	n	%	n	%	
Gender							
Male	25	86.2	21	77.8	21	8.,0	χ^2=0.737
Woman	4	13.8	6	22.2	4	16.0	p=0.692
Side							
Right	17	58.6	17	63.0	15	60.0	χ^2=0.114
Left	12	41.4	10	37.0	10	40.0	p=0.945
Anesthesia type							
Spinal	26	89.7	23	85.1	22	88.0	χ^2=0.262
General	3	10.3	4	14.8	3	12.0	p=0.877
Sports-related							
Related	18	62.1	16	59.3	16	64.0	χ^2=0.126
Not related	11	37.9	11	40.7	9	36.0	p=0.939
Mechanism							
Non-contact	25	86.2	22	81.5	22	88.0	χ^2=0.474
Contact	4	13.8	5	18.5	3	12.0	p=0.789
Injury (month)							
0-6	21	72.4	17	63.0	9	36.0	χ^2=20.029
7-12	7	24.1	2	7.4	2	8.0	**p<0.001**
>12	1	3.5	8	29.6	14	56.0	

*: Pearson's χ^2 cross-tabulations evaluate the association between two qualitative variables, ACL: Anterior cruciate ligament

Table 2. Examination of the relationship between groups and meniscus type

Variable	ACL R+ meniscus repair (n=27)		ACL R+ meniscectomy (n=25)		Statiscical analysis* probability
	n	%	n	%	
Meniscus type					
Flap	-	-	7	28.0	χ^2=11.577
Horizontal	3	11.1	2	8.0	**p=0.041**
Complex	3	11.1	4	16.0	
Bucket handle	10	37.0	8	32.0	
Longitudinal	5	18.6	3	12.0	
Radial	6	22.2	1	4.0	

*: Pearson's χ^2 cross-tabulations were used to examine the relationship between two categorical variables, ACL: Anterior cruciate ligament

Table 3. Comparison of socio-demographic quantitative findings according to groups

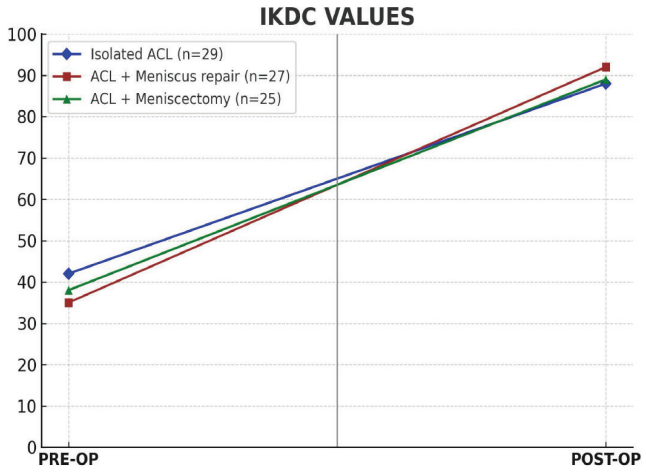
Variable	Isolated ACL R (n=29)		ACL R+ meniscus repair (n=27)		ACL R+ meniscectomy (n=25)		Statiscical analysis * probability
	$\underline{X}$ ± SD	Median [IQR]	$\underline{X}$ ± SD	Median [IQR]	$\underline{X}$ ± SD	Median [IQR]	
Age (years)	31.83±6.79	32.0 [8.0]	28.00±7.49	28.0 [9.0]	31.44±6.58	31.0 [9.5]	χ^2=5.644 p=0.059
Follow-up period	17.83±4.77	18.0 [7.5]	20.59±6.94	18.0 [8.0]	22.56±10.12	18.0 [21.0]	χ^2=2.489 p=0.288
BMI (kg/m^2)	27.16±3.05	27.2 [3.9]	27.21±3.09	26.6 [3.2]	25.89±2.96	25.6 [4.8]	χ^2=3.034 p=0.219

*: The Kruskal-Wallis H test (χ^2 table value) statistics were used to compare the measurement values of three or more independent groups in data that did not show a normal distribution, ACL: Anterior cruciate ligament, BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range

Table 4. Comparison of IKDC values by groups and processes

Variable	Isolated ACL R (n=29)		ACL R+ meniscus repair (n=27)		ACL R+ meniscectomy (n=25)		Statistical analysis* probability
	X ± SD	Median [IQR]	X ± SD	Median [IQR]	X ±SD	Median [IQR]	
IKDC							
Pre-op	41.55±16.17	42.0 [24.5]	34.00±13.61	25.0 [28.0]	39.92±13.92	40.0 [21.5]	χ^2=4.723 p=0.094
Post-op	86.41±10.37	90.0 [13.0]	92.89±6.26	94.0 [10.0]	87.80±10.18	90.0 [12.5]	χ^2=4.840 p=0.089
Analysis probability	Z=-4.706 **p<0.001**		Z=-4.543 **p<0.001**		Z=-4.376 **p<0.001**		

*: To compare measurements between two related groups for non-normally distributed data, the Wilcoxon test (Z-value) was employed, whereas comparisons across three or more independent groups were conducted using the Kruskal-Wallis H test (χ^2 value), SD: Standard deviation, IKDC: International Knee Documentation Committee, ACL: Anterior cruciate ligament, IQR: Interquartile range



Graphic 1. Distribution of IKDC values by groups and processes

IKDC: International Knee Documentation Committee, ACL: Anterior cruciate ligament

Patients with ACL R+ meniscus repair had significantly higher preoperative Tegner scores than those with isolated ACL R.

When postoperative Tegner scores were examined by group, a statistically significant difference was found (χ^2=7.410; p=0.025). To determine the group in which this difference occurred, a significant difference was found between those with ACL R+ meniscus repair and those with ACL R+ meniscectomy. Patients undergoing ACL R+ meniscectomy showed significantly higher postoperative Tegner scores than those with isolated ACL R.

The isolated ACL R group exhibited a statistically significant difference in Tegner activity scores across the treatment process (Z=-2.828; p=0.005). Patients' postoperative Tegner scores decreased significantly compared to their preoperative scores.

The ACL R+ meniscal repair group exhibited a statistically significant difference in Tegner activity scores across the treatment process (Z=-3.419; p<0.001). Postoperative Tegner values were significantly lower compared to preoperative values.

The ACL R+ meniscectomy group exhibited a statistically significant difference in Tegner activity scores across the treatment process (Z=-3.100; p=0.002). Postoperative Tegner values were significantly lower compared to preoperative values (Table 5, Graphic 2).

Preoperative and postoperative Lysholm activity scores did not differ significantly across the groups (p>0.05).

The isolated ACL R group exhibited a statistically significant difference in Lysholm scores across procedures (Z=-4.706; p<0.001). Postoperative Lysholm values were significantly higher compared to preoperative values.

The ACL R+ meniscal repair group exhibited a statistically significant difference in Lysholm scores across procedures (Z=-4.543; p<0.001). Postoperative Lysholm values were significantly higher compared to preoperative values.

The ACL R+ Meniscectomy group exhibited a statistically significant difference in Lysholm scores across procedures (Z=-4.373; p<0.001). Postoperative Lysholm values were significantly higher compared to preoperative values (Table 6, Graphic 3).

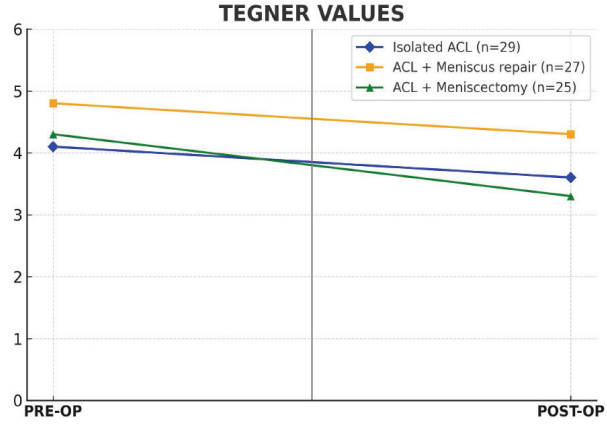
Preoperative and postoperative Cincinnati values did not differ significantly among the groups (p>0.05).

The isolated ACL R group exhibited a statistically significant difference in Cincinnati scores across procedures (Z=-4.706; p<0.001). Postoperative Cincinnati values were significantly higher than preoperative values.

Table 5. Comparison of Tegner values by groups and processes

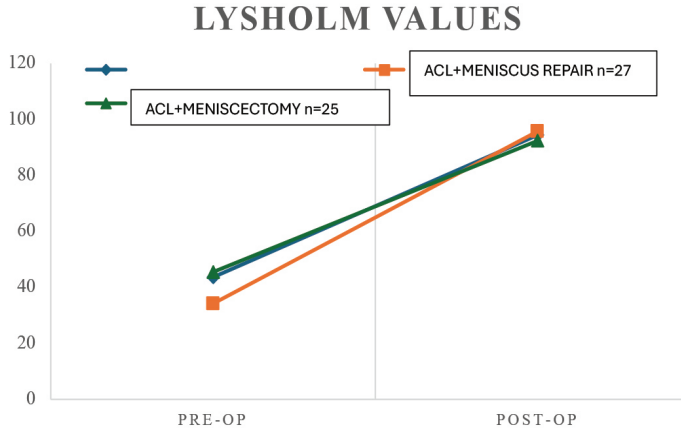
Variable	Isolated ACL R (n=29)		ACL R+ meniscal repair (n=27)		ACL R+ meniscectomy (n=25)		Statistical analysis* probability
	X̲ ± SD	Median [IQR]	X̲ ± SD	Median [IQR]	X̲ ± SD	Median [IQR]	
Tegner							
Pre-op	4.00±0.80	4.0 [0.5]	4.78±1.05	4.0 [1.0]	4.28±1.14	4.0 [1.0]	χ^2=9.749 **p=0.008** **[1-2]**
Post-op	3.72±0.95	4.0 [1.0]	4.22±1.21	4.0 [2.0]	3.40±1.00	3.0 [1.0]	χ^2=7.410 **p=0.025** **[2-3]**
Analysis probability	Z=-2.828 **p=0.005**		Z=-3.419 **p<0.001**		Z=-3.100 **p=0.002**		

*: For data not normally distributed, the Wilcoxon test (Z statistic) was applied to compare two dependent groups, while the Kruskal-Wallis H test (χ^2 statistic) was applied to compare three or more independent groups, SD: Standard deviation, ACL: Anterior cruciate ligament, IQR: Interquartile range



Graphic 2. Distribution of Tegner values according to groups and processes

ACL: Anterior cruciate ligament



Graphic 3. Distribution of Lysholm values according to groups and processes

ACL: Anterior cruciate ligament

Table 6. Comparison of Lysholm values by groups and processes

Variable	Isolated ACL R (n=29)		ACL R+ meniscal repair (n=27)		ACL R+ meniscectomy (n=25)		Statistical analysis* probability
	X̲ ± SD	Median [IQR]	X̲ ± SD	Median [IQR]	X̲ ± SD	Median [IQR]	
Lysholm							
Pre-op	43.62±14.93	45.0 [20.0]	34.18±16.17	40.0 [25.0]	45.48±19.37	48.0 [32.0]	χ^2=4.583 p=0.101
Post-op	94.41±7.06	98.0 [10.0]	95.74±6.57	98.0 [5.0]	92.36±10.11	97.0 [10.0]	χ^2=1.508 p=0.470
Analysis probability	Z=-4.706 **p<0.001**		Z=-4.543 **p<0.001**		Z=-4.373 **p<0.001**		

*: To compare two related groups for non-normally distributed data, the Wilcoxon test (Z value) was employed, whereas comparisons involving three or more independent groups were conducted using the Kruskal-Wallis H test (χ^2 value), SD: Standard deviation, ACL: Anterior cruciate ligament, IQR: Interquartile range

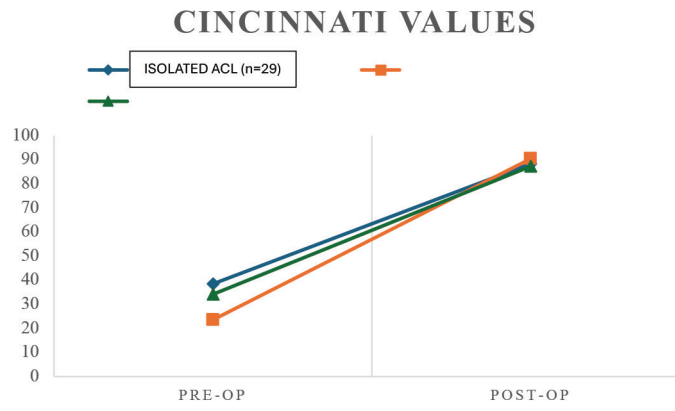
The ACL R+ meniscal repair group exhibited a statistically significant difference in Cincinnati scores across procedures (Z=-4.545; p<0.001). Postoperative Cincinnati values were significantly higher than preoperative values.

The ACL R+ meniscectomy group exhibited a statistically significant difference in Cincinnati scores across procedures (Z=-4.375; p<0.001). Postoperative Cincinnati scores were significantly higher compared with preoperative scores (Table 7, Graphic 4).

Table 7. Comparison of Cincinnati values by group and process

Variable	Isolated ACL R (n=29)		ACL R+ meniscal repair (n=27)		ACL R+ meniscectomy (n=25)		Statistical analysis* probability
	X ± SD	Median [IQR]	X ± SD	Median [IQR]	X ± SD	Median [IQR]	
Cincinnati							
Pre-op	30.48±21.65	20.0 [26.0]	23.56±12.24	23.0 [16.0]	34.16±21.82	30.0 [41.0]	χ^2=2.065 p=0.356
Post-op	88.38±14.89	96.0 [27.0]	90.44±12.36	94.0 [17.0]	87.32±13.42	92.0 [25.5]	χ^2=0.393 p=0.822
Analysis probability	Z=-4.706 **p<0.001**		Z=-4.545 **p<0.001**		Z=-4.375 **p<0.001**		

*: For data not following a normal distribution, comparisons between two related groups were performed via the Wilcoxon test (Z-value), and comparisons across three or more independent groups were conducted via the Kruskal-Wallis H test (χ^2 value), ACL: Anterior cruciate ligament, SD: Standard deviation, IQR: Interquartile range



Graphic 4. Distribution of Cincinnati values according to groups and processes
ACL: Anterior cruciate ligament

Comparison of the groups revealed no statistically significant differences in Lachman test results at either the preoperative or postoperative assessment (p>0.05).

The groups did not differ significantly in Lachman test results at preoperative or postoperative assessment (p>0.05) (Table 8).

The groups did not differ significantly regarding Tegner score differences or posterior tibial slope (p>0.05).

The groups exhibited significant differences in the interval between injury and surgery (in months) (χ^2=12.533; p=0.002). Bonferroni-corrected pairwise comparisons were performed to identify the source of this difference. The isolated ACL R group differed significantly from the ACL R+ meniscus repair and ACL R+ meniscectomy groups. Specifically, patients in the ACL R and ACL R+ meniscectomy groups exhibited a significantly shorter time from injury to

Table 8. Examining the association between groups and the qualitative characteristics of the study

Variable	Pre-op						Statistical analysis* probability	Post-op						Statistical analysis* probability
	Isolated ACL R (n=29)		ACL R+ meniscal repair (n=27)		ACL R+ meniscectomy (n=25)			Isolated ACL R (n=29)		ACL R+ meniscectomy (n=27)		ACL R+ meniscectomy (n=25)		
	n	%	n	%	n	%		n	%	n	%	n	%	
Lachman														
Negative (-)	9	31.0	5	18.5	6	24.0		29	100.0	26	96.3	23	92.0	
(+)	17	58.6	19	70.4	15	60.0	χ^2=3.524	-	-	1	3.7	2	8.0	χ^2=2.409
(++)	3	10.4	3	11.1	3	12.0	p=0.741	-	-	-	-	-	-	p=0.300
(+++)	-	-	-	-	1	4.0		-	-	-	-	-	-	
Anterior drawer														
Negative (-)	6	20.7	2	7.4	3	12.0		22	75.9	22	81.5	19	76.0	
(+)	13	44.8	8	29.6	6	24.0		7	24.1	5	18.5	5	20.0	χ^2=2.539
(++)	9	31.0	16	59.3	16	64.0	χ^2=8.173	-	-	-	-	1	4.0	p=0.638
(+++)	1	3.5	1	3.7	-	-	p=0.226	-	-	-	-	-	-	

*: The association between two qualitative variables was analyzed by Pearson χ^2 cross-tabulation, ACL: Anterior cruciate ligament

surgery (in months) compared to those undergoing ACL R+ meniscectomy (Table 9).

Postoperative anteroposterior and lateral knee radiographs of all study groups are presented to illustrate the surgical reconstruction characteristics. Representative images demonstrate (Figure 1) ACL reconstruction combined with meniscal repair, (Figure 2) isolated ACL reconstruction, and (Figure 3) ACL reconstruction with concomitant meniscectomy.

Discussion

This study aimed to compare one-year postoperative clinical outcomes among patients undergoing isolated ACL-R, ACL-R following ACL rupture, and ACL-R combined with meniscal repair or meniscectomy. The outcomes of 29 patients in the isolated ACL R group, 27 in the ACL R+ meniscus repair group, and 25 in the ACL R+ meniscectomy group were evaluated. The advantages of our study were the homogeneity of the groups regarding age, gender, BMI, follow-up duration, and surgical side, and the fact that it was conducted by the same surgical team. While the follow-up period was sufficient for comparing early-term results, its inadequacy in terms of long-term outcomes is a drawback. Long follow-up is required to evaluate complications such as the development of osteoarthritis, tunnel widening, and re-tear or rupture of the ACL and meniscus. Another drawback was that the majority of the participants were not professional athletes and, therefore, did not return to their prior activities.

Ageberg et al. (5) found that 70% of ACL injuries are non-contact, whereas the remaining 30% are contact injuries. Michalitsis et al. (4) reported non-contact mechanisms in 72% of cases and contact injuries in 28% of cases in a survey of athletes regarding the mechanisms of ACL injuries. There is broad consensus in previous studies that approximately 70% of ACL injuries result from non-contact events (5).

Table 9. Comparison of some quantitative findings by groups

Variable	Isolated ACL R (n=29)		ACL R+ meniscal repair (n=27)		ACL R+ meniscectomy (n=25)		Statistical analysis* probability
	$\underline{X}$ ± SD	Median [IQR]	$\underline{X}$ ± SD	Median [IQR]	$\underline{X}$ ± SD	Median [IQR]	
Tegner score difference	0.28±0.45	0.0 [1.0]	0.56±0.64	0.0 [1.0]	0.88±1.09	0.0 [2.0]	χ^2=4.992 p=0.082
Posterior tibial slope	9.80±2.63	9.9 [4.5]	8.82±2.70	8.8 [3.1]	9.59±2.96	9.2 [4.2]	χ^2=1.641 p=0.440
Time to injury (months)	5.55±5.40	3.0 [8.0]	10.18±10.64	6.0 [15.0]	21.20±17.73	24.0 [32.0]	χ^2=12.533 **p=0.002 [1.2-3]**

*: The Kruskal-Wallis H test (χ^2-table value) was applied to compare measurements among three or more independent groups for data not following a normal distribution, SD: Standard deviation, ACL: Anterior cruciate ligament, IQR: Interquartile range

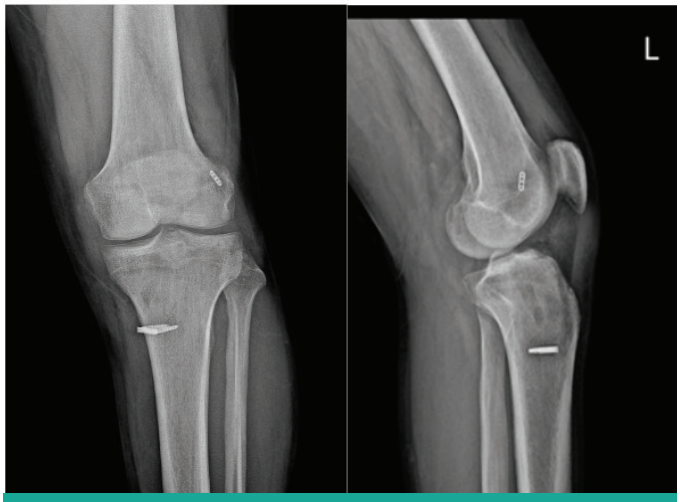


Figure 1. ACL reconstruction combined with meniscal repair

ACL: Anterior cruciate ligament

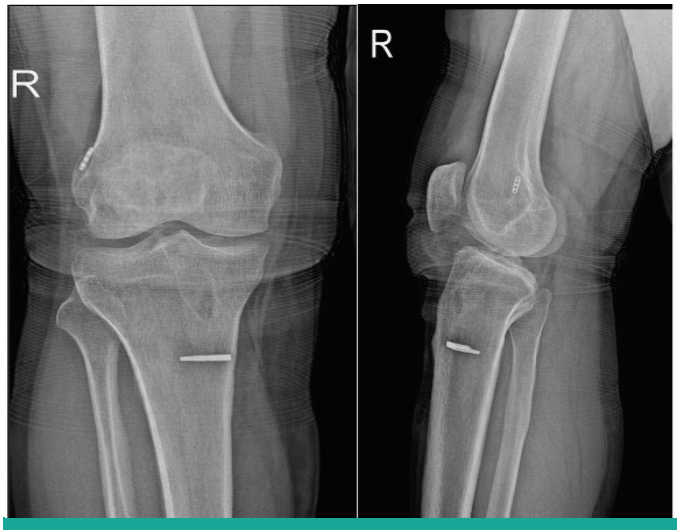


Figure 2. Isolated ACL reconstruction

ACL: Anterior cruciate ligament

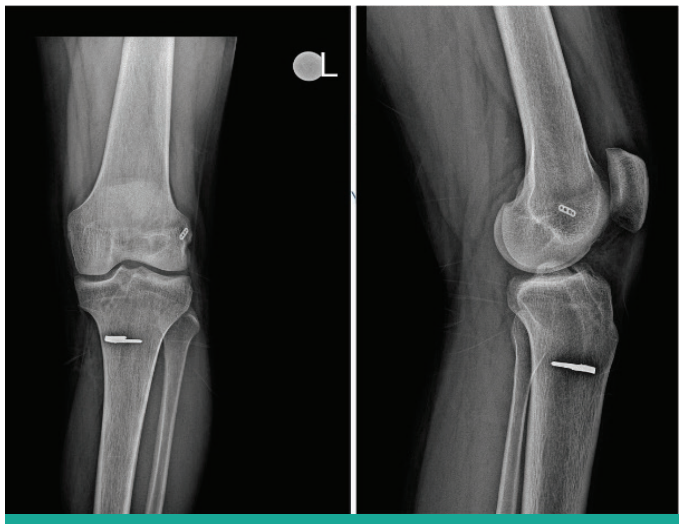


Figure 3. ACL reconstruction with concomitant meniscectomy

ACL: Anterior cruciate ligament

In line with the literature 85% of cases in our study were non-contact, while 15% were contact. An estimated 70% of ACL injuries are sports-related (6). In our patients, the etiology of injuries was found to be sports-related in 61.2% of the isolated ACL R group, 59.3% in the ACL R+meniscus repair group, and 64% in the ACL R+meniscectomy group. The analysis did not reach statistical significance across the groups. Although the risk of injury was higher in women, only one in every five of our patients was female (5). This can be attributed to football being the leading cause of sports-related injuries, with men participating more frequently in such activities. High-energy events, such as construction accidents and traffic collisions, were the most frequent causes of non-sports injuries. This may also be another reason for the low number of female patients presenting.

The mean age of the patient groups treated with isolated ACL R, ACL R+ meniscus repair, and ACL R+ meniscectomy was 31.83, 28.0, and 31.44, respectively, and their BMIs were 27.16, 27.21, and 25.89, respectively. Age, gender, BMI, and injury mechanism did not differ significantly among the groups. The impact of patient age on meniscal repair is debated. Many studies suggest that meniscus tears in the vascular zone, performed with or without ACL reconstruction, have a similar recovery prognosis up to age 58, regardless of age (7,8). Conversely, there are studies showing histologically that menisci in patients over 40 years of age have poorer cellularity and healing potential (9). Another study found that with increasing age, the likelihood of encountering a meniscal tear pattern that is not amenable to repair increases (10).

Meniscal repair rates have been consistently higher in younger patients and those with lower BMI across multiple studies (11-14). Conversely, Abram et al. (12), in a study spanning 1997 to 2017, observed a 2.4-fold increase in meniscal repair incidence among patients aged 30-39 and a 1.3-fold increase among those aged 40-49 during ACL reconstruction. Similar findings have also been reported in other studies (15). Partan et al. (16) observed similar patterns of meniscal preservation among older patients undergoing ACL reconstruction. They also reported a higher proportion of overweight and obese patients receiving concurrent meniscal repair with ACL reconstruction, with only minor differences in mean BMI between those undergoing meniscal repair and those undergoing partial meniscectomy Sommerfeldt et al. (17) investigated the association between BMI and meniscal repair failure, reporting that while higher BMI was linked to an increased likelihood of degenerative meniscal lesions, patients with BMI up to 35 were not at greater risk of repair failure.

In our study, a statistically significant difference was found among the groups with respect to the interval between injury and surgery (χ^2=20.029; p<0.001). It was determined that 21 individuals (72.4%) in the isolated ACL R group and 17 individuals (63.0%) in the ACL R+ meniscus repair group had a mean age of 0-6 months, while 14 individuals (56.0%) with ACL R+ meniscectomy had a mean age of >12 months. The mean interval from injury to surgery was predominantly 0-6 months in patients with isolated ACL R and ACL R+ meniscectomy, it was predominantly >12 months in those with ACL R+ meniscectomy.

The optimal timing for ACL reconstruction following an ACL tear remains a topic of debate (17). Early ACL reconstruction is theoretically advantageous, as it may lower the risk of cartilage or meniscal damage caused by recurrent instability and facilitate a quicker return to sports (18). ACL injury has been linked to a higher risk of osteoarthritis, with cartilage and meniscal lesions in an unstable knee experiencing recurrent sprains potentially playing a contributing role (19-21). ACL injury also affects the patellofemoral joint (22).

Chen et al. (23) reported that medial meniscus tears were more common in ACL reconstructions performed after 12 months compared to those performed before 12 months Allen et al. (11), using a biomechanical force-moment sensor testing system, demonstrated that the medial meniscus experiences significantly higher forces in ACL-deficient knees, highlighting its role in knee stabilization. They

proposed this mechanism to explain the higher prevalence of medial meniscus tears in chronic ACL reconstructions. Most publications indicate that lateral meniscus tears are associated with acute injuries, but the incidence is no different in patients with early and chronic ACL tears. This is thought to result from the greater mobility of the lateral meniscus and the comparatively lower load it experiences during ACL tears (23,24). There is also a relationship between anterior cruciate ligament reconstruction and surgical timing, as well as patients' age, sex, and body mass index (25).

According to Tenuta and Arciero (26), patients receiving acute meniscal repair alongside ACL reconstruction exhibited higher meniscal healing rates than those who underwent delayed meniscal repair. Delayed ACL reconstruction also reduces the likelihood of meniscal repair (26). In our study, 56% of patients who underwent meniscectomy after 12 months were operated on, consistent with literature. Delayed ACL-R is linked to a higher rate of bucket-handle meniscal tears (27). We observed bucket-handle tears as the most common tear type in the group that underwent both meniscal repair and meniscectomy.

Although there is a lack of high-level comparative studies to date, available evidence indicates that meniscal repairs combined with ACL reconstruction are associated with faster healing and lower failure rates compared with isolated repairs. In other words, ACL-R is a protective factor against meniscal repair failure and reoperation. This positive effect is thought to be due to the slower rehabilitation process in meniscal repairs performed simultaneously with ACL-R and the influence of biological factors released by bone tunnels. Another explanation is that meniscal repairs performed alone may cause occult knee instability, which is believed to reduce the success of meniscal repair (27). Therefore, early ACL-R is crucial for reducing the incidence of meniscal tears, preventing joint degeneration, and increasing the likelihood of meniscal repair and healing.

Our results demonstrated satisfactory postoperative IKDC, Lysholm, and Cincinnati scores in all groups, without any statistically significant intergroup differences ($p>0.05$). However, postoperative Tegner scores differed significantly between the groups. ACL R+ meniscus repair patients had significantly higher rates compared to ACL R+ meniscectomy and isolated ACL reconstruction groups.

Eken et al., in a study assessing clinical outcomes of meniscus repair and meniscectomy in chronic bucket-handle tears with ACL reconstruction, found that IKDC scores were significantly higher in the meniscus repair group, although clinical outcomes did not differ. The meniscal repair group exhibited slightly higher Lysholm and Tegner scores; however, these differences did not reach statistical significance (28). Shelbourne and Gray reported that 87% of patients in the isolated ACL reconstruction group, 63% in the medial meniscectomy group, and 60% in the lateral meniscectomy group, who underwent ACL reconstruction with concurrent meniscal intervention, had normal or near-normal IKDC scores (29). In another study, Melton et al. found that after 12.6 years of follow-up, the mean IKDC score in patients with meniscal repair was 14 points higher than in patients with meniscal resection (30,31).

Byrne et al. (32) reported similar results in all three groups at ten months postoperatively in terms of objective measurements, including IKDC scores and return to sports, and that meniscal surgery had no effect on ACL reconstruction. In their meta-analysis, Sarraj et al. (33) found that patients with ACL reconstruction combined with meniscal resection experienced better symptoms at 2-year follow-up than those treated ACL reconstruction with meniscal repair. However, they also reported that ACL-R combined with meniscal repair led to reduced knee joint laxity, better long-term patient-reported outcomes, and higher reoperation rates (32).

In their kinematic analysis, Wang et al. (34) revealed that patients with partial medial meniscectomy had significantly elevated adduction angle during early and mid-stance phases, tibial internal rotation during early stance phases, and anterior tibial translation during the swing phase compared with healthy knees, whereas patients with medial meniscus repair had increased adduction angle and anterior tibial translation only at the beginning of the terminal stance phase (33). According to Seon et al. (35), anterior tibial translation was higher in the partial meniscectomy group than in the isolated ACL reconstruction group, indicating that ACL reconstruction alone may not completely restore normal sagittal kinematics (34).

Our study found that Lachman and anterior drawer test outcomes did not differ significantly between preoperative and postoperative assessments ($p>0.05$). At the one-year postoperative evaluation, the anterior drawer test revealed ++ anterior tibial translation in only one patient (4%) from the meniscectomy group. Downhill running kinematics research has shown that meniscal damage contributes to greater tibial anterior translation at two years following ACL reconstruction (35). In their biomechanical analysis,

Papageorgiou et al. (36) demonstrated that medial meniscus resection led to a 33-50% increase in the forces applied to the ACL graft. Consequently, increased tibial translation, combined with elevated graft tension due to meniscal tissue removal, may predispose the graft to failure.

Most surgeons implement a weight-bearing and knee range of motion restriction protocol following meniscus repair. This significantly limits patient rehabilitation compared to meniscectomy or isolated ACL R (36). Spang et al. (37) assessed biomechanical stresses using a cadaver model in which they created and repaired a meniscal tear and reported no significant changes in the meniscus. The literature does not associate early joint motion resumption with a higher rate of weight-bearing failure after meniscal repair. Our findings suggest that weight-bearing and range of motion restriction do not affect return to sports at 6 months.

Study Limitations

Di Miceli et al. (38) have shown that bracing and delayed weightbearing after ACL repair reduce functional outcomes according to IKDC scores. However, their effect on ACL repair performed in conjunction with meniscal repair has not been investigated. While early motion and early weightbearing may provide functional benefits or, some detrimental effects on limitation in the medium term for isolated ACL repair, our study found this not to be the case for concurrent meniscal repair (37). Di Miceli et al. (38) reported no differences in IKDC and Tegner scores among the three groups in their study. In contrast to these studies, our study found significantly higher Tegner activity scores in the meniscus repair group. We believe that the weightbearing and range of motion restriction protocol positively influences both meniscal and ACL healing.

Conclusion

This study evaluated the one-year postoperative clinical outcomes of patients undergoing meniscal surgery in combination with ACL-R for ACL insufficiency. The key findings and recommendations are summarized below.

Most injuries are sports-related, highlighting the importance of recognizing external and individual risk factors and educating athletes to prevent injury.

An increased interval between injury and surgery raises the likelihood of injury to other knee structures due to instability resulting from an ACL injury. Patients undergoing surgical treatment after 12 months are more likely to exhibit meniscal tear patterns unsuitable for repair. In patients who undergoing surgery in the acute phase, surgery is recommended early, after the exacerbation period (the first 3-4 weeks) has passed, due to the risk of developing arthrofibrosis.

Our study shows that the early clinical outcomes of isolated ACL-R and ligament reconstruction combined with meniscal repair or resection are satisfactory and not poor. However, in the long term, osteoarthritis development is accelerated in patients undergoing meniscectomy. Preserving meniscal integrity whenever possible is recommended to prevent osteoarthritis.

Although the literature indicates that anterior knee stability is lower in patients who undergo meniscal repair compared with those who undergo meniscectomy, the present study found that patients undergoing meniscal repair had higher Tegner activity scores than those undergoing meniscectomy. Weight-bearing and movement restrictions were prescribed for patients with meniscal repair. These results suggest that weight-bearing and movement restrictions have no impact on clinical outcomes. Patients should be supported to safely and promptly return to sports or other pre-injury activities.

Ethics

Ethics Committee Approval: This study was conducted after the approval received from the Tekirdağ Namık Kemal University Local Ethics Committee meeting dated 28.11.2023 (protocol number 2023.197.11.11.11).

Informed Consent: Informed consent was obtained.

Footnotes

This study was presented as an oral presentation at the "6th Bilsel International World Science and Research Congress, 28-29 December 2024, İstanbul/Turkey".

Authorship Contributions

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

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ORIGINAL RESEARCH

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Clinical and Demographic Characteristics of Newborns with Meconium-stained Amniotic Fluid: A Retrospective Single-centre Study

Mekonyumlu Amniyotik Sıvı Boyalı Yenidoğanların Klinik ve Demografik Özellikleri: Retrospektif Tek Merkezli Bir Çalışma

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Abstract

Objective: This study examines which clinical and demographic risk factors are associated with early complications in full-term infants born through meconium-stained amniotic fluid (MSAF).

Method: A retrospective cohort study included 76 term newborns delivered with MSAF at University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, in İstanbul, between May 2023 and May 2025. Data covered maternal age, nationality, number of prenatal visits, Apgar scores, delivery method, and neonatal outcomes within 72 hours. Adequate prenatal care was defined as at least four antenatal visits, per World Health Organization standards. Maternal infections were noted based on symptoms or lab results. Multivariable logistic regression was used to identify predictors of early sepsis or referral.

Results: More than half of the infants were born to non-Turkish mothers. Adequate prenatal care was reported in 62.5% of these mothers, compared to 88.9% in Turkish mothers. Sepsis occurred in 17.1% of all cases, more frequently among non-Turkish newborns. A 1-minute Apgar score below 7, maternal infection, and fewer prenatal visits were each linked to increased risk of early complications. Nationality alone was not statistically significant after adjustment.

Conclusion: Among infants born with MSAF, low Apgar scores and insufficient prenatal care were the clearest indicators of early sepsis or referral. Strengthening prenatal support and education for migrant families may help reduce preventable neonatal risks.

Keywords: Apgar score, meconium-stained amniotic fluid, maternal infection, neonatal sepsis, prenatal care

Öz

Amaç: Bu çalışma, mekonyumla boyalı amniyotik sıvı (MSAF) ile doğan term bebeklerde erken komplikasyonlarla ilişkili klinik ve demografik risk faktörlerini incelemektedir.

Yöntem: Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi'nde Mayıs 2023 ile Mayıs 2025 tarihleri arasında MSAF ile doğan 76 term yenidoğanı içeren retrospektif bir kohort çalışması yapılmıştır. Veriler; anne yaşı, uyruk, doğum öncesi ziyaret sayısı, Apgar skorları, doğum şekli ve ilk 72 saatteki neonatal sonuçları kapsamaktadır. Yeterli doğum öncesi bakım, Dünya Sağlık Örgütü standartlarına göre en az dört antenatal ziyaret olarak tanımlanmıştır. Maternal enfeksiyonlar semptomlara veya laboratuvar sonuçlarına göre kaydedilmiştir. Erken sepsis veya sevki öngören faktörleri belirlemek için çok değişkenli lojistik regresyon analizi kullanılmıştır.

Bulgular: Bebeklerin yarısından fazlası Türk olmayan annelerden doğmuştur. Yeterli doğum öncesi bakım oranı Türk annelerde %88,9 iken, bu gruptaki annelerde %62,5 olarak bildirilmiştir. Sepsis tüm olguların %17,1'inde görülmüş olup, Türk olmayan yenidoğanlarda daha sık izlenmiştir. Birinci dakika Apgar skorunun 7'nin altında olması, maternal enfeksiyon varlığı ve yetersiz doğum öncesi ziyaret sayısının her biri, artmış erken komplikasyon riski ile ilişkilendirilmiştir. İstatistiksel düzeltme yapıldıktan sonra uyruk tek başına anlamlı bir faktör olarak saptanmamıştır.

Sonuç: MSAF ile doğan bebekler arasında, düşük Apgar skorları ve yetersiz doğum öncesi bakım, erken sepsis veya sevkin en belirgin göstergeleridir. Göçmen aileler için doğum öncesi desteğin ve eğitimin güçlendirilmesi, önlenebilir neonatal risklerin azaltılmasına yardımcı olabilir.

Anahtar kelimeler: Apgar skoru, doğum öncesi bakım, maternal enfeksiyon, mekonyumla boyalı amniyotik sıvı, neonatal sepsis

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Introduction

Meconium-stained amniotic fluid (MSAF) occurs in approximately 8% to 15% of deliveries. It is often a physiological response to fetal stress or a sign of fetal maturation, particularly in term or post-term pregnancies (1,2). While frequently benign, MSAF is associated with adverse outcomes such as meconium aspiration syndrome (MAS), respiratory distress, and early-onset neonatal infections (3).

Modern obstetric and neonatal care practices, including the avoidance of routine tracheal suctioning in vigorous infants and prompt resuscitation, have significantly improved outcomes in recent years (4). Nevertheless, MSAF requires vigilant monitoring. In diverse urban hospital settings, infants born to migrant mothers may face compounded risks due to inconsistent access to prenatal services and varying levels of health literacy (5).

Research indicates that early and regular prenatal care plays a pivotal role in mitigating neonatal risks (6). Mothers with fewer antenatal visits are more likely to deliver infants with lower Apgar scores, signs of infection, or requirements for neonatal intensive care unit (NICU) admission (7). Migrant women often encounter structural barriers including language difficulties, unfamiliarity with local healthcare systems, and socioeconomic constraints that limit their utilization of prenatal services (8,9).

Rather than attributing adverse outcomes solely to systemic issues, this study aims to identify specific clinical markers that predict risks in MSAF-exposed newborns. Identifying these factors could enable healthcare providers to intervene earlier and tailor care, particularly for families from migrant backgrounds (10).

Materials and Methods

Study Design and Ethics

This retrospective cohort study was conducted at University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, a tertiary care center in İstanbul. Ethical approval was granted by the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (decision no: 2025/08/20/983, date: 07.07.2025). Since only anonymized patient data were used, individual consent was not necessary.

Population and Data Collection

All singleton term newborns delivered with MSAF between May 1, 2023, and May 31, 2025, were eligible for inclusion. Newborns with congenital anomalies, multiple gestations, or incomplete records were excluded. A total of 76 cases were included in the final analysis.

Maternal data collected included age, nationality, number of prenatal visits, and the presence of infections. Neonatal variables included sex, gestational age, birth weight, Apgar scores at 1 and 5 minutes, need for respiratory support, occurrence of MAS or sepsis, NICU admission, and referrals. Adequate prenatal care was defined as attending at least four antenatal visits, in accordance with World Health Organization guidelines (11).

Outcome Definition

The primary outcome was any early neonatal complication occurring within the first 72 hours of life, defined as suspected or confirmed sepsis, or referral to another facility. Maternal infection was recorded if the mother had a documented bacterial or viral illness requiring treatment during pregnancy.

Statistical Analysis

All data were analyzed using IBM SPSS version 28. The Shapiro-Wilk test was applied to assess normality. Continuous variables were presented as means with standard deviations or medians with interquartile ranges. Categorical data were summarized as frequencies and percentages (n, %). For comparisons, Student's t-test or Mann-Whitney U test was applied to continuous variables, and the chi-square or Fisher's exact test for categorical variables. Variables with p-values below 0.20 in univariate analysis were included in the multivariable logistic regression model. Statistical significance was set at $p<0.05$.

Results

Among the 76 newborns included in the study, 36 (47.4%) were born to Turkish mothers and 40 (52.6%) to non-Turkish mothers. The median maternal age was slightly lower in the non-Turkish group. Infants in the non-Turkish group had slightly lower gestational ages and birth weights compared to the Turkish group, though these differences were not statistically significant (Table 1).

Adequate prenatal care was reported in 32 (88.9%) Turkish mothers compared to only 25 (62.5%) non-Turkish mothers, a difference that was statistically significant ($p<0.01$).

Sepsis was diagnosed in 13 (17.1%) of all infants. The incidence was higher among non-Turkish newborns [9 (22.5%)] compared to Turkish newborns [4 (11.1%)], with a p-value of 0.03. Oxygen therapy was administered in 11 (14.5%) cases, and one infant required intubation. NICU referrals occurred in 12 (15.8%) of the cohort, with no statistically significant difference between the two groups (p=0.65) (Table 2, Figure 1).

Table 1. Maternal and neonatal characteristics of newborns with MSAF

Parameter	Turkish (n=36)	Non-Turkish (n=40)	p
Maternal age (years)	30.8±6.3	27.9±7.1	0.04
Gestational age (weeks)	40.1±1.2	39.5±1.4	0.07
Birth weight (g)	3492±487	3350±526	0.12
Male gender, n (%)	20 (55.6%)	21 (52.5%)	0.78
Cesarean section, n (%)	10 (27.8%)	6 (15.0%)	0.17
Adequate prenatal care, n (%)	32 (88.9%)	25 (62.5%)	<0.01

MSAF: Meconium-stained amniotic fluid

Table 2. Clinical outcomes and delivery room interventions

Outcome/ intervention	Total (n=76)	Turkish (n=36)	Non-Turkish (n=40)	p
Sepsis, n (%)	13 (17.1%)	4 (11.1%)	9 (22.5%)	0.03
Referral to NICU, n (%)	12 (15.8%)	5 (13.9%)	7 (17.5%)	0.65
Oxygen support, n (%)	11 (14.5%)	4 (11.1%)	7 (17.5%)	0.43
PPV and/or intubation, n (%)	1 (1.3%)	0 (0%)	1 (2.5%)	0.34

NICU: Neonatal intensive care unit, PPV: Positive predictive value

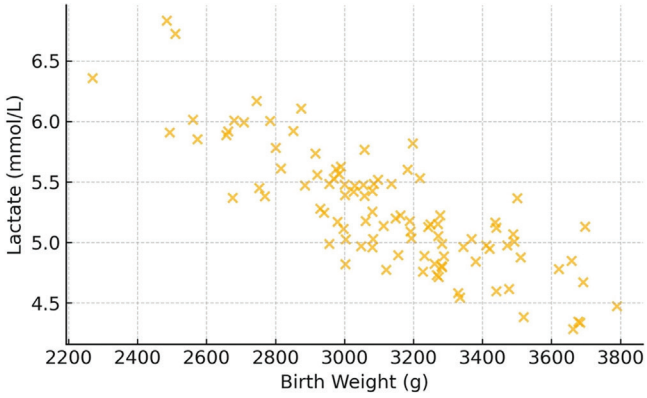

Figure 1. Prevalence of early neonatal sepsis by maternal nationality. The bar chart compares sepsis rates between newborns of Turkish mothers (11.1%) and those of non-Turkish mothers (22.5%), showing a statistically significant difference (p=0.03)

In the univariate analysis, a 1-minute Apgar score <7 (p<0.01) and the presence of maternal infection (p=0.02) were identified as significant risk factors associated with adverse outcomes. These factors were subsequently included in the multivariate model. Logistic regression analysis revealed that three factors significantly increased the odds of early complications: a 1-minute Apgar score below 7 [odds ratio (OR) 3.4, 95% confidence interval (CI) 1.1-9.8], maternal infection (OR 2.8, 95% CI 1.0-8.2), and inadequate prenatal care (OR 2.5, 95% CI 1.0-6.9). Nationality was not an independent predictor once these variables were controlled for (Table 3).

Discussion

The findings from this study reinforce the importance of specific clinical factors in predicting early complications among term infants exposed to MSAF. Specifically, low Apgar scores, the presence of maternal infection, and limited access to prenatal care emerged as key risk indicators. These results are consistent with previous research highlighting the protective effects of early and adequate antenatal monitoring (5-7).

Although higher rates of complications were noted among infants born to non-Turkish mothers, these outcomes were more likely tied to differences in care access and maternal health parameters rather than nationality itself (8). Once confounding variables such as prenatal care adequacy were incorporated into the analysis, nationality no longer had a significant independent impact.

Barriers such as language, socioeconomic status, and unfamiliarity with the healthcare system may limit how often migrant mothers seek or receive prenatal care (9,10). Addressing these gaps through community outreach programs, language support services, and culturally tailored health education could make a meaningful difference (12). Explaining the value of prenatal visits in multiple languages and encouraging early care enrollment may also improve continuity (13).

Table 3. Multivariate logistic regression analysis

Risk factor	OR	95% CI	p
Apgar 1-min <7	3.2	1.4-7.3	<0.01
Maternal infection	2.8	1.2-6.5	0.02
Non-Turkish nationality	1.9	0.9-4.1	0.09
No prenatal care	2.1	1.0-4.5	0.04

OR: Odds ratio, CI: Confidence interval

Study Limitations

This study was conducted in a single tertiary center, which may limit the generalizability of the findings. The retrospective nature of the study carries inherent limitations, including the possibility of incomplete records. Additionally, long-term neonatal outcomes beyond the first 72 hours were not evaluated. However, the findings remain relevant for urban centers serving diverse patient populations.

Conclusion

In term infants with MSAF, early complications were most strongly predicted by a low 1-minute Apgar score, maternal infection, and inadequate prenatal care. These factors had a greater impact than maternal nationality, which lost significance after statistical adjustment. Enhancing outreach and prenatal education, particularly for migrant families, while ensuring consistent follow-up for all mothers, may help reduce early neonatal complications.

Ethics

Ethics Committee Approval: This retrospective cohort study was conducted at University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, a tertiary care center in İstanbul. Ethical approval was granted by the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (decision no: 2025/08/20/983, date: 07.07.2025).

Informed Consent: Since only anonymized patient data were used, individual consent was not necessary.

Footnotes

Authorship Contributions

Concept: Y.K., E.C., Design: Y.K., E.C., Data Collection or Processing: Y.K., E.C., Analysis or Interpretation: Y.K., E.C., Literature Search: Y.K., Writing: Y.K., E.C.

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ORIGINAL RESEARCH

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Investigation of Predictive and Prognostic Factors in Metastatic Renal Cell Carcinoma (mRCC) Patients Receiving First-line Treatment: A Retrospective Single-center Experience

Birinci Basamak Tedavi Alan Metastatik Renal Hücreli Karsinom (mRCC) Hastalarında Prediktif ve Prognostik Faktörlerin Araştırılması: Retrospektif Tek Merkez Deneyimi

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Abstract

Objective: We conducted this study to assess the efficacy and identify prognostic factors associated with immunotherapy (IO) combination therapies—including IO+IO and IO+tyrosine kinase inhibitor (TKI) regimens—in patients with metastatic renal cell carcinoma (RCC).

Method: We examined 24 patients with metastatic RCC who received first-line IO+IO or IO+TKI combination therapy at Department of Medical Oncology, İstanbul Medipol University between 2022 and 2025. Demographic and clinicopathological characteristics of the patients, along with their treatment responses, were evaluated. An analysis of progression-free survival (PFS) and overall survival (OS) was conducted using Kaplan-Meier and Cox regression models. We also analyzed various prognostic factors to see how they impacted survival.

Results: Most patients were male (79.2%), and the median age was 56 years. The most common metastatic sites were lymph nodes (63%) and lungs (50.3%). The majority of patients had clear cell carcinoma histology (83.3%). Treatment responses observed were 16.7% complete response, 62.5% partial response, 12.5% stable disease, and 8.3% progressive disease. Thus, the overall response rate was found to be 79.2%. The median OS was 41.8 months, and the median PFS was 25.87 months. In the univariate analysis, the stage at diagnosis,

Öz

Amaç: Bu retrospektif, tek merkezli çalışma, metastatik renal hücreli karsinom (RCC) tanılı hastalarda immünoterapi (İO) ve İO kombinasyonu veya İO ile tirozin kinaz inhibitörü (TKİ) tedavilerinin (İO+İO veya İO+TKİ) etkinliğini ve prognostik faktörleri değerlendirmeyi amaçlamıştır.

Yöntem: 2022-2025 yılları arasında İstanbul Medipol Üniversitesi Tıbbi Onkoloji Kliniği'nde metastatik RCC tanısı ile birinci basamakta İO+İO veya İO+TKİ kombinasyon tedavisi alan 24 hasta incelendi. Hastaların demografik ve klinikopatolojik özellikleri ile tedavi yanıtları değerlendirildi. Progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) analizleri Kaplan-Meier ve Cox regresyon modelleri kullanılarak yapıldı. Sağkalımlar üzerine etkili prognostik faktörler analiz edildi.

Bulgular: Hastaların çoğu erkekti (%79,2) ve ortanca yaş 56 yıldı. En sık metastaz bölgeleri lenf nodu (%63) ve akciğer (%50,3) idi. Hastaların büyük çoğunluğu berrak hücreli karsinom histolojisine sahipti (%83,3). Tedavi yanıtları %16,7 tam yanıt, %62,5 kısmi yanıt, %12,5 stabil hastalık ve %8,3 progresif hastalık (PD) olarak gözlendi. Böylece, objektif yanıt oranı %79,2 olarak bulundu. Medyan genel sağkalım (OS) 41,8 ay, medyan PFS 25,87 ay olarak hesaplandı. Tek değişkenli analizde tanı evresi, histoloji, ve nefrektomi varlığı PFS

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Abstract

histology, and presence of nephrectomy were found to be significant for PFS, whereas in the multivariate analysis, only the stage at diagnosis was identified as an independent prognostic factor (p=0.03, hazard ratio: 5.64). For OS, while the stage at diagnosis, histology, and presence of nephrectomy were significant in the univariate analysis, no independent prognostic factors were identified in the multivariate analysis.

Conclusion: IO+IO or IO+TKI combination therapies in metastatic RCC are associated with high response rates and long survival durations. The stage at diagnosis is an independent prognostic factor for PFS. This factor is of critical importance in evaluating patient prognosis and personalizing treatment decisions.

Keywords: First-line treatment, immunotherapy, metastatic renal cell carcinoma, side effects, survival, tyrosine kinase inhibitors

Öz

için anlamlı bulunurken, çok değişkenli analizde sadece tanı evresi bağımsız prognostik faktör olarak belirlendi (p=0,03, tehlike oranı: 5,64). OS için tek değişkenli analizde ise, tanı evresi, histoloji ve nefrektomi varlığı anlamlı iken, çok değişkenli analizde herhangi bir bağımsız prognostik faktör bulunamadı.

Sonuç: Metastatik RCC'de İO+İO veya İO+TKİ kombinasyon tedavileri yüksek yanıt oranları ve uzun sağkalım süreleri ile ilişkilidir. Tanı anındaki evre PFS için bağımsız prognostik faktördür. Bu faktör, hastaların prognozunu değerlendirmede ve tedavi kararlarını kişiselleştirmede kritik öneme sahiptir.

Anahtar kelimeler: Birinci basamak tedavi, immünoterapi, metastatik renal hücreli karsinom, sağkalım, tirozin kinaz inhibitörleri, yan etkiler

Introduction

Renal cell carcinoma (RCC) is a significant global health issue. In 2022, there were 434,840 new cases, and in 2020, it was the 15th leading cause of cancer-related deaths, resulting in over 179,000 fatalities (1,2). The disease is most prevalent in those aged 60 to 70 and is more common in men, with about three male cases for every two in women (3).

Risk factors associated with RCC include systolic hypertension [relative risk (RR) 1.4], diastolic hypertension (RR: 2.3), smoking (RR: 1.6), kidney disease (up to RR: 12.3 in dialysis patients), environmental exposures, and obesity (RR 1.9), which accounts for over 16% of global cases. Obese patients are less likely to present with advanced-stage disease compared to patients with a normal weight (4-9).

RCC starts in the epithelial cells of the kidney's outer layer, the renal cortex. It is diagnosed by examining a tissue sample's appearance and through immunohistochemistry (10). Based on the World Health Organization classification, there are over 20 subtypes of malignant renal cell tumors (11). The three most common are clear cell RCC (75-80%), papillary RCC (10-15%), and chromophobe RCC (5%) (11).

Most cases of clear cell RCC—up to 90%—are associated with a loss of the Von Hippel-Lindau (VHL) tumor suppressor gene (12). While the majority of RCC cases are sporadic (not inherited), 5% to 16% of advanced (Stage III or IV) cases are due to hereditary syndromes (13). VHL disease accounts for 2% of all cases (13).

The classic signs of kidney cancer—flank pain, a lump in the abdomen, and blood in the urine—are rarely seen together, appearing in less than 10% of new RCC diagnoses (14).

Additionally, paraneoplastic syndromes, which are symptoms caused by the cancer's effect on other organs, occur in 10% to 40% of patients (15). These can include fever, high blood calcium, anemia, an increase in platelets, an increase in red blood cells, and high blood pressure (16-18).

When RCC is diagnosed, 70% of cases are in Stage I, while 11% are already in Stage IV (19-21). The prognosis is closely tied to both the tumor's stage and grade (22). Approximately 10% of new RCC patients have metastatic disease at the time of diagnosis (23). The cancer most commonly spreads to the lungs (70%), followed by the lymph nodes (45%), bones (32%), liver (18%), adrenal gland (10%), and the brain (8%) (24,25).

According to the International Metastatic RCC Database Consortium (IMDC), a patient's chances of survival are lower if they have any of the following six risk factors: an elevated neutrophil-to-lymphocyte ratio (NLR), a high platelet count, low hemoglobin, high calcium, a Karnofsky performance score below 80%, or if they required systemic treatment less than a year after their diagnosis (26). In patients with metastatic RCC receiving modern systemic combination therapies, 18-month overall survival (OS) rates have been reported to be 90% to 93% in the favorable risk group, 78% to 83% in the intermediate-risk group, and 50% to 74% in the poor-risk group (26). In a study of 645 patients with metastatic RCC, the median OS was found to be 22 months, with a 95% CI ranging from 20.2 to 26.5 months (27). These rates show a significant improvement compared to the period before the use of immune checkpoint therapies.

Cytotoxic chemotherapy is typically not effective for metastatic RCC (28). Instead, the main treatments are

immunotherapy (IO) and tyrosine kinase inhibitors (TKIs) (28). Current IOs work by blocking specific protein interactions, such as those involving progressive disease (PD)-1/PD-L1/PD-L2 and CTLA-4/CD80/CD86 (28). For advanced and metastatic RCC, the initial treatment is a combination of therapies that use IOs (28). For patients with metastatic clear cell RCC who have an intermediate or poor risk score based on the IMDC criteria, the approved initial treatment is a combination of ipilimumab and nivolumab (28). When patients with metastatic RCC achieve a complete response to IO or have oligometastatic disease, they may become disease-free. A three-year disease-free survival rate of approximately 22% to 27% can be achieved (29). A striking example of this success is seen with high-dose interleukin-2-based IO. While only 5% of patients had a complete response, 59% of those who did remained alive and cancer-free for a median of 10.5 years without needing further treatment (30,31).

The regimen demonstrated a superior OS profile compared to sunitinib, yielding a 5-year OS probability of 43% (32,33). While direct head-to-head comparisons of different IO+TKI combinations are lacking, these regimens consistently achieve higher overall response rate (ORR)—ranging from 55% to 71%—than the ipilimumab plus nivolumab combination (34-36). However, most patients experience side effects such as hypertension and diarrhea with TKI treatment (34). Treatment decisions should be individualized, considering the patient's risk tolerance. Based on the results of the CARMENA study, for most patients with advanced or metastatic disease, cytoreductive nephrectomy is no longer recommended (37).

In RCC patients receiving systemic treatment, potential immune-related side effects should be managed by a multidisciplinary team. Clinically useful predictive biomarkers to guide RCC treatment have not yet been identified. While molecular subtypes based on gene expression profiling have been reported, they have not been prospectively validated for clinical use (38).

Therefore, we retrospectively evaluated the data of patients who received IO+IO or IO+TKI as first-line treatment at our center between 2022 and 2025 and investigated the predictive and prognostic factors that may influence response and survival.

Materials and Methods

Ethics Committee Approval

All patients or their immediate family members provided informed consent to participate in the study. The İstanbul Medipol University Ethics Committee approved the study on August 6, 2025 (decision no: E-10840098-202.3.02-5070).

Patients

Between 2022 and 2025, 200 patients who received treatment for metastatic RCC at the Medical Oncology Department of İstanbul Medipol University were retrospectively screened, and data from 24 patients who received IO+IO or IO+TKI therapy as first line treatment were analyzed. Patients who received single IO or TKI were not included in the study. In addition, patients with missing information were excluded from the analysis. Patients receiving adjuvant IO were also excluded from the study. Early-stage patients receiving adjuvant therapy were not included in the study. Patients receiving post-first-line therapy were also excluded from the study.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), and categorical variables as frequencies and percentages.

Survival analyses, including progression-free survival (PFS) (time from metastatic diagnosis to progression or death) and OS (time from metastatic diagnosis to death), were performed with the Kaplan-Meier method and compared using the log-rank test.

We used univariate analysis to screen for potential prognostic factors, followed by multivariate Cox proportional hazards modeling to identify independent predictors for both PFS and OS. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to express the RR.

Data are reported as mean (standard deviation), median (min-max), 95% CI, and percentages. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

In the study of 24 patients, the demographic and clinical characteristics showed that 79.2% (19 patients) were male, and 20.8% (5 patients) were female. The median age was 56.00 years, ranging from 28 to 76 years. Thirteen patients (54.2%) were under 60 years of age, while 45.8% (n=11) were 60 years or older. At the time of diagnosis, 50.0% (n=12) of the patients were staged as Stage IV, 33.3% (n=8) as Stage II, 12.5% (n=3) as Stage III, and 4.2% (n=1) as Stage I. According to the Eastern cooperative oncology group (ECOG) performance status (PS), 79.2% (n=19) of the

patients had an ECOG PS of 0, while the remaining 20.8% (n=5) had an ECOG PS of 1.

Regarding metastasis sites, the most common site was the lymph node, found in 62.5% of patients. Additionally, lung metastasis was detected in 50%, bone in 33.3%, liver in 12.5%, and adrenal metastasis in 12.5%. It should be noted that one patient could have more than one metastatic site.

None of the patients had received prior adjuvant therapy. Histologically, the vast majority of patients (83.3%, n=20) had clear cell carcinoma histology, while 12.5% (n=3) had papillary and 4.2% (n=1) had chromophobe histology. Two patients (8.3%) had a sarcomatoid component. 62.5% (n=15) of the patients were in the IMDC intermediate-risk group, and 37.5% (n=9) were in the IMDC poor-risk group. There were no patients in the favorable-risk group.

Eleven patients (45.8%) had undergone nephrectomy, while 54.2% (n=13) had not. The mean NLR was 4.49 (median: 2.99), and the mean platelet-to-lymphocyte ratio (PLR) was 183.20 (median: 161.56).

Regarding the treatments administered, 50% (n=12) of the patients received nivolumab-cabozantinib, 25% (n=6) received pembrolizumab-axitinib, and 25% (n=6) received nivolumab-ipilimumab. Treatment responses were evaluated according to RECIST 1.1 criteria: Four patients (16.7%) showed complete response (CR), 15 patients (62.5%) showed partial response, three patients (12.5%) had stable disease (SD), and two patients (8.3%) had PD. The ORR was calculated as 79.2%. As of the time of data analysis, progression was observed in 54.2% (n=13) of patients under these treatments, while no progression was observed in 45.8% (n=11). The mean duration of treatment was 16.6 months (median: 17.10 months).

When survival data were examined, The median OS was 41.8 months, with a 95% CI of 10-115.6. On the other hand, the median PFS was 25.87 months, with a 95% CI of 12.89-38.83. PFS durations differed according to age groups; the median PFS was 21.2 months in patients under 60 years (<60), and 62.8 months in patients aged 60 and over (≥60) (p=0.5).

In the univariate analysis for PFS, only the stage at initial diagnosis (p=0.004), histology (p=0.04), and presence/absence of nephrectomy (p=0.038) were statistically significant prognostic factors. In other words, patients diagnosed at an earlier stage (stage 1 and stage 2) had significantly longer PFS durations compared to patients at a more advanced stage (stage 3 and stage 4). Other factors examined, such as age (p=0.503), gender (p=0.339), ECOG PS (p=0.216), NLR (p=0.57), PLR (p=0.6), presence of sarcomatoid component (p=0.885), and IMDC score (p=0.698) did not show a statistically significant effect on PFS. The treatment modality showed a borderline non-significance (p=0.067).

Multivariate models were constructed using factors significantly associated with outcomes in univariate analysis. For PFS, the model included stage at initial diagnosis, histology, nephrectomy status, and IMDC score. The OS analysis was further adjusted for treatment modality in addition to these factors.

In the multivariate Cox regression analysis for PFS, only the stage at initial diagnosis was found to be a statistically significant and independent prognostic factor (p=0.03, HR: 5.64, 95% CI: 1.18-26.96). A more advanced stage significantly increased the risk of progression. Histology, the presence of nephrectomy, and the IMDC score were not found to be influential factors for PFS in this model.

According to the univariate analysis for OS, the stage at initial diagnosis (p=0.005), histology (p=0.006), and presence or absence of nephrectomy (p=0.017) were statistically significant variables affecting OS. In other words, the median OS durations of patients diagnosed at an earlier stage were significantly longer than those of patients at a more advanced stage (p=0.005). Patients with clear cell histology had significantly longer OS durations than those with papillary and especially chromophobe histology (p=0.006). The presence or absence of nephrectomy also significantly affected OS (p=0.017). Patients who underwent nephrectomy had longer OS durations than those who did not.

For OS, while the stage at diagnosis, histology, and presence of nephrectomy were significant in the univariate analysis, no independent prognostic factors were identified in the multivariate analysis. Factors, such as stage at initial diagnosis (p=0.075, HR: 4.0, 95% CI: 0.87-18.36) histology (p=0.55, HR: 1.5, 95% CI: 0.38-5.94), nephrectomy (p=0.87, HR: 0.82, 95% CI: 0.079-8.54), and the treatment received (p=0.76, HR: 0.90, 95% CI: 0.47-1.72), did not show a statistically significant independent effect on OS in this model.

The most common side effects included hypothyroidism (6 patients, 25.0%), diarrhea (5 patients, 20.8%), and hepatitis (5 patients, 20.8%). Additionally, pruritus was observed in two patients (8.3%), Grade 2 hypertension related to axitinib in one patient, Grade 3 orthohyperkeratosis in one patient, and IO-related bullous pemphigoid in

one patient. When the grades of the side effects were examined, 77.8% (n=14) were reported as Grade 2, 16.7% (n=3) as Grade 3, and 5.6% (n=1) as Grade 1. Three patients experienced Grade 3 immune-related adverse events (hepatitis, orthohyperkeratosis, bullous pemphigoid) required steroid intervention. Importantly, no patient discontinued treatment as a result of these side effects.

The results of univariate and multivariate analyses for OS and PFS are summarized in Tables 1 and 2. Toxicity type, grade, and number of patients affected (Grade 1-2 vs. ≥3) are summarized in Table 3.

Kaplan-Meier survival curves for PFS and OS are presented in Figure 1 and Figure 2.

Table 1. Univariate and multivariate analysis for PFS

Variable	Median PFS (months)	Univariate p-value	HR (95% CI)	Multivariate p-value
Age, years		0.50		
<60	21.23			
>60	32.83			
Gender		0.33		
Female	19.33			
Male	28.23			
Stage at initial diagnosis		0.004	5.64 (1.18-26.96)	0.03
Stage 1 Stage 2 Stage 3	165.43 117.06 25.86			
Stage 4	10.03			
ECOG PS		0.21		
0	62.83			
1	21.23			
Histology		0.04	1.83 (0.67-4.98)	0.23
Clear cell	25.86			
Papiller	28.23			
Chromophobe	6.36			
Sarcomatoid component		0.88		
Present	4.53			
Absent	25.86			
IMDC score		0.698		
Intermediate	28.23			
Poor	21.23			
Nephrectomy		0.038	0.39 (0.03-3.93)	0.42
Present	62.83			
Absent	19.33			
Treatment modality		0.067		
Pembrolizumab-axitinib	10.03			
Nivolumab-cabozantinib Nivolumab-ipilimumab	19.33 117.06			
NLR		0.57		
<2.98	25.86			
≥2.98	19.33			
PLR		0.60		
<161.5	62.83			
≥161.5	21.23			

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, ECOG PS: Eastern cooperative oncology group performance status, IMDC: International metastatic RCC database consortium, CI: Confidence interval, HR: Hazard ratio, RCC: Renal cell carcinoma, PFS: Progression-free survival

Table 2. Univariate and multivariate analysis for OS

Variable	Median OS (months)	Univariate p-value	HR (95% CI)	Multivariate p-value
Age, years		0.78		
<60	35.76			
>60	41.80			
Gender		0.086		
Female	19.33			
Male	124.4			
Stage at initial diagnosis		0.005	4.0 (0.87-18.36)	0.075
Stage 1 Stage 2 Stage 3	167.4 124.4 35.76			
Stage 4	16.06			
ECOG PS		0.084		
0	167.4			
1	21.23			
Histology		0.006	1.5 (0.38-5.94)	0.55
Clear cell	124.43			
Papiller	41.80			
Chromophobe	6.36			
Sarcomatoid component		0.61		
Present	7.0			
Absent	41.8			
IMDC score		0.26		
Intermediate	41.8			
Poor	21.23			
Nephrectomy		0.017	0.82 (0.079-8.54)	0.87
Present	124.43			
Absent	21.23			
Treatment modality		0.059	0.90 (0.47-1.72)	0.76
Pembrolizumab-axitinib	16.06			
Nivolumab-cabozantinib Nivolumab-ipilimumab	NR 124.43			
NLR		0.74		
<2.98	35.76			
≥2.98	124.43			
PLR		0.21		
<161.5	167.4			
≥161.5	28.76			

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, ECOG PS: Eastern cooperative oncology group performance status, IMDC: International metastatic RCC database consortium, CI: Confidence interval, HR: Hazard ratio, RCC: Renal cell carcinoma, NR: Not reached, OS: Overall survival

Discussion

The main findings of our study show that the stage at initial diagnosis is an independent prognostic factor for PFS. In the OS analyses, the univariate analysis showed that the stage at initial diagnosis, histology, and the presence of nephrectomy were significant prognostic factors influencing OS. It is widely accepted that the stage at the time of diagnosis is a critical indicator for prognosis, and our finding was consistent with the literature (22,23). Similarly, it is known that the histological subtype, especially clear cell carcinoma, is associated with a better prognosis (11).

Table 3. Toxicity type, grade, and number of patients affected (Grade 1-2 vs. ≥3)

Toxicity type	Patients affected (n)	Incidence (%)	Grade 1 (n)	Grade 2 (n)	Grade ≥3 (n)	Key notes/association
Hypothyroidism	6	25.0%	Included in n=1 (total Grade 1)	Included in n=14 (total Grade 2)	0	Most common side effect.
Diarrhea	5	20.8%	-	Included in n=14	0	-
Hepatitis	5	20.8%	-	Included in n=14	1	One of the Grade 3 events requiring intervention.
Pruritus (itching)	2	8.3%	-	Included in n=14	0	-
Hypertension	1	4.2%	0	1	0	Grade 2; related to axitinib.
Orthohyperkeratosis	1	4.2%	0	0	1	Grade 3.
Bullous pemphigoid	1	4.2%	0	0	1	IO-related Grade 3 event.
Total events graded	-	-	1	14	3	77.8% were Grade 2, and 16.7% were Grade 3.

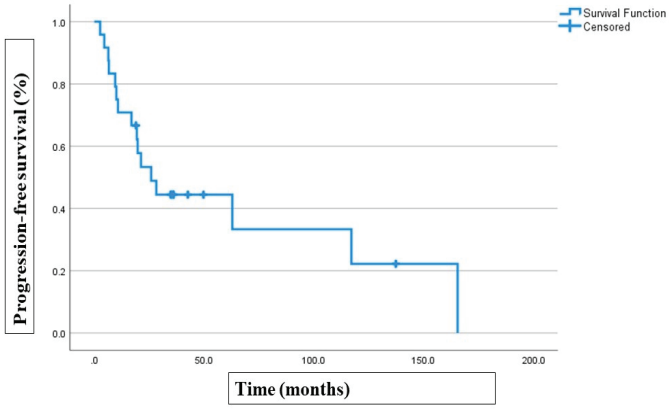

Figure 1. Kaplan-Meier curves for progression-free survival

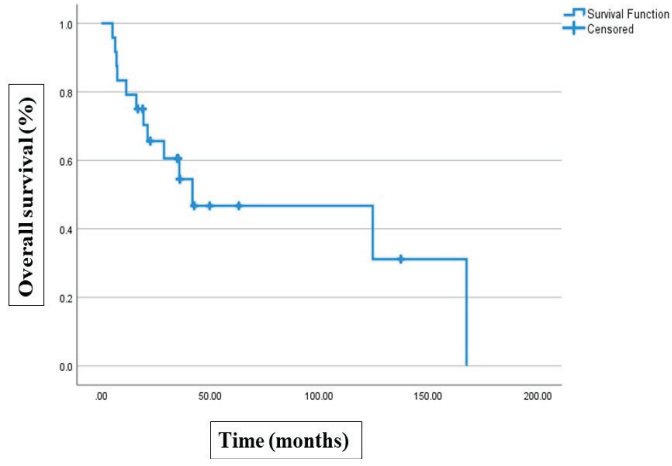

Figure 2. Kaplan-Meier curves for overall survival

Although the significant effect of nephrectomy in the univariate analysis highlights the importance of primary tumor control, its failure to be an independent factor in the multivariate analysis supports the existing conflicting literature.

While the stage at diagnosis, histology, and presence of nephrectomy were significant in the univariate analysis for OS, no independent prognostic factors were identified in the multivariate analysis.

Interestingly, factors that appeared significant in the univariate analysis, such as histology and whether a nephrectomy was performed, were not significant in the multivariate OS analysis. This suggests that the prognostic effects of these variables may be partially explained by or are correlated with more powerful prognostic factor included in the model, such as the stage at initial diagnosis. The role of cytoreductive nephrectomy in metastatic kidney cancer is changing with the development of modern systemic therapies, and it is no longer routinely recommended for some patient groups based on the results of the CARMENA study (37). Our study's finding suggests that the independent prognostic effect of nephrectomy may be overshadowed by other clinical prognostic factors in a multivariate model. This may be related to the small number of patients in our study.

In the PFS analyses, the univariate analysis found the stage at initial diagnosis and histology to be significant,

while only the stage at initial diagnosis was identified as an independent prognostic factor for PFS in the multivariate analysis. This indicates that the initial stage of the disease plays a critical and independent role in determining the risk of progression. The lack of significance for histology in the multivariate PFS analysis may again be due to the influence of other strong factors. Other factors such as ECOG PS, NLR, PLR, and the presence of a sarcomatoid component did not show a significant prognostic effect in the univariate analyses for both PFS and OS. The lack of statistical significance for these factors, which have been shown to be prognostic in larger cohorts (NLR, PLR), is primarily attributed to the limited sample size (n=24). The low statistical power prevented these factors from reaching the threshold of significance. Additionally, the NLR and PLR values were treated as continuous variables, but defining a specific cut-off point (e.g., NLR >3 or 5) might have revealed prognostic value. Although some studies have shown the prognostic importance of these markers (26), this significance may not have been reached in our small patient group.

Due to the relatively small sample size, inclusion of multiple covariates in the multivariable Cox model may have introduced a risk of overfitting, potentially affecting the stability of HR estimates. Therefore, multivariable findings should be interpreted cautiously.

The median OS of 41.8 months and the median PFS of 25.87 months observed under treatment reflect a significant improvement compared to the period before the use of immune checkpoint therapies in metastatic RCC patients (26,27). The observed side effects (such as hypothyroidism, diarrhea, and hepatitis) also overlap with the known toxicity profiles of IO and TKI combinations (28). The treatment response rates of the patients included in the study appear to be consistent with the high ORR reported in the literature for modern immuno-oncology-based combination therapies (rates ranging from 55% to 71% have been reported) (34-36).

Study Limitations

Our study has some important limitations. The most notable limitation is the small sample size of only 24 patients. This may have reduced the statistical power, causing some clinically important factors to fail to reach statistical significance. Since this was a retrospective study conducted at a single center, its findings may not apply to a wider patient population and introduces potential biases in data collection. The presentation of multi-categorical variables (such as histology, treatment modality) with a single degree of freedom (df=1) in the multivariate analysis prevented us from providing detailed results for specific subcategory comparisons.

Conclusion

Our findings re-emphasize that the stage at initial diagnosis is critically important independent prognostic factor for predicting PFS in metastatic RCC patients. This factor maintains its place in clinical practice for evaluating patient prognosis and individualizing treatment strategies. Future research should validate these findings in larger, multi-center, and prospective patient cohorts. Additionally, the investigation of new and validated biomarkers to further guide RCC treatment will help us predict treatment response and survival more accurately. Such studies will contribute to the development of personalized medicine approaches.

Ethics

Ethics Committee Approval: The İstanbul Medipol University Ethics Committee approved the study on August 6, 2025 (decision no: E-10840098-202.3.02-5070).

Informed Consent: All patients or their immediate family members provided informed consent to participate in the study.

Footnotes

Authorship Contributions

Concept: J.H., E.K., Ö.F.Ö., Ö.Y., A.B., Design: J.H., E.K., Ö.A., A.B., Data Collection or Processing: J.H., E.K., Ö.A., Analysis or Interpretation: J.H., E.K., Ö.F.Ö., Ö.Y., A.B., Literature Search: J.H., Ö.A., Ö.F.Ö., Ö.Y., Writing: J.H., A.B.

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

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ORIGINAL RESEARCH

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Palliative Care in the Age of Artificial Intelligence: Evaluation of Healthcare Workers' Awareness and Attitudes

Yapay Zeka Çağında Palyatif Bakım: Sağlık Çalışanlarının Farkındalık Düzeyi ve Tutumlarının Değerlendirilmesi

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Abstract

Objective: Palliative care plays a critical role in improving quality of life for patients with life-limiting illnesses; however, misconceptions, educational gaps, and emerging technological challenges continue to affect its clinical implementation. This study aimed to evaluate healthcare professionals' awareness and attitudes toward palliative care and to explore their perceptions of artificial intelligence (AI) applications in palliative care practice.

Method: This descriptive cross-sectional study was conducted between September 1 and 30, 2025, among healthcare professionals working in tertiary care hospitals. A structured questionnaire, developed through literature review and expert consultation, was administered to physicians, nurses, and allied health professionals. The questionnaire included items on palliative care awareness and attitudes, as well as perceptions of AI applications. Content validity was confirmed (=0.88), and internal consistency was satisfactory (Cronbach's α=0.82-0.86). Data were analyzed using descriptive statistics.

Results: A total of 337 participants were included in the analysis (response rate: 96.3%). Most participants demonstrated high awareness of palliative care principles, with 91.6% correctly identifying quality of life improvement as its primary goal. The majority rejected misconceptions that palliative care is limited to terminal stages (73.8%) or oncology patients (88.1%). Despite this, 49.6% reported insufficient training in opioid use, and 19.8% felt inadequately prepared for difficult patient-family conversations.

Öz

Amaç: Palyatif bakım, yaşamı tehdit eden hastalıklarda yaşam kalitesini artırmada temel bir rol oynamaktadır; ancak yanlış inanışlar, eğitim eksiklikleri ve gelişen teknolojilere ilişkin belirsizlikler klinik uygulamayı etkilemektedir. Bu çalışmanın amacı, sağlık profesyonellerinin palyatif bakıma yönelik farkındalık ve tutumlarını değerlendirmek ve palyatif bakımda yapay zeka (YZ) uygulamalarına ilişkin algılarını incelemektir.

Yöntem: Bu tanımlayıcı kesitsel çalışma, 1-30 Eylül 2025 tarihleri arasında üçüncü basamak sağlık kuruluşlarında çalışan sağlık profesyonelleri ile yürütülmüştür. Literatür taraması ve uzman görüşleri doğrultusunda geliştirilen yapılandırılmış bir anket; hekimlere, hemşirelere ve yardımcı sağlık personeline uygulanmıştır. Anket palyatif bakım farkındalık ve tutumları ile YZ algılarını içermektedir. İçerik geçerliği sağlanmış (=0,88) ve iç tutarlılık katsayıları kabul edilebilir düzeyde bulunmuştur (Cronbach α=0,82-0,86). Veriler tanımlayıcı istatistiklerle analiz edilmiştir.

Bulgular: Toplam 337 katılımcı çalışmaya dahil edilmiştir (yanıt oranı: %96,3). Katılımcıların büyük çoğunluğu palyatif bakımın temel amacını doğru şekilde tanımlamış (%91,6) ve palyatif bakımın yalnızca terminal dönem (%73,8) veya onkoloji hastalarıyla (%88,1) sınırlı olduğu yönündeki yanlış inanışları reddetmiştir. Buna karşın, katılımcıların %49,6'sı opioid kullanımı konusunda ek eğitime ihtiyaç duyduğunu, %19,8'i ise hasta-aile görüşmelerinde kendini yetersiz hissettiğini belirtmiştir. YZ'ye yönelik tutumlar heterojen olup, %37,7'si YZ kullanımını desteklerken gizlilik (%86,7) ve empati

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Abstract

Attitudes toward AI showed a heterogeneous distribution: 37.7% supported broader AI implementation, while 45.7% remained undecided. Concerns regarding patient confidentiality (86.7%) and loss of empathy (54.0%) were prominent, although most participants expressed willingness to receive training on AI applications.

Conclusion: Healthcare professionals demonstrated generally positive awareness of palliative care; however, important gaps persist in clinical competencies such as opioid management and communication skills. AI offers potential benefits for palliative care delivery, but ethical concerns highlight the need for cautious, human-centered integration supported by structured education and governance frameworks.

Keywords: AI-assisted healthcare, healthcare professionals, palliative care awareness

Öz

kaybı (%54,0) önemli kaygılar olarak öne çıkmıştır. Buna rağmen katılımcıların çoğu YZ eğitimi almaya isteklidir.

Sonuç: Sağlık profesyonellerinin palyatif bakıma yönelik farkındalığı genel olarak olumlu olmakla birlikte, klinik becerilerde önemli eksiklikler bulunmaktadır. YZ, palyatif bakımda potansiyel katkılar sunsa da etik ve insani boyutlar gözetilerek, yapılandırılmış eğitim ve düzenleyici çerçevelerle desteklenen bir entegrasyon gerekmektedir.

Anahtar kelimeler: Palyatif bakım farkındalığı, sağlık profesyonelleri, YZ-destekli sağlık

Introduction

Palliative care is a holistic and multidisciplinary care model that aims to improve the quality of life of individuals living with life-limiting illnesses by addressing physical, psychological, social, and spiritual needs. The World Health Organization emphasizes that palliative care should not be restricted to terminal stages but should be integrated early in the disease trajectory (1). Nevertheless, the integration of palliative care into routine clinical practice remains heterogeneous worldwide, with persistent variations in healthcare workers' awareness, misconceptions regarding eligibility criteria, and uncertainty about the appropriate timing of referral (2-4).

Although recent literature suggests an overall improvement in conceptual knowledge of palliative care, this knowledge is not consistently translated into clinical practice. A meta-analysis including more than 30 international studies demonstrated that misconceptions such as "palliative care begins only when curative treatment ends" remain prevalent, particularly among non-specialist clinicians (4). These findings indicate that increasing awareness alone is insufficient unless it is supported by structured educational programs and implementable care models.

At the same time, the growing demand for palliative care services — driven by population aging, increasing cancer prevalence, and the rising burden of chronic diseases — has further underscored the need for adequately trained healthcare professionals (5). However, several barriers continue to limit effective palliative care delivery, including hesitancy toward opioid use, moral distress during end-of-life decision-making, communication challenges with patients and families, and insufficient interdisciplinary collaboration (6,7). The palliative care knowledge scale, developed and validated by Kozlov et al. (6), has demonstrated that education significantly improves knowledge; yet notable gaps persist in translating this knowledge into routine clinical practice. Therefore, systematically assessing healthcare workers' perceptions and attitudes toward palliative care is essential for identifying educational needs and informing service planning.

In parallel with these traditional challenges, healthcare systems are undergoing a rapid digital transformation in which artificial intelligence (AI) is increasingly being introduced as a supportive tool for clinical decision-making. In the context of palliative care, AI-based applications have shown potential in prognostication, early identification of symptom trajectories, patient monitoring, risk stratification for clinical deterioration, and decision support systems (8,9). In oncology settings, AI-assisted mortality prediction models have been reported to estimate 6-12-month survival with accuracies ranging from 75% to 92% (10). Additionally, emerging studies have explored the use of natural language processing–based systems to support empathic communication and detect early pain signals through physiological pattern recognition (11).

Despite these promising developments, the adoption of AI in palliative care remains limited. Ethical concerns—including patient privacy, algorithmic transparency, accountability in clinical decision-making, and the potential erosion of human empathy—represent major barriers to implementation in this sensitive, human-centered field (12-14). Importantly, previous research has demonstrated

that healthcare professionals' acceptance and readiness are key determinants of successful technology integration, highlighting the need to understand their perceptions toward AI applications.

Against this background, a combined examination of healthcare workers' knowledge and attitudes toward palliative care, together with their perceptions of AI-based applications, is both timely and necessary. However, the existing literature addressing this dual perspective remains scarce, particularly in healthcare systems where AI integration is still emerging and palliative care education varies considerably. Therefore, the present study aims to evaluate healthcare workers' awareness of and attitudes toward palliative care and to explore their perceptions of AI applications in this field. If both traditional and technological dimensions are addressed, the findings may inform targeted training programs, guide resource allocation, and support the development of ethical, human-centered AI integration policies to strengthen future palliative care delivery.

Materials and Methods

Study Design and Setting

This study was designed as a descriptive cross-sectional survey and was primarily aimed at providing an exploratory assessment of healthcare workers' awareness and attitudes rather than testing predefined hypotheses. Data were collected from healthcare professionals working in tertiary care hospitals between September 1 and September 30, 2025. Ethical approval was obtained from the İstanbul Medipol University Ethics Committee (decision no: 1137, date: 23.09.2025). Participation was voluntary, and written informed consent was obtained from all participants. This study was primarily designed as an exploratory assessment to map awareness and attitudes rather than to test predefined hypotheses.

Participants

The study population comprised physicians (specialists, residents, associate professors, and professors), nurses, and allied health professionals. Inclusion criteria were: (i) age ≥18 years, (ii) current employment in the hospital, and (iii) voluntary participation. Exclusion criteria included refusal to participate and incomplete survey responses.

Questionnaire Development and Validation

The questionnaire was developed through an extensive literature review and consultation with three palliative care specialists and one academic with expertise in AI. Content validity was assessed using expert ratings, yielding a content validity index of 0.88.

A pilot study was conducted with 30 healthcare professionals to assess clarity, relevance, and completion time. Based on pilot feedback, minor wording adjustments were made. Pilot data were excluded from the final analysis.

Internal consistency reliability was evaluated using Cronbach's alpha coefficients:

- Palliative care awareness/attitude section: α=0.82
- AI perception section: α=0.86.

Data Collection Tool

The questionnaire consisted of two main sections.

Palliative care awareness and attitudes (21 items):

- Profession and years of professional experience
- Referral practices to palliative care services
- Likert-scale items (1= strongly disagree, 5= strongly agree) assessing scope and objectives of palliative care, holistic approach, family involvement, opioid use, communication skills, training needs, psychosocial support, and ethical considerations
- Open-ended items for additional comments.

AI in palliative care (15 items):

For the purpose of this study, AI applications were defined as clinical decision-support tools, prognostic models, symptom-monitoring systems, and communication-support technologies potentially applicable in palliative care settings.

- Awareness of AI applications in symptom management, prognosis prediction, and patient communication
- Perceived benefits, risks, and ethical concerns related to AI use
- Likert-scale items evaluating attitudes toward AI-based patient monitoring, clinical decision-support systems, empathetic communication support, and family support
- Training needs and willingness to receive education on AI.

Variables such as medical specialty and duration of direct experience in palliative care were not included to limit questionnaire length and reduce response burden, given the exploratory nature of the study.

Sample Size

The required sample size was calculated using a prevalence-based approach with a 95% confidence level and a 5% margin of error. Given the descriptive and exploratory design of the study, a minimum sample size of 350 participants was determined. After exclusion of incomplete questionnaires, 337 valid responses were analyzed, yielding a response rate of 96.3%.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies and percentages for categorical variables and as mean ± standard deviation for continuous variables.

Consistent with the exploratory and descriptive design, no hypothesis-driven comparisons or multivariable inferential analyses (e.g., chi-square tests or logistic regression) were planned. Therefore, the analysis focused exclusively on descriptive statistics to summarize overall response patterns and trends.

Results

A total of 350 healthcare professionals were approached, and after excluding incomplete responses, 337 participants were included in the final analysis, yielding a response rate of 96.3%. The study population consisted of physicians (specialists, residents, and academic faculty), nurses, and allied health professionals. The distribution of professional experience was as follows: 0-1 years (15.0%), 2-4 years (23.3%), 5-10 years (33.4%), and ≥11 years (28.3%) (Figure 1). Both early-career and experienced healthcare workers were represented in the study sample.

Overall awareness of palliative care was high (Table 1). Forty-one percent of participants reported referring at least one patient to palliative care services within the past three years. A majority of participants disagreed with the statement that palliative care is intended only for terminal patients (73.8%), while 10.9% agreed with this statement and 15.3% were neutral. Similarly, 88.1% of respondents disagreed that palliative care is limited to oncology patients, 6.4% agreed, and 5.5% were neutral.

Most participants correctly identified improvement in quality of life as the primary goal of palliative care (91.6%) and more than 85% agreed that psychosocial support is an essential component of palliative care. Regarding perceived competencies, 49.6% of participants reported a need for additional training in opioid use, while 50.4% indicated that they felt sufficiently trained. With respect to communication skills, 19.8% reported feeling inadequately prepared for difficult patient-family conversations, 56.8% reported feeling adequately prepared, and 23.4% reported feeling neutral (Table 1).

Attitudes toward AI in palliative care showed a heterogeneous distribution of responses (Table 2). While 37.7% of participants supported broader implementation of AI applications in palliative care, 45.7% remained undecided and 16.6% opposed broader implementation. Opinions regarding the role of AI in supporting ethical decision-making were divided: 27.0% agreed, 28.5% disagreed, and 44.5% reported neutral responses.

Concerns related to patient confidentiality were prominent, with 86.7% of participants indicating that AI poses at least a moderate risk to data privacy, while 2.1% perceived no such risk. Perceptions of AI's ability to replicate empathy were mixed: 19.5% evaluated this capacity positively, 20.2% evaluated this capacity negatively, and 54.0% reported uncertainty. Despite these concerns, the majority of participants expressed willingness to receive training related to AI applications in palliative care (Table 2).

Discussion

This study evaluated healthcare professionals' awareness and attitudes toward palliative care and explored their perceptions of integrating AI into clinical practice. By addressing both traditional palliative care knowledge and emerging technological perspectives, the findings provide contemporary insights into the evolving landscape of palliative medicine.

Awareness levels regarding the fundamental goals of palliative care were generally encouraging. Most participants rejected the misconceptions that palliative care is limited to terminal patients (73.8%) or to oncology settings (88.1%); most recognized quality-of-life enhancement as its central aim (91.6%). These observations indicate progress compared with earlier reports in which palliative care was frequently perceived as synonymous with end-of-life care (2,3). However, the persistence of misconceptions in the literature (4) and variability across healthcare systems suggest that continuous education and institutional standardization remain necessary.

Despite favorable overall awareness, this study revealed marked gaps in essential competencies. Nearly half of respondents (49.6%) reported insufficient opioid

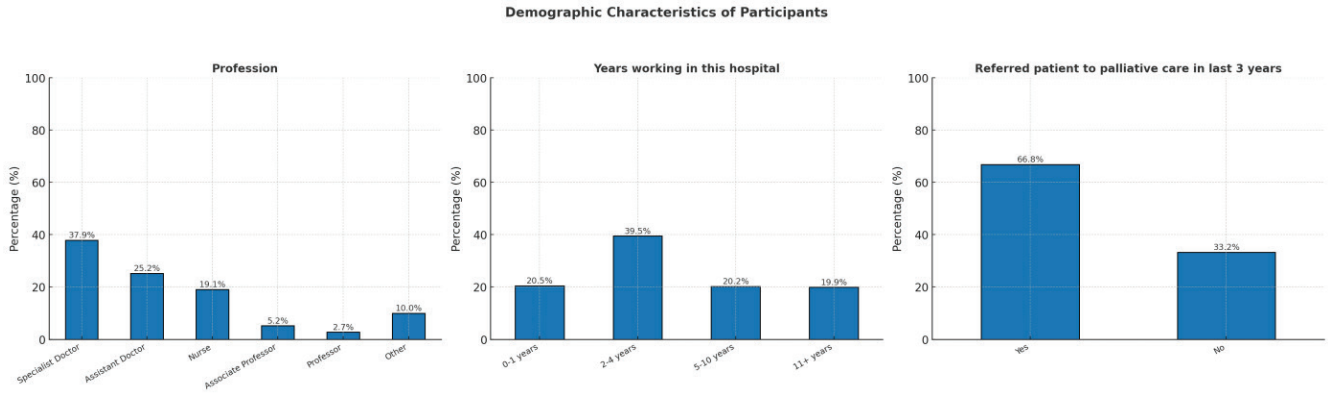

Figure 1. Demographic characteristics of participants

Table 1. Awareness and attitudes toward palliative care among healthcare professionals (n=337)

Statement	Agree n (%)	Neutral n (%)	Disagree n (%)
Palliative care aims to improve quality of life	309 (91.6)	-	-
Palliative care is only for terminal patients	37 (10.9)	52 (15.3)	248 (73.8)
Palliative care is limited to oncology patients	22 (6.4)	19 (5.5)	296 (88.1)
Psychosocial support is an essential component of palliative care	≥287 (≥85.0)	-	
I feel sufficiently trained in opioid use for palliative care	170 (50.4)	-	167 (49.6)
I feel adequately prepared for difficult patient–family conversations	191 (56.8)	79 (23.4)	67 (19.8)
I have referred at least one patient to palliative care in the last three years	138 (41.0)	-	-

Table 2. Attitudes toward AI in palliative care (n=337)

Statement	Agree n (%)	Neutral n (%)	Disagree n (%)
AI should be more widely implemented in palliative care	127 (37.7)	154 (45.7)	56 (16.6)
AI can support ethical decision-making in palliative care	91 (27.0)	150 (44.5)	96 (28.5)
AI poses a risk to patient confidentiality	292 (86.7)	38 (11.2)	7 (2.1)
AI can adequately replicate empathy in patient care	66 (19.5)	182 (54.0)	68 (20.2)
Willingness to receive training on AI applications in palliative care	Majority	-	-

AI: Artificial intelligence

knowledge, and 19.8% reported feeling inadequately prepared for difficult conversations with patients and families. Previous research similarly highlights deficiencies in pain management and communication as recurrent barriers to high-quality palliative care (5,6). These findings reinforce the need for comprehensive, multidisciplinary training programs that combine theoretical knowledge with structured clinical experience (10).

Perceptions toward AI demonstrated cautious optimism. While 37.7% supported broader integration of AI, only 27.0% believed it could assist with ethically complex decision-making; major concerns were identified regarding data privacy (86.7%) and loss of empathy (54.0%). This aligns with emerging evidence indicating that AI shows promise in symptom monitoring, prognostic modeling, and clinical decision support; however, adoption remains hindered by concerns regarding transparency, accountability, and explainability (7-9,11). Notably, the strong willingness of participants to receive AI training highlights an opportunity for capacity-building, particularly given the early stage of AI integration in palliative care practice. Educational initiatives should therefore address not only technical competencies but also ethical boundaries, data security, and the preservation of human-centered care (12,13).

Study Limitations

This study has several limitations. As the data were obtained through self-reported responses, the possibility of response

bias and social desirability bias cannot be excluded. Additionally, perceptions regarding artificial intelligence were assessed based on conceptual understanding rather than direct clinical experience, as AI-based applications are not yet widely implemented in routine palliative care practice. Finally, the absence of subgroup analyses according to specialty or duration of palliative care experience may have limited a more detailed exploration of variations in attitudes.

Conclusion

Collectively, these findings suggest that improving palliative care in the digital era requires a dual strategy: addressing existing deficits in opioid-related knowledge and communication skills, and promoting the ethical, transparent, and human-centered integration of AI, supported by structured training and regulatory oversight.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the İstanbul Medipol University Ethics Committee (decision no: 1137, date: 23.09.2025).

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.G., S.K.S., Concept: C.G., S.K.S., Design: C.G., S.K.S., Data Collection or Processing: C.G., S.K.S., Analysis or Interpretation: C.G., S.K.S., Literature Search: C.G., S.K.S., Writing: C.G., S.K.S.

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ORIGINAL RESEARCH

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Acute Liver and Kidney Damage Due to Ethanol: The Impact of Disulfiram Treatment

Etil Alkol Nedeniyle Oluşan Akut Karaciğer ve Böbrek Hasarı: Disülfiram Tedavisinin Etkisi

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Abstract

Objective: Acute ethanol (EtOH) exposure is known to induce oxidative stress, inflammation, and cellular injury in various organs, particularly the liver and kidneys. Disulfiram (DSF), a drug used in alcohol cessation therapy, also exhibits anti-inflammatory and antioxidant properties. This study aimed to evaluate the extent of liver and kidney damage induced by acute EtOH exposure and to investigate the potential therapeutic effects of DSF using histopathological and immunohistochemical methods.

Method: Twenty-eight male Sprague-Dawley rats were randomly divided into four groups: Control, EtOH, EtOH+DSF, and DSF. The EtOH group received 5 g/kg EtOH orally, while the EtOH+DSF group additionally received 100 mg/kg DSF administered intraperitoneally. Tissue sections were stained with hematoxylin and eosin, Masson's trichrome, and periodic scid-Schiff for semiquantitative evaluation. Interleukin-1beta (IL-1β) expression was assessed using avidin-biotin immunohistochemistry and quantified with ImageJ software.

Results: Histopathological examination revealed significant hepatocyte degeneration, inflammatory cell infiltration, and fibrosis in the EtOH group, along with tubular degeneration, hemorrhage, and structural disorganization in the kidneys. DSF treatment markedly ameliorated these histological alterations. Immunohistochemical analysis demonstrated that IL-1β expression was significantly increased following EtOH exposure but was notably reduced in the DSF-treated group.

Öz

Amaç: Akut etanol (EtOH) maruziyetinin, özellikle karaciğer ve böbreklerde olmak üzere çeşitli organlarda oksidatif stres, enflamasyon ve hücresel hasara yol açtığı bilinmektedir. Alkol bırakma tedavisinde kullanılan bir ilaç olan disülfiram (DSF), aynı zamanda anti-enflamatuvar ve antioksidan özellikler de göstermektedir. Bu çalışma, akut EtOH maruziyetinin neden olduğu karaciğer ve böbrek hasarının boyutunu değerlendirmeyi ve DSF'nin olası terapötik etkilerini histopatolojik ve immünohistokimyasal yöntemler kullanarak araştırmayı amaçlamıştır.

Yöntem: Yirmi sekiz erkek Sprague-Dawley sıçanı rastgele dört gruba ayrılmıştır: Kontrol, EtOH, EtOH+DSF ve DSF. EtOH grubuna oral yolla 5 g/kg EtOH verilmiş, EtOH+DSF grubuna ise ek olarak 100 mg/kg DSF intraperitoneal yolla uygulanmıştır. Doku kesitleri yarı kantitatif değerlendirme için hematoksilen-eozin, Masson's trikom ve periyodik asit-Schiff ile boyanmıştır. İnterlökin-1beta (IL-1β) ekspresyonu avidin-biotin immünohistokimya yöntemiyle değerlendirilmiş ve ImageJ yazılımı kullanılarak kantitatif olarak analiz edilmiştir.

Bulgular: Histopatolojik inceleme, EtOH grubunda belirgin hepatosit dejenerasyonu, enflamatuvar infiltrasyon ve fibrozis; böbreklerde ise tübüler dejenerasyon, hemoraji ve yapısal bozulma olduğunu ortaya koymuştur. DSF tedavisi bu histolojik değişiklikleri belirgin şekilde hafifletmiştir. İmmünohistokimyasal olarak, EtOH maruziyeti sonrasında IL-1β ekspresyonu anlamlı düzeyde artmış, ancak DSF tedavisi uygulanan grupta belirgin biçimde azalmıştır.

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Abstract

Conclusion: These findings suggest that DSF exerts therapeutic and anti-inflammatory effects against EtOH-induced hepatic and renal injury, primarily through modulation of IL-1β-mediated inflammatory pathways.

Keywords: Disulfiram, ethanol, kidney, liver

Öz

Sonuç: Bu bulgular, DSF'nin EtOH kaynaklı karaciğer ve böbrek hasarına karşı terapötik ve anti enflamatuvar etkilere sahip olduğunu ve bu etkinin büyük ölçüde IL-1β aracılı enflamatuvar yolların düzenlenmesiyle ilişkili olduğunu göstermektedir.

Anahtar kelimeler: Böbrek, disülfiram, etanol, karaciğer

Introduction

Ethyl alcohol is one of the most widely used psychoactive substances worldwide. Chemically known as ethanol (EtOH), it is a colorless, flammable liquid with a slightly pleasant odor (1). It causes significant health problems through both chronic and acute exposure, contributing to morbidity and mortality at individual and societal levels. Acute EtOH exposure usually occurs as a result of consuming large amounts of alcohol in a short period of time (2). This exposure can affect many systems such as the central nervous system, gastrointestinal system, and cardiovascular system. It can also suppress the immune system and cause harm to a wide range of individuals. However, one of the most serious and common form of organ damage caused by EtOH occurs in the liver (1). Short-term high doses of EtOH disrupt hepatic metabolism and cause lipid accumulation (steatosis) in liver cells (3). Furthermore, acetaldehyde and reactive oxygen species (ROS) formed during the metabolism of alcohol cause oxidative stress in hepatocytes, leading to cell damage. This process can lead to apoptosis and necrosis of hepatocytes. The presence of necrotic cells triggers an inflammatory response (4). Acute EtOH exposure has also been found to have nephrotoxic effects on the kidneys. Histopathologic changes such as dilatation of glomerular capillaries, interstitial edema and tubular degeneration may lead to decreased glomerular filtration rate and electrolyte imbalances (5).

Interleukin-1beta (IL-1β) is a key proinflammatory cytokine that contributes significantly to inflammation. Whenever pathogens or tissue injury are present, IL-1β activates a signaling cascade that leads to a multi-phase inflammatory response at the cell level (6,7). Excessive EtOH exposure induces oxidative stress and cell death, leading to increased IL-1β levels. This elevation further exacerbates inflammation-associated tissue damage, particularly in organs such as the liver (8). Experimental data has shown that consumption of alcohol triggers the tumor necrosis factor-alpha (TNF-α)/nuclear factor Kappa B (NF-κB) signaling pathway in kidney tissue, which leads to alterations in the kidney that are linked to inflammation (9).

Disulfiram (DSF) is a drug used in the treatment of EtOH dependence that exerts its main effect by inhibiting the enzyme aldehyde dehydrogenase. It increases the level of acetaldehyde in the blood by preventing the metabolism of acetaldehyde produced after EtOH intake. This build-up leads to unpleasant symptoms such as dizziness, palpitations, nausea and flushing of the face, with the aim of getting the patient to stop drinking alcohol (10). In addition to its well-known aversive effects, DSF has recently been shown to have antioxidant and anti-inflammatory properties (11). Through lowering ROS, which are significant triggers of intracellular oxidative stress, DSF exhibits antioxidant properties. In this regard, DSF reduces oxidative cellular processes including DNA damage and lipid peroxidation (12). Furthermore, by blocking NF-κB and inflammasome signaling pathways, DSF lowers the synthesis of proinflammatory cytokines including IL-1β and TNF-α. By reducing the intensity of the inflammatory response, this impact might stop tissue damage from getting deeper (13). The goal of our investigation was to use histopathologic and immunohistochemical analysis to examine the impact of DSF, a compound with therapeutic potential, on the structural changes brought on by acute EtOH exposure in tissues.

Materials and Methods

Ethical Approval

All animal procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council). This study was reviewed by the Local Ethics Committee of Kırşehir Ahi Evran University Animal Experiments and this committee approved our experimental guidelines (decision no: 24/057, date: 19.01.2024).

Animals and Experimental Groups

The Experimental Research Center of Kırşehir Ahi Evran University served as the site for this investigation. We used stress-free circumstances (21 °C; 12-h light/12-h dark cycles) to examine adult male Sprague-Dawley rats (n=28), which

were 8-10 weeks old and weighed 200-250 g. Four distinct experimental groups were created for this investigation, each with seven rats: Control, EtOH, EtOH+DSF, and DSF. A total of fifteen days were allocated for the investigation. At the conclusion of the fifteenth day, the control group was euthanized under anesthesia, and tissue and blood samples were collected without any treatment. EtOH group rats were given EtOH orally at a dose of 5 g/kg (14) three times a week at 12-hour intervals. Following EtOH administration, a 100 mg/kg dose of DSF (15) was diluted in 0.9% saline and administered intraperitoneally once daily for seven days in the EtOH+DSF group. The DSF group received only DSF at a dosage of 100 mg/kg (Table 1). All animals were euthanized at the end of the experimental period under general anesthesia with xylazine (10 mg/kg) and ketamine (60 mg/kg). Afterwards, the liver and kidney tissue were taken for histopathological and immunohistochemical analyses.

Histopathological Evaluation

The tissue samples collected at the end of the experiment were kept in a 10% formaldehyde solution to histologically assess liver and kidney tissue changes in each experimental group. 72 hours of formaldehyde fixation, the tissues were rinsed under running water. Following a series of alcohol dehydrations, they were cleaned in xylene, embedded in paraffin, and paraffin blocks were formed. Rat liver and kidney tissue paraffin blocks were cut into sections 5 µm in thickness, which were then put on poly-L-lysine-coated slides. Sections were stained with hematoxylin & eosin, Masson trichrome (MT) and periodic acid-schiff (PAS). Following staining, the sections were handled by a series of increasing alcohol passes, xylene cleaning, entellan mounting on a coverslip, and light microscopy analysis (Nikon Eclipse Si, Tokyo, Japan). For histological scoring, ten randomly selected microscopic fields were evaluated in each section. Furthermore, liver tissue damage included hepatocyte degeneration and fibrosis, while renal tissue damage was assessed and scored for tubule degeneration and hemorrhage. These parameters were scored semiquantitatively for each criterion on a scale of 0 to 3 (0: None, 1: Mild, 2: Moderate, 3: Severe).

Immunohistochemical Evaluation

The expression of IL-1β in liver and kidney tissue was shown by immunohistochemistry. For immunohistochemical staining, the avidin-biotin peroxidase assay was used. To stain, 5 µm slices of paraffin blocks were created on polylysine slides. Sections were deparaffinized with xylene, then preserved with a declining alcohol before their rehydration in distilled water. Sections were heated in a 600 W microwave oven with 5% citrate buffer for antigen retrieval, then rinsed with phosphate buffered saline (PBS) and treated with 3% H_2O_2 to suppress endogenous peroxidase activity. The immunohistochemical staining kit (Thermo Scientific/TS-125-HR, Thermo Fisher Scientific Inc., Waltham, MA, USA) was used in all subsequent steps, and the entire treatment carried out in a room that prevents tissue drying. Block serum was applied into PBS-washed sections for 10 minutes at room temperature to cover the areas external of the antigenic regions. The primary antibody for IL-1β (Proteintech, 26048-1-ap, 1:200) was then incubated at 4 °C overnight. Biotinylated secondary antibodies were subsequently used to incubate the sections. Streptavidin-peroxidase mixture was applied after washing with PBS. Following that was amino-9-ethylcarbazole (HA53704, Thermo Scientific, USA) that highlighted the immunoreactivity. To boost nuclear staining, Gill's hematoxylin was used as a counterstain. Sections of liver

Table 1. Overview of the treatment protocols applied to each experimental group during the 15-day study period, including administered substances, dosages, routes, frequency, and duration

Group	Number of animals	Treatment	Dose	Route	Frequency	Duration
Control	7	No treatment	-	-	-	No treatment for 15 days; sacrificed on day 15
EtOH	7	Ethanol	5 g/kg	Oral gavage	Three times per week; two doses at 12-hour intervals on each administration day	During the 15-day experimental period
EtOH+ DSF	7	Ethanol+disulfiram	EtOH: 5 g/kg DSF: 100 mg/kg	EtOH: oral DSF: intraperitoneal	EtOH: three times per week DSF: once daily	Ethanol administered first; DSF administered once daily for 7 consecutive days after ethanol exposure
DSF	7	Disulfiram	100 mg/kg	Intraperitoneal	Once daily	7 consecutive days during the experimental period

DSF: Disulfiram, EtOH: Ethanol

and kidney stained with immunohistochemistry were examined under light microscopy, and microscopic images from randomly selected locations were acquired. Twenty distinct microscopic fields were assessed from each section for quantitative analysis. Immunoreactivity examination was conducted specifically in the pericentral (central vein-adjacent) regions of the liver tissue and in the cortical region of the kidney. ImageJ software was used for assessing the immunoreactivity intensities of the markers identified in the images. The overall immunoreactivity was evaluated using ImageJ software's color threshold plugin.

Statistical Analysis

For all research involving statistics, Graphpad Prism version 9 was applied. The data distribution was determined using the Shapiro-Wilk test. The Kruskal-Wallis test and One-Way Analysis of Variance (ANOVA) were the methods used for comparisons involving more than two groups. Significant post-hoc comparisons of the variables were found using the Dunn test for the Kruskal-Wallis analysis and the Bonferroni test for the One-Way ANOVA. In all data, a p-value of less than 0.05 was accepted as statistically significant.

Results

Body Weight

Both before and after the experiment, the rats' body weights were measured. Figure 1 compares body weight changes among the groups. Rats in the EtOH group experienced a significant ($p<0.01$) weight loss at the conclusion of the experiment. Upon completion of the assessment, the weights of the DSF group ($p<0.01$) and the control group ($p<0.01$) were both greater than their initial weights.

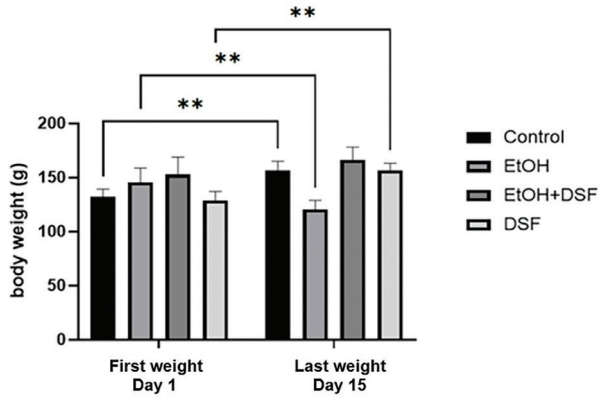

Figure 1. Comparison of body weights of rats belonging to all groups before and after the study

**: p<0.05, **: p<0.01, ***: p<0.001, DSF: Disulfiram, EtOH: Ethanol*

Histopathology of Liver and Kidney Tissues

Liver Assessment

Figure 2A illustrates the histologic evaluation of liver tissues from all groups. Hepatocytes in the control group's histologic sections had a regular organization, homogenous cellular architecture, and a normal sinusoidal structure. The DSF group had a histologic appearance similar to the control group. There was healthy cellular integrity. When analyzing the control liver stained with MT, we observed minimal collagen deposition around the vessels (Figure 3A). PAS staining demonstrated a normal glycogen distribution in the hepatocyte cytoplasm (Figure 4A). The DSF group showed results that were similar to these assessments. In the EtOH group, hepatocytes degenerated ($p<0.001$) and vacuolized. This group's liver sections showed inflammatory cell infiltration, among additional findings. Necrotic cells were also found in a few locations (Figure 2A). Fibrosis development was observed in the MT-treated EtOH group due to alcohol toxicity ($p<0.001$) (Figure 3A). PAS staining revealed a reduction in PAS-positive staining intensity compared to the control group (Figure 4A). In the EtOH group treated with DSF, hepatocyte structure was found to be more regular, and inflammatory cells were diminished. There were also reduced regions of degeneration and fibrosis ($p<0.05$) (Figures 2-5, Table 2).

Kidney Assessment

When the kidney tissue was investigated, it showed that the control group had a regular, round glomerulus structure with established boundaries. Tubule epithelial cells were normal, the lumen was visible, and the nuclei had a typical appearance. There were no significant pathologic findings in the DSF group, and the histologic structure was maintained. The basement membrane and tubule structure were comparable to the control group (Figure 2B). The connective tissue in the control group was found to be within normal boundaries by MT staining (Figure 3B). Furthermore, glomerular basement membranes were clearly visible and tubule brush borders were preserved in the control group, according to PAS staining (Figure 4B). The findings of the DSF group were similar to these assessments. In the EtOH group, the glomerular structure was retracted, and degenerative glomeruli with hypocellularity were observed. Tubular degradation was additionally noted during vacuolization, especially in the proximal tubules ($p<0.001$). In this group, there was also hemorrhage in the kidney tissue ($p<0.001$) (Figure 2B). In contrast to liver tissue, no fibrosis was found in the kidney on MT staining (Figure 3B). PAS staining reveals abnormalities in the glomerular basement membranes and a decrease in tubular damage and preservation of brush border architecture (Figure 4B).

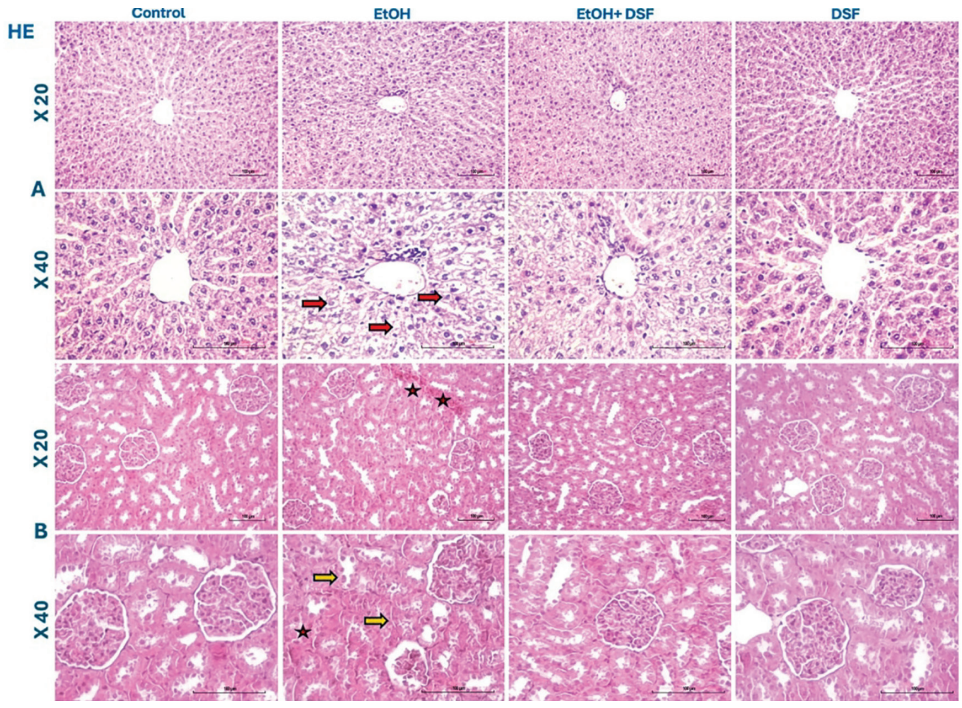

Figure 2. Light microscopic images of rat liver and kidney tissues stained with hematoxylin and eosin (H&E), (Nikon Eclipse Si, Tokyo, Japan. X200 and X400). Hepatocyte degeneration (red arrow), tubular degeneration (orange arrow) and hemorrhage (red star) in the experimental groups

DSF: Disulfiram, EtOH: Ethanol

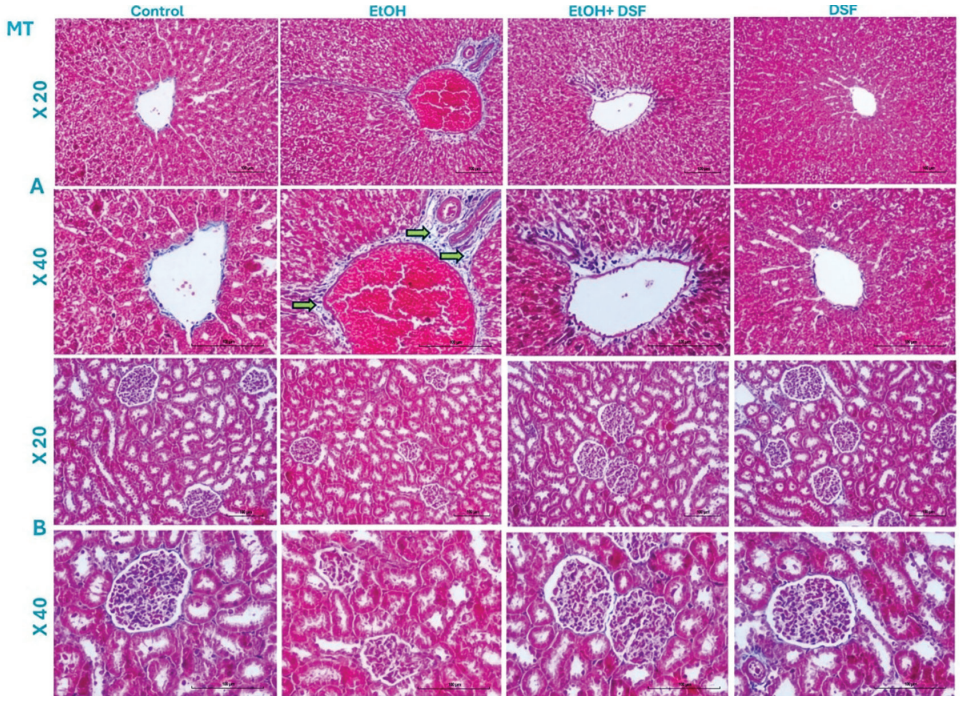

Figure 3. Light microscopic images of rat liver and kidney tissues stained with Masson trichrome (MT). Increased collagen deposition indicative of fibrosis (green arrow) was observed in the liver tissue (Nikon Eclipse Si, Tokyo, Japan. X200 and X400)

DSF: Disulfiram, EtOH: Ethanol

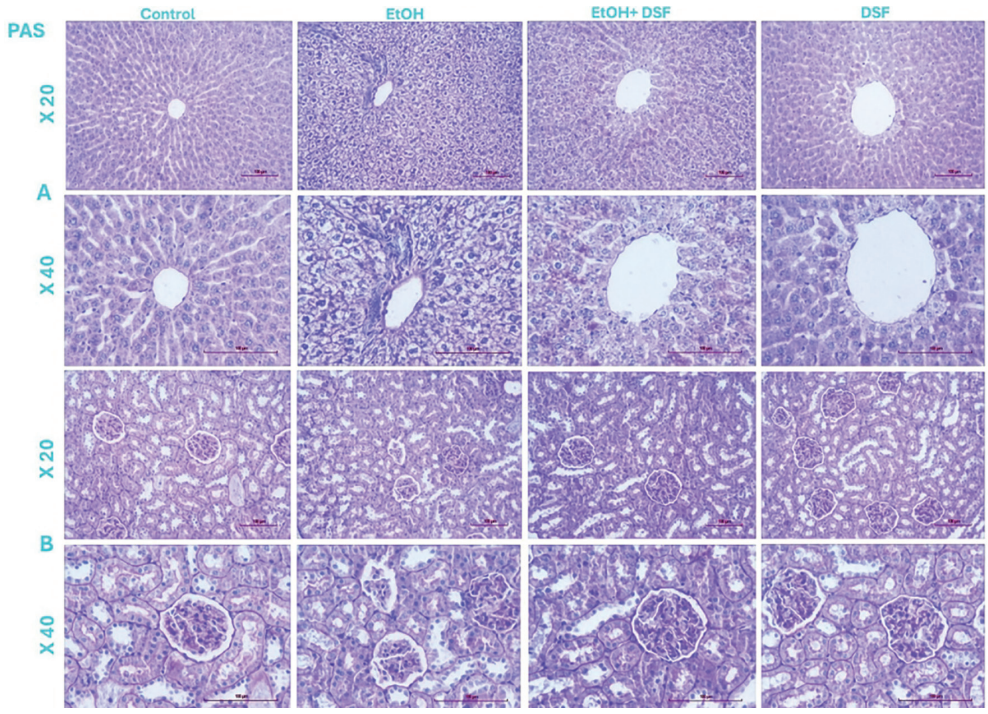

Figure 4. Light microscopic images of rat liver and kidney tissues stained with periodic acid-schiff (PAS), (Nikon Eclipse Si, Tokyo, Japan. X200 and X400)

DSF: Disulfiram, EtOH: Ethanol

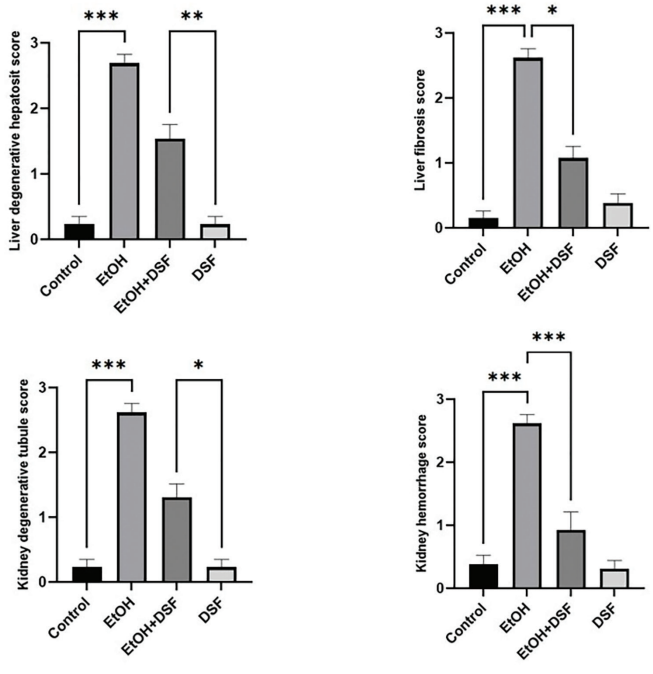

Figure 5. Histopathological findings of rat liver and kidney tissues. Graph exhibiting hepatocyte degeneration, fibrosis, tubular degeneration and hemorrhage in the experimental groups. Data were presented as mean ± standard deviation and median (min-max)

**: p<0.05, **: p<0.01, ***: p<0.001, DSF: Disulfiram, EtOH: Ethanol*

Table 2. Histological scoring of rat liver and kidney tissues showing hepatocyte degeneration, fibrosis, tubular degeneration, and hemorrhage in the experimental groups

Liver	Control	EtOH	EtOH + DSF	DSF	p
Hepatocyte degeneration	0.000 (0.000-1.000)	3.000 (2.000-3.000)	1.000 (1.000-3.000)	0.000 (0.000-1.000)	<0.001
Fibrosis	0.000 (0.000-1.000)	3.000 (2.000-3.000)	1.000 (0.000-2.000)	0.000 (0.000-1.000)	<0.001
Kidney					
Tubular degeneration	0.000 (0.000-1.000)	3.000 (2.000-3.000)	1.000 (0.000-3.000)	0.000 (0.000-1.000)	<0.001
Hemorrhage	0.000 (0.000-1.000)	3.000 (2.000-3.000)	1.000 (0.000-3.000)	0.000 (0.000-1.000)	<0.001

Data are presented as mean ± standard deviation and median (min-max). p<0.05, DSF: Disulfiram, EtOH: Ethanol

The glomerular structures in the EtOH+DSF group treated with DSF are relatively preserved, and the basement membrane is clearly visible. Furthermore, it was found that the protective action of DSF reduced tubular damage and mostly preserved the brush-like edge structure. Hemorrhage was markedly reduced in this group throughout the tissue (p<0.001) (Figures 2-5, Table 2).

Immunohistochemical Results of Liver and Kidney Tissues

Liver Assessment

In the control group, IL-1β expression in liver tissue was minimal and weak immunoreactivity was observed around the vessels. Similarly, in the DSF group, IL-1β staining was very weak and did not indicate inflammatory activity. IL-1β density and prevalence were significantly higher in the EtOH group compared to the control group (p<0.001). This marker showed reactivity around the vessels in the tissue. IL-1β expression was considerably lower in the EtOH +DSF group than in the EtOH group (p<0.001) (Figure 6A, Table 3).

Kidney Assessment

The expression of IL-1β in kidney tissue was low in both the control and DSF groups. IL-1β expression was significantly elevated in the EtOH group, particularly in proximal tubular cells. When compared to the control group, this rise was statistically significant (p<0.001). In the EtOH + DSF group, IL-1β expression was significantly lower than in the EtOH group (p<0.01) (Figure 6B), with tubular locations showing reduced staining intensity (Table 3).

Discussion

Acute toxic effects of EtOH lead to pronounced histopathological and immunohistochemical alterations, particularly in metabolically active organs such as the liver and kidneys. In the present study, EtOH administration resulted in marked structural disorganization, cellular damage, and enhanced inflammatory responses in both tissues. DSF treatment, on the other hand, was associated with alleviation of these pathological alterations, potentially related to modulation of IL-1β-mediated inflammatory responses. Carmiel-Haggai et al. (16) treated genetically obese and thin rats with 4 g/kg EtOH every 12 hours for three days. This therapy resulted in a 6.4% loss in body weight in thin rats. According to this study, acute EtOH consumption significantly affects body weight (16). Yoladi et al. (17) reported that rats treated with EtOH had a statistically important decrease in body weight. This conclusion indicates that EtOH has a detrimental effect on food intake and energy balance by altering metabolic processes during the experiment (17). Consistent with our study, in a recent study, rats were given a single injection of EtOH at a dose of 3 g/kg and it was observed that this high dose caused a significant decrease in body weight by suppressing appetite (18). In a study, 6-month-old male Wistar rats were given EtOH in drinking water at a volumetric concentration of 20% for 30 days. Histopathological examination of the liver revealed significant shrinking of the sinusoids, disruption of hepatocyte cords, and complete loss of sinusoidal architecture in some areas. Hepatocytes demonstrated significant vacuolization and degenerative alterations. Renal tissue investigation revealed a considerable reduction in Bowman's space, massive vacuolization in tubular epithelial cells, luminal displacement of nuclei and hydropic degeneration in certain tubular cell nuclei (5). In another study, an acute toxicity model was established by giving 5 g/kg EtOH orally to rats consistent with our dosing protocol. When the liver tissue was examined, ballooning degeneration in hepatocytes, vacuolization in the cytoplasm and also sinusoidal enlargement were observed (19).

These findings were consistent with our findings. These pathologies are associated with oxidative stress at the cellular level caused by toxic intermediates such as ROS and acetaldehyde released as a result of EtOH metabolism. In addition, inflammatory cell infiltration and the presence of necrotic cells were reported (20). In a study, it was reported that IL-1β expression increased in the central amygdala of mice after chronic EtOH exposure and this increase was

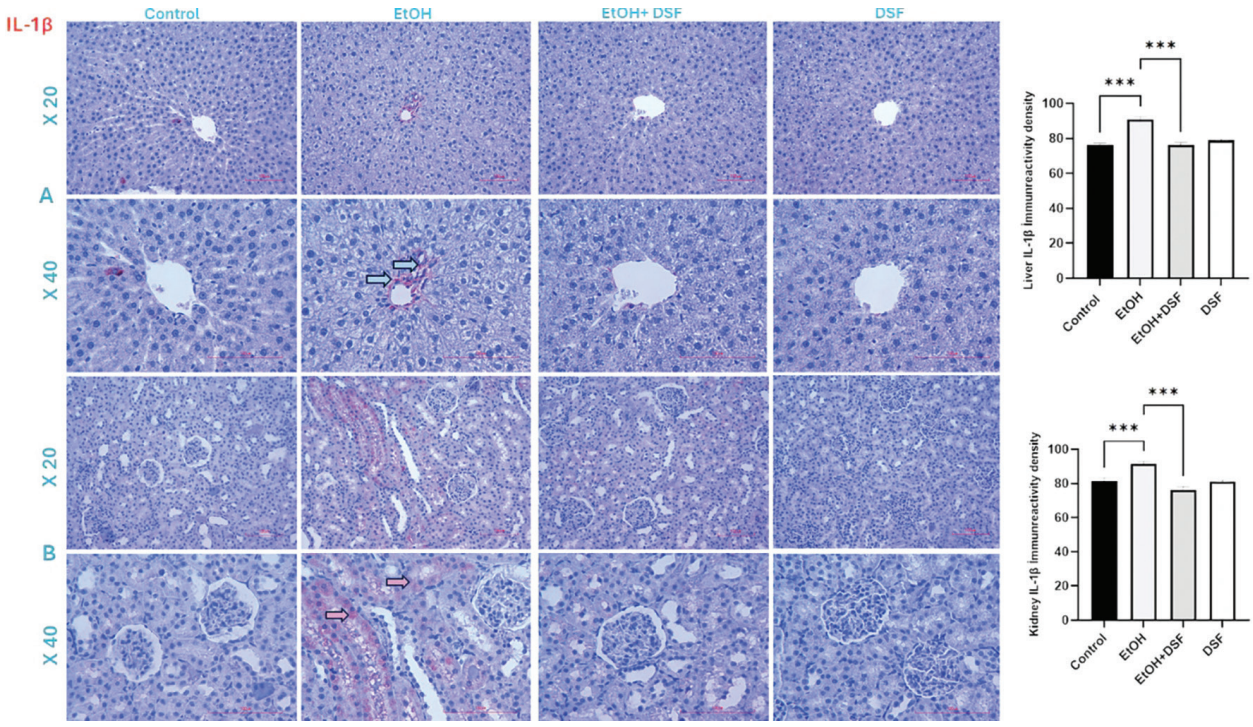

Figure 6. Immunohistochemical microscopic images and quantitative analysis of interleukin-1beta (IL-1β) expression in liver and kidney tissues of all experimental groups. Red areas indicate immunopositive staining. Increased IL-1β-positive immunoreactivity in the central vein and surrounding pericentral regions of the liver tissue (blue arrows) and in tubular epithelial cells in kidney tissue, with prominent inflammatory changes (pink arrows). The slides had been counterstained with hematoxylin. Data were presented as mean ± standard deviation and median (min-max), (Nikon Eclipse Si, Tokyo, Japan. X200 and X400)

**: p<0.05, **: p<0.01, ***: p<0.001, DSF: Disulfiram, EtOH: Ethanol*

Table 3. Immunoreactivity intensity of the IL-1β marker in the experimental groups

Liver	Control	EtOH	EtOH + DSF	DSF	p
IL-1β immunoreactivity density	76.25±3.353	90.88±5.251	76.27±5.044	78.87±2.784	<0.001
Kidney					
IL-1β immunoreactivity density	81.6±5.758	91.65±4.528	76.27±6.908	81.18±3.221	<0.001

Data are presented as mean ± standard deviation and median (min-max)
DSF: Disulfiram, EtOH: Ethanol, IL-1β: Interleukin-1beta

confirmed by immunohistochemistry. In this study, the expression of IL-1β in microglia and neurons was evaluated by confocal microscopy (21). In another study, mice were injected with lipopolysaccharide (LPS) 4 hours after oral administration of a single dose of 3 g/kg EtOH. The results showed that EtOH pretreatment significantly increased the mRNA and protein levels of proinflammatory cytokines such as IL-1β, and IL-6 induced by LPS (22). In one study, researchers administered an acute single dose of 5 g/kg EtOH intragastrically and 9 hours later the animals were sacrificed and tissues were taken. They showed that EtOH exposure increased IL-1β and inflammatory response in the liver (23). These findings were consistent with our results regarding IL-1β. Our immunohistochemistry investigations revealed that IL-1β expression was markedly elevated in liver and kidney tissues, suggesting an association between IL-1β immunoreactivity and histopathological findings. Beyond its conventional application, DSF's regulatory function on indicators linked to inflammation and oxidative stress has been investigated in several experimental animal studies (24-26). In a study investigating the hepatoprotective effects of DSF, DSF treatment was shown to significantly reduce fibrotic changes in experimental liver fibrosis models induced by carbon tetrachloride administration and bile duct ligation in rats (27). Lei et al. (28) showed that DSF treatment significantly reduced liver steatosis and fibrosis in a non-alcoholic steatohepatitis (NASH) model and suppressed inflammation and oxidative stress. Zhang et al. (29) used DSF therapy in

a rat model of renal fibrosis caused by unilateral ureteral obstruction. DSF therapy was found to significantly reduce the accumulation of collagen and the expression of fibrotic markers in histopathological examination. Furthermore, the findings demonstrated that DSF inhibited the gasdermin D protein, which in turn decreased inflammation and pyroptosis (29). Another recent study reported that NLRP3 inflammasome activity was inhibited by DSF. This was supported by decreased expression levels of NLRP3, caspase-1 (p20) and IL-1β proteins (30). A model of fungal keratitis caused by Aspergillus fumigatus was used to assess the effects of DSF. According to the study, DSF therapy blocked IL-1β release, reduced neutrophil and macrophage infiltration into ocular tissue, and regulated the inflammatory response. These results imply that DSF may lessen inflammation and thereby minimize tissue damage (31). In another study, the effects of DSF were examined in a peritendinous fibrosis model that developed after tendon injury in mice. In this study, it was shown that DSF treatment significantly decreased the levels of proinflammatory cytokines such as IL-1β and IL-1α prevented the development of fibrosis (32). All these results were in parallel with our results in terms of IL-1β. DSF decreased IL-1β reactivity, which was increased in liver and kidney in our study. Immunohistochemical analysis showed that IL-1β expression was markedly increased in the EtOH group. These findings suggest that IL-1β may play an important role in the acute inflammatory response under the present experimental conditions. DSF treatment was associated with reduced IL-1β immunoreactivity in liver and kidney tissues. Numerous studies have previously demonstrated that DSF modulates inflammatory processes (33-35). DSF has been highlighted for its ability to prevent tissue damage by inhibiting the NLRP3 inflammasome and attenuating oxidative stress. The results of the present study further support the anti-inflammatory properties of DSF against EtOH-induced acute toxicity (36).

Study Limitations

Despite these promising findings, certain limitations should be acknowledged. In the present study, IL-1β was evaluated as the primary inflammatory marker, while other relevant cytokines were not assessed, which may limit a more comprehensive understanding of the inflammatory response. Additionally, the absence of complementary quantitative analyses, such as Western blotting or ELISA, to validate the immunohistochemical findings may restrict the precision of molecular-level interpretations.

Conclusion

In summary, our investigation showed that acute EtOH intake significantly damaged the liver and kidneys both structurally and through inflammatory mechanisms, a process that was primarily linked to elevated IL-1β levels. By lowering histopathological degradation and inhibiting the inflammatory process, particularly IL-1β-mediated inflammation, DSF therapy demonstrated a significant protective effect. These findings suggest that DSF may represent a potential candidate for further experimental investigation in the modulation of alcohol-induced inflammatory organ damage, in addition to its established use in the treatment of alcohol dependence. Future studies should thoroughly examine DSF's optimal dosage range, molecular mechanisms of action, and potential synergistic effects with other anti-inflammatory drugs.

Ethics

Ethics Committee Approval: All animal procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council). This study was reviewed by the Local Ethics Committee of Kırşehir Ahi Evran University Animal Experiments and this committee approved our experimental guidelines (decision no: 24/057, date: 19.01.2024).

Informed Consent: N/A.

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Footnotes

Authorship Contributions

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

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ORIGINAL RESEARCH

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Ultrasonographic Assessment of Thumb Muscle Thickness and Evaluation of Pinch and Grip Strength in First Carpometacarpal Joint Osteoarthritis: A Comparison of Early and Advanced Stages

Birinci Karpometakarpal Eklem Osteoartritinde Başparmak Kası Kalınlığı ile Parmak ve El Kavrama Kuvveti Değerlendirilmesi: Erken ve İlerlemiş Evrelerin Karşılaştırılması

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Abstract

Objective: This study investigated the ultrasonographic thickness of the thenar muscles and assessed pinch and grip strength in patients with first carpometacarpal (CMC) osteoarthritis by comparing early and advanced stages of the disease.

Method: A total of 34 female patients aged 50-80 years with early- or advanced-stage first CMC osteoarthritis were included in this cross-sectional study. Patients were classified as early-stage (Eaton stages 1-2) or advanced-stage (Eaton stages 3-4). The thicknesses of the abductor pollicis brevis (APB), opponens pollicis (OPP), and first dorsal interosseous (FD I) muscles were measured by ultrasound on both the dominant and non-dominant hands. Grip and key pinch strengths were assessed with a hand dynamometer and a hydraulic pinch meter, respectively.

Results: Muscle thicknesses of APB, OPP, and the dominant-side FDI, as well as key pinch strength, were significantly higher in early-stage patients ($p<0.05$). Grip strength did not differ significantly. Dominant OPP thickness was positively correlated with pinch strength ($r=0.382$, $p=0.026$), while APB thickness was negatively correlated with age and pain severity.

Öz

Amaç: Bu çalışmanın amacı, birinci karpometakarpal (KMK) eklem osteoartriti olan hastalarda tenar kasların ultrasonografik kalınlığını incelemek ve erken ile ilerlemiş evreleri karşılaştırarak parmak ve el kavrama kuvvetini değerlendirmektir.

Yöntem: Bu kesitsel çalışmaya, erken veya ilerlemiş evre birinci KMK eklem osteoartriti tanısı konmuş, 50-80 yaş aralığında toplam 34 kadın hasta dahil edildi. Hastalar erken evre (Eaton evre 1-2) veya ilerlemiş evre (Eaton evre 3-4) olarak sınıflandırıldı. abduktor pollicis brevis (APB), opponens pollicis (OPP) ve birinci dorsal interosseöz (FDI) kaslarının kalınlıkları, hem dominant hem de non-dominant ellerde ultrason kullanılarak ölçüldü. El kavrama kuvveti el dinamometresiyle, parmak kavrama kuvveti ise hidrolik pinçmetre ölçer ile değerlendirildi.

Bulgular: APB, OPP ve dominant taraftaki FDI kas kalınlıkları ile parmak kavrama kuvveti erken evre hastalarda anlamlı olarak daha yüksekti ($p<0,05$). El kavrama kuvvetinde ise anlamlı bir fark saptanmadı. Dominant OPP kalınlığı, parmak kavrama kuvveti ile pozitif korelasyon gösterirken ($r=0,382$, $p=0,026$), APB kalınlığı yaş ve ağrı şiddeti ile negatif ilişki içindeydi.

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Abstract

Conclusion: In first CMC osteoarthritis, muscle thickness and pinch strength decrease as the disease progresses. Early ultrasound detection of thenar changes may help guide treatment to preserve thumb function.

Keywords: Carpometacarpal joints, osteoarthritis, pinch strength, ultrasonography

Öz

Sonuç: Birinci KMK osteoartritinde kas kalınlığı ve parmak kavrama kuvveti, hastalığın ilerlemesiyle birlikte azalmaktadır. Tenar kaslardaki değişikliklerin ultrasonografi ile erken tespiti, başparmak fonksiyonunu korumaya yönelik tedavi rehberliğine yardımcı olabilir.

Anahtar kelimeler: Karpometakarpal eklemler, osteoartrit, sıkma kuvveti, ultrasonografi

Introduction

First carpometacarpal (CMC) joint osteoarthritis is a common degenerative condition that can lead to significant functional limitations in affected individuals. First CMC osteoarthritis, which predominantly affects postmenopausal women, has been reported in 17-33% of this population, while its prevalence among men of the same age group ranges from 5% to 11% (1-3).

The first CMC joint is a saddle-type joint, and its stabilization is primarily provided by ligaments rather than bony structures (2,4). Laxity in the supporting ligaments increases mechanical load on the joint and contributes to the development of osteoarthritis. This increase in load is particularly evident during pinch grip, and it has been shown that a 1 kg pinch force at the fingertip translates into a 13.42 kg load on the first CMC joint (5). A reduction in pinch strength in patients with first CMC joint osteoarthritis has been demonstrated (6). Grip strength, on the other hand, is a commonly used method in the literature to assess hand function in patients with thumb osteoarthritis (7).

In addition to ligamentous structures, the abductor pollicis brevis (APB) and opponens pollicis (OPP) muscles, located on the palmar surface of the hand, along with the first dorsal interosseous (FDI) muscle, contribute to stabilization of the CMC joint (8). It is known that pain and structural changes secondary to osteoarthritis can lead to muscle atrophy. This muscle loss can be evaluated indirectly through various muscle strength measurements or directly by measuring muscle thickness using imaging methods. Ultrasonography (USG) is a safe alternative for muscle assessment due to its rapid application, cost-effectiveness, and lack of radiation exposure (9). For the evaluation of intrinsic hand muscles, USG is recommended by many studies and has been shown to be valid (9-11). Test-retest reliability of ultrasonographic muscle thickness measurements has previously been reported for intrinsic hand muscles (e.g., dorsal interossei and lumbricals), with high intraclass correlation coefficients and low measurement error (10). In addition, ultrasonographic measurements of intrinsic hand muscle size (cross-sectional area) have been shown to correlate strongly with muscle strength and to demonstrate excellent intra-rater and good inter-rater reliability (9). However, studies using USG to evaluate hand muscles in first CMC joint osteoarthritis are limited. Lai et al. (8) evaluated thumb muscles using USG in patients with early-stage first CMC osteoarthritis and found a weak association between OPP muscle thickness and presence of early-stage osteoarthritis.

To the best of our knowledge, no study has ultrasonographically evaluated muscle thickness in both early and advanced stages of first CMC joint osteoarthritis and compared the findings with grip and pinch strength. The present study aims to address this gap. We hypothesized that patients with advanced first CMC joint osteoarthritis would have significantly reduced muscle thickness, pinch strength, and grip strength compared with patients with early-stage osteoarthritis. The findings of this study may provide insights into muscle involvement across disease stages and support future research focusing on muscle-oriented assessment approaches, particularly in early disease stages.

Materials and Methods

Study Design and Participants

This cross-sectional study included patients who presented to the physical therapy and rehabilitation outpatient clinics at Beylikdüzü State Hospital between 10.12.2024 and 20.01.2025. Ethical approval for the study was obtained from the Ethics Committee of İstanbul Physical Therapy and Rehabilitation Training and Research Hospital with protocol number: 2024-73, date: 05.12.2024. Informed consent was obtained from all participants before the study, and the study was conducted in accordance with the Declaration of Helsinki.

Inclusion criteria were being between 50-80 years of age, having bilateral hand radiographs taken within the last three months, having a diagnosis of early or advanced stage first CMC osteoarthritis, and being female. Exclusion criteria were refusal to participate in the study,

use of medications that suppress osteoarthritis flare-ups, presence of rheumatologic diseases that may cause peripheral joint involvement, history of fracture or surgery in the first CMC joint, presence of cervical disc herniation, presence of entrapment neuropathies such as carpal tunnel syndrome that may cause muscle atrophy in the thenar region,presence of de Quervain's tenosynovitis or other tendon inflammations in the wrist area, psychiatric disorders, and cognitive impairments.

At the beginning of the study, the participants' socio-demographic, anthropometric, and clinical data—such as age, height, weight, marital status, and comorbidities—were recorded. Pain intensity was evaluated using the visual analogue scale (VAS); patients rated their pain from 0 (no pain) to 100 (worst pain imaginable) (12). Hand radiographs were evaluated, and osteoarthritis severity was classified using the Eaton classification. According to this classification: Stage 1: The joint space is normal, but mild joint widening may be present due to ligament laxity and effusion. Stage 2: Joint space narrowing, osteophytes and debris smaller than 2 mm, and subluxation of more than one-third of the metacarpal bone are observed. Stage 3: Joint space narrowing is more pronounced, with osteophytes and debris larger than 2 mm present. Stage 4: The scaphotrapezoid joint is also involved (13,14). The Eaton classification was conducted by an experienced physical medicine and rehabilitation specialist, who was blinded to all ultrasonographic and clinical assessment results.

Patients classified as Stages 1 and 2 were considered early-stage, and those classified as Stages 3 and 4 were considered late-stage (15). Patients whose dominant and non-dominant hands were at different stages were excluded from the study. Grip strength and pinch strength were measured and recorded separately for the dominant and non-dominant hands. Subsequently, APB, OPP, and FDI muscle thicknesses were measured by USG on both the dominant and non-dominant sides. Ultrasonographic evaluations were performed by a second examiner with expertise in musculoskeletal USG, who was blinded to the Eaton classification and functional assessment findings (ClinicalTrials.gov ID: NCT06730698).

Outcomes

Handgrip Strength

We measured handgrip strength using a Jamar handgrip dynamometer. We had the patient sit upright in a chair with back support but no armrests, ensuring their feet were flat on the floor. The wrist was held in a neutral position, and the elbow was flexed 90 degrees. We instructed the patient to grasp the dynamometer and squeeze with maximum effort. We performed measurements separately for the dominant and non-dominant hands. Each measurement was repeated three times with 45-second rest intervals, and the highest value was recorded (16).

Pinch Strength

Pinch strength was measured with a Jamar hydraulic pinch gauge. The patient maintained the same posture during the handgrip strength measurement. We placed the pinch gauge between the pulp of the thumb and the lateral surface of the index finger and instructed the patient to squeeze with maximal force (Figure 1A, B). Measurements were performed separately for each hand. We took three measurements at 45-second intervals and recorded the highest value (8).

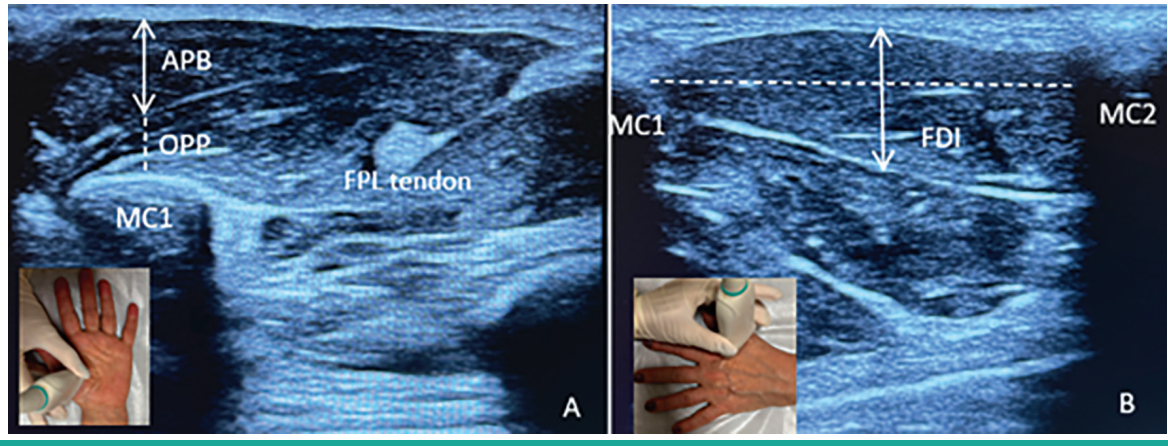

Figure 1. (A) Grip strength assessment using a hand dynamometer. (B) Lateral pinch strength measurement using a pinch meter

FDI: First dorsal interosseous, APB: Abductor pollicis brevis, OPP: Opponens pollicis, MC: Metacarpal, FLP: Flexor pollicis longus

Ultrasonographic Assessment

All muscle thickness measurements were performed using a high-frequency (3-11 MHz) linear ultrasound probe (Mindray DC-8 EXP). We positioned the patient facing the examiner. To ensure consistency, the same experienced examiner performed all measurements. We held the probe upright using ultrasound gel to avoid compression.

We imaged the APB, OPP, and FDI muscles in both the dominant and non-dominant hands. During the assessment of the APB and OPP muscles, the patient was positioned with the elbow in flexion and the forearm in full supination. The probe was placed in the short-axis of the thenar eminence, at the proximal one-third of the first metacarpal, ensuring visualization of the flexor pollicis longus tendon. Muscle thicknesses of the APB and OPP were measured perpendicular to the first metacarpal, which served as the reference point (Figure 2A). To image the FDI muscle, the probe was placed on the dorsal surface of the hand in the short-axis orientation, aligned with the proximal one-third of both the first and second metacarpals. Thickness was measured perpendicular to the muscle, at the midpoint between the two bones (Figure 2B). Each measurement was repeated three times, and the average was recorded.

Statistical Analysis

Categorical variables were presented as numbers and percentages; numerical data as mean ± standard deviation, median, and interquartile range. Normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Either an independent-samples t-test or the Mann-Whitney U test was used, depending on the data distribution. Pearson or Spearman correlation tests were applied as appropriate. Analyses were conducted using SPSS 21.0.

Sample Size Calculation

Based on the referenced study, the effect size was calculated as 1.52 using the mean pinch-strength values (7). Assuming an alpha level of 0.05 and a power of 99%, the minimum required sample size per group was 17, resulting in a total of 34 patients.

Results

All 34 patients with first CMC osteoarthritis included in the study were female. The mean age was 65.82±8.6 in the early-stage group and 69.76±8.04 in the late-stage group, with no significant difference. Body mass index (BMI) was significantly higher in the late-stage group (p=0.028). Comorbidities did not differ significantly between groups. VAS scores were significantly lower in the early-stage group (p=0.012). Pinch strength was higher in the early-stage group for both the dominant (p=0.026) and non-dominant (p=0.021) hands. However, no significant difference was found in handgrip strength (p>0.05) (Table 1).

Ultrasonographic measurements of thumb muscle thickness are presented in Table 2. The thicknesses of the APB and OPP muscles were greater in the early-stage osteoarthritis group than in the advanced-stage group on both dominant and non-dominant sides (p<0.05). The FDI muscle thickness was also greater in the dominant hand of the early-stage group (p=0.007). Although the FDI thickness

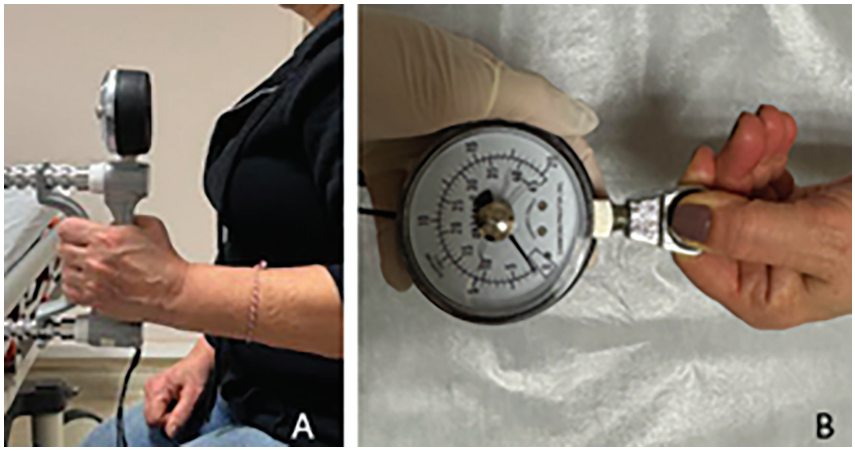

Figure 2. Ultrasonographic assessment of thenar and first dorsal interosseous (FDI) muscle thickness. (A) Short-axis ultrasonographic image showing the abductor pollicis brevis (APB) and opponens pollicis (OPP) muscles overlying the first metacarpal (MC1). The flexor pollicis longus tendon is also visualized in the deeper layer. The vertical dashed line indicates the measurements of APB and OPP muscle thicknesses taken perpendicular to MC1. (B) Short-axis ultrasonographic image of the FDI muscle between the first (MC1) and second metacarpal (MC2) bones. The vertical arrow represents the muscle thickness measured from the midpoint between MC1 and MC2

in the non-dominant hand was also higher in the early-stage group, this difference was not statistically significant (p=0.158) (Table 2).

In our study, pinch strength on the dominant side was positively correlated with the OPP muscle thickness on the that side (r=0.382, p=0.026). No significant relationship was observed between pinch strength and the thickness of other muscles. Handgrip strength was not correlated with the thickness of the APB, OPP, or FDI muscles (p>0.05). A negative correlation was found between APB muscle thickness and age, whereas no such relationship was observed between age and the thicknesses of the other muscles. A significant negative correlation was observed between BMI and the thickness of the dominant OPP muscle (r=-0.487, p=0.003), the non-dominant OPP muscle (r=-0.518, p=0.002), and the dominant FDI muscle (r=-0.343, p=0.047). While handgrip strength significantly decreased with age (r=-0.470, p=0.005), pinch strength was not significantly affected (p>0.05). No significant relationship was found between pain severity and either pinch strength or handgrip strength, but a negative correlation was observed only between pain severity and APB muscle thickness (Table 3).

Discussion

In this study, the muscle thicknesses of APB, OPP, and FDI were evaluated using USG in patients with early- and advanced-stage first CMC osteoarthritis. It was found that in early-stage patients, the thicknesses of the APB and OPP muscles were greater on both the dominant and non-dominant sides than in advanced-stage patients. In early-stage osteoarthritis, the FDI muscle thickness was higher in the dominant hand, whereas no significant difference was found between the groups for the non-dominant hand. In addition, pinch strength was higher in patients with early-stage first CMC osteoarthritis compared to those

Table 1. Descriptive statistics

		Early stage (n=17)		Late stage (n=17)		
		Mean ± SD/n (%)	**Median (IQR)**	**Mean ± SD/n (%)**	**Median (IQR)**	**p-value**
Age(year)		65.82±8.6	67 (13)	69.76±8.04	72 (15)	0.178[t]
BMI [kg (m²)]		27.72±4.51	28.19 (4.75)	30.87±3.40	31.22 (4.03)	**0.028[t]**
Marital status	Married	11 (64.7%)		10 (58.8%)		1.000
	Single	6 (35.3%)		7 (41.2%)		
Hypertension		6 (35.3%)		10 (58.8%)		0.303[x]
Diabetes mellitus		1 (5.9%)		5 (29.4%)		0.175[f]
CAD		1 (5.9%)		5 (29.4%)		0.175[f]
Hypothyroidism		7 (41.2%)		5 (29.4%)		0.720[x]
VAS		49.71±20.95	50 (25)	70±20.31	70 (40)	**0.012[m]**
Pinch dominant (lb)		10.71±2.95	10 (6)	8.47±3.28	8 (3)	**0.026[m]**
Pinch non-dominant (lb)		9.35±3.06	9 (5)	7.06±2.41	7 (2)	**0.021[t]**
Handgrip dominant (kg)		16.24±5.14	16 (5)	14.94±6.37	12 (8)	0.374[m]
Handgrip non-dominant (kg)		15.29±4.58	16(6)	12.76±6.40	12 (8)	0.194[t]

[t]: Independent sample t-test, [m]: Mann-Whitney U test, [x]: Chi-square test, [f]: Fisher's exact test, SD: Standard deviation, IQR: Interquartile range, BMI: Body mass index, CAD: Coronary artery disease, VAS: Visual analogue scale

Table 2. Comparison of muscle thickness measurements between early and late stage first carpometacarpal osteoarthritis

	Early stage		Late stage			
	Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	**p-value**	**95% CI**
APB dominant (cm)	0.49±0.05	0.5 (0.09)	0.41±0.09	0.40 (0.15)	**0.002**	0.032-0.130
APB non-dominant (cm)	0.48±0.05	0.49 (0.1)	0.39±0.08	0.40 (0.11)	**0.001**	0.035-0.132
OPP dominant (cm)	0.57±0.08	0.57 (0.14)	0.43±0.08	0.40 (0.12)	**0.000**	0.088-0.197
OPP non-dominant (cm)	0.52±0.07	0.52 (0.11)	0.42±0.09	0.42 (0.16)	**0.001**	0.046-0.158
FDI dominant (cm)	0.92±0.09	0.93 (0.16)	0.84±0.09	0.82 (0.12)	**0.007**	0.025-0.145
FDI non-dominant (cm)	0.82±0.09	0.81 (0.10)	0.77±0.12	0.80 (0.17)	0.158	-0.021-0.122

SD: Standard deviation, IQR: Interquartile range, CI: Confidence interval, APB: Abductor pollicis brevis, OPP: Opponens pollicis, FDI: First dorsal interosseous

Table 3. Correlation between muscle thickness and grip/pinch strength, age, BMI, and pain severity (VAS)

	Pinch dominant		Hangrip dominant		APB dominant		APB non-dominant		OPP dominant		OPP non-dominant		FDI dominant		FDI non-dominant	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Age (year)	-0.113[s]	0.523	-0.470**[s]	**0.005**	-0.446**	**0.008**	-0.488**	**0.003**	-0.121	0.496	-0.119	0.503	-0.279	0.110	-0.181	0.307
BMI (kg/m²)	-0.280[s]	0.109	-0.166[s]	0.349	-0.026	0.885	-0.115	0.519	-0.487**	**0.003**	-0.518**	**0.002**	-0.343*	**0.047**	-0.298	0.087
VAS	-0.142[s]	0.424	-0.069	0.699	-0.346*[s]	**0.045**	-0.381*[s]	**0.026**	-0.109[s]	0.541	0.091	0.611	-0.156[s]	0.377	-0.010[s]	0.956
Pinch dominant (lb)	1.000[s]		0.660**[s]	**0.000**	0.208[s]	0.237	0.188[s]	0.288	0.382*[s]	**0.026**	0.257	0.142	0.037[s]	0.837	0.075[s]	0.673
Pinch non-dominant (lb)	0.793**[s]	**0.000**	0.737**[s]	**0.000**	0.240	0.171	0.201	0.254	0.240	0.172	0.170	0.336	0.154	0.384	0.131	0.460
Hangrip dominant (kg)	0.660**[s]	**0.000**	1.000[s]		0.053[s]	0.765	0.096[s]	0.588	0.122[s]	0.492	0.087	0.625	0.206[s]	0.242	0.178[s]	0.313
Handgrip non-dominant (kg)	0.427*[s]	**0.012**	0.653**[s]	**0.000**	0.179	0.310	0.270	0.122	0.260	0.138	0.156	0.377	0.133	0.452	0.168	0.343
APB dominant (cm)	0.208[s]	0.237	0.053[s]	0.765	1.000		0.842**	**0.000**	0.271	0.122	0.329	0.057	0.215	0.222	0.053	0.765
APB non-dominant (cm)	0.188[s]	0.288	0.096[s]	0.588	0.842**	**0.000**	1.000		0.407*	**0.017**	0.463**	**0.006**	0.360*	**0.037**	0.159	0.368
OPP dominant (cm)	0.382*[s]	**0.026**	0.122[s]	0.492	0.271	0.122	0.407*	**0.017**	1.000		0.862**	**0.000**	0.438**	**0.009**	0.341*	**0.048**
OPP non-dominant (cm)	0.257[s]	0.142	0.087[s]	0.625	0.329	0.057	0.463**	**0.006**	0.862**	**0.000**	1.000		0.453**	**0.007**	0.288	0.099
FDI dominant (cm)	0.037[s]	0.837	0.206[s]	0.242	0.215	0.222	0.360*	**0.037**	0.438**	**0.009**	0.453**	**0.007**	1.000		0.621**	**0.000**
FDI non-dominant (cm)	0.075[s]	0.673	0.178	0.313	0.053	0.765	0.159	0.368	0.341*	**0.048**	0.288	**0.099**	0.621**	**0.000**	1.000	

Pearson correlation test; *: Spearman correlation test, BMI: Body mass index, VAS: Visual analogue scale, APB: Abductor pollicis brevis, OPP: Opponens pollicis, FDI: First dorsal interosseous, *:Correlation is significant at the 0.05 level (2-tailed), **: Correlation is significant at the 0.01 level (2-tailed)

with advanced-stage disease, while handgrip strength was found to be similar between the two groups.

Few studies focus on thumb muscles in first CMC osteoarthritis. In a previous study, OPP muscle thickness was greater in patients with early-stage first CMC osteoarthritis than in healthy controls. In multivariate analysis, only OPP muscle thickness was significantly associated with early-stage osteoarthritis, whereas no significant relationship with early-stage osteoarthritis was found for the APB and FDI muscles (8). In the study by Karademir et al. (17), a total of 24 patients with first CMC osteoarthritis (according to the Eaton classification: 7 stage-1, 9 stage-2, 6 stage-3, and 2 stage-4 patients) and 8 healthy controls were evaluated by water-bath USG to assess the thenar muscles. As a result, APB, OPP, and FDI muscle thicknesses on the dominant side did not differ between the two groups. On the non-dominant side, only APB muscle thickness was found to be higher in the control group (17). In this study, the lack of homogeneity in sample sizes across groups and the relatively small number of advanced-stage patients, among whom muscle atrophy would be more pronounced, may have prevented obtaining the expected results (17). In the present study, a comparison of early- and advanced-stage first CMC osteoarthritis revealed that the muscle thicknesses of APB, OPP, and FDI (FDI measured only on the dominant side) were significantly greater in the early-stage group. These findings suggest that thumb muscle thickness varies by disease stage and that muscle involvement is more pronounced in advanced stages of first CMC osteoarthritis.

In our study, no significant difference was observed in handgrip strength between patients with early-stage and advanced-stage osteoarthritis, whereas pinch strength was notably higher in the early-stage group. In the study by Lai et al. (8), pinch strength and cylindrical grip strength were found to be similar between patients with early-stage first CMC osteoarthritis and healthy controls. In another study evaluating patients with first CMC osteoarthritis, tip and tripod pinch strength measurements were significantly lower in the osteoarthritis group (7). In the study by McQuillan et al. (6), patients with early-stage first CMC osteoarthritis were compared with healthy controls; key pinch strength was significantly lower in the osteoarthritis group. Moreover, compared with tip and tripod pinch grips, the association between key pinch and osteoarthritis was more pronounced (6). In our study, as in that study, key pinch strength was assessed and found to be significantly lower. Previous studies have shown that the key-pinch position is associated with CMC joint instability, trapezium

translation (18), and increased mechanical load on the trapezium (19). In light of this information, it is reasonable to conclude that key pinch strength is more strongly affected by muscle weakness and functional loss associated with first CMC osteoarthritis (6).

Other studies have supported our findings, reporting that handgrip strength in patients with first CMC osteoarthritis is similar to that of the control group (8,20), whereas one study, contrary to our results, found lower handgrip strength in the osteoarthritis group (7). Handgrip strength is influenced not only by the intrinsic muscles of the hand but also by the extrinsic muscles forearm. In a study of older women and men, handgrip strength was correlated with forearm muscle thickness (21). These contradictory findings in the literature may be attributed to the more prominent compensatory effect of forearm muscles during handgrip than during pinch grip. Furthermore, because CMC joint osteoarthritis is more closely related to the thumb muscles, it may affect key pinch strength more than handgrip strength.

A study showed negative correlations between age and handgrip strength and between age and tip and tripod pinch strengths in patients with first CMC osteoarthritis. However, key pinch strength was not evaluated. In the control group, the negative relationship between age and muscle strength was found to be stronger than in the osteoarthritis group (7). Jansen et al. (22) found a negative association between age and grip and pinch strength in elderly women and men, independent of osteoarthritis. In our study, age showed a significant negative correlation with handgrip strength, but no such relationship was observed with key pinch strength. Because CMC osteoarthritis was present in our patient population, pinch strength may have decreased because of osteoarthritis rather than age, which may have led to the loss of correlation with age. Additionally, in our study, a negative correlation was observed between age and APB muscle thickness.

Study Limitations

This study has strengths and limitations. To the best of our knowledge, no study has comparatively evaluated the thumb muscles in patients with early- and advanced-stage first CMC osteoarthritis using USG or investigated their relationship with handgrip and pinch strength. Our study is, to our knowledge, the first study of its kind. All USG measurements were performed by the same specialist experienced in the field, ensuring measurement standardization, which is one of our strengths. Participants may compensate during daily activities by using the extremity with a lower stage of osteoarthritis, which may result in unpredictable changes in muscle thickness and strength independent of pathology. To minimize this issue, only patients whose dominant and non-dominant sides were classified in the same Eaton classification stage were included in the study.

Although the sample size was determined by power analysis, our sample remains relatively small. To ensure standardization of measurements and eliminate sex-related confounders, only female patients were included. The absence of a control group is another limitation; however, in this age group, it is extremely difficult to recruit patients without any signs of first CMC osteoarthritis, which limits the feasibility of establishing a truly “healthy” comparison group. The study was also conducted at a single-center. Additionally, due to the cross-sectional design of our study, it is difficult to establish causal relationships among the development of hand osteoarthritis, the loss of muscle strength, and the decrease in muscle thickness. Future multi-center studies with larger sample sizes, including both genders and appropriate control groups, may yield more generalizable results. Moreover, longitudinal follow-up studies may allow clearer conclusions to be drawn about the effects of hand osteoarthritis on muscle strength and thickness.

Conclusion

In conclusion, examination of patients with first CMC osteoarthritis revealed that the USG-measured thicknesses of the APB, OPP, and FDI muscles, as well as pinch strength, were greater in patients in the early stage than in those in the advanced stage. These findings indicate that both muscle thickness and muscle strength significantly decrease as the disease progresses. The data obtained suggest that early identification of the functional effects of CMC osteoarthritis may be important for the timely implementation of interventions aimed at preserving muscle strength and structure. In this context, USG may be a useful assessment tool for evaluating muscle involvement and functional impairment in patients with first CMC osteoarthritis.

Ethics

Ethics Committee Approval: This cross-sectional study included patients who presented to the physical therapy and rehabilitation outpatient clinics at Beylikdüzü State Hospital between 10.12.2024 and 20.01.2025. Ethical approval for the study was obtained from the Ethics

Committee of İstanbul Physical Therapy and Rehabilitation Training and Research Hospital with protocol number: 2024-73, date: 05.12.2024.

Informed Consent: Informed consent was obtained from all participants, and their confidentiality was strictly protected.

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Footnotes

Authorship Contributions

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

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

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ORIGINAL RESEARCH

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The Relationship Between Sleep Quality and Clinical and Demographic Factors After Stroke

İnme Sonrası Uyku Kalitesi ile Klinik ve Demografik Faktörler Arasındaki İlişki

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Abstract

Objective: Post-stroke sleep disturbances are significant complications that impact the rehabilitation process. This study aimed to evaluate sleep quality in post-stroke patients and examine its relationship with clinical and demographic factors, including functional and psychological status.

Method: This cross-sectional study included 92 post-stroke patients in inpatient rehabilitation. Sleep quality was assessed using the Pittsburgh sleep quality index (PSQI), with patients categorized into good (≤5) and poor (>5) sleep groups. Depression and anxiety symptoms were measured with the hospital anxiety and depression scale (HADS). Functional status and motor recovery were evaluated using the modified Barthel index (MBI) and the Brunnstrom motor assessment, respectively.

Results: Fifty percent of participants had poor sleep quality. No significant differences were observed between groups in age, gender, stroke type, or body mass index (p>0.05). Compared with the good sleep quality group, the poor sleep quality group had significantly shorter time since stroke (p=0.013), lower Brunnstrom motor stage scores (p<0.001), greater dependency as indicated by MBI scores (p<0.001), and higher HADS depression scores (p<0.001) and anxiety scores (p=0.002). In addition, PSQI scores were significantly negatively correlated with stroke duration, Brunnstrom stages, and MBI scores, and were positively correlated with HADS scores.

Conclusion: Half of the stroke patients in this study had poor sleep quality, which was significantly associated with impaired motor recovery, reduced independence in daily activities, and

Öz

Amaç: İnme sonrası uyku bozuklukları, rehabilitasyon sürecini olumsuz etkileyen önemli komplikasyonlar arasında yer almaktadır. Bu çalışmanın amacı, inme sonrası hastalarda uyku kalitesini değerlendirmek ve uyku kalitesinin fonksiyonel ve psikolojik durum da dahil olmak üzere klinik ve demografik faktörlerle ilişkisini incelemektir.

Yöntem: Bu kesitsel çalışmaya, yataklı rehabilitasyon programına alınan 92 inme hastası dahil edilmiştir. Uyku kalitesi Pittsburgh uyku kalitesi indeksi (PUKİ) kullanılarak değerlendirilmiş ve hastalar iyi (≤5) ve kötü (>5) uyku kalitesi gruplarına ayrılmıştır. Depresyon ve anksiyete belirtileri hastane anksiyete ve depresyon ölçeği (HADÖ) ile değerlendirilmiştir. Fonksiyonel durum ve motor iyileşme düzeyi sırasıyla modifiye Barthel indeksi (MBİ) ve Brunnstrom motor değerlendirmesi kullanılarak ölçülmüştür.

Bulgular: Katılımcıların %50'sinin kötü uyku kalitesine sahip olduğu saptanmıştır. Gruplar arasında yaş, cinsiyet, inme tipi veya vücut kitle indeksi açısından anlamlı bir fark bulunmamıştır (p>0,05). İyi uyku kalitesine sahip grupla karşılaştırıldığında, kötü uyku kalitesine sahip grupta inme süresinin daha kısa olduğu (p=0,013), Brunnstrom motor evrelerinin daha düşük olduğu (p<0,001), MBİ puanlarına göre bağımlılık düzeyinin daha yüksek olduğu (p<0,001) ve HADÖ depresyon (p<0,001) ve anksiyete (p=0,002) puanlarının daha yüksek olduğu bulunmuştur. Ayrıca, PUKİ puanlarının inme süresi, Brunnstrom evreleri ve MBİ puanları ile negatif; HADÖ puanları ile ise pozitif yönde anlamlı korelasyon gösterdiği saptanmıştır.

Sonuç: Bu çalışmada, inme hastalarının yarısının kötü uyku kalitesine sahip olduğu ve bu durumun bozulmuş motor iyileşme, günlük

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Abstract

increased anxiety and depression. These findings emphasize the importance of regular sleep assessments and multidisciplinary sleep management within post-stroke rehabilitation programs.

Keywords: Activities of daily living, depression, rehabilitation, sleep quality, stroke

Öz

yaşam aktivitelerinde azalmış bağımsızlık ve artmış anksiyete ve depresyon düzeyleriyle anlamlı derecede ilişkili olduğu gösterilmiştir. Bu sonuçlar, inme sonrası rehabilitasyon programları kapsamında düzenli uyku değerlendirmesinin yapılması ve multidisipliner bir yaklaşımla uyku yönetiminin sağlanmasının gerekliliğini vurgulamaktadır.

Anahtar kelimeler: Günlük yaşam aktiviteleri, depresyon, rehabilitasyon, uyku kalitesi, inme

Introduction

Stroke is one of the leading causes of long-term disability worldwide, resulting in significant physical, cognitive, and psychological impairments that affect patients' quality of life (1). While the primary focus of rehabilitation is often motor recovery, secondary complications can significantly hinder this process (2). Sleep disorders exhibit a complex, bidirectional relationship with stroke; they not only act as a risk factor for stroke but also serve as a significant post-stroke complication that adversely affects rehabilitation outcomes (3,4).

Post-stroke sleep disturbances, encompassing insomnia, fragmented sleep, and hypersomnia, may arise from direct structural damage to sleep-regulating brain centers (e.g., thalamus, brainstem) or secondary to psychological factors such as depression and anxiety (5).

Previous studies have reported that up to 60% of post-stroke patients experience poor sleep quality or related sleep disorders (6). This is clinically important because sleep is not merely a resting state but a vital physiological process that supports neuroplasticity, memory consolidation, and motor learning, which are foundational to stroke rehabilitation (7). Sleep disorders have also been associated with worsening functional status and poor prognosis, which are key targets of post-stroke rehabilitation (8). However, the relationships between sleep quality and demographic factors, stroke characteristics, and psychological status remain heterogeneous in the literature, and conflicting results have been reported. Furthermore, the relationship between sleep and psychological status creates a "vicious cycle". Post-stroke depression and anxiety are strong predictors of poor sleep, yet sleep disturbances themselves can exacerbate these psychiatric symptoms, further hindering functional independence and activities of daily living (9). Given the growing evidence supporting improved clinical outcomes following stroke rehabilitation, it is critical to more fully understand how post-stroke sleep disorders relate to clinical and demographic variables.

This study aimed to evaluate post-stroke patients' sleep quality and to examine its relationship with clinical and demographic factors, including motor function, independence in daily activities, and psychological symptoms.

Materials and Methods

This cross-sectional, descriptive, observational study was designed and conducted in accordance with STROBE guidelines (10). It was conducted between 15.02.2025 and 28.02.2025 at a tertiary hospital. Of 138 post-stroke patients assessed for eligibility, 92 were included in the study. A detailed analysis of the patient selection process and exclusion criteria is shown in the Figure 1. Patients were categorized into two groups based on sleep quality using the Pittsburgh sleep quality index (PSQI) cut-off values.

This study was conducted following approval by the Local Ethics Committee of İstanbul Physical Therapy Rehabilitation Training and Research Hospital (approval number: 2025-02, date: 06.02.2025). All volunteers provided written informed consent for this study, which adhered to the principles outlined in the Declaration of Helsinki.

Inclusion Criteria

- Patients were between 18 and 80 years old
- History of hemorrhagic or ischemic stroke
- Voluntarily agreed to participate in the study.

Exclusion Criteria

- History of pre-stroke insomnia
- Pre-existing psychiatric diseases (e.g., bipolar disorder, depression, schizophrenia, or anxiety)
- Pre-stroke psychiatric medication use
- History of sleep apnea syndrome (confirmed via medical records and patient self-reports)
- Inability to cooperate or complete study-related questionnaires
- Presence of other neurological diseases.

Data for all patients, including demographic details (age, gender, level of education, occupation, marital status), were recorded. Stroke-specific characteristics, such as time since onset, etiology, lesion location, and the affected side, were also evaluated.

Outcomes

PSQI

The PSQI was developed by Buysse et al. (11). The Turkish version, whose validity and reliability were established by Agargun et al. (12), was used to assess patients' sleep quality. The PSQI evaluates sleep quality over the past month through 24 items addressing various components such as sleep duration, sleep latency, subjective sleep quality, use of sleep medication, habitual sleep efficiency, sleep disturbances, and daytime dysfunction. The total score ranges from 0 to 21, with scores above 5 indicating poor sleep quality (12).

Hospital Anxiety and Depression Scale (HADS)

The Turkish validity and reliability study of the HADS was conducted by Aydemir (13). HADS is a 14-item self-assessment tool designed to assess anxiety and depression symptoms, with seven items per subscale. Patients are asked to rate each item on a scale from 0 to 3. The maximum score for both the anxiety and depression subscales is 21. A score of 8 or higher on the depression subscale indicates clinically significant depressive symptoms, and a score of 11 or higher on the anxiety subscale indicates clinically significant anxiety (14).

Modified Barthel Index (MBI)

To evaluate the functional status and dependency level of patients, the Turkish version of the MBI, whose reliability and validity have been confirmed, was used. This index comprises 10 key items assessing various aspects of daily living, including feeding, transfers between bed and wheelchair, personal hygiene, toilet use, bathing, mobility on flat surfaces or in a wheelchair, stair climbing, dressing, and control of bladder and bowel functions. The total score ranges from 0 to 100, with interpretation as follows: 0-20 points indicate total dependence, 21-61 points indicate severe dependence, 62-90 points indicate moderate dependence, 91-99 points indicate mild dependence, and 100 points indicate full independence (15).

Brunnstrom Motor Assessment

The Brunnstrom motor assessment was employed to evaluate motor function in the hemiplegic upper extremity, the lower extremity, and the hand in patients following stroke.

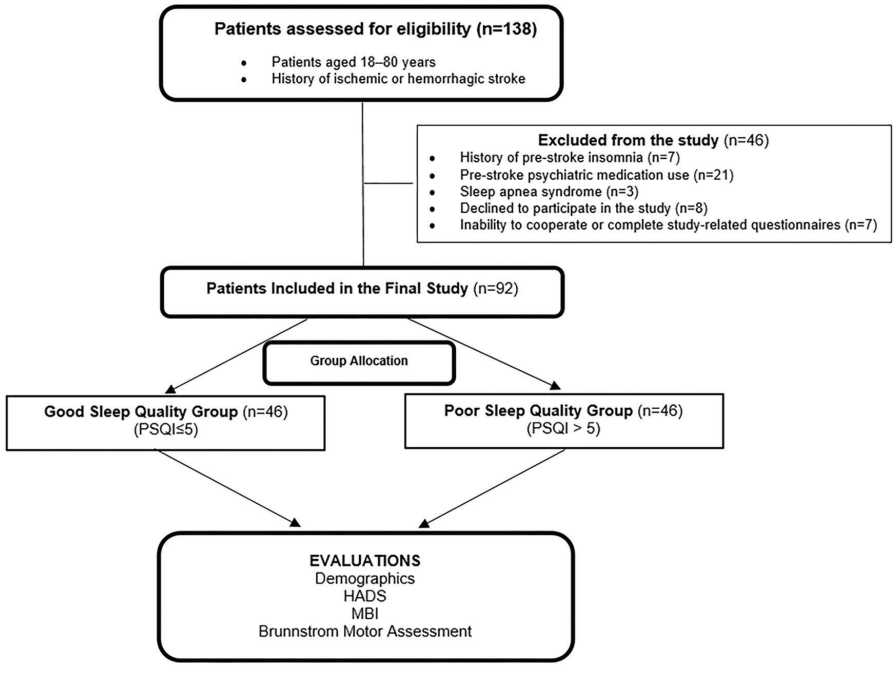

Figure 1. Flow chart of the study

Of the 138 patients assessed for eligibility, 92 were included in the final study after excluding 46 patients who did not meet the inclusion criteria, declined to participate, or were unable to cooperate. Participants were allocated into two groups based on their Pittsburgh sleep quality index (PSQI) scores: the good sleep quality group (PSQI ≤5, n=46) and the poor sleep quality group (PSQI >5, n=46)

This scale classifies motor recovery into six stages, with Stage 1 representing the absence of voluntary movement and Stage 6 indicating near-normal motor control (16).

Sample Size

The sample size of the study was calculated using G*Power software (version 3.1.9.4; Franz Faul, Universität Kiel, Germany). Based on a medium effect size of 0.3 for the correlation test, a significance level of 5% (α=0.05), and a statistical power of 90%, the minimum required sample size was calculated to be 92 participants in total (17).

Statistical Analysis

The normality of the distribution of continuous variables was assessed using the Kolmogorov-Smirnov test with Lilliefors correction. Continuous variables were summarized as mean ± standard deviation and minimum-maximum values, whereas non-normally distributed data were summarized as median (interquartile range). Categorical variables were summarized as frequencies (percentages). Comparisons between two independent groups were made using the Mann-Whitney U test for non-normally distributed data. The homogeneity of categorical variables between groups was assessed using the Pearson chi-square test. Statistical significance was set at $p<0.05$. Spearman's rank correlation coefficient was used to evaluate the relationships between PSQI scores and clinical variables because the data did not meet the normality assumption. Data analyses were performed using IBM SPSS Statistics version 21.0.

Results

A total of 92 patients with stroke were included in the study. The mean age was 65.63 ± 7.94 years. 65.2% of the patients were male. 71.7% of the patients had a history of ischemic stroke. The majority of patients (63%) had lesions in the middle cerebral artery territory, and 55.4% had left hemiplegia (Table 1).

Participants were divided into two groups with good (PSQI≤5) and poor (PSQI>5) sleep quality according to the cut-off values of PSQI scores. Fifty percent of patients had poor sleep quality. There were no statistically significant differences between the groups with good and poor sleep quality in terms of age, gender, etiology, and body mass index (BMI) ($p>0.05$). Compared with the good sleep quality group, the poor sleep quality group had a significantly shorter time since stroke ($p=0.013$), lower Brunnstrom motor stages ($p<0.001$), greater dependency as indicated by MBI scores ($p<0.001$), and higher HADS depression ($p<0.001$) and anxiety scores ($p=0.002$) (Table 2).

Analysis of the relationship between PSQI scores and clinical and demographic parameters revealed no significant correlation with age or BMI. However, significant negative correlations were observed between PSQI scores and stroke duration ($r=-0.269$, $p=0.010$); Brunnstrom stages of the upper extremity ($r=-0.615$, $p<0.001$), hand ($r=-0.523$, $p<0.001$), and lower extremity ($r=-0.575$, $p<0.001$); and the MBI ($r=-0.605$, $p<0.001$). Additionally, there was a significant positive correlation between PSQI scores and HADS depression ($r=0.503$, $p<0.001$) and anxiety ($r=0.393$, $p<0.001$) scores (Table 3).

Table 1. Patients' demographic and stroke characteristics

		n (%)	Mean ± SD	Min-max
Age (years)			65.63±7.94	45-78
Height (cm)			164.98±8.69	148-181
Weight (kg)			79.29±12.77	48-110
BMI (kg/m²)			29.23±4.90	21.72-41.02
Stroke duration (months)			4.64±2.77	1-14
Gender	Male	60 (65.2%)		
	Female	32 (34.8%)		
Marital status	Married	72 (78.3%)		
	Single	20 (21.7%)		
Etiology	Ischemic	66 (71.7%)		
	Hemorrhagic	26 (28.3%)		
Plegic side	Right	41 (44.6%)		
	Left	51 (55.4%)		
Lesion location	MCA	58 (63.0%)		
	ACA	15 (16.3%)		
	Posterior circulation	19 (20.7%)		

SD: Standard deviation, BMI: Body mass index, MCA: Middle cerebral artery, ACA: Anterior cerebral artery, Min-max: Minimum-maximum

Table 2. Comparison of clinical characteristics by PSQI

		Sleep quality		
		Good	Poor	p-value
		(n=46)	(n=46)	
Age (years)		65.04±7.92	66.21±8.01	0.484[U]
BMI (kg/m²)		29.03±4.50	29.42±5.32	0.749[U]
Gender	Male	34 (56.67%)	26 (43.33%)	0.080[P]
	Female	12 (37.5%)	20 (62.5%)	
Etiology	Ischemic	34 (50.75%)	33 (49.25%)	0.815[P]
	Hemorrhagic	12 (48%)	13 (52%)	
Stroke duration (months)		5.46±3.26	3.82±1.90	**0.013**[U]
Brunnstrom upper extremity		5.00 (3.00-6.00)	2.00 (1.00-2.00)	**<0.001**[U]
Brunnstrom hand		5.00 (3.00-6.00)	2.00 (1.00-3.00)	**<0.001**[U]
Brunnstrom lower extremity		4.00 (3.00-5.25)	3.00 (2.00-3.00)	**<0.001**[U]
MBI		77.50 (63.75-85.00)	35.00 (20.00-56.25)	**<0.001**[U]
HADS depression		7.00 (6.00-11.25)	13.00 (10.75-16.25)	**<0.001**[U]
HADS anxiety		6.00 (4.00-14.00)	12.50 (7.75-18.00)	**0.002**[U]

[P]: Pearson chi-square, [U]: Mann-Whitney U test, the data were presented as mean ± standard deviation or frequency (percentage) or median (interquartile range). HADS: Hospital anxiety and depression scale, BMI: Body mass index, MBI: Modified Barthel index

Table 3. Correlation between PSQI scores and other parameters

	PSQI scores	
	r	p-value
Age (years)	0.091	0.391
BMI (kg/m²)	0.080	0.448
Stroke duration (months)	-0.269	**0.010**
Brunnstrom upper extremity	-0.615	**<0.001**
Brunnstrom hand	-0.523	**<0.001**
Brunnstrom lower extremity	-0.575	**<0.001**
MBI	-0.605	**<0.001**
HADS depression	0.503	**<0.001**
HADS anxiety	0.393	**<0.001**

PSQI: Pittsburgh Sleep quality index, BMI: Body mass index, HADS: Hospital anxiety and depression scale, MBI: Modified Barthel index

Discussion

In this study, 50% of stroke patients had poor sleep quality. Significant relationships were found between sleep quality and functional staging, and between sleep quality and the level of independence in activities of daily living. Moreover, as sleep quality worsened, patients also exhibited higher depression and anxiety symptom scores.

In a study conducted in Canada, 61.6% of 682 stroke patients reported at least one type of sleep-related complaint (18). In a prospective cohort study conducted among 403 stroke patients in Northwest Ethiopia, 50.1% were evaluated as having poor sleep quality based on PSQI scores (8). In another study, 60% of 100 stroke patients had poor sleep quality, and the mean global PSQI score was reported as 9.13±14.40 (6). In a study evaluating chronic stroke patients, the mean global PSQI score was found to be 6.5±4.2, and 53% of the patients were reported to have sleep disturbances (19). In the study by Silva et al. (20), the PSQI scores were reported as 8.5±4.4. In our study, the mean total PSQI score was 7.47±5.75, which was lower compared to other studies in the literature. However, when the sample was divided into two groups according to clinically significant cut-off values, 50% of patients had poor sleep quality, which is consistent with the literature.

In our study, the mean age of the patients was 65.63±7.94 (range: 45-78), and no significant relationship was found between age and sleep quality. Conflicting findings exist in the literature on this subject. Nilsson et al. (19) did not find a significant relationship between sleep problems and age (73±11; range: 30-91). Alabdali et al. (6) found no association between age and sleep quality in patients, most of whom were aged 51-59 years. Similarly, other studies have reported no significant association between age and sleep quality, which aligns with our findings (3,18,20). In contrast to these findings, a study involving 277 patients with a mean age of 70.7±7.5 (range: 55-85) reported that the mean age was higher in the group with insomnia (21). Likewise, in the study by Palomäki et al. (22), age (mean 55.2 years; range 27-70 years) was identified as an independent risk factor for insomnia-related symptoms. Further research with

larger sample sizes and more homogeneous patient groups is needed to clarify the relationship between age and sleep quality.

In this study, sleep quality was rated as "poor" in 62.5% of female stroke patients, compared with 43.3% of male patients. Although this difference was not statistically significant, it may be considered clinically meaningful. Several studies have reported inconsistent results on this subject. A study of 682 stroke patients found no significant association between gender and sleep problems (18). Similarly, other studies have reported no association between sleep quality and gender (3,6). In the study by Nilsson et al. (19), however, sleep quality was significantly lower in female patients. In the study by Bakken et al. (23), PSQI total scores were higher in women during the acute phase, whereas actigraphy showed that total sleep duration was longer in women than in men. At the 6-month follow-up, the differences between genders in both objective and subjective measures were no longer observed (23). In our study, sleep quality was assessed only subjectively. Moreover, no specific distinction was made between the acute and chronic phases, and our study population consisted of patients between 1 and 14 months post-stroke. Such variations may account for the differing results regarding the relationship between gender and sleep quality across studies.

In a study conducted in a rehabilitation unit that followed post-stroke patients, improvements in sleep quality paralleled improvements in FIM scores (3). In the study by Silva et al. (20), functional status was assessed using the modified rankin scale and was found to be significantly associated with sleep quality. Although our study did not involve longitudinal follow-up, a significant relationship was found between sleep quality and Brunnstrom stages and MBI scores, both of which reflect functional independence. We believe this may be explained by better adherence to and participation in rehabilitation among patients with good sleep quality, resulting in more favorable functional recovery outcomes.

In a previous study, PSQI scores were >5 in 69.3% of patients with hemorrhagic stroke, indicating poorer sleep quality than in those with ischemic stroke (6). Similarly, other studies have reported a more pronounced deterioration in sleep quality following hemorrhagic stroke. In the study by Kojic et al. (24), sleep disorders were found to be 1.41 times more common after hemorrhagic stroke. Although Pasic et al. (25) observed no statistically significant difference in sleep disorders between the two groups, higher rates were reported in the hemorrhagic stroke group (76.8% vs. 82.5%). It has been suggested that the extensive damage and inflammatory response caused by hemorrhagic strokes in regions such as the brainstem and thalamus—areas critical for sleep regulation—may contribute to the development of sleep disturbances (6). Contrary to these findings, our study found similar rates of sleep problems in both hemorrhagic and ischemic stroke patients. Other studies have reported no significant difference in this regard (19,26). The discrepancies in the literature may be due to various factors such as lesion location, the extent of the affected brain region, patient clinical parameters, the presence or absence of cerebral edema following hemorrhagic stroke, and differences in treatment approaches.

In a study of chronic stroke patients, a significant relationship was found between depression and sleep quality (27). Similarly, Silva et al. (20) found that sleep quality was associated with depressive symptoms. In a study that followed stroke patients under the age of 65, those classified as having chronic insomnia at 12 months showed higher rates of depression, anxiety, and physical limitations (26). Another study demonstrated that depression is an independent factor associated with insomnia (22). Leppävuori et al. (21) reported an independent association between insomnia and anxiety. Consistent with the literature, our study found that HADS scores for anxiety and depression were significantly higher in participants with poor sleep quality.

This study has strengths. One of its strengths is that all assessments were conducted in face-to-face interviews by the same physiatrist, an expert in the field. Additionally, the sample size was determined based on a power analysis. Moreover, the PSQI, which was used to assess sleep quality, is a widely accepted tool with proven validity and reliability.

Study Limitations

An important limitation of our study is that we used a subjective assessment based solely on patient self-reports to evaluate sleep quality, rather than using objective tools such as polysomnography or actigraphy. Furthermore, the study was conducted at a single center. Additionally, since the analyses were primarily bivariate, potential confounding between variables such as stroke duration, motor stage, functional independence, and HADS scores cannot be ruled out. Consequently, independent associations and causality cannot be inferred from our results. Due to its cross-sectional design, patients' pre-stroke sleep patterns and mood states are unknown. Future multicenter studies with larger sample sizes, multivariable analyses, and longitudinal follow-up designs are needed to obtain more comprehensive results.

Conclusion

In conclusion, the study showed that sleep quality was significantly impaired in 50% of stroke patients. Sleep quality is a key parameter that influences patient participation in rehabilitation and alters treatment response. Furthermore, psychological conditions such as anxiety and depression appear to affect sleep quality. Therefore, assessing and improving sleep quality in stroke patients is an integral part of rehabilitation.

Ethics

Ethics Committee Approval: This study was conducted following approval by the Local Ethics Committee of İstanbul Physical Therapy Rehabilitation Training and Research Hospital (approval number: 2025-02, date: 06.02.2025).

Informed Consent: All volunteers provided written informed consent for this study, which adhered to the principles outlined in the Declaration of Helsinki.

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Footnotes

Authorship Contributions

Concept: E.K., B.Ş.A., M.A., N.K., N.P., Design: E.K., B.Ş.A., M.A., N.K., N.P., Data Collection or Processing: E.K., M.A., Analysis or Interpretation: E.K., Literature Search: E.K., B.Ş.A., M.A., Writing: E.K., B.Ş.A., M.A.

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

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ORIGINAL RESEARCH

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Evaluation of the Views of Patients Receiving ECT and Their Parents Regarding ECT, Along with Sociodemographic and Clinical Data

EKT Alan Hastaların ve Ebeveynlerin EKT ile İlgili Görüşlerinin, Sosyodemografik ve Klinik Verilerle Birlikte Değerlendirilmesi

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Abstract

Objective: Electroconvulsive therapy (ECT) represents an efficacious therapeutic approach for managing refractory psychiatric conditions among pediatric and adolescent patients. However, parental authorization is necessary for ECT administration within this age group, and parents' attitudes toward treatment directly influence clinical decision-making processes. This research sought to evaluate parental understanding, attitudes, and experiences among parents whose children received ECT.

Method: This descriptive cross-sectional research was carried out with parents of patients aged 12-18 years who underwent ECT within a tertiary-level psychiatric hospital between 2015 and 2024. Records of 78 patients were accessed, and interviews were conducted with

Öz

Amaç: Elektrokonvülsif terapi (EKT), çocuk ve ergenlerde tedaviye dirençli psikiyatrik bozuklukların yönetiminde etkili bir tedavi seçeneğidir. Ancak bu yaş grubunda EKT uygulaması için ebeveyn onayı gereklidir ve ebeveynlerin tedaviye yönelik tutumları klinik karar süreçlerini doğrudan etkilemektedir. Bu çalışma, EKT uygulanan çocuk ve ergen hastaların ebeveynlerinin tedaviye ilişkin bilgi düzeylerini, tutumlarını ve deneyimlerini değerlendirmeyi amaçlamıştır.

Yöntem: Bu kesitsel ve tanımlayıcı çalışma, 2015-2024 yılları arasında üçüncü basamak bir psikiyatri hastanesinde EKT uygulanan 12-18 yaş arasındaki hastaların ebeveynleri ile yürütülmüştür. Toplam 78 hastanın kayıtlarına ulaşılmış ve 31 ebeveyn ile görüşme yapılmıştır.

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Abstract

31 parents. A structured 30-item questionnaire compiled from the literature was administered to the parents.

Results: Of the patients, 67.7% were male, averaging 16.5±1.1 years of age. The most frequently encountered diagnostic groups were bipolar disorder (38.7%) and schizophrenia spectrum and other psychotic disorders (38.7%). The primary indication for ECT administration was aggression (41.9%). Of the parents, 74.2% reported a reduction in their children's psychiatric symptoms following ECT, and 64.5% reported decreased suicidal ideation. While 71.0% of parents observed no side effects, 35.5% reported experiencing fear during the treatment process. Agreement with the notion that ECT is inhuman was only 12.9%. While 45.2% of parents preferred earlier treatment initiation, 41.9% believed that ECT should be a last resort. Notable moderate to strong inverse associations were identified between parental age and perceived level of information provision.

Conclusion: Parents of young patients who received ECT largely perceive the treatment as effective and safe. However, older parents appear to require more support during the information provision process. It is recommended that clinicians more effectively involve parents in the treatment process through structured psychoeducation programs.

Keywords: Child and adolescent psychiatry, electroconvulsive therapy, parental attitudes

Öz

Ebeveynlere, literatürden derlenen 30 maddelik yapılandırılmış bir anket formu uygulanmıştır.

Bulgular: Hastaların %67,7'si erkek olup yaş ortalaması 16,5±1,1 idi. En sık tanı grupları bipolar bozukluk (%38,7) ve şizofreni spektrumu ve diğer psikotik bozukluklardı (%38,7). En sık EKT endikasyonu saldırganlıktı (%41,9). Ebeveynlerin %74,2'si EKT sonrası çocuklarının psikiyatrik belirtilerinin azaldığını, %64,5'i intihar düşüncesinin gerilediğini bildirdi. Ebeveynlerin %71,0'ı yan etki gözlemlemezken, %35,5'i tedavi sürecinde korku yaşadığını belirtti. EKT'nin insancıl olmadığı düşüncesine katılım yalnızca %12,9 idi. Ebeveynlerin %45,2'si tedavinin daha erken uygulanmasını tercih ederken, %41,9'u EKT'nin son çare olması gerektiğini düşünüyordu. Ebeveyn yaşı ile bilgilendirilme düzeyi arasında orta-güçlü düzeyde negatif yönlü anlamlı korelasyonlar saptandı.

Sonuç: EKT uygulanan çocuk ve ergen hastaların ebeveynleri, tedaviyi büyük oranda etkili ve güvenli olarak değerlendirmektedir. Ancak özellikle ileri yaş ebeveynlerin bilgilendirme süreçlerinde daha fazla desteğe ihtiyaç duyduğu görülmektedir. Klinisyenlerin yapılandırılmış psikoeğitim programları ile aileleri tedavi sürecine daha etkin dahil etmesi önerilmektedir.

Anahtar kelimeler: Çocuk ve ergen psikiyatrisi, ebeveyn tutumları, elektrokonvülsif terapi

Introduction

Electroconvulsive therapy (ECT) represents a neuromodulatory technique applied within psychiatric practice for nearly eight decades, exerting therapeutic effects by inducing controlled seizures in the brain through electrical stimulation (1-3). Modern ECT constitutes a secure treatment modality administered with anesthetic agents alongside muscle relaxation, carrying a low risk of serious complications and enabling rapid response (4,5). As an effective treatment modality, it finds application in the management of conditions such as treatment-resistant depression, mania, schizophrenia, plus catatonia (6-9). ECT stands out as a primary treatment option, particularly in cases unresponsive to pharmacotherapy or in life-threatening clinical situations (10,11). Furthermore, ECT is regarded as the benchmark approach for managing mood or psychotic disorders with severe symptoms or treatment resistance (12,13).

Although ECT effectiveness in adults is well established, its application among pediatric and adolescent populations remains controversial. Nevertheless, current scientific evidence indicates that ECT may be safely administered to young patients without serious side effects and offers a rapid and effective treatment option, particularly in acute clinical situations such as mood disorders, psychotic disorders, catatonia, significant suicide risk, or violent behavior (14-16). Additionally, the United States Food and Drug Administration approved (in 2018) ECT devices as Class II (moderate risk) for managing depression as well as catatonic states in individuals 13 years of age or above (17,18). Furthermore, the American Academy of Child and Adolescent Psychiatry 2025 policy statement regarding "electroconvulsive therapy" emphasizes that ECT represents a safe and efficacious therapeutic option for appropriate indications among youth, therefore access to ECT should be supported (19,20).

The decision to use ECT among pediatric and adolescent patients represents a process that must be evaluated not only based on clinical indication but also considering ethical, legal, and familial dimensions (21-23). Obtaining treatment consent from the patient is generally not a legal requirement for ECT administration in the pediatric patient population; however, written consent needs to be secured from parents or guardians before initiating treatment (21,24,25). Since the decision to initiate and continue ECT in this age group is typically made with parental consent, the knowledge level, beliefs, and concerns of families directly influence their approach to treatment (26,27). There are findings indicating that both patients and families may

initially harbor fear, uncertainty, and negative prejudices toward ECT; however, after treatment, most report benefits and their attitudes shift to more positive ones (27-30).

Despite its documented clinical efficacy, ECT continues to be one of the most stigmatized treatments in psychiatry. This stigma stems from multiple sources, including historical practices before the introduction of anesthesia and muscle relaxants, sensationalized and inaccurate portrayals in popular media, and persistent public misconceptions about the treatment's safety profile (31-33). Research indicates that negative media representations significantly influence both patient and family attitudes, often creating barriers to accessing effective treatment. A recent analysis of social media discussions revealed that misconceptions about ECT remain prevalent, with many posts reflecting outdated fears rather than contemporary evidence-based practice (31). This stigma affects not only patients but also their families, who may face social judgment when considering ECT for their loved ones. Understanding and addressing these negative perceptions is particularly important in the pediatric context, where parental consent is essential and family attitudes directly influence treatment decisions. On the other hand, evidence that modern ECT applications in pediatric patients can provide high rates of clinical improvement and significantly enhance quality of life has strengthened considerably in recent years (34-36).

A critical, yet often overlooked factor in the surrogate decision-making process is the potential influence of parental demographics, particularly age, on the interpretation of medical information. Prior research indicates that relatives' knowledge and attitudes toward ECT are significantly shaped by sociodemographic variables and personal context (27). We hypothesized that parental age may influence ECT perceptions through two potential mechanisms: First, parents of different age cohorts may have varying degrees of exposure to negative media portrayals of ECT, as older generations were more likely to encounter sensationalized depictions during the pre-modern ECT era, while recent studies demonstrate that misconceptions continue to circulate widely on contemporary social media platforms (31). Second, older parents may face additional challenges in processing complex medical information, which could affect their perceived adequacy of information provision. Furthermore, qualitative research with parents of adolescents who received ECT has highlighted the emotional complexity of the decision-making process and the critical role of adequate information provision (21). Understanding these potential age-related differences is clinically relevant, as it could inform the development of tailored, age-appropriate communication strategies for families considering ECT for their children.

Evaluating the experiences and views held by families of young patients who received ECT is important for reducing misconceptions about treatment and supporting informed parental decision-making processes. Although numerous studies in the international literature address the knowledge, attitudes, and experiences of parents or caregivers toward ECT, no study focusing on parents of pediatric patients who received ECT exists in our country. This study was conducted to evaluate the knowledge levels, emotions, experiences, and preferences held by parents of young patients who received ECT regarding ECT, and to reveal how these views relate to the treatment process. Thus, it aims to contribute to filling the gap in the literature regarding the clinical position of ECT within pediatric and adolescent psychiatry and how patient parents perceive this treatment.

Materials and Methods

Study Design

This investigation was carried out following a descriptive cross-sectional framework. This research adhered to the ethical principles outlined in the Declaration of Helsinki by the World Medical Association. The study protocol received approval from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2024-02-09, dated: February 09, 2024).

Population and Sample

A total of 78 patients aged 12-18 years who were hospitalized and received ECT within the child and adolescent psychiatry unit of a tertiary psychiatric hospital in İstanbul between 2015 and 2024 were identified. The parents belonging to these patients were contacted, and 31 parents who provided written informed consent and could be interviewed constituted the study sample. Of the remaining 47 parents who did not participate, 34 could not be reached due to outdated contact information, relocation, or unavailable records, and 13 declined to participate (response rate: 31/78, 39.7%). A participant flow diagram is presented in Figure 1.

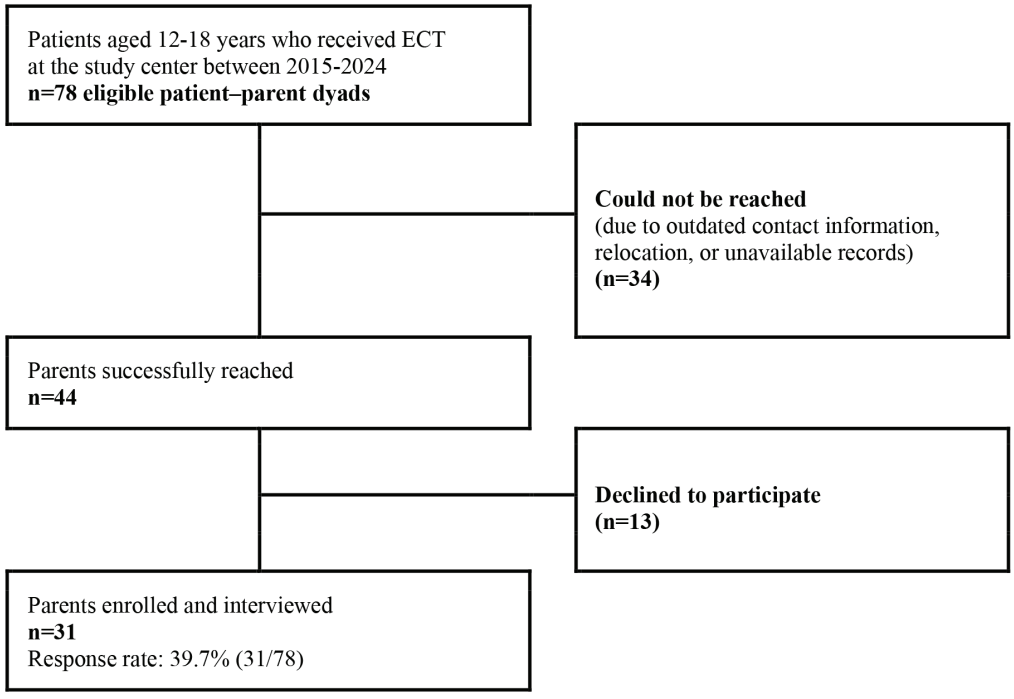

Figure 1. Participant flow diagram
ECT: Electroconvulsive therapy

Inclusion Criteria

The inclusion criteria were: (1) Being a parent of a patient aged 12-18 years who received ECT at the study center during the specified period; (2) having been directly involved in the ECT decision-making and consent process; (3) ability to communicate effectively in Turkish; and (4) provision of written informed consent.

Exclusion Criteria

The exclusion criteria were: (1) Cognitive impairment that could prevent the parent from understanding or answering the questions; (2) inability to reach the parent; (3) parent's refusal to participate in the study. Advanced parental age was not considered an exclusion criterion, as excluding older parents would reduce the representativeness of the sample. Similarly, parental psychiatric history or prior personal exposure to ECT were not included among the exclusion criteria, given that our study aimed to capture the full spectrum of parental perspectives representative of the real-world clinical population, and excluding parents with psychiatric conditions could introduce selection bias (Table 1).

Data Collection Instrument

A structured 30-item questionnaire was developed by the research team following a systematic review of existing instruments used in ECT-related perception and attitude studies. The questionnaire development process involved the following steps: (1) Comprehensive literature review to identify validated instruments and commonly used items in ECT perception research (26,37-42); (2) selection of items addressing key domains relevant to the pediatric ECT context, including ease of use, emotional experiences, perceived clinical benefits, side effect experiences, adequacy of information provision, and treatment preferences regarding ECT; (3) linguistic adaptation of selected items to ensure cultural appropriateness for the Turkish context; and (4) face validity assessment through review by three child and adolescent psychiatrists with ECT experience.

The final questionnaire comprised 30 items distributed across six thematic domains: (a) Ease of use and accessibility (3 items); (b) emotional responses to treatment (4 items); (c) perceived clinical benefits (6 items); (d) side effect experiences (9 items); (e) treatment preferences (4 items); and (f) information provision process (4 items). Items were adapted from questionnaires used in previous international studies assessing ECT-related knowledge, attitudes, and experiences among patients, caregivers, and families (26,37-39,41,42).

Table 1. Parental demographic and patient clinical characteristics

Parental role	**n**	**%**
Mother	16	51.6
Father	15	48.4
Parental education level		
Illiterate	3	9.7
Literate (no formal education)	1	3.2
Primary school graduate	15	48.4
Middle school graduate	2	6.5
High school graduate	6	19.4
University graduate	4	12.9
Patient psychiatric diagnoses		
Bipolar disorder	12	38.7
Schizophrenia spectrum and other psychotic disorders	12	38.7
Major depressive disorder	5	16.1
Autism spectrum disorder	2	6.5
Indications for ECT		
Aggression	13	41.9
Suicidality	4	12.9
Non-suicidal self-injury	3	9.7
Refusal of treatment	4	12.9
Treatment resistance	5	16.1
Catatonia	1	3.2
Neuroleptic malignant syndrome	1	3.2
Patient history		
Prior substance use	2	6.5
History of forensic incidents	6	19.4
Prior suicide attempts	6	19.4
ECT-related side effects (observed in patient)		
Prolonged seizure	1	3.2
Other neurological or cardiac side effects	0	0.0
Clinical characteristics		
Prior psychiatric hospitalizations, mean ± SD	1.6±0.9	
Hospitalization duration during ECT admission (days), mean ± SD	60.9±44.0	
Number of ECT sessions, median (range)	9.0 (4-63)	

ECT: Electroconvulsive therapy, SD: Standard deviation

Procedure

The questionnaire was administered to parents via in-person interviews. Questions were structured employing a Likert-type format ranging from 0 to 5; scores of 0-1 were evaluated as negative, 2-3 as partially positive, and 4-5 as positive views. Answer options spanned from 0 (strongly disagree) to 5 (strongly agree). For the purpose of descriptive reporting and to facilitate interpretation, responses were collapsed into three categories for presentation in Table 2: Scores of 0-1 were categorized as "disagree" (indicating negative or disagreeing views); scores of 2-3 were categorized as "partially agree" (indicating ambivalent or neutral views); and scores of 4-5 were categorized as "agree" (indicating positive or agreeing views). This approach of collapsing scores into three descriptive categories is conceptually aligned with analytical strategies used in similar ECT perception studies (26,38,39) and allows for clearer presentation of the overall direction of parental attitudes while reducing the complexity of presenting full 6-point distributions for 30 items. The original continuous scores (0-5) were retained and used for all correlation analyses presented in Table 3, as these analyses require continuous variables to assess linear relationships between parental age and perception-related variables.

Variables

Variables evaluated within this research included sociodemographic characteristics, medical and psychiatric features of the child, and parental perceptions, attitudes, expectations, satisfaction, side effect experiences, and information provision processes regarding ECT.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY, USA). Skewness and Kurtosis were used to assess the normality of continuous data. Descriptive statistics (frequency, standard deviation, mean, and percentage distributions) were used. Chi-square testing was utilized to compare groups, and correlation analyses were performed to evaluate relationships between variables. Pearson correlation analysis was applied to normally distributed variables. For correlation analyses examining associations between parental age and perception-related variables, the original Likert scores (0-5) were retained rather than collapsed categories to maximize variability. The magnitude of Pearson correlation coefficients was categorized as weak (r=0.10-0.29), moderate (r=0.30-0.49), or strong (r≥0.50).

Results

Records of a total of 78 patients aged 12-18 years who received ECT were accessed within the scope of the study. The parents of these patients were contacted, and face-to-face interviews were conducted with 31 parents who agreed to participate. Thus, the study sample consisted of 31 patients and their parents. All clinical and demographic data presented in this study pertain exclusively to these

31 patient-parent dyads, and all reported frequencies and percentages are calculated using n=31 as the denominator. Of the patients included in the study, 10 were female (32.3%) and 21 were male (67.7%), with a mean age of 16.5±1.1 years at the time of ECT administration.

Of the interviewed parents, 16 (51.6%) were mothers and 15 (48.4%) were fathers, averaging 48.5±5.3 years of age. Regarding parental education levels: 3 (9.7%) were illiterate, 1 (3.2%) was literate but had not completed primary school, 15 (48.4%) were primary school graduates, 2 (6.5%) were middle school graduates, 6 (19.4%) were high school graduates, and 4 (12.9%) were university graduates. The demographic characteristics of parents along with patient clinical features are summarized within Table 1.

Twelve patients (38.7%) were diagnosed with bipolar disorder and 12 cases (38.7%) with schizophrenia spectrum and other psychotic disorders. Among the remaining individuals, 5 (16.1%) had major depressive disorder and 2 (6.5%) had autism spectrum disorder.

ECT was administered due to aggression in 13 patients (41.9%), suicidality in 4 patients (12.9%), non-suicidal self-injury in 3 patients (9.7%), refusal of treatment in 4 patients (12.9%), treatment resistance in 5 patients (16.1%), catatonia in 1 patient (3.2%), and neuroleptic malignant syndrome in 1 patient (3.2%).

The average count of psychiatric hospitalizations was 1.6±0.9, and patients remained hospitalized for an average of 60.9±44.0 days during the admission when ECT was applied. The median ECT session count was 9.0, with values spanning from 4 at the lowest to 63 at the highest.

Two patients (6.5%) presented with prior substance use, 6 patients (19.4%) had a history of forensic incidents, while 6 patients (19.4%) reported previous suicide attempts.

Table 2. Parental perceptions, attitudes, and experiences of ECT

Statement	Disagree n (%)	Partially agree n (%)	Agree n (%)
ECT is more effective than medications.	7 (22.6)	5 (16.1)	19 (61.3)
ECT acts more rapidly than medications.	8 (25.8)	4 (12.9)	19 (61.3)
ECT is an inhuman treatment.	21 (67.7)	6 (19.4)	4 (12.9)
ECT is not an appropriate treatment for my child.	18 (58.1)	7 (22.6)	6 (19.4)
I experienced fear during my child's ECT treatment.	9 (29.0)	11 (35.5)	11 (35.5)
ECT reduced my child's illness symptoms.	2 (6.5)	6 (19.4)	23 (74.2)
My child's suicidal ideation decreased after ECT.	7 (22.6)	4 (12.9)	20 (64.5)
My child experiences fewer illness-related relapses after ECT.	5 (16.1)	7 (22.6)	19 (61.3)
ECT is more dangerous than medications.	18 (58.1)	7 (22.6)	6 (19.4)
ECT is a safe treatment option.	6 (19.4)	7 (22.6)	18 (58.1)
I observed side effects after ECT.	22 (71.0)	4 (12.9)	5 (16.1)
I wish ECT had been administered earlier.	12 (38.7)	5 (16.1)	14 (45.2)
I would prefer ECT over medications.	11 (35.5)	5 (16.1)	15 (48.4)
ECT should only be used in severely ill patients.	7 (22.6)	9 (29.0)	15 (48.4)
ECT should be used as a last resort.	8 (25.8)	10 (32.3)	13 (41.9)

ECT: Electroconvulsive therapy

Table 3. Correlations between parental age and ECT-related perceptions

Variable	p	r
Perceived adequate knowledge about ECT	0.009	-0.462
Perceived adequate information on therapeutic effects and procedure	0.001	-0.563
Perceived adequate information on side effects	0.034	-0.382
Perceived adequate information on risks	0.038	-0.374
Belief that ECT is frequently used in adolescents	0.037	-0.376

ECT: Electroconvulsive therapy, r: Pearson correlation coefficient
All correlations indicate that older parents reported lower perceived information adequacy

Regarding side effects evaluated during or after ECT administration, prolonged seizure was observed in only 1 patient (3.2%). No other neurological or cardiac side effects were observed.

The majority of parents evaluated ECT to be an efficacious, rapid, and secure therapeutic approach. Most parents indicated that ECT was both more effective and faster than medications. Agreement with the notion that ECT is an inhuman method remained low (12.9%).

A total of 58.1% of parents viewed ECT as an appropriate treatment option for their child; although 35.5% of parents reported experiencing fear during the ECT process, the general tendency was that the child benefited from treatment. Indeed, 74.2% of participants reported that their children's psychiatric symptoms decreased after ECT, and 64.5% reported that suicidal ideation decreased. Additionally, 61.3% of participants stated that there were fewer illness-related relapses after ECT.

Overall, 58.1% of parents believed that the method was not more dangerous than medications and was a safe treatment. Furthermore, 71.0% of parents reported not observing any side effects after ECT. A total of 45.2% of participants expressed that ECT should have been administered earlier; 48.4% indicated that they could prefer ECT over medication treatment. On the other hand, 48.4% of parents expressed the view that ECT ought to remain reserved for patients presenting serious psychiatric conditions, while 41.9% believed it should be administered as a last resort. In comparisons, mothers' and fathers' responses showed no statistically meaningful variations across all items. Parental attitudes and experiences regarding ECT are summarized in Table 2.

When parents were grouped according to their children's diagnoses, no significant differences were found in their views regarding benefit from ECT, side effects, emotions about ECT, or beliefs about ECT's effectiveness and speed.

Correlation analyses between parental age and views on ECT were also examined (Table 3). A significant negative moderate correlation was found between parental age and perceived adequate knowledge about ECT (p=0.009, r=-0.462); a significant strong negative correlation with the belief of perceived adequate information on therapeutic effects and procedure (p=0.001, r=-0.563); a significant negative moderate correlation with the belief of perceived adequate information on side effects (p=0.034, r=-0.382); a significant negative moderate correlation with the belief of perceived adequate information on risks (p=0.038, r=-0.374); and a significant negative moderate correlation with the belief that ECT is frequently used in adolescents (p=0.037, r=-0.376).

Parental perceptions and attitudes toward ECT were compared according to parental role (mothers vs. fathers) using chi-square tests (Table 4). No statistically significant differences were observed between mothers and fathers across any of the questionnaire items (all p>0.05). Specifically, mothers and fathers demonstrated comparable views regarding perceived efficacy, with similar proportions agreeing that ECT reduced their child's symptoms (68.8% vs. 80.0%; χ^2=0.7, p=0.712) and that ECT acts more rapidly than medications (62.5% vs. 60.0%; χ^2=0.0, p=0.990). Similarly, no significant differences emerged in safety perceptions, including views on whether ECT is a safe treatment option (χ^2=3.9, p=0.141) or observations of side effects following treatment (χ^2=3.5, p=0.174). Emotional responses to treatment were also comparable between groups, with 43.8% of mothers and 26.7% of fathers reporting fear during their child's ECT treatment (χ^2=1.0, p=0.610). Furthermore, treatment preferences showed no significant variation, as similar proportions expressed a preference for ECT over medications (43.8% vs. 53.3%; χ^2=0.3, p=0.850) and agreement that ECT should be used as a last resort (37.5% vs. 46.7%; χ^2=0.4, p=0.800). These findings suggest that parental role does not significantly influence perceptions and attitudes toward ECT in this sample. Given the non-significant chi-square results (all p>0.05), Fisher's exact test, as a more conservative statistical approach, was not implemented in the current study.

Discussion

This research sought to describe parental perceptions, attitudes, and experiences regarding ECT administered to their children. Our descriptive findings indicate that the majority of parents in this sample reported positive perceptions of ECT. However, these findings represent reported perceptions rather than objective measures of treatment efficacy or safety. Our findings indicate that parents' general attitudes toward ECT are positive, and they largely view the treatment as "life-saving" and "more effective than medications". These findings are consistent with the results of the systematic review by Boone et al. (27), which included 29 studies; this review indicated that caregivers' perceptions regarding ECT are predominantly favorable, and that most caregivers would recommend ECT in the future if needed.

Table 4. Comparison of ECT-related perceptions and attitudes between mothers and fathers

Statement	Answer	Mothers, n=16	Fathers, n=15	X^2	p
ECT is more effective than medications.	Disagree	4 (25.0)	3 (20.0)	0.4	0.834
	Partially agree	3 (18.8)	2 (13.3)		
	Agree	9 (56.3)	10 (66.7)		
ECT acts more rapidly than medications.	Disagree	4 (25.0)	4 (26.7)	0.0	0.990
	Partially agree	2 (12.5)	2 (13.3)		
	Agree	10 (62.5)	9 (60.0)		
ECT is an inhuman treatment.	Disagree	11 (68.8)	10 (66.7)	1.7	0.431
	Partially agree	2 (12.5)	4 (26.7)		
	Agree	3 (18.8)	1 (6.7)		
ECT is not an appropriate treatment for my child.	Disagree	9 (56.3)	9 (60.0)	1.9	0.382
	Partially agree	5 (31.3)	2 (13.3)		
	Agree	2 (12.5)	4 (26.7)		
I experienced fear during my child's ECT treatment.	Disagree	4 (25.0)	5 (33.3)	1.0	0.610
	Partially agree	5 (31.3)	6 (40.0)		
	Agree	7 (43.8)	4 (26.7)		
ECT reduced my child's illness symptoms.	Disagree	1 (6.3)	1 (6.7)	0.7	0.712
	Partially agree	4 (25.0)	2 (13.3)		
	Agree	11 (68.8)	12 (80.0)		
My child's suicidal ideation decreased after ECT.	Disagree	3 (18.8)	4 (26.7)	1.1	0.574
	Partially agree	3 (18.8)	1 (6.7)		
	Agree	10 (62.5)	10 (66.7)		
My child experiences fewer illness-related relapses after ECT.	Disagree	4 (25.0)	1 (6.7)	3.1	0.211
	Partially agree	2 (12.5)	5 (33.3)		
	Agree	10 (62.5)	9 (60.0)		
ECT is more dangerous than medications.	Disagree	8 (50.0)	10 (66.7)	3.0	0.223
	Partially agree	3 (18.8)	4 (26.7)		
	Agree	5 (31.3)	1 (6.7)		
ECT is a safe treatment option.	Disagree	5 (31.3)	1 (6.7)	3.9	0.141
	Partially agree	2 (12.5)	5 (33.3)		
	Agree	9 (56.3)	9 (60.0)		
I observed side effects after ECT.	Disagree	9 (56.3)	13 (86.7)	3.5	0.174
	Partially agree	3 (18.8)	1 (6.7)		
	Agree	4 (25.0)	1 (6.7)		
I wish ECT had been administered earlier.	Disagree	6 (37.5)	6 (40.0)	0.2	0.919
	Partially agree	3 (18.8)	2 (13.3)		
	Agree	7 (43.8)	7 (46.7)		
I would prefer ECT over medications.	Disagree	6 (37.5)	5 (33.3)	0.3	0.850
	Partially agree	3 (18.8)	2 (13.3)		
	Agree	7 (43.8)	8 (53.3)		
ECT should only be used in severely ill patients.	Disagree	5 (31.3)	2 (13.3)	1.4	0.489
	Partially agree	4 (25.0)	5 (33.3)		
	Agree	7 (43.8)	8 (53.3)		
ECT should be used as a last resort.	Disagree	4 (25.0)	4 (26.7)	0.4	0.800
	Partially agree	6 (37.5)	4 (26.7)		
	Agree	6 (37.5)	7 (46.7)		

ECT: Electroconvulsive therapy

In our study, 74.2% of parents reported that their children's psychiatric symptoms decreased after ECT, and 64.5% reported that suicidal ideation decreased. Furthermore, the fact that no parent characterized the treatment as "completely ineffective" and that 48.4% indicated they could prefer ECT over medication treatment suggests that ECT was perceived favorably by families in this sample. This high perception of efficacy is consistent with the literature. Flamarique et al. (42), in their study with families of teenage patients carrying schizophrenia spectrum diagnoses, reported that 73.7% of parents found the treatment beneficial for their children and no parent thought the condition worsened. Walter et al. (37) reported that 50% of patients found ECT beneficial, while the same study noted that 61% of parents reported improvement. The 74.2% symptom reduction rate we observed aligns with these findings and even suggests a somewhat higher satisfaction level compared to these data. Additionally, in the study by Rajagopal et al. (39), 94% of patient relatives agreed with the statement "I am satisfied that my relative received ECT", supporting that parents/caregivers are highly satisfied with treatment outcomes.

One of the most notable findings of our study is that 71% of parents reported not observing any side effects in their children after ECT. This rate reveals similar results to some studies in the literature. Similarly, Rajagopal et al. (38) reported that a large proportion (83%) of patient relatives did not have negative experiences with long-term side effects. However, Deng et al. (26) noted that 62% of participants experienced adverse effects, with memory disturbance emerging as the predominant complaint at 72.8% The low rate of side effect reporting in our study (no serious side effects except for prolonged seizure at 3.2%) suggests that parents can tolerate mild cognitive effects or prioritize clinical improvement from treatment over side effects. In the study by Flamarique et al. (42), 80% of parents also described the illness itself as a worse experience than ECT or medications.

Our analysis revealed notable negative associations between parental age and the beliefs of "perceived adequate knowledge about ECT" and "perceived adequate information on therapeutic effects and procedure". This indicates that older parents experience more difficulty in the information provision process. The literature also frequently emphasizes deficiencies in information provision processes. Rajagopal et al. (39) reported that although 100% of patient relatives stated they had sufficient information to decide on treatment and all their questions were answered, and 96% reported that the treatment team devoted sufficient time to them, complete satisfaction with information was not achieved. In the same study, 90% of patient relatives agreed with the statement "we did not receive adequate information", and 80% disagreed with the statement "we received the right amount of information", emphasizing that the information was insufficient. Gunasekera et al. (41) reported that physicians served as the primary information source (43%), yet 69% felt that medical staff failed to offer sufficient explanation before treatment. Similarly, in the study by Deng et al. (26), only 55.4% of caregivers indicated they were informed before ECT. Our findings indicate that, particularly for parents in older age groups, there is a need for structured and repetitive information sessions beyond standard consent forms. However, alternative interpretations should be considered; this association may also reflect generational differences in expectations regarding medical communication, varying levels of health literacy, or differences in willingness to express dissatisfaction rather than actual deficits in information comprehension.

The rate of agreement with the notion that ECT is an "inhuman" method was found to be quite low (12.9%) in our study. This outcome aligns with what Rajagopal et al. (38) observed; in that study, 96% of patient relatives disagreed with the view that ECT is an inhuman treatment, and only 3.9% agreed or were undecided. Nevertheless, 35.5% of parents reported experiencing fear about their child during the ECT process. Our findings parallel those documented in previous research. Our results are comparable to the 26% noted by Rajagopal et al. (39) in adult patient relatives and the 31.5% found by Deng et al. (26) in caregivers. Flamarique et al. (42) identified a notably higher fear rate (52.6%) among families of adolescent patients with schizophrenia spectrum conditions. Such variation suggests the impact of the child's diagnosis and age on parental anxiety.

In our study, 41.9% of parents believed that ECT should be administered as a last resort. This rate is similar to the 51.1% found by Deng et al. (26) in caregivers in China. On the other hand, 45.2% of parents in our study expressed the view that "ECT should have been administered earlier". This rate is higher than the 19.5% "treatment was delayed" rate reported by Rajagopal et al. (38) in patient relatives and the 31.6% rate of parents who responded "would accept immediately" in the study by Flamarique et al. (42). These findings may reflect positive parental experiences in our sample and a possible preference toward earlier initiation of treatment.

Study Limitations

Our research has certain limitations. First, data collection occurred at a single institution with a limited number of participants (n=31). This may restrict how broadly the results can be applied. Second, the cross-sectional nature of this work does not permit assessment of how parental attitudes evolve over time. Third, data were collected retrospectively, and parental recall bias may have affected the results. Since the time elapsed since ECT administration varied, some parents may have remembered their experiences more positively or negatively. Fourth, of the 78 parents contacted, 34 could not be reached due to outdated contact information, relocation, or unavailable records, and 13 declined to participate, resulting in a response rate of 39.7% (31/78); this may have led to selection bias, as parents with more positive experiences regarding ECT may have been more inclined to participate. This potential bias should be considered when interpreting the predominantly favorable attitudes reported. Finally, the questionnaire used was not a standardized scale but was compiled from the literature by the researchers; therefore, its psychometric properties, including internal consistency and reliability, have not been formally evaluated. Additionally, formal pilot testing was not conducted prior to data collection. These factors limit our ability to determine whether the items function coherently to measure the intended constructs and should be considered when interpreting the findings.

Nevertheless, our study has notable strengths. First, this is the first study in Turkey to assess parental perspectives regarding minors treated with ECT, addressing a significant gap in this field. Second, the study encompasses cases spanning approximately a decade (2015-2024), capturing a wide range of clinical experience. Third, the questionnaire used was compiled from studies with demonstrated validity in the international literature, providing a multidimensional assessment. Finally, our study includes views of both mothers and fathers, showing a balanced distribution by gender.

Conclusion

In conclusion, our descriptive study indicates that parents of pediatric patients who received ECT at our center reported predominantly positive perceptions regarding the treatment's effectiveness and safety. A large proportion of parents reported reduction in their children's psychiatric symptoms after ECT and found the treatment beneficial. The perception that ECT is an "inhuman" method remained at a very low level. However, it was found that older parents in particular experienced more difficulty in the information provision process, and greater emphasis should be placed on structured psychoeducation programs and family education in clinical practice. Future studies conducted with larger samples, prospective designs, and qualitative methods will increase the body of knowledge in this field. Additionally, developing and implementing psychoeducation programs aimed at reducing social stigma toward ECT is important.

Ethics

Ethics Committee Approval: This research adhered to the ethical principles outlined in the Declaration of Helsinki by the World Medical Association. The study protocol received approval from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2024-02-09, dated: February 09, 2024).

Informed Consent: Written permission was secured from all parents or legal guardians of the participants.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: M.T., C.Y., S.A., İ.E.G.F., K.K., Ç.E., S.T., R.O.Ç., E.H., G.A., Ö.A.C., G.K. Concept: M.T., G.K., Ç.E., S.T., C.Y., S.A., İ.E.G.F., K.K. Design: M.T., G.K., Ç.E., S.T., C.Y., S.A., R.O.Ç., Ö.A.C. Data Collection or Processing: M.T., C.Y., S.A., İ.E.G.F., K.K., Ç.E., S.T., R.O.Ç., E.H., G.A., Ö.A.C. Analysis or Interpretation: M.T., G.K., Ç.E., S.T., C.Y., S.A., İ.E.G.F., K.K. Literature Search: M.T., C.Y., S.A., İ.E.G.F., K.K., E.H., G.A., Ö.A.C., R.O.Ç. Writing: M.T., G.K., C.Y., S.A., Ç.E., S.T.

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ORIGINAL RESEARCH

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The Impact of the Systemic Immune-inflammation Index and the Systemic Inflammatory Response Index on Progression-free Survival and Overall Survival in Second-line Immunotherapy for Metastatic Non-small Cell Lung Cancer

Metastatik Küçük Hücreli Dışı Akciğer Kanserinde İkinci Basamak İmmünoterapide Sistemik İmmün-enflamatuvar İndeks ve Sistemik Enflamatuvar Yanıt İndeksinin Progresyonsuz Sağkalım ve Genel Sağkalıma Etkisi

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Abstract

Objective: Systemic inflammation plays a key role in tumor progression and treatment response in advanced non-small cell lung cancer (NSCLC). Among inflammation-based biomarkers, the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) have recently gained attention as potential prognostic tools. This study aimed to evaluate the prognostic impact of SII and SIRI on progression-free survival (PFS) and overall survival (OS) in metastatic NSCLC patients receiving second-line nivolumab.

Method: A retrospective analysis was conducted in 216 patients with metastatic NSCLC who were treated with second-line nivolumab. Baseline hematologic parameters were used to calculate SII and SIRI.

Öz

Amaç: Sistemik enflamasyon, ileri evre küçük hücreli dışı akciğer kanserinde (KHDAK) tümör progresyonu ve tedavi yanıtında önemli bir rol oynamaktadır. Enflamasyon temelli biyobelirteçler arasında sistemik immün-enflamasyon indeksi (SII) ve sistemik enflamatuvar yanıt indeksi (SIRI), son yıllarda prognostik araçlar olarak dikkat çekmiştir. Bu çalışma, ikinci basamak nivolumab tedavisi alan metastatik KHDAK hastalarında SII ve SIRI'nın progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) üzerindeki etkisini değerlendirmeyi amaçlamıştır.

Yöntem: İkinci basamak nivolumab tedavisi alan 216 metastatik KHDAK hastasının retrospektif analizi gerçekleştirildi. SII ve SIRI değerleri başlangıç hematolojik parametrelerden hesaplandı. Eğri

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Receiver operating characteristic analysis was used to determine optimal cut-off values, and associations between these values and OS and PFS were examined. Clinical variables—including metastatic distribution, response to prior therapy, and nivolumab cycle number—were incorporated into univariate and multivariate Cox regression models.

Results: Median OS and PFS were 27.7 and 12.6 months, respectively, with a median follow-up of 24 months. A SIRI cut-off of ≥2086 was strongly associated with increased mortality and progression risk, while SII demonstrated no significant discriminatory value. An association was observed between the number of nivolumab cycles and survival outcomes, with shorter survival among patients who received fewer cycles. Additionally, the presence of multiorgan metastases and disease progression during prior treatment independently predicted worse outcomes.

Conclusion: SIRI and the nivolumab cycle count appear to be clinically relevant parameters associated with survival outcomes. The lack of prognostic significance for SII suggests that SIRI may be a more reliable inflammation-based marker in this treatment setting. These findings highlight the potential of integrating inflammatory indices with clinical parameters to refine risk stratification and optimize patient management.

Keywords: Nivolumab, non-small cell lung cancer, overall survival, progression-free survival, prognostic biomarkers, systemic immune-inflammation index, systemic inflammatory response index

altında kalan alan analizi ile optimal kesim noktaları belirlendi ve bu indekslerin OS ve PFS ile ilişkileri değerlendirildi. Metastatik dağılım, önceki tedavi yanıtı ve nivolumab kür sayısı gibi klinik değişkenler univaryant ve multivaryant Cox regresyon modellerine dahil edildi.

Bulgular: Ortalama 24 aylık takip sonrasında medyan OS 27,7 ay, medyan PFS ise 12,6 ay olarak hesaplandı. SIRI için ≥2086 kesim değeri, artmış mortalite ve progresyon riski ile güçlü şekilde ilişkili bulundu. Buna karşın SII anlamlı bir ayırt edici değer göstermedi. Nivolumab kür sayısı, hastalık seyri ile ilişkili prognostik bir gösterge olarak değerlendirildi; daha az kür alabilen hastalarda daha kısa sağkalım gözlenmiştir. Ayrıca çoklu organ metastazı ve önceki tedavi sırasında progresyon, bağımsız kötü prognostik faktörler olarak saptandı.

Sonuç: SIRI ve nivolumab kür sayısı, ikinci basamak immünoterapi alan metastatik KHDAK hastalarında sağkalım ile ilişkili, klinik olarak uygulanabilir prognostik parametreler olarak değerlendirilebilir. SII'nın anlamlı prognostik katkı sağlamaması, bu tedavi bağlamında SIRI'nın daha güvenilir bir enflamasyon temelli belirteç olabileceğini düşündürmektedir. Bulgular, enflamatuvar indekslerin klinik parametrelerle birlikte kullanılarak risk sınıflamasının iyileştirilebileceğini ve hasta yönetiminin optimize edilebileceğini göstermektedir.

Anahtar kelimeler: Genel sağkalım, küçük hücreli dışı akciğer kanseri, nivolumab, prognostik biyobelirteçler, progresyonsuz sağkalım, sistemik enflamatuvar yanıt indeksi, sistemik immün-enflamasyon indeksi

Introduction

Cancer, excluding non-melanoma skin cancers, remains the most frequently diagnosed malignancy worldwide and represents a major public health problem in terms of both incidence and mortality (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers and is associated with poor overall survival (OS), largely due to diagnosis at advanced stages and the limited availability of effective treatment options (2,3). Because most patients are diagnosed at an advanced stage, survival outcomes remain suboptimal despite current therapeutic strategies (4). In recent years, the introduction of immune checkpoint inhibitors (ICIs), particularly anti-PD-1/PD-L1 agents, has marked a major breakthrough in the management of advanced NSCLC and has led to significant improvements in survival outcomes (5). However, the response to immunotherapy (IT) varies substantially among patients, highlighting the need for reliable and easily accessible biomarkers that can predict treatment outcomes (6).

With increasing understanding of the role of systemic inflammation in tumor development, progression, and metastasis, inflammatory indices derived from peripheral blood parameters have attracted increasing attention (7). Among these, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI) are the most commonly investigated biomarkers (8). Large-scale meta-analyses in NSCLC populations have demonstrated that elevated NLR levels are significantly associated with poor survival (9). Similarly, C-reactive protein (CRP)–based inflammatory scores have been shown to have strong prognostic value across large patient cohorts (10).

SIRI is a recently defined index calculated as (neutrophils×monocytes)/lymphocytes (11). Meta-analyses including more than 3.000 patients with NSCLC have shown that elevated SIRI levels are consistently associated with poor OS and progression-free survival (PFS) (8). Moreover, this association has been reported to remain consistent regardless of differences in country, tumor stage, histology, or cut-off values (8).

Recent findings also suggest that SIRI and SII may serve as potential biomarkers for predicting treatment response among patients with advanced NSCLC receiving IT (8). However, most existing meta-analyses involve heterogeneous patient populations and

combine different treatment modalities, limiting the generalizability of their conclusions. Data specifically evaluating the prognostic roles of SIRI and SII in patients with metastatic NSCLC treated with second-line nivolumab remain limited (12). Furthermore, comprehensive studies assessing these inflammatory indices together with clinical features such as metastatic patterns, prior treatment response, and the number of nivolumab cycles are still needed (12).

In this study, we aimed to evaluate the prognostic significance of SIRI and SII for OS and PFS in metastatic NSCLC patients receiving second-line nivolumab, as well as their associations with metastatic distribution, number of nivolumab cycles administered, and prior treatment response (12).

Materials and Methods

This retrospective study included patients with metastatic NSCLC who received second-line nivolumab treatment at the İstanbul Medipol University Medical Oncology Clinic. Ethics committee approval: Permission was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (decision no: 1238, date: 16.10.2025). Electronic medical records and radiological data of eligible patients were reviewed.

Patients aged ≥18 years, histologically diagnosed with NSCLC, who had received at least one cycle of nivolumab as second-line therapy and who had accessible baseline laboratory parameters and radiological assessments were included. Patients with insufficient laboratory data, active infections, autoimmune diseases requiring immunosuppressive therapy, hematologic malignancies, or missing follow-up information were excluded.

Demographic characteristics (age, sex), Eastern Cooperative Oncology Group (ECOG) performance status, histopathological subtype, primary tumor location, initial clinical stage, comorbidities, prior treatments, metastatic sites, metastatic tumor burden, number of nivolumab cycles, and radiological treatment responses were obtained from medical records. Pre-treatment neutrophil, lymphocyte, monocyte, and platelet counts, as well as CRP and albumin levels, were retrieved from the hospital laboratory information system. Hemogram analyses were performed on the Mindray CAL 8000 analyzer (Shanghai, China) using electrical-impedance and optical methods, while CRP and albumin levels were measured on Cobas 702 analyzers (Roche Diagnostics, Mannheim, Germany) using the electrochemiluminescence method.

Systemic inflammation indices were calculated using the following formulas:

SII = platelet count × neutrophil count/lymphocyte count

SIRI = neutrophil count × monocyte count/lymphocyte count.

OS was defined as the time from nivolumab initiation until death from any cause. PFS was defined as the time from treatment initiation until radiologically confirmed disease progression or death. Treatment responses were evaluated according to RECIST 1.1 criteria.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean ± standard deviation, whereas non-normally distributed variables were expressed as median (minimum-maximum). Categorical variables were summarized as frequencies and percentages.

Comparisons between groups were performed using the chi-square or Fisher's exact test for categorical variables, and the independent samples t-test or Mann-Whitney U test for continuous variables. OS and PFS were analyzed using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Prognostic factors affecting survival were examined using Cox proportional hazards regression analysis; hazard ratios (HRs) and 95% confidence intervals (CIs) were reported.

The predictive performance of continuous variables was assessed using receiver operating characteristic (ROC) curve analysis, and optimal cut-off values were determined by the Youden index. The number of nivolumab cycles was included in the analyses as a treatment exposure-related variable, defined as the total number of administered cycles during follow-up. In this study, ≥2086 was used as the cut-off value for SIRI, and ≤10.5 for the number of nivolumab cycles. A p-value <0.05 was considered statistically significant.

To address the potential risk of immortal time bias associated with treatment duration, a landmark analysis was performed for progression-free survival. The landmark time point was defined at 3 months following nivolumab initiation, corresponding to the first routine radiological response assessment. Only patients who were alive and progression-free at the landmark time point were included in the landmark-adjusted multivariate Cox regression

model. OS analyses were performed using the full cohort, as the predefined landmark did not result in exclusion of patients or alteration of the OS risk set.

Results

In the present study, 216 patients were included (Table 1). The mean age of the patients was 62.56±8.53 years, with a median age of 62.5 (range: 24-88). Among all cases, 64.4% were older than 60 years, and 35.6% were younger than 60 years. The gender distribution revealed that 86.1% of the patients were male and 13.9% were female, indicating a clear predominance of male patients. Regarding performance status, 13.5% of the patients had ECOG 0, 84.2% had ECOG 1, and 2.3% had ECOG 2.

Table 1. Distribution of socio-demographic and clinical variables

Variables	n	%
Age		
Mean ± SD	62.56±8.53	
Median (min-max)	62.5 (24-88)	
<60	77	35.6
>60	139	64.4
Sex		
Female	30	13.9
Male	186	86.1
ECOG		
0	18	13.5
1	112	84.2
2	3	2.3
Comorbidity		
Absent	95	44.0
COPD	34	15.7
CHF-CAD	25	11.6
History of an other malignancy in remission	9	4.2
DM or HT	48	22.2
Other	5	2.3
Histopathology		
ADC	99	45.8
SCC	81	37.5
Mixed type	31	14.4
Other	5	2.3
Primary tumor location		
Right upper lobe	83	38.4
Right middle lobe	17	7.9
Right lower lobe	31	14.4
Left upper lobe	41	19.0
Left lower lobe	29	13.4
Central	15	6.9
Initial stage		
Early stage at diagnosis	99	45.8
Metastatic at diagnosis	117	54.2
Vascular invasion		
Unknown	175	81.0
Present	19	8.8
Absent	22	10.2
Lymphatic invasion		
Unknown	175	81.0
Present	19	8.8
Absent	22	10.2
Perineural invasion		
Unknown	172	79.6
Present	14	6.5
Absent	30	13.9
RT type		
Received adjuvant RT	1	1.9
Definitive CRT	44	84.6
Sequential CT and RT	7	13.5
RT with concurrent CT		
No concurrent chemotherapy	7	13.5
Concurrent carboplatin–paclitaxel	44	84.6
Concurrent chemotherapy unknown	1	1.9
Metastasis sites		
Lung widespread	50	23.1
Lung local	34	15.7
Brain metastasis	24	11.1
Bone metastasis	27	12.5
Multiorgan	77	35.6
Adrenal	4	1.9
Tumor burden in metastatic disease		
Oligometastatic 1-2-3 lesions	72	33.3
Oligometastatic 4-5 lesions	39	18.1
No Oligometastatic disease	75	34.7
Local-regional recurrence only	30	13.9
Initial treatment summary		
Induction CT then CRT	16	7.4
CRT then consolidation CT	12	5.6
Received sequential RT/CT	5	2.3
Previously operated + adjuvant CT	25	11.6

Table 1. Continued

Variables	n	%
Previously operated + adjuvant RT/CT	6	2.8
Follow-up after definitive CRT	31	14.4
Postoperative follow-up, recurrence treated with RT/CT	8	3.7
Nivolumab cycle count		
Mean ± SD	13.96±11.07	
Median (min-max)	10.00 (1.00-50.00)	
SUV_{max} on PET before nivolumab		
Mean ± SD	12.65±6.85	
Median (min-max)	11.30 (2.80-42.80)	
Received RT during immunotherapy		
No	184	85.2
Yes	32	14.8
Radiologic interim response to immunotherapy		
Complete response	11	5.3
Partial response	64	30.8
Stable disease	43	20.7
Unconfirmed progression	4	1.9
Confirmed progression	84	40.4
Pseudoprogression	2	1.0
Recurrence sites after immunotherapy		
Absent	62	32.8
Lung local	27	14.3
Brain metastasis	10	5.3
Bone metastasis	9	4.8
Liver metastasis	1	0.5
Multiorgan	80	42.3
Relationship to prior treatment		
Progressed during prior treatment	154	71.3
Progressed during drug-free follow-up	62	28.7
Chemotherapy response before immunotherapy		
Complete response	8	3.7
Partial response	55	25.5
Stable response	20	9.3
Progressive disease	127	58.8
Unknown	6	2.8
SII		
Mean ± SD	286219.00±110497.80	
Median (min-max)	260847.0 (21995.0-736000.0)	
SIRI		
Mean ± SD	3002.84±2847.96	
Median (min-max)	2086.00 (175.0-21144.0)	
Progression		
No	91	42.1
Yes	125	57.9
Mortality		
Alive	107	49.5
Dead	109	50.5
Follow-up duration (months)		
Mean ± SD	24.43±17.28	
Median (min-max)	20.16 (1.03-117.20)	

SD: Standard deviation, ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, CHF: Congestive heart failure, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension, ECOG: Eastern Cooperative Oncology Group, SIRI: Systemic inflammatory response index, SII: Systemic immune-inflammation index, PET: Positron emission tomography, CRT: Chemoradiotherapy, RT: Radiotherapy, CT: Computed tomography

Regarding comorbidities, 44.0% of patients had none. The most common comorbidities were diabetes mellitus or hypertension (22.2%), COPD (15.7%), and heart failure-coronary artery disease (11.6%). A history of another malignancy in remission was reported in 4.2% of patients, whereas 2.3% had other less frequent comorbidities.

Histopathological evaluation showed that 45.8% of cases had adenocarcinoma, 37.5% had squamous cell carcinoma, 14.4% had mixed type, and 2.3% had other histological subtypes. Regarding primary tumor localization, the most common site was the right upper lobe (38.4%), followed by the left upper lobe (19.0%), the right lower lobe (14.4%), the left lower lobe (13.4%), and the right middle lobe (7.9%). Centrally located tumors accounted for 6.9% of all cases.

At diagnosis, 54.2% of the patients presented with metastatic disease, while 45.8% were diagnosed at an early stage. Vascular, lymphatic, and perineural invasion rates were 8.8%, 8.8%, and 6.5%, respectively.

Regarding radiotherapy, the majority of patients (84.6%) underwent definitive chemoradiotherapy. The most commonly administered regimen among those receiving

concurrent chemotherapy was carboplatin-paclitaxel (84.6%); 13.5% did not receive concurrent chemotherapy.

Assessment of metastatic involvement revealed that 23.1% of patients had diffuse lung metastases, 15.7% had localized lung metastases, 11.1% had brain metastases, 12.5% had bone metastases, 1.9% had adrenal metastases, and 35.6% had multiple-organ metastatic involvement. Based on metastatic tumor burden, 33.3% were classified as oligometastatic with 1-3 lesions, 18.1% with 4-5 lesions, 34.7% had no oligometastatic disease, and 13.9% had locoregional recurrence only.

Evaluation of initial treatment strategies demonstrated that 52.3% of patients presented with metastatic disease at diagnosis and received systemic therapy. Additionally, 11.6% underwent surgery followed by adjuvant chemotherapy; 14.4% were monitored after definitive chemoradiotherapy; 7.4% received induction chemotherapy followed by chemoradiotherapy; 5.6% received consolidation chemotherapy following chemoradiotherapy; 2.3% received sequential radiotherapy/chemotherapy; and 3.7% were treated with radiotherapy/chemotherapy for recurrence after surgery.

Regarding IT, patients received a mean of 13.96±11.07 cycles of nivolumab (median: 10 cycles; range: 1-50). The mean pre-IT baseline PET SUV_{max} value was 12.65±6.85 (median: 11.30; range: 2.80-42.80). Radiotherapy during IT was administered to 14.8% of patients.

Radiological response analysis showed complete response in 5.3% of patients, partial response in 30.8%, stable disease in 20.7%, confirmed progression in 40.4%, and pseudoprogression in 1.0%. Following IT, multiorgan recurrence was the most common relapse pattern (42.3%), followed by localized lung (14.3%), brain (5.3%), bone (4.8%), and liver (0.5%) recurrences; no recurrence was observed in 32.8% of patients.

Regarding pre-IT treatment status, 71.3% of patients had progressed during prior therapy, while 28.7% experienced progression during treatment-free follow-up. Pre-IT chemotherapy response assessment showed complete response in 3.7%, partial response in 25.5%, stable disease in 9.3%, and progressive disease in 58.8% of patients.

Evaluation of systemic inflammatory markers revealed a mean SII of 286219.00±110497.80 and a mean SIRI of 3002.84±2847.96. The mean follow-up duration was 24.43±17.28 months (median: 20.16; range: 1.03-117.20 months). The progression rate was 57.9%, and the mortality rate was 50.5%.

As shown in Table 2, the predictive value of various clinical parameters for distinguishing mortality was evaluated using ROC analysis. According to the results, the number of nivolumab cycles demonstrated discriminative ability with respect to mortality [area under the curve (AUC)=0.843; 95% confidence interval (CI): 0.792-0.893; p<0.001]. The determined cut-off value was ≤10.50, indicating that patients receiving nivolumab below this threshold had a significantly higher risk of mortality. Sensitivity and specificity at this cut-off were calculated as 77.1% and 76.4%, respectively.

SIRI was also found to be a significant predictor of mortality (AUC=0.652; 95% CI: 0.578-0.725; p<0.001). The cut-off value of ≥2086.00 was identified as the threshold associated with increased mortality risk, with sensitivity of 60.6% and specificity of 61.0%.

In contrast, SII did not demonstrate a statistically significant discriminative ability for mortality (AUC=0.554; 95% CI: 0.477-0.631; p=0.173).

As shown in Table 3, the median OS for all patients was 27.66 months (95% CI: 19.31-36.01). Median OS differed significantly according to several clinical variables, including initial disease stage (p=0.001), metastatic sites (p=0.008), initial treatment summary (p=0.034), number of nivolumab cycles (p<0.001), the relationship between prior treatment and IT (p=0.002), chemotherapy response before initiation of IT (p=0.004), and SIRI groups (p<0.001) (Figure 1A-D).

As shown in Table 4, the overall median PFS was 12.56 months (95% CI: 9.09-16.03). Median PFS differed significantly by metastasis site (p=0.026), number of

Table 2. Analysis of the predictive value of various clinical parameters in distinguishing mortality

Variables	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	p
SII	0.554	0.477-0.631	≥260847.00	55.0	55.2	0.173
SIRI	0.652	0.578-0.725	≥2086.00	60.6	61.0	**<0.001**
Number of nivolumab cycles	0.843	0.792-0.893	≤10.50	77.1	76.4	**<0.001**

AUC: Area under the curve, CI: Confidence interval, SIRI: Systemic inflammatory response index, SII: Systemic immune-inflammation index

Table 3. OS comparisons of the patients

Variables	2-year %	5-year %	Median months (95% CI)	p
Overall	56.8	37.1	27.66 (19.31-36.01)	
Age				
<60	60.0	35.7	34.80 (11.92-57.67)	0.478
>60	55.2	36.8	27.16 (17.67-36.66)	
Sex				
Female	54.0	-	26.33 (15.20-37.45)	0.941
Male	57.1	37.1	27.66 (19.17-36.15)	
Initial stage				
Early stage at diagnosis	67.9	44.2	43.46 (18.60-68.32)	0.001
Metastatic at diagnosis	43.8	35.3	22.13 (18.75-25.50)	
Lymphatic invasion				
Present	69.4	39.2	29.66 (6.39-52.93)	0.766
Absent	61.3	51.1	- (-)	
PNI				
Present	64.3	48.2	27.16 (0.0-73.79)	0.966
Absent	68.8	41.6	43.46 (34.50-52.42)	
RT type				
Definitive CRT	60.9	36.9	36.33 (7.83-64.83)	0.213
Sequential CT and RT	42.9	-	24.00 (11.51-36.48)	
Metastasis sites				
Lung widespread	74.3	58.1	67.73 (0.00-140.77)	0.008
Lung local	7.5	46.4	60.00 (25.62-94.37)	
Brain metastasis	46.0	-	23.66 (17.78-29.54)	
Bone metastasis	43.6	43.6	20.20 (18.40-21.99)	
Multiorgan	44.4	27.1	19.63 (14.77-24.48)	
Tumor burden in metastatic disease				
Oligometastatic 1-2-3 lesions	57.4	38.7	34.80 (18.12-51.47)	0.178
Oligometastatic 4-5 lesions	58.6	37.5	36.33 (14.62-58.04)	
No Oligometastatic disease	46.1	32.3	20.96 (13.33-28.59)	
Local-regional recurrence only	76.4	47.8	60.00 (20.63-99.36)	
Initial treatment summary				
Induction CT then CRT	61.9	37.7	26.33 (24.05-28.61)	0.034
CRT then consolidation CT	43.8	32.8	23.66 (17.05-30.28)	
Received sequential RT/CT	26.7	-	24.00 (17.05-30.94)	
Previously operated + adjuvant CT	79.6	56.5	60.40 (20.98-99.81)	
Metastatic at diagnosis	46.0	34.8	22.13 (18.45-25.80)	
Previously operated + adjuvant RT/CT	83.3	62.5	78.23 (-)	
Follow-up after definitive CRT	71.0	42.4	60.00 (22.74-97.25)	
Post-op follow-up, recurrence treated with RT/CT	62.5	31.3	43.46 (10.02-76.90)	
Nivolumab cycle count				
>10.50	83.9	64.9	117.20 (-)	<0.001
≤10.50	30.2	14.1	15.63 (12.59-18.67)	
Relationship to prior treatment				
Progressed during prior treatment	49.3	29.4	24.00 (16.38-31.61)	0.002
Progressed during drug-free follow-up	74.3	52.7	60.40 (11.52-109.27)	

Table 3. Continued

Variables	2-year %	5-year %	Median months (95% CI)	p
Chemotherapy response before immunotherapy				
Complete response	87.5	87.5	60.40 (13.85-106.94)	0.004
Partial response	68.7	42.9	29.93 (18.06-41.79)	
Stable response	69.6	58.0	- (-)	
Progressive disease	44.9	26.8	20.96 (16.36-25.56)	
SIRI				
<2086.00	71.9	46.6	60.00 (31.70-88.29)	<0.001
≥2086.00	41.5	26.6	19.63 (15.09-24.17)	

Kaplan-Meier analysis and log-rank test were applied; p<0.05 was considered statistically significant, SIRI: Systemic inflammatory response index, RT: Radiotherapy, CRT: Chemoradiotherapy, CT: Computed tomography, OS: Overall survival, CI: Confidence interval, PNI: Perineural invasion

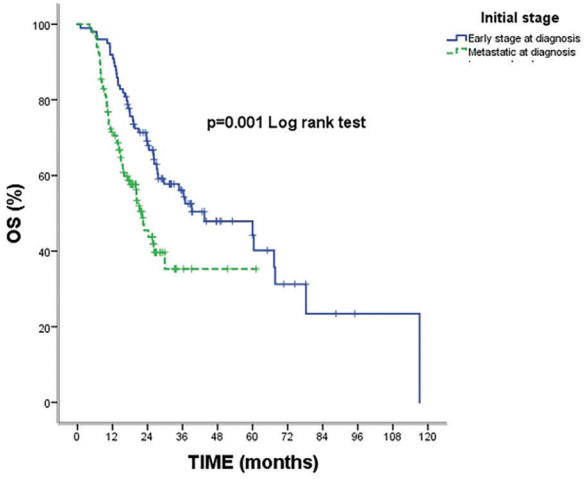

Figure 1. Kaplan-Meier curves for overall survival (OS) according to (A) initial stage at diagnosis, (B) metastatic sites, (C) number of nivolumab cycles, and (D) SIRI groups; Figure 1A. Overall survival according to initial stage

SIRI: Systemic inflammatory response index

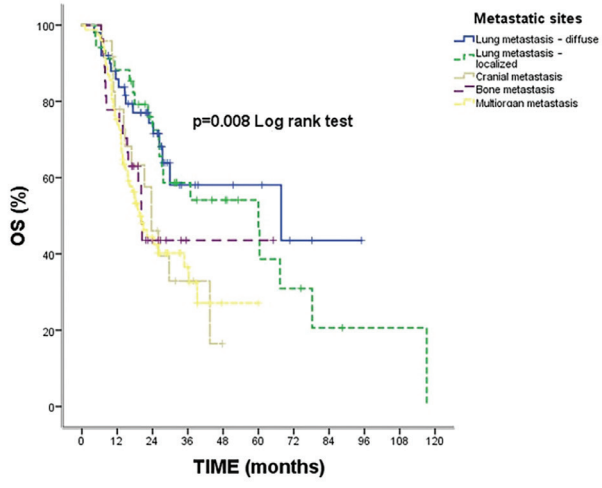

Figure 1B. Overall survival (OS) according to metastatic sites

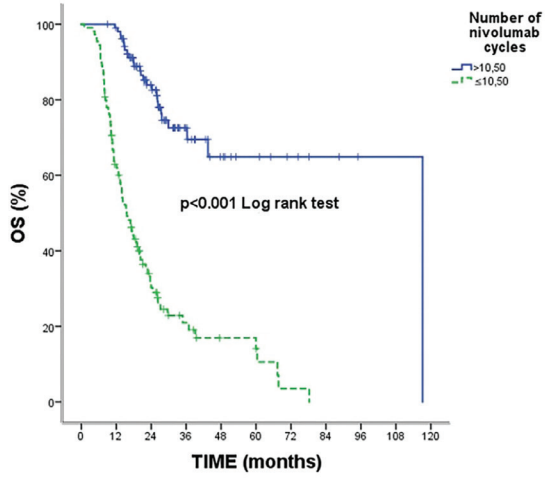

Figure 1C. Overall survival (OS) according to number of nivolumab cycles

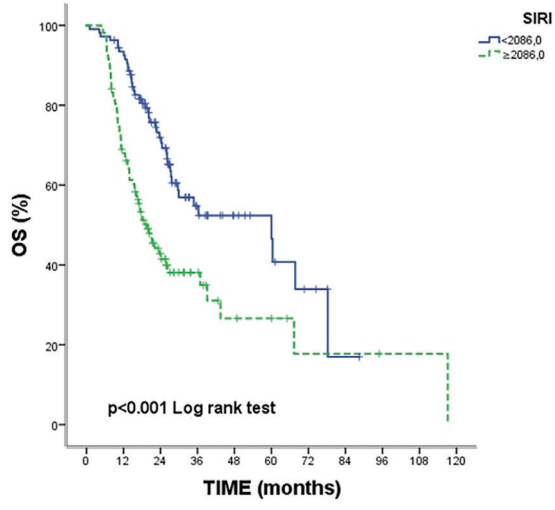

Figure 1D. Overall survival (OS) according to SIRI groups

SIRI: Systemic inflammatory response index

Table 4. PFS comparisons of the patients

Variables	2-year %	5-year %	Median months (95% CI)	p
Overall	37.0	13.9	12.56 (9.09-16.03)	
Age				
<60	46.2	-	19.86 (11.73-27.99)	0.054
>60	32.6	20.7	11.36 (8.81-13.91)	
Sex				
Female	34.3	-	13.50 (8.49-18.50)	0.899
Male	37.3	13.3	12.56 (8.69-16.43)	
Initial stage				
Early stage at diagnosis	39.9	27.6	18.16 (13.32-23.01)	0.056
Metastatic at diagnosis	37.1	-	9.90 (7.90-11.80)	
Lymphatic invasion				
Present	31.4	-	18.16 (6.85-29.47)	0.851
Absent	45.9	-	12.66 (1.80-23.52)	
PNI				
Present	45.1	-	16.16 (-)	0.788
Absent	34.7	-	18.16 (8.07-28.25)	
RT type				
Definitive CRT	43.3	11.9	15.56 (7.67-23.46)	0.074
Sequential CT and RT	-	-	9.86 (8.92-10.80)	
Metastasis sites				
Lung widespread	54.4	-	25.53 (-)	0.026
Lung local	44.9	22.5	15.56 (8.56-22.56)	
Brain metastasis	20.6	-	16.16 (5.69-26.63)	
Bone metastasis	42.3	-	11.13 (7.61-14.65)	
Multiorgan	26.4	-	8.06 (5.64-10.48)	
Tumor burden in metastatic disease				
Oligometastatic 1-2-3 lesions	40.9	14.7	17.56 (9.90-25.22)	0.065
Oligometastatic 4-5 lesions	29.3	-	7.93 (2.01-13.86)	
No oligometastatic disease	31.2	-	9.86 (5.27-14.46)	
Local-regional recurrence only	51.7	-	25.03 (-)	
Initial treatment summary				
Induction CT then CRT	36.5	-	11.73 (7.48-15.98)	0.179
CRT then consolidation CT	31.3	-	11.13 (7.96-14.30)	
Received sequential RT/CT	-	-	9.50 (7.78-11.21)	
Previously operated + adjuvant CT	48.4	-	19.86 (-)	
Metastatic at diagnosis	35.9	-	9.66 (7.15-12.18)	
Previously operated + adjuvant RT/CT	50.0	-	6.56 (-)	
Follow-up after definitive CRT	49.7	19.0	18.73 (7.73-29.73)	
Post-op follow-up, recurrence treated with RT/CT	34.3	-	21.43 (0.00-45.53)	
Nivolumab cycle count				
>10.50	60.5	23.5	35.63 (24.25-47.01)	<0.001
≤10.50	10.4	-	5.80 (5.20-6.39)	
Relationship to prior treatment				
Progressed during prior treatment	33.4	-	9.13 (6.64-11.62)	0.001
Progressed during drug-free follow-up	48.6	16.5	19.86 (13.03-26.69)	

Table 4. Continued

Variables	2-year %	5-year %	Median months (95% CI)	p
Chemotherapy response before immunotherapy				
Complete response	75.0	-	25.60 (15.68-35.52)	0.162
Partial response	34.8	27.8	15.56 (10.96-20.17)	
Stable response	40.2	-	11.73 (8.14-15.32)	
Progressive disease	36.3	-	9.13 (6.15-12.10)	
SIRI				
<2086.00	47.0	17.8	18.73 (10.62-26.84)	<0.001
≥2086.00	17.3	-	8.76 (6.34-11.18)	

Kaplan-Meier survival analysis and log-rank test were applied; p<0.05 was accepted as statistically significant, PFS: Progression-free survival, CT: Computed tomography, RT: Radiotherapy, CRT: Chemoradiotherapy, SIRI: Systemic inflammatory response index, PNI: Perineural invasion, CI: Confidence interval

nivolumab cycles (p<0.001), the relationship between prior treatment and IT (p=0.001), and SIRI group (p<0.001). Patients with multiorgan metastasis and those who received ≤10.50 nivolumab cycles had markedly shorter PFS (Figure 2A-D).

As shown in Table 5, the variables initial stage, metastasis sites, initial treatment summary, number of nivolumab cycles, relationship to prior treatment, chemotherapy response before IT, and SIRI were found to be significant in the univariate analyses. Variables identified as significant in the univariate analyses were included in the multivariate Cox regression model. According to the model results, being in the lung local group increased the risk of death by 2.29-fold (HR: 2.29, 95% CI: 1.01-5.24, p=0.050), having brain metastases by 2.67-fold (HR: 2.67, 95% CI: 1.19-5.98, p=0.017), having bone metastasis by 2.45-fold (HR: 2.45,

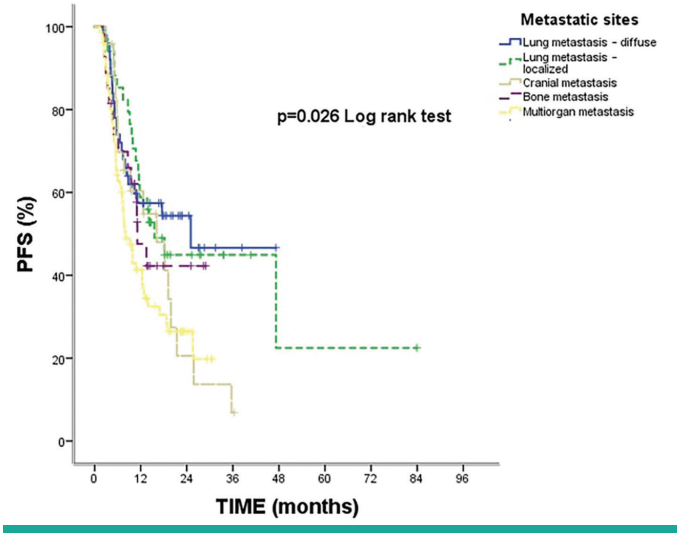

Figure 2. Kaplan-Meier curves for progression-free survival (PFS) according to (A) metastatic sites, (B) number of nivolumab cycles, (C) relation to previous treatment, and (D) SIRI groups; Figure 2A. Progression-free survival according to metastatic sites

SIRI: Systemic inflammatory response index

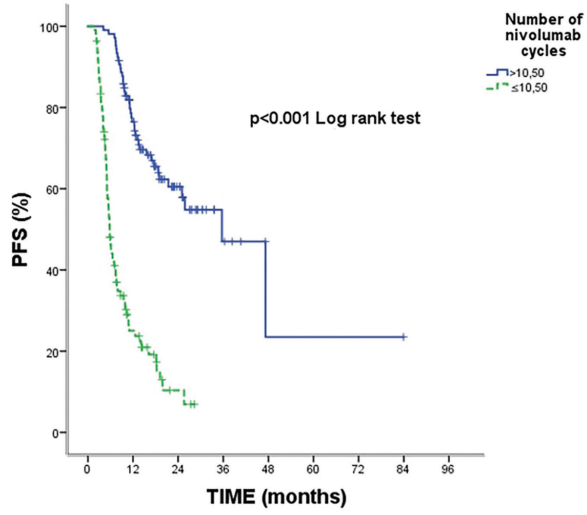

Figure 2B. Progression-free survival (PFS) according to number of nivolumab cycles

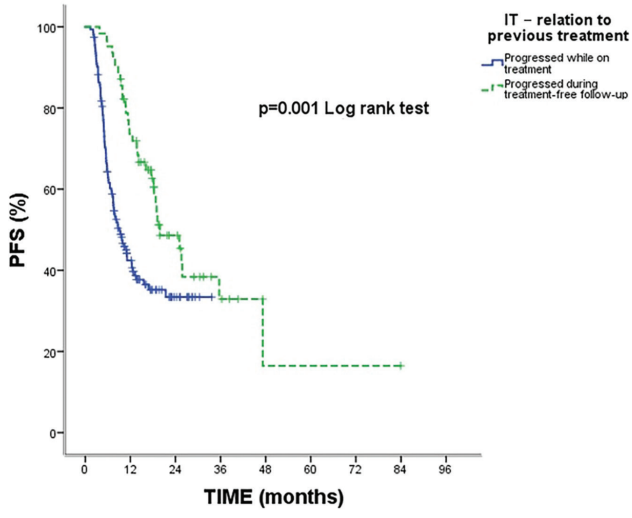

Figure 2C. Progression-free survival (PFS) according to relation to previous treatment

IT: Immunotherapy

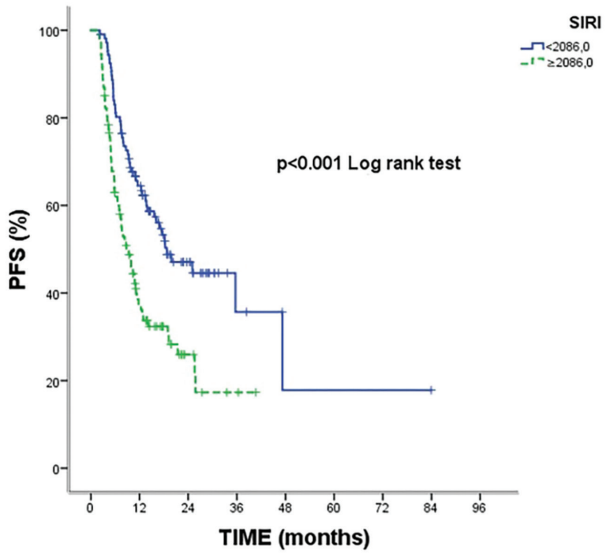

Figure 2D. Progression-free survival (PFS) according to SIRI groups

SIRI: Systemic inflammatory response index

95% CI: 1.15-5.21, p=0.019), having multiorgan metastasis by 2.69-fold (HR: 2.69, 95% CI: 1.45-5.02, p=0.002), having ≤10.50 nivolumab cycles by 6.38-fold (HR: 6.38, 95% CI: 3.90-10.43, p<0.001), and having progressive disease by 5.24-fold (HR: 5.24, 95% CI: 1.09-25.07, p=0.038) were determined to increase the risk of death.

As shown in Table 6, metastatic sites, number of nivolumab cycles, relationship to prior treatment, and SIRI were found to be significant in the univariate analyses. To minimize potential immortal time bias related to treatment duration, a landmark analysis was performed, and patients who were alive and progression-free at the predefined landmark time point were included in the multivariate Cox regression model. According to the landmark-adjusted model results, having multiorgan metastasis was associated with an increased risk of progression (HR: 1.77, 95% CI: 0.54-2.98, p=0.051), and receiving ≤10.50 nivolumab cycles by the landmark time point was associated with a markedly higher risk of progression (HR: 6.48, 95% CI: 4.13-10.16, p<0.001). In contrast, progression during drug-free follow-up was associated with a reduced risk (HR: 0.30, 95% CI: 0.19-0.49, p<0.001).

Table 5. Multivariate Cox regression results of various clinical variables on mortality risk

Variables	HR (95% CI)	p
Initial stage		
Early stage at diagnosis	ref	0.249
Metastatic at diagnosis	2.40 (0.54-10.69)	
Metastasis sites		0.032
Lung widespread	ref	
Lung local	2.29 (1.01-5.24)	0.050
Brain metastasis	2.67 (1.19-5.98)	0.017
Bone metastasis	2.45 (1.15-5.21)	0.019
Multiorgan	2.69 (1.45-5.02)	0.002
Initial treatment summary		0.381
Induction CT then CRT	ref	
CRT then consolidation CT	0.69 (0.20-1.70)	0.333
Received sequential RT/CT	0.63 (0.16-2.47)	0.512
Previously operated + adjuvant CT	0.29 (0.10-0.89)	0.055
Metastatic at diagnosis	0.52 (0.21-1.29)	0.633
Previously operated + adjuvant RT/CT	0.19 (0.04-0.88)	0.065
Follow-up after definitive CRT	0.52 (0.21-1.29)	0.161
Post-op follow-up, recurrence treated with RT/CT	0.53 (0.16-1.71)	0.294
Nivolumab cycle count		
>10.50	ref	<0.001
≤10.50	6.38 (3.90-10.43)	
Relationship to prior treatment		
Progressed during prior treatment	ref	0.400
Progressed during drug-free follow-up	1.35 (0.66-2.77)	
Chemotherapy response before immunotherapy		0.018

Table 5. Continued

Variables	HR (95% CI)	p
Complete response	ref	
Partial response	2.02 (0.44-9.17)	0.359
Stable response	4.12 (0.77-21.88)	0.096
Progressive disease	5.24 (1.09-25.07)	0.038
SIRI		
<2086.00	ref	0.111
≥2086.00	1.41 (0.92-2.17)	
-2 Log Likelihood:865.04, p<0.001, SIRI: Systemic inflammatory response index, CT: Computed tomography, RT: Radiotherapy, CRT: Chemoradiotherapy, HR: Hazard ratio, CI: Confidence interval		

Table 6. Landmark-adjusted multivariate Cox regression analysis of clinical variables associated with progression risk

Variables	HR (95% CI)	p
Metastasis sites		0.057
Lung widespread	ref	
Lung local	1.13 (0.59-2.17)	0.709
Brain metastasis	1.42 (0.73-2.76)	0.298
Bone metastasis	0.73 (0.35-1.51)	0.401
Multiorgan	1.77 (0.54-2.98)	0.051
Nivolumab cycle count		
>10.50	ref	<0.001
≤10.50	6.48 (4.13-10.16)	
Relationship to prior treatment		
Progressed during prior treatment	ref	<0.001
Progressed during drug-free follow-up	0.30 (0.19-0.49)	
SIRI		
<2086.00	ref	0.280
≥2086.00	1.24 (0.83-1.83)	
-2 Log Likelihood:1073.11, p<0.001, HR: Hazard ratio, CI: Confidence interval, SIRI: Systemic inflammatory response index		

Discussion

In this study, the relationship among SIRI, SII, and prognosis was evaluated using real-world data from patients with metastatic NSCLC treated with second-line nivolumab. With a mean follow-up of 24 months, the median OS and PFS were 27.7 and 12.6 months, respectively. In the ROC analysis, a SIRI cut-off value of ≥2086 was associated with an increased risk of both mortality and progression, whereas SII did not demonstrate similar discriminatory performance. One of the notable findings of our study was that the number of nivolumab cycles was consistently associated with both OS and progression-free survival. This association should be interpreted with caution because treatment duration is closely linked to underlying disease biology and treatment response; patients with better disease control are therefore more likely to receive a greater number of treatment cycles. Therefore, the number of nivolumab cycles should be considered a surrogate marker of clinical course rather than an independent causal determinant of survival. In the multivariate analyses, multiorgan metastasis remained an independent adverse prognostic factor, whereas progression during drug-free follow-up was associated with a reduced risk of death.

The relatively long median OS and PFS observed in our cohort, compared with pivotal randomized trials of second-line nivolumab, may be explained by differences in patient selection and disease characteristics. Nearly half of the patients were initially diagnosed at an early stage and received definitive local treatment before recurrence, a subgroup known to have more favorable tumor biology and a lower metastatic burden. In addition, a considerable proportion of patients experienced progression during drug-free follow-up; this progression is generally associated with better prognosis and treatment sensitivity. Therefore,

the observed survival outcomes likely reflect real-world population heterogeneity rather than methodological bias.

Systemic inflammation-based indices have strong prognostic value in many solid tumors, as demonstrated consistently in large meta-analyses across various cancer types. Several studies have reported that SIRI, which reflects the combined dynamics of neutrophils, monocytes, and lymphocytes, is an independent poor prognostic factor for both OS and PFS in gastrointestinal, gynecological, and genitourinary malignancies (13-15). Similarly, meta-analytic findings have demonstrated that SII is associated with high tumor burden, advanced stage, and poor survival, particularly in gastrointestinal system tumors (16,17). In our study, the finding that SIRI was significant for both OS and PFS in univariate analyses is consistent with the broader cancer literature and suggests that SIRI may be a sensitive indicator of systemic inflammatory burden in metastatic NSCLC patients receiving IT.

When studies focusing specifically on NSCLC are examined, the prognostic role of peripheral blood inflammation indices becomes even more prominent. Systematic reviews and meta-analyses including patients with advanced lung cancer have shown that elevated SII levels adversely affect both OS and PFS in both early-stage resected patients and metastatic cases, and that SII often demonstrates stronger prognostic performance than traditional parameters such as NLR and PLR (18-20). Likewise, retrospective cohorts have shown that SIRI is associated with tumor stage, metastatic burden, and survival in NSCLC (21). The observation in our cohort that SII did not show significant discriminatory ability in either the ROC analysis or the survival curves is partially inconsistent with the literature. This may be related to the structure of our selected cohort, differences in SII cut-off values, sample size, and the effects of radiotherapy on PLRs (22-24).

Although both SII and SIRI are derived from peripheral blood inflammatory parameters, they reflect distinct biological aspects of the host–tumor interaction. SIRI incorporates monocytes in addition to neutrophils and lymphocytes, thereby better capturing monocyte-driven immunosuppressive mechanisms that are particularly relevant in the context of immune checkpoint inhibitor therapy (7,11). Monocytes and tumor-associated macrophages play pivotal roles in shaping the tumor microenvironment and facilitating immune evasion, which may directly influence the response to nivolumab (7). In contrast, SII does not directly account for monocyte-related immune suppression and may be more susceptible to treatment-related fluctuations in platelet and lymphocyte counts, such as those induced by radiotherapy or peri-treatment inflammatory changes (22-24). These biological and treatment-related differences may partly explain the observed discrepancy between the prognostic performances of SIRI and SII in our cohort.

In recent years, a growing body of evidence suggests that SII and SIRI may serve as useful biomarkers for predicting treatment response and survival in patients with metastatic lung cancer treated with ICIs. Meta-analyses including large patient series have shown that elevated pre-treatment SII levels are associated with significantly worse OS and PFS, and that this relationship is maintained across different tumor types and treatment lines (25-27). Meta-analyses specific to advanced lung cancer have also reported markedly shortened survival for patients with high baseline SII despite ICI therapy. The lack of significance of SII in our study suggests that SII may be less predictive than expected in a homogeneous subgroup of metastatic NSCLC patients receiving IT, and is consistent with the literature suggesting that dynamic changes in SII may be more meaningful (28).

In our univariate analyses, SIRI was found to be significant for both OS and PFS, a finding that is more consistent with the IT literature. Studies including lung cancer patients treated with ICIs have reported that high SIRI levels are associated with low treatment response rates, shorter PFS, and shorter OS (21). The ability of SIRI to predict IT response has been proposed to be related to neutrophil- and monocyte-mediated immunosuppression. The loss of significance of SIRI in our multivariate model may be due to its coexistence with other strong prognostic factors, such as nivolumab cycle count and metastatic burden.

One of the key findings of our study was that the number of nivolumab cycles was independently associated with both OS and PFS. The ROC analysis yielded an AUC of 0.84, and patients who received ≤10.5 cycles experienced a markedly higher risk of mortality and progression. However, this association should be interpreted cautiously, as patients with better disease control are more likely to receive a higher number of treatment cycles. In the literature, the optimal duration of immune checkpoint inhibitor therapy and the concept of treatment beyond progression remain controversial, with most available evidence derived from secondary or exploratory analyses. In this context, our real-world data highlight a strong prognostic association between treatment duration and clinical outcomes in patients with metastatic NSCLC receiving second-line nivolumab.

To mitigate the potential risk of immortal time bias related to treatment duration, a landmark analysis was applied to progression-free survival, with the landmark time point defined as 3 months after nivolumab initiation. Only patients who were alive and progression-free at the landmark were included in the landmark-adjusted multivariate Cox regression model. OS analyses were performed using the full cohort, as the predefined landmark did not result in exclusion of patients or alteration of the OS risk set.

Findings regarding patterns of metastasis and tumor burden were consistent with those observed in inflammation-based indices. The finding that multiorgan metastasis was an independent poor prognostic factor for both OS and PFS is consistent with studies reporting higher SII levels in patients with brain and bone metastases (29,30). In our study, the inclusion of metastatic burden in the model, independent of SIRI/SII, indicates that inflammation scores alone may not fully explain the prognostic heterogeneity. Therefore, using SIRI and SII together with metastatic burden may provide a more accurate risk stratification.

Treatment response prior to IT and timing of progression are also important prognostic indicators. Poorer survival among patients who progressed on prior therapy reflects biological aggressiveness and reduced sensitivity to treatment. In contrast, longer OS in patients who progressed during drug-free follow-up after chemotherapy is consistent with the concept of "chemo-sensitive disease" (31,32). These findings suggest that SIRI and SII should be evaluated together with clinical parameters.

A key clinical contribution of our study is the introduction of a practical basis for risk stratification that combines SIRI with nivolumab cycle count in metastatic NSCLC patients receiving second-line IT. Patients with high SIRI who discontinue nivolumab early may be defined as a high-risk group, whereas those with low SIRI receiving prolonged nivolumab therapy may represent a subgroup likely to derive long-term benefit (12,21). Validation of this approach in prospective studies may contribute to the development of risk-based treatment and follow-up algorithms in real-world practice.

Study Limitations

This study has several limitations, including its retrospective design, single-center setting, heterogeneity of cut-off values, lack of biomarker data, such as PD-L1 and TMB, and the assessment of SIRI and SII only at baseline. Literature suggests that dynamic measurements may provide greater prognostic insight (33). Although a landmark approach was applied to mitigate immortal time bias, residual confounding related to treatment duration cannot be completely excluded.

Conclusion

In conclusion, in this real-world cohort of patients with metastatic NSCLC treated with second-line nivolumab, SIRI demonstrated significant prognostic value for both OS and progression-free survival. Although SII did not show discriminatory performance, elevated SIRI levels were associated with poorer outcomes. The strongest prognostic factor identified in the study was the number of nivolumab cycles received; patients who discontinued treatment early (≤10.5 cycles) had a markedly higher risk of both mortality and progression. In addition, multiorgan metastatic disease was confirmed as an independent adverse prognostic factor.

These findings highlight the clinical utility of SIRI and treatment duration as practical, easily accessible parameters for risk stratification in patients receiving ICIs. Combining systemic inflammation markers with treatment-related variables, such as nivolumab cycle count, may facilitate more individualized prognostic assessment. Prospective studies evaluating dynamic changes in inflammatory indices and integrating additional biomarkers, including PD-L1 and TMB, are needed to further refine prognostic models and guide treatment optimization in metastatic NSCLC.

Ethics

Ethics Committee Approval: Permission was obtained from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (decision no: 1238, date: 16.10.2025).

Informed Consent: This retrospective study included patients with metastatic NSCLC who received second-line nivolumab treatment at the İstanbul Medipol University Medical Oncology Clinic.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Ç.D., Ş.B., S.T., M.Ö., J.H., A.Ö., A.G.D., A.B., Concept: B.Ç.D., M.Ö., A.Ö., J.H., Design: B.Ç.D., J.H., A.B., Data Collection or Processing: B.Ç.D., Ş.B., S.T., A.Ö., Analysis or Interpretation: B.Ç.D., Ş.B., S.T., A.G.D., A.B., A.G.D., Literature Search: B.Ç.D., Writing: B.Ç.D.

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

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ORIGINAL RESEARCH

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Quercetin Protects Against Doxorubicin-induced Cardiac Injury Through Stress Modulation: Evidence from Electrocardiographic, Scintigraphic, and Biochemical Analyses in Rats

Quercetin, Stres Modülasyonu Yoluyla Doksorubisin Kaynaklı Kalp Hasarına Karşı Koruma Sağlar: Sıçanlarda Elektrokardiyografik, Sintigrafik ve Biyokimyasal Analizlerden Elde Edilen Kanıtlar

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Abstract

Objective: Doxorubicin (DOX) induces cardiotoxicity via oxidative and endoplasmic reticulum (ER) stress. This study evaluated the cardioprotective effects of quercetin against DOX-induced cardiac injury in rats, focusing on ER stress and SIRT1 signaling.

Method: Wistar Albino rats were used. Rats were allocated into control, DOX, low-dose quercetin (10 mg/kg) + DOX, and high-dose quercetin (100 mg/kg) + DOX groups. Cardiac function was assessed by lead II electrocardiography, while myocardial injury was evaluated using Tc-99m pyrophosphate (PYP) scintigraphy. Cardiac biomarkers, inflammatory cytokines, oxidative stress parameters, ER stress markers, and SIRT1 expression were analyzed.

Results: DOX induced marked electrocardiogram abnormalities, including Q wave-T wave interval- prolongation and ST-segment elevation, increased myocardial ^{99}mTc-PYP uptake, elevated cardiac injury biomarkers, renal and hepatic markers, enhanced

Öz

Amaç: Doksorubisin (DOX), oksidatif ve endoplazmik retikulum (ER) stresi yoluyla kardiyotoksisiteye neden olur. Bu çalışma, ER stresi ve SIRT1 sinyaline odaklanarak, sıçanlarda DOX'in neden olduğu kalp hasarına karşı quercetinin kardiyoprotektif etkilerini değerlendirmiştir.

Yöntem: Wistar Albino sıçanlar kullanılmıştır. Sıçanlar kontrol, DOX, düşük doz quercetin (10 mg/kg) + DOX ve yüksek doz quercetin (100 mg/kg) + DOX gruplarına ayrılmıştır. Kardiyak fonksiyon II elektrokardiyografi ile değerlendirilirken, miyokardiyal hasar Tc-99m pirofosfat (PYP) sintigrafisi kullanılarak değerlendirilmiştir. Kardiyak biyobelirteçler, enflamatuvar sitokinler, oksidatif stres parametreleri, ER stres belirteçleri ve SIRT1 ekspresyonu analiz edildi.

Bulgular: DOX, Q dalgası-T dalgası aralığı uzaması ve ST segment yükselmesi, miyokardiyal ^{99}mTc-PYP alımında artış, kardiyak hasar biyobelirteçlerinde, böbrek ve karaciğer belirteçlerinde yükselme,

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Abstract

oxidative stress, inflammatory responses (tumor necrosis factor-α, interleukin-6), upregulation of GRP78 and C/EBP homologous protein, and suppression of SIRT1 and glutathione ($p<0.05$). Quercetin significantly attenuated these alterations in a dose-dependent manner, with greater protection observed at the higher dose.

Conclusion: Quercetin mitigates DOX-induced cardiotoxicity by suppressing oxidative stress, ER stress, and inflammation via restoration of SIRT1 signaling. The integration of electrocardiography and Tc-99m PYP scintigraphy provides novel multimodal evidence of quercetin's cardioprotective effects.

Keywords: Cardiotoxicity, doxorubicin, ER stress, oxidative stress, quercetin, scintigraphy

Öz

oksidatif stres artışı, enflamatuvar yanıtlarda (tümör nekroz faktörü-α, interlökin-6) artış, GRP78 ve C/EBP homolog proteinin yukarı regülasyonu ve SIRT1 ve glutatyonun baskılanması ($p<0,05$) gibi belirgin elektrokardiyografi anormalliklerine neden olmuştur. Quercetin, bu değişiklikleri doz bağımlı bir şekilde önemli ölçüde azalttı ve daha yüksek dozda daha fazla koruma gözlendi.

Sonuç: Quercetin, SIRT1 sinyalini geri yükleyerek oksidatif stresi, ER stresini ve enflamasyonu baskılayarak DOX'in neden olduğu kardiyotoksisiteyi hafifletir. Elektrokardiyografi ve Tc-99m PYP sintigrafisinin entegrasyonu, quercetinin kardiyoprotektif etkilerine ilişkin yeni multimodal kanıtlar sağlar.

Anahtar kelimeler: Doksorubisin, ER stresi, kardiyotoksisite, oksidatif stres, quercetin, sintigrafi

Introduction

Cancer incidence is steadily rising worldwide (1). Chemotherapy has significantly improved survival outcomes in oncology (2). Doxorubicin (DOX) (Adriamycin), an anthracycline antibiotic, is widely used for treating both solid and hematological malignancies, including breast cancer, lymphomas, leukemias, and sarcomas (2,3). Despite its potent antitumor efficacy, the clinical utility of DOX is limited by its dose-dependent cardiotoxicity (4), which is often irreversible and may result in long-term cardiac morbidity (5). Preventing these side effects remains a key challenge in oncology.

DOX cardiotoxicity is multifactorial, with oxidative stress and inflammation playing central roles. In addition to mitochondrial oxidative injury, DOX promotes cardiomyocyte apoptosis and inflammatory signaling, thereby contributing to cardiac dysfunction (6). Notably, recent studies indicate that SIRT1 exerts cardioprotective effects through modulating cellular stress responses.

Flavonoid antioxidants have shown promise in mitigating DOX-induced toxicity. Quercetin (QRC), a natural flavonol found in various yellow and orange fruits and vegetables (7,8), exhibits anti-inflammatory, antioxidant, anticancer, and cytoprotective properties, attributed to its five hydroxyl groups (8-10). Experimental models suggest that QRC exerts cardioprotective effects by scavenging reactive oxygen species (ROS), enhancing antioxidant enzyme activity, and attenuating endoplasmic reticulum (ER) stress. However, while QRC's cardioprotective effects are promising, the precise mechanisms by which it confers protection, particularly its influence on less-studied pathways like ER stress in DOX-induced toxicity, remain to be determined.

We hypothesize that QRC exerts therapeutic effects against DOX-induced cardiotoxicity by modulating pathways including SIRT1, GRP78–CHOP, malondialdehyde (MDA)–glutathione (GSH), and tumor necrosis factor (TNF)-α–interleukin (IL)-6. This study aims to evaluate the cardioprotective potential of QRC through biochemical, scintigraphic, and electrocardiographic parameters. Furthermore, the use of clinically relevant diagnostic modalities—such as pyrophosphate (PYP) scintigraphy, serum troponin and creatine kinase (CK)- myocardial band (MB) levels, and electrocardiography (ECG)-derived conduction and arrhythmia metrics—may offer a novel translational approach.

Materials and Methods

Animal

All procedures were approved by the Local Animal Experiments Ethics Committee of Tokat Gaziosmanpaşa University (approval no: 2019-HADYEK-15, date: 09.06.2019). Male Wistar Albino rats were housed under standard laboratory conditions with ad libitum access to food and water and allowed a one-week acclimatization period before experimentation. This is an experimental animal study conducted in accordance with national and institutional guidelines for the care and use of laboratory animals.

Experimental groups and procedures

The animals were randomly allocated into four experimental groups, and the following procedures were applied:

Group I (Control group): Rats in the control group received no treatment throughout the experimental period.

Group II (DOX group): DOX was administered intraperitoneally (i.p) on experimental days 12, 13, and 14, at a cumulative dose of 18 mg/kg.

Group III (Low-dose QRC + DOX group; QRC 10 mg/kg + DOX): QRC was administered i.p at a dose of 10 mg/kg once daily for 14 consecutive days. In addition, DOX was injected (i.p) on days 12, 13, and 14 at a cumulative dose of 18 mg/kg.

Group IV (High-dose QRC + DOX group; QRC 100 mg/kg + DOX): QRC was administered i.p. at a dose of 100 mg/kg once daily for 14 consecutive days. DOX was additionally administered (i.p) on days 12, 13, and 14 at a cumulative dose of 18 mg/kg.

Scintigraphic imaging

For scintigraphic evaluation, 1 millicurie (mCi) of 99mTc-(99mTc-PYP) radiopharmaceutical (TechneScan PYP, Mallinckrodt) was diluted with 5 mL of isotonic saline, and 0.1 mL of the prepared solution was administered intravenously to each rat. One hour after injection, static planar scintigraphic imaging was performed with a gamma camera (Siemens Symbia, USA).

To facilitate scintigraphic imaging, rats were anesthetized with ketamine (Ketalar®, 75 mg/kg; Pfizer, İstanbul, Turkey) and xylazine (Rompun®, 10 mg/kg; Bayer, İstanbul, Turkey) administered at the indicated doses. Scintigraphic acquisition was conducted for 15 minutes under anesthesia.

Regions of interest (ROIs) were manually defined over the affected myocardial area, and seven separate measurements were obtained for each animal. The mean ROI value was calculated and used for quantitative analysis.

Radiation safety considerations

The 1 Technetium-99m pyrophosphate (99mTc-PYP) mCi dose used in rats in the present study, therefore, represents a relatively low activity level. Following completion of scintigraphic imaging, animals were kept in lead-shielded containers for 24 hours to allow radioactive decay and reduction of residual activity. Accordingly, no radiation exposure to personnel or the environment was anticipated during or after the experimental procedures.

Electrocardiographic recording

Following scintigraphic imaging, the depth of anesthesia in rats was assessed by measuring pedal withdrawal reflexes. Subsequently, needle electrodes were inserted subcutaneously into the right and left forelimbs and the left hind limb of each rat.

ECG recordings were obtained for 1 minute using a MP-150 multi-channel physiological data acquisition system (BIOPAC Systems Inc., USA) with the accompanying software (version 3.8). Changes in ECG patterns, including ST-segment elevation, QT interval duration, and heart rate, were analyzed (Figure 1).

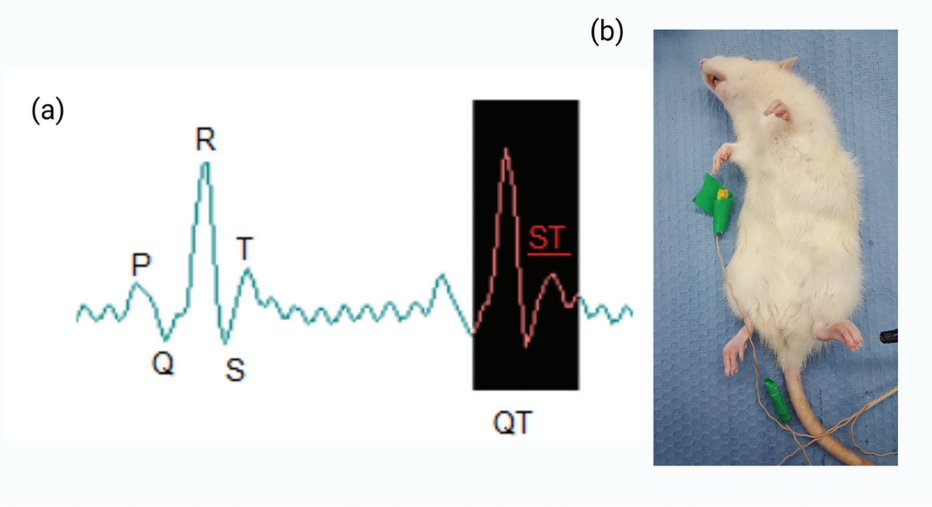

Figure 1. Electrocardiographic assessment in rats.

(a) Representative ECG waveform illustrating the P, QRS, and T waves, with indication of the QT interval and ST-segment elevation.

(b) Electrocardiographic recordings were obtained using a single-lead configuration (Lead II) with subcutaneous needle electrodes placed on the right and left forelimbs and the left hind limb

ECG: Electrocardiography, QT: Q wave-T wave interval

Quantification of Serum Cardiac, Renal, Hepatic Biomarkers and Cardiac Tissues

Serum markers of cardiac, renal, and hepatic injury [aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), gamma-glutamyl transferase (GGT), CK-MB, creatinine, and cardiac troponin T (cTnT) were quantified using kinetic spectrophotometric assays on a Beckman Coulter LX-2000 autoanalyzer (Brea, CA, USA).

Cardiac tissues were homogenized in cold phosphate-buffered saline (pH 7.4), centrifuged, and the supernatants were analyzed. Tissue levels of SIRT1, MDA, GSH, TNF-α, IL-6, GRP78, and CHOP were quantified using ELISA. Results were normalized to wet tissue weight and expressed in appropriate units. Rats received QRC (10 or 100 mg/kg, i.p.) for 14 days, with DOX administered on days 12-14 (cumulative dose: 18 mg/kg, i.p.) (Figure 2).

Statistical Analysis

Statistical analyses were performed using SPSS software (version 19.0; IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 10.0; GraphPad Software, San Diego, CA, USA). Data normality was assessed using the Shapiro-Wilk test. Variables that did not follow a normal distribution were analyzed using the Kruskal-Wallis test, followed by pairwise Mann-Whitney U tests with Bonferroni correction for multiple comparisons, including ^{99}mTc-PYP uptake, MDA, creatinine, and ALT. Normally distributed variables were analyzed using One-Way Analysis of Variance (ANOVA) followed by Tukey's post-hoc test. Data are presented as mean ± standard error of the mean (SEM) (mean ± SEM). A value of $p<0.05$ was considered statistically significant.

Results

Scintigraphic results

Kruskal-Wallis analysis revealed a significant overall difference among the groups in myocardial 99mTc-PYP uptake [$\chi^2(3) = 21.849$, $p<0.001$]. Consistent with this finding, myocardial radiotracer uptake was markedly increased in the DOX group compared with the control group ($p<0.0001$). Although myocardial 99mTc-PYP uptake remained higher than control values in both QRC-treated groups [DOX + QRC (10 mg/kg), $p<0.0001$; DOX + QRC (100 mg/kg), $p=0.0106$], direct comparison with the DOX group demonstrated a significant dose-dependent reduction in tracer accumulation (10 mg/kg: $p=0.0329$; 100 mg/kg: $p=0.0006$). Comparison between the two QRC-treated groups revealed that administration of 100 mg/kg QRC resulted in significantly lower myocardial radiotracer uptake than 10 mg/kg, indicating a dose-dependent effect ($p=0.0106$). These findings demonstrate that QRC administration significantly attenuates DOX-induced myocardial accumulation of 99mTc-PYP in a dose-dependent manner, suggesting a protective effect of QRC against DOX-related myocardial injury (Figure 3, Table 1).

Red circles indicate ROIs placed over the cardiac area for quantitative analysis. DOX administration resulted in markedly increased myocardial radiotracer accumulation compared with controls, whereas QRC treatment reduced myocardial 99mTc-PYP uptake in a dose-dependent manner.

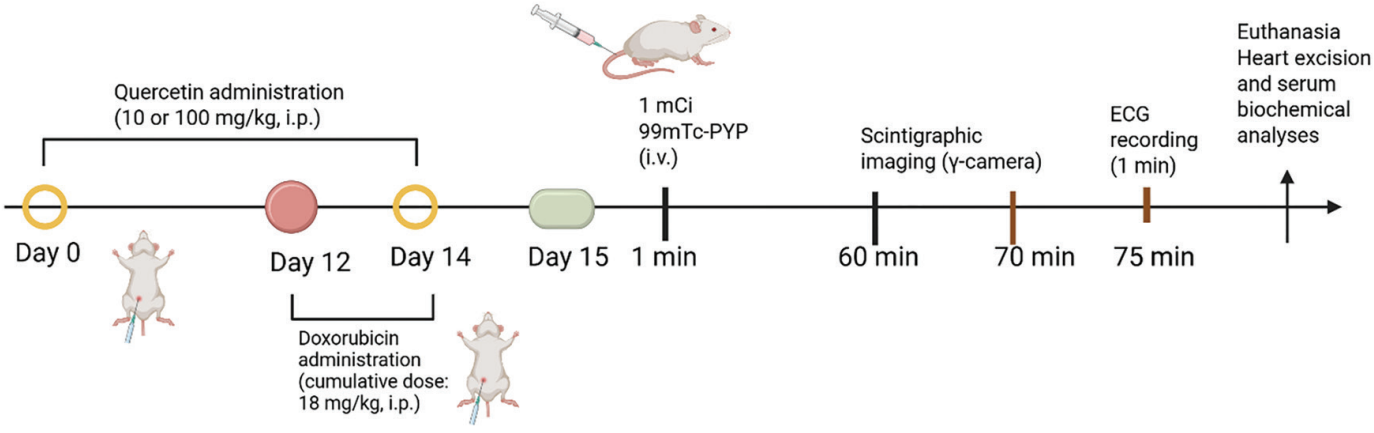

Figure 2. Experimental timeline
ECG: Electrocardiography, PYP: Pyrophosphate

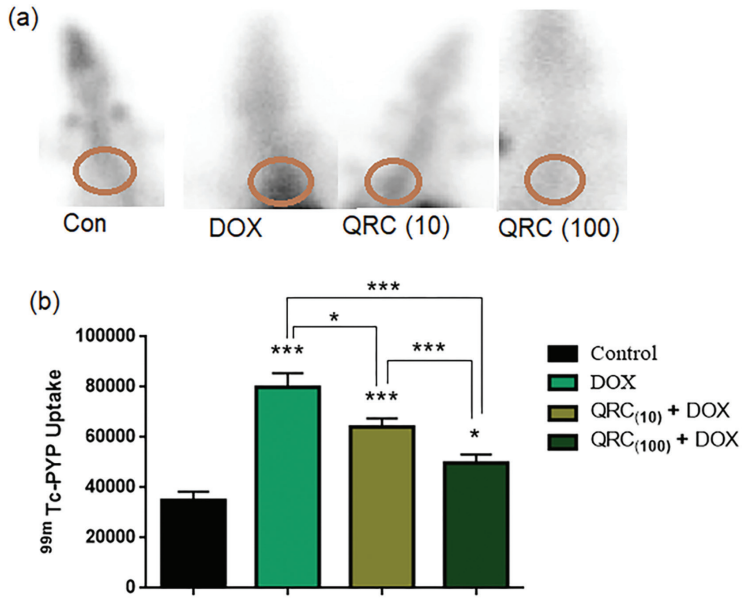

Figure 3. Effects of quercetin on doxorubicin-induced myocardial 99mTc-PYP uptake

Representative planar myocardial scintigraphic images obtained 1 h after intravenous injection of 99mTc-PYP are shown for the (a) Control, (b) DOX, (c) DOX + QRC (10 mg/kg), and (d) DOX + QRC (100 mg/kg) groups.

The lower panel shows quantitative analysis of myocardial ^{99}mTc-PYP uptake, expressed as mean ± SEM (n=7 per group). Differences among groups were analyzed using the Kruskal-Wallis test followed by pairwise Mann-Whitney U tests with Bonferroni correction for multiple comparisons

**: p<0.05, **: p<0.01, ***: p<0.001 were considered statistically significant, PYP: Pyrophosphate, DOX: Doxorubicin, SEM: Standard error of the mean, QRC: Quercetin*

Table 1. Scintigraphic and electrocardiographic findings in control and experimental groups

	Control	DOX	QRC (10) + DOX	QRC (100) + DOX
99mTc-PYP uptake	34914±3583	79943±5613[b]	64171±3365[b,c]	49829±3393[a,d,f]
Heart rate (bpm)	307±3.92	225±8.69 [b]	256±8.5[b,c]	293±4.18[d]
QT interval (duration, s)	0.070±0.002	0.110±0.006[b]	0.082±0.003[c]	0.075±0.003[d,e]
ST-segment amplitude (mV)	0.037±0.002	0.116±0.007[b]	0.068±0.003[b,d]	0.045±0.003[d,e]

[a]: p<0.05, [b]: p<0.001, all groups when compared to control group, [c]: p<0.05, [d]: p<0.001 QRC (10) + DOX and QRC (100) + DOX groups when compared to DOX group, [e]: p<0.01, [f]: p<0.001, QRC (10) + DOX group when compared to QRC (100) + DOX group.
Data are presented as mean ± SEM (n=7 per group). 99mTc-PYP uptake was analyzed using the Kruskal-Wallis test followed by pairwise Mann-Whitney U tests with Bonferroni correction for multiple comparisons. Electrocardiographic parameters (heart rate, QT interval, and ST-segment amplitude) were analyzed using One-Way ANOVA followed by Tukey's post-hoc test, DOX: Doxorubicin, SEM: Standard error of the mean, QT: Q wave-T wave interval, QRC: Quercetin

Effects on ECG parameters

Heart rate analysis revealed a significant overall group effect [F(3.24) =30.32, p<0.0001], with marked heart rate alteration in the DOX group compared with controls (p<0.0001), while both QRC doses significantly improved heart rate relative to DOX (10 mg/kg: p=0.0175; 100 mg/kg: p<0.0001), and the higher dose restored values to control levels (p=0.4687).

QT interval duration and ST segment elevation differed significantly among groups [QT: F(3.24) =18.42, p<0.0001; ST: F(3.24) =58.56, p<0.0001], with DOX inducing pronounced QT prolongation and ST elevation compared with controls (both p<0.0001). While QT interval prolongation was only partially reduced in the DOX + QRC (10 mg/kg) group and did not reach statistical significance compared with the DOX group (p=0.1935), treatment with DOX + QRC (100 mg/kg) resulted in a significant shortening of the QT interval (p<0.0001). ST-segment elevation was significantly attenuated in both QRC-treated groups compared with the DOX group (DOX + QRC 10 mg/kg, p=0.0005; DOX + QRC 100 mg/kg, p<0.0001). Notably, ST segment values were significantly lower in the DOX + QRC (100 mg/kg)

group than in the DOX + QRC (10 mg/kg) group (p=0.0098), indicating a dose-dependent cardioprotective effect (Figure 4, Table 1).

Biochemical Parameters

Serum cardiac injury markers (cTnT and CK-MB)

Data presented in Table 2 and Figure 5 revealed significant group differences in serum cardiac injury markers. One-Way ANOVA showed significant overall effects for both cTnT [F(3.24) =28.96, p<0.0001] and CK-MB [F(3.24) =22.75, p<0.0001]. Both markers were significantly elevated in the DOX group compared with controls (both p<0.0001), indicating marked myocardial injury.

Post-hoc Tukey analysis demonstrated that QRC treatment significantly reduced cTnT and CK-MB levels compared with the DOX group (cTnT: QRC 10 mg/kg, p=0.0005; QRC 100 mg/kg, p<0.0001; CK-MB: QRC 10 mg/kg, p=0.0016; QRC 100 mg/kg, p<0.0001). No significant differences were observed between the two QRC doses for either marker (cTnT, p=0.0289; CK-MB, p=0.1589), and biomarker levels in QRC-treated groups did not differ significantly from controls (p>0.05) (Figure 5, Table 2).

ER stress-related parameters (GRP78 and CHOP)

Data presented in Table 2 and Figure 6 show that ER stress-related markers were significantly affected by DOX treatment. One-Way ANOVA revealed significant overall group differences for both GRP78 [F(3.24) =16.65, p<0.0001] and CHOP [F(3.24) =106.0, p<0.0001]. Both GRP78 and CHOP levels were significantly increased in the DOX group compared with the control group (p<0.0001 for both), indicating pronounced ER stress induction following DOX administration (Figure 6, Table 2).

Administration of QRC at both doses significantly reduced GRP78 content and CHOP activity compared with the DOX group (QRC 10 mg/kg: GRP78 p=0.0244, CHOP p<0.0001; QRC 100 mg/kg: GRP78 p=0.0002, CHOP p<0.0001). When the two QRC doses were compared, no statistically significant difference was observed in GRP78 levels

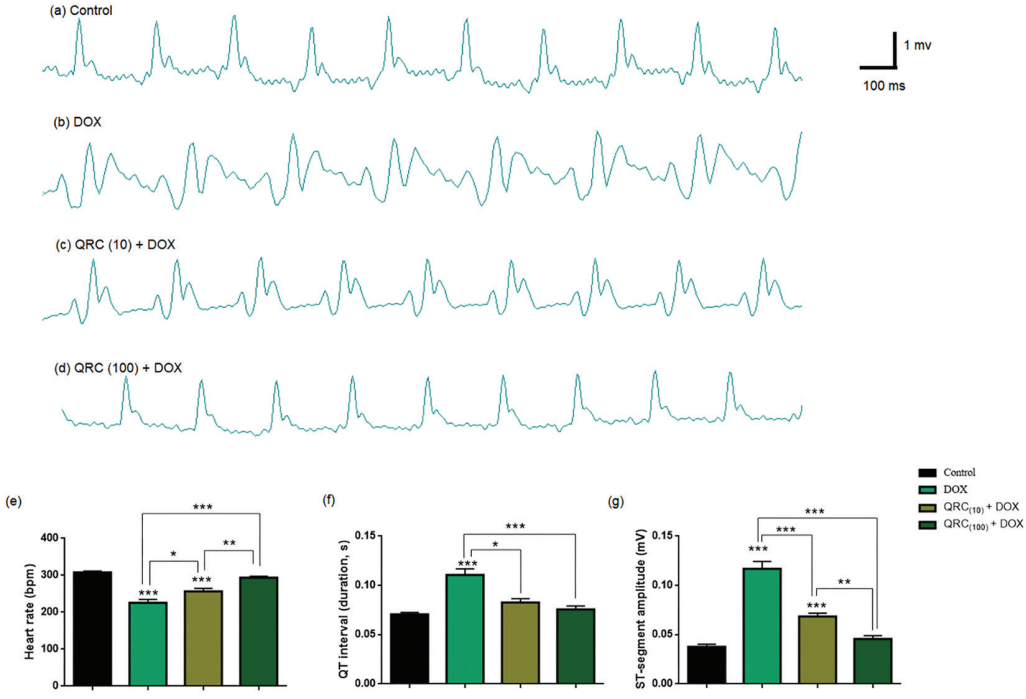

Figure 4. Effects of quercetin on doxorubicin-induced electrocardiographic alterations

Representative electrocardiographic (ECG) recordings obtained from rats in the (a) Control, (b) DOX, (c) DOX + QRC (10 mg/kg), and (d) DOX + QRC (100 mg/kg) groups are shown.

Quantitative analyses of (e) heart rate, (f) QT interval duration, and (g) ST segment amplitude are presented as mean ± SEM (n=7 per group). Statistical comparisons were performed using One-Way ANOVA followed by Tukey's multiple comparisons test

**: p<0.05, **: p<0.01, ***: p<0.001 indicate significant differences between groups, as specified, DOX: Doxorubicin, QRC: Quercetin, QT: Q wave-T wave interval*

(p=0.1923), whereas CHOP levels were significantly lower in the QRC (100 mg/kg) group than in the QRC (10 mg/kg) group (p<0.0001), indicating a dose-dependent attenuation of CHOP-mediated ER stress and apoptotic signaling.

Oxidative stress-related parameters (MDA and GSH)

Kruskal-Wallis analysis revealed a significant overall difference among the groups in MDA levels [$\chi^2(3) = 19.619$, p<0.001]. Consistent with this finding, MDA levels were significantly increased in the DOX group compared with the control group (p<0.0001), indicating enhanced lipid peroxidation. QRC treatment significantly reduced MDA levels compared with the DOX group (QRC 10 mg/kg, p=0.002; QRC 100 mg/kg, p<0.0001). In parallel, reduced GSH levels showed a significant overall group effect by One-Way ANOVA [F(3.24) =28.01, p<0.0001], with a marked decrease observed in the DOX group relative to controls (p<0.0001). QRC administration significantly increased GSH levels in both treatment groups (QRC 10 mg/kg and QRC 100 mg/kg, p=0.024, p<0.0001, respectively). Notably, MDA levels were significantly lower in the QRC (100 mg/kg) group than in the QRC (10 mg/kg) group (p=0.0148), whereas no significant difference was observed in GSH levels between the two QRC-treated groups (p>0.05) (Figure 6, Table 2).

Table 2. Biochemical parameters in heart tissue and serum

	Control	DOX	QRC (10) + DOX	QRC (100) + DOX
cTnT (pg/mL)	785±221	3731±418[c]	2091±126[b,f]	1031±88[f,g]
CK-MB (U/L)	462±26	868±37[c]	646±22[b,e]	531±54[f]
GRP78 (ng/mg protein)	0.73±0.07	2.13±0.23[c]	1.49±0.13[b,d]	1.05±0.10[f]
CHOP (pg/mg protein)	44.77±3.10	182.5±7.40[c]	127±6.89[c,f]	77.32±4.94[b,f,h]
TNF-a (pg/mg)	128±10	282±27[c]	170±17[f]	125±11[f]
IL-6 (pg/mg)	4.96±0.58	11.10±0.99[c]	6.92±0.85[e]	5.16±0.56[f]
MDA (nmol/mg)	1.60±0.15	5.17±0.43[c]	2.91±0.29[b,e]	1.92±0.18[f,g]
GSH (µmol/g)	47.87±2.47	18.43±1.61[c]	28.76±2.89[c,d]	37.29±2.29[a,f]
SIRT1 (ng/mg)	3.40±0.15	1.45±0.06[c]	2.21±0.18[c,d]	2.76±0.23[f]

[a]: p<0.05, [b]: p<0.01, [c]: p<0.001, all groups when compared to control group, [d]: p<0.05, [e]: p<0.01, [f]: p<0.001, QRC (10) + DOX and QRC (100) + DOX groups when compared to DOX group, [g]: p<0.05, [h]: p<0.001 QRC (10) + DOX group when compared to QRC (100) + DOX group, data are presented as mean ± SEM (n=7 per group) DOX: Doxorubicin, GSH: Glutathione, QRC: Quercetin, MDA: Malondialdehyde, CK-MB: Creatine kinase-myocardial band, TNF: Tumor necrosis factor, SEM: Standard error of the mean

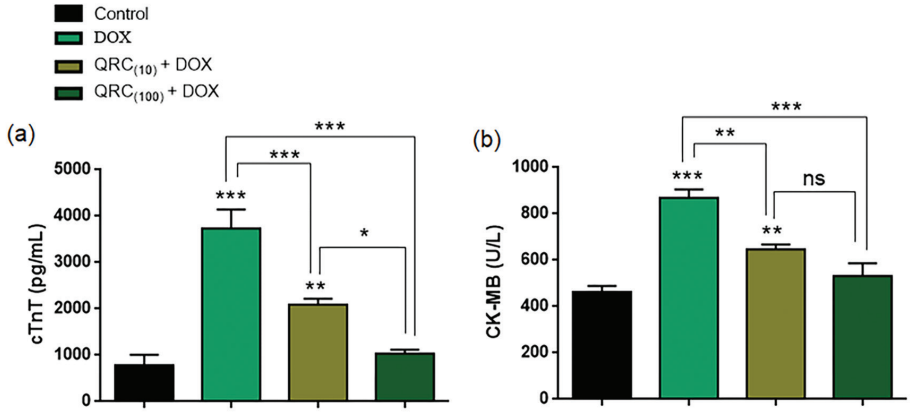

Figure 5. Serum cardiac injury markers. (a) cTnT and (b) CK-MB levels in control, DOX, QRC (10 mg/kg) + DOX, and QRC (100 mg/kg) + DOX groups. Data are presented as mean ± SEM (n=7). Statistical analysis was performed using One-Way ANOVA followed by Tukey's post-hoc test

**: p<0.05, **: p<0.01, ***: p<0.001, ns: Not significant, DOX: Doxorubicin, QRC: Quercetin, CK-MB: Creatine kinase-myocardial band, cTnT: Cardiac troponin T, SEM: Standard error of the mean*

Inflammation-related cytokines (TNF-α and IL-6)

Data presented in Table 2 and Figure 7 demonstrate significant alterations in pro-inflammatory cytokine levels among the experimental groups. One-Way ANOVA revealed significant overall group differences for both TNF-α [F(3.24) =16.97, p<0.0001] and IL-6 [F(3.24) =13.55, p<0.0001]. TNF-α and IL-6 levels were significantly increased in the DOX group compared with the control group (both 0.0001), indicating a pronounced inflammatory response following DOX administration. QRC treatment significantly reduced TNF-α and IL-6 levels compared with the DOX group at both doses (TNF-α: QRC 10 mg/kg p=0.0009, QRC 100 mg/kg p<0.0001; IL-6: QRC 10 mg/kg p=0.0044, QRC 100 mg/kg p<0.0001). However, no statistically significant difference was observed between the two QRC-treated groups for either TNF-α (p=0.3131) or IL-6 (p=0.3912) (Figure 7, Table 2).

SIRT1

Data presented in Table 2 and Figure 7 demonstrate significant alterations in SIRT1 levels among the experimental groups. One-Way ANOVA revealed a significant overall group effect for SIRT1 [F(3.24) =23.64, p<0.0001]. SIRT1 levels were significantly reduced in the DOX group compared with the control group (p<0.0001), indicating suppression of SIRT1–mediated cytoprotective signaling following DOX administration (Figure 7, Table 2).

QRC treatment significantly restored SIRT1 levels compared with the DOX group at both doses (QRC 10 mg/kg, p=0.0218; QRC 100 mg/kg, p<0.0001). However, no statistically significant difference was observed between the two QRC-treated groups (p=0.1274), suggesting that QRC-induced SIRT1 activation was not dose-dependent under the present experimental conditions.

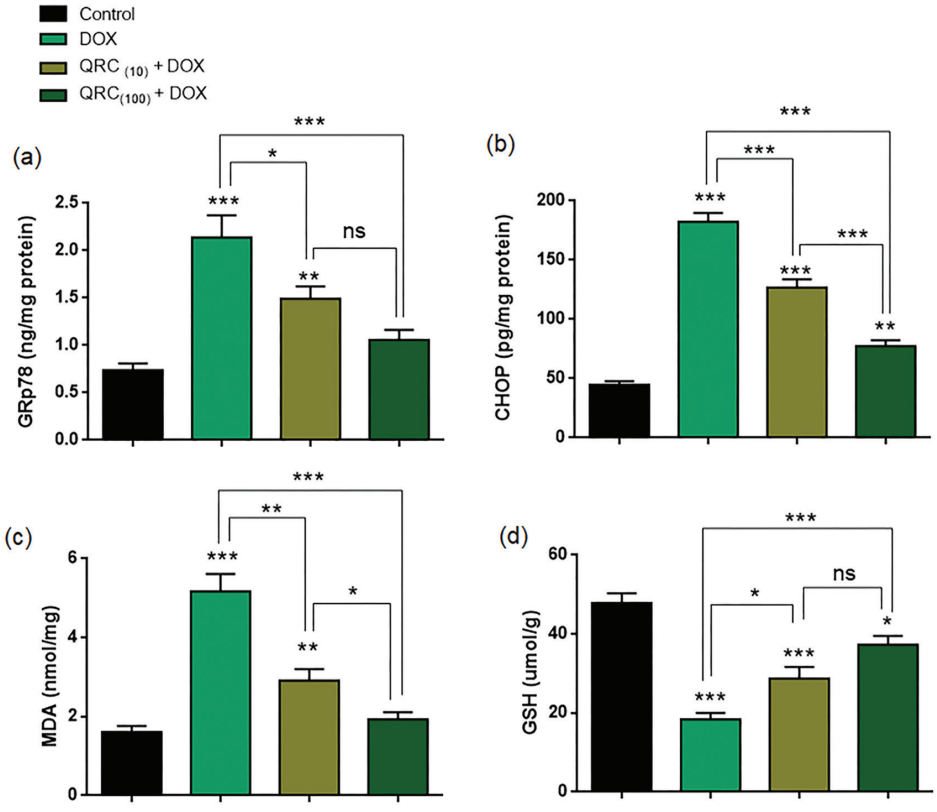

Figure 6. Effects of quercetin on ER stress and oxidative stress markers in cardiac tissue. Levels of (a) GRP78, (b) CHOP, (c) malondialdehyde (MDA), and (d) reduced (GSH) in control, DOX, QRC (10 mg/kg) + DOX, and QRC (100 mg/kg) + DOX groups. Data are expressed as mean ± SEM (n=7 per group).

GRP78, CHOP, and GSH were analyzed using One-Way ANOVA followed by Tukey's post-hoc test, whereas MDA levels were analyzed using the Kruskal-Wallis test followed by pairwise Mann-Whitney U tests with Bonferroni correction for multiple comparisons

**: p<0.05, **: p<0.01, ***: p<0.001, ns: Not significant, GSH: Glutathione, DOX: Doxorubicin, QRC: Quercetin, ER: Endoplasmic reticulum, CHOP: C/EBP homologous protein, SEM: Standard error of the mean*

Normally distributed variables were analyzed using One-Way ANOVA followed by Tukey's post-hoc test. Non-normally distributed variables (MDA) were analyzed using the Kruskal-Wallis test followed by pairwise Mann-Whitney U tests with Bonferroni correction for multiple comparisons.

Biochemical renal and hepatic markers

Renal Function Markers: BUN and Creatinine

BUN values showed a normal distribution. They were therefore analyzed using One-Way ANOVA, which revealed a significant overall group effect [$F(3.24) = 48.04$, $p<0.0001$], indicating that DOX administration significantly increased BUN levels compared with the Control group ($p<0.0001$), while co-treatment with QRC at 10 mg/kg (QRC 10 + DOX) and 100 mg/kg (QRC 100 + DOX) significantly attenuated this increase relative to the DOX group ($p<0.001$ and $p<0.001$, respectively), with no significant difference between the two QRC doses ($p=0.069$).

In contrast, serum creatinine levels did not follow a normal distribution and were therefore analyzed using the Kruskal-Wallis test, which revealed a significant overall difference among the groups [$\chi^2(3) = 23.485$, $p<0.001$]. Pairwise comparisons demonstrated that DOX significantly increased creatinine levels compared with the control group ($p<0.0001$). Treatment with QRC significantly reduced creatinine levels relative to the DOX group in both treatment groups (QRC 10 + DOX, $p=0.0379$; QRC 100 + DOX, $p<0.0001$). Moreover, creatinine levels were significantly lower in the QRC 100 + DOX group than in the QRC 10 + DOX group ($p=0.0015$), indicating a stronger protective effect at the higher dose.

Hepatic Enzymes: AST, ALT, and GGT

As shown in Table 3 and Figure 8, normality testing indicated that AST and GGT values were normally distributed, and these variables were therefore analyzed using One-Way ANOVA. A significant overall treatment effect was observed for AST [$F(3.24) = 27.91$, $p<0.0001$] and GGT [$F(3.24) = 33.41$, $p<0.0001$]. Post-hoc Tukey's multiple comparisons test demonstrated that DOX administration markedly increased serum AST and GGT levels compared with the control group (both $p<0.001$), indicating pronounced hepatocellular injury (Figure 8).

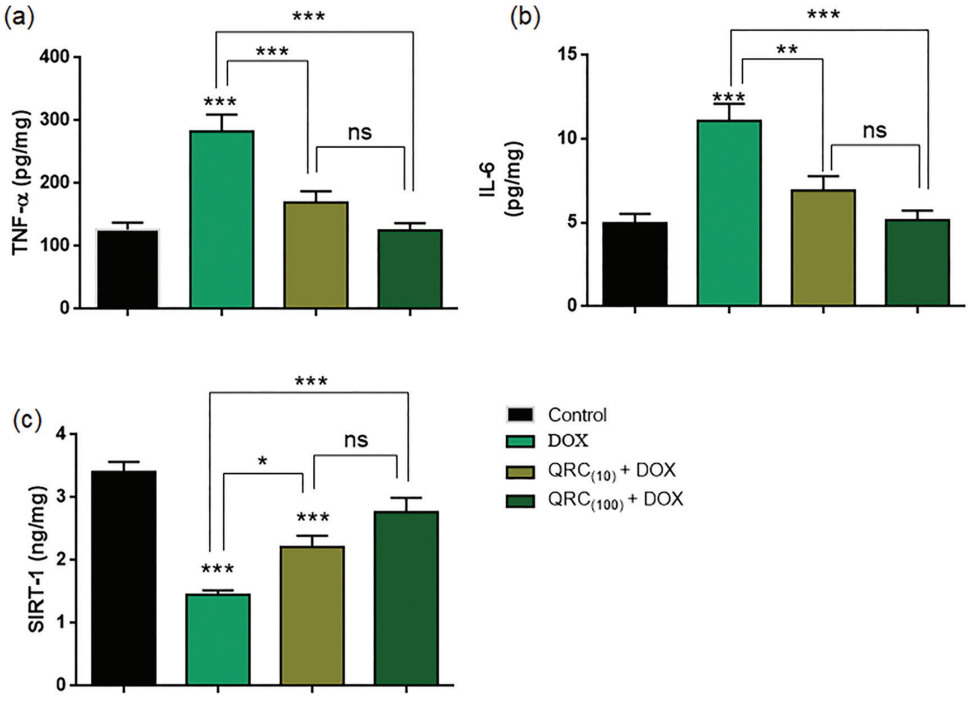

Figure 7. Effects of quercetin on inflammatory and SIRT1 signaling markers in cardiac tissue. (a) TNF-α, (b) IL-6, and (c) SIRT1 levels in control, DOX, QRC (10 mg/kg) + DOX, and QRC (100 mg/kg) + DOX groups. Data are expressed as mean ± SEM (n=7). One-Way ANOVA followed by Tukey's post-hoc test

**: p<0.05, **: p<0.01, ***: p<0.001, ns: Not significant, SEM: Standard error of the mean, TNF: Tumor necrosis factor, DOX: Doxorubicin, QRC: Quercetin*

Table 3. Renal and hepatic biochemical markers

	Control	DOX	QRC (10) + DOX	QRC (100) + DOX
Creatinine (mg/dL)	0.40±0.02	2.11±0.20[c]	1.54±0.14[c,d]	0.86±0.08[c,f,g]
BUN (mg/dL)	25.14±1.42	97.43±6.84[c]	64.43±4.19[c,f]	48.29±3.21[b,f]
AST (U/L)	191.9±8.54	581.6±48.71[c]	407.4±24.74[c,e]	300±29.96[f]
ALT (U/L)	62±2.58	287.6±24.24[b]	192.1±14.21[b,d]	139.1±5.0[b,e,g]
GGT (U/L)	5.28±0.42	18.71±1.16[c]	13.14±1.26[c,e]	9.85±0.82[a,f]

[a]: p<0.05, [b]: **p<0.01, [c]: *** p<0.001 vs. control; [d]: p<0.05, [e]: **p<0.01, [f]: ***p<0.001 vs. DOX;
[g]: p<0.01 QRC (10) + DOX group when compared to QRC (100) + DOX, DOX: Doxorubicin, QRC: Quercetin, BUN: Blood urea nitrogen, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: Gamma-glutamyl transferase

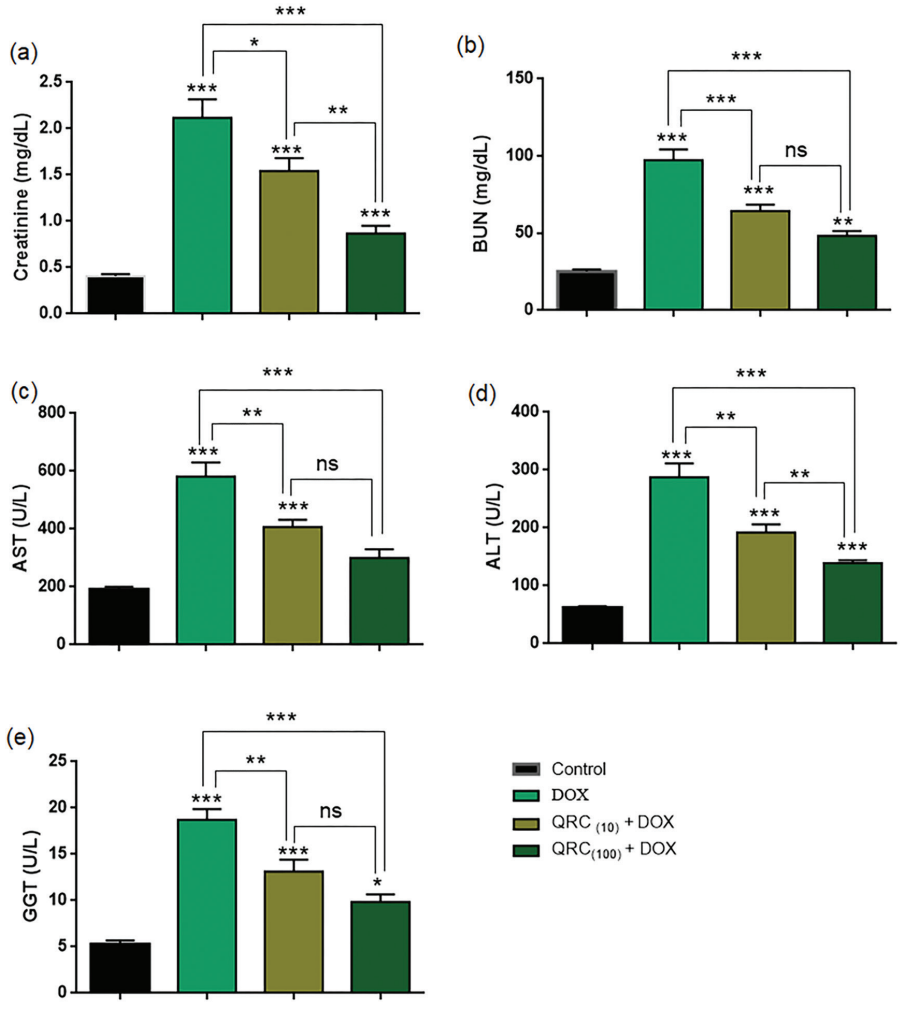

Figure 8. Effects of quercetin on doxorubicin-induced renal and hepatic injury markers.

Serum levels of (a) creatinine (mg/dL), (b) blood urea nitrogen [(BUN), mg/dL], (c) aspartate aminotransferase [(AST), U/L], (d) alanine aminotransferase [(ALT), U/L], and (e) gamma-glutamyl transferase [(GGT), U/L] in Control, doxorubicin (DOX), QRC 10 mg/kg + DOX [QRC (10) + DOX], and QRC 100 mg/kg + DOX (QRC (100) + DOX) groups. One-Way ANOVA followed by Tukey's multiple comparisons test was used for normally distributed variables (BUN, AST, and GGT). ALT and creatinine values were analyzed using the Kruskal-Wallis test followed by Mann-Whitney U post-hoc comparisons, *: p<0.05, **: p<0.01, ***: p<0.001 vs. control;

Brackets indicate comparisons between treatment groups; ns: Not significant.

Normally distributed variables were analyzed using One-Way ANOVA followed by Tukey's post-hoc test. Non-normally distributed variables (ALT and creatinine) were analyzed using the Kruskal-Wallis test followed by pairwise Mann-Whitney U tests with Bonferroni correction for multiple comparisons

Co-treatment with QRC at 10 mg/kg (QRC 10 + DOX) significantly attenuated the DOX-induced elevations in AST (p=0.0003) and GGT (p=0.0026) relative to the DOX group. Similarly, QRC at 100 mg/kg (QRC 100 + DOX) produced a more pronounced reduction in AST and GGT (both p<0.001) compared with DOX alone. Direct comparison between QRC 10 + DOX and QRC 100 + DOX revealed no statistically significant difference for AST (p=0.1016) or GGT (p=0.1090).

In contrast, serum ALT values did not follow a normal distribution and were therefore analyzed using the Kruskal-Wallis test, which demonstrated a significant overall difference among the experimental groups [$\chi^2(3) = 24.416$, p<0.001].

ALT levels were significantly higher in the DOX group compared with the control group (p=0.002). QRC treatment significantly reduced ALT levels relative to the DOX group in both treatment groups (QRC 10 + DOX, p=0.013; QRC 100 + DOX, p=0.002). Furthermore, ALT levels were significantly lower in the DOX + QRC (100 mg/kg) group than in the DOX + QRC (10 mg/kg) group (p=0.002), indicating a dose-dependent hepatoprotective effect of QRC.

Discussion

In the present study, DOX administration induced marked ER stress and oxidative-inflammatory damage in cardiac tissue, as evidenced by increased GRP78, CHOP, MDA, TNF-α, and IL-6 levels together with reduced SIRT1 and GSH, which were paralleled by significant electrocardiographic abnormalities and increased myocardial uptake on Tc-99m PYP scintigraphy. Notably, QRC dose-dependently attenuated these biochemical, electrophysiological, and scintigraphic alterations, with the higher dose conferring more pronounced cardioprotection.

In this study, Electrocardiographic analysis revealed significant QT interval prolongation, ST-segment elevation, and bradycardia in the DOX-treated rat. QT prolongation is a well-established marker of impaired ventricular repolarization and is closely associated with malignant arrhythmias and increased cardiovascular mortality (11,12). DOX has been shown to prolong cardiac action potential duration by disrupting delayed rectifier potassium currents (IKr/IKs) and calcium handling (13,14). At the same time, the accompanying ST-segment elevation likely reflects myocardial membrane injury and necrosis-related injury currents. The accompanying reduction in heart rate may be attributed to DOX-induced sinus node dysfunction and autonomic imbalance, which have previously been linked to mitochondrial damage and oxidative stress in pacemaker cells (15,16).

Tc-99m PYP is a radiopharmaceutical that binds to calcium complexes and preferentially accumulates in necrotic tissue. It has been routinely used in nuclear medicine for the imaging of myocardial and tissue necrosis (17-20). Consistent with this study, diffuse myocardial PYP uptake occurs in anthracycline-injured hearts (21). Miyagawa et al. (22) evaluated chronic DOX-induced myocardial injury in a rat model using 201Tl-thallium and ^{99}mTc-PYP uptake. They reported that cardiac accumulation of ^{99}mTc-PYP occurred only in the presence of advanced necrotic myocardial damage. In the present study, PYP uptake was markedly reduced in QRC-treated groups compared to DOX alone, indicating that QRC mitigated DOX-induced myocardial injury and supporting its cardioprotective role.

Consistent with the ECG and scintigraphic findings, DOX administration resulted in marked elevations in serum cTnT and CK-MB levels, confirming substantial cardiomyocyte injury and membrane disruption. Troponin elevation is widely accepted as a sensitive indicator of anthracycline-induced myocardial damage and has been correlated with both acute and long-term cardiac dysfunction (23). Consistent with previous reports, DOX administration resulted in significant elevations in cTnT and CK-MB levels, confirming myocardial injury (24,25).

DOX-induced oxidative stress primarily arises from excessive ROS generation during mitochondrial metabolism in cardiomyocytes, which are particularly susceptible due to their high mitochondrial density and limited antioxidant capacity (26,27). Excess ROS damages lipid membranes, proteins, and nucleic acids, promoting cardiomyocyte dysfunction and death (28), while simultaneously triggering inflammatory signaling. In this context, DOX has been shown to activate NF-κB, TLR4, and the NLRP3 inflammasome, leading to increased TNF-α and IL-6 production (29,30), consistent with the elevated cytokine levels observed in the present study. Oxidative stress is also closely linked to ER stress, as ROS disrupts protein folding and activates the unfolded protein response. The concurrent upregulation of GRP78 and CHOP suggests a shift toward ER stress–mediated apoptosis, consistent with reports of CHOP-dependent cardiomyocyte death in DOX models (31).

In the current study, the observed reduction in SIRT1 expression in DOX-treated hearts provides important mechanistic insight into DOX cardiotoxicity. SIRT1 is a NAD^+-dependent deacetylase that plays a central role in

cellular stress adaptation, and previous studies have shown that DOX exposure suppresses cardiac SIRT1 expression and activity, thereby enhancing ROS generation and myocardial injury (32,33). Under physiological conditions, SIRT1 negatively regulates both ER stress and inflammatory signaling by modulating UPR activity and limiting NF-κB-dependent cytokine transcription (34). Thus, DOX-mediated SIRT1 suppression likely contributes to sustained ER stress activation and increased TNF-α and IL-6 production. Supporting this interpretation, experimental models have demonstrated that SIRT1 deficiency markedly increases GRP78 and CHOP expression, whereas SIRT1 overexpression attenuates ER stress responses (35). Moreover, cardiomyocyte-specific SIRT1 deletion has been shown to activate multiple UPR branches and promote CHOP-dependent cell death (36), findings further corroborated in sepsis and aging models (37,38). Collectively, these data indicate that SIRT1 functions as a key negative regulator of the ER stress–UPR–CHOP axis in the heart.

QRC treatment markedly reversed the pathological alterations induced by DOX in the present study. QRC-treated groups exhibited significant reductions in GRP78 and CHOP expression, restoration of SIRT1 levels, attenuation of lipid peroxidation, and recovery of GSH content. In parallel, TNF-α and IL-6 levels were substantially reduced. These findings indicate that QRC simultaneously targets oxidative, ER, and inflammatory stress. Extensive evidence supports QRC's potent antioxidant capacity and cardioprotective efficacy across diverse cardiac injury models, including ischemia-reperfusion injury, myocardial infarction, and diabetic cardiomyopathy (39-43).

Mechanistically, QRC activates the Nrf2 signaling pathway, leading to enhanced expression of endogenous antioxidant defenses, including SOD, GSH, and HO-1 (44-46). Concurrently, QRC suppresses stress-activated inflammatory pathways by inhibiting NF-κB signaling, thereby reducing pro-inflammatory cytokine production. Notably, emerging evidence indicates that QRC can also enhance SIRT1 activity. Through SIRT1-dependent mechanisms, including XBP1 deacetylation, QRC dampens excessive UPR activation and alleviates ER stress (47-49).

In the present study, DOX administration significantly increased renal and hepatic injury markers, whereas QRC co-treatment partially but significantly reversed these alterations in a dose-dependent manner. Consistent with our findings, numerous experimental studies have demonstrated that DOX induces marked renal and hepatic dysfunction – reflected by elevations in serum creatinine, BUN, and hepatic transaminases – primarily through mechanisms involving oxidative stress, ER stress, and inflammatory signaling (50,51). Previous reports have shown that various antioxidant agents attenuate DOX-induced renal and hepatic injury by suppressing oxidative damage, reducing ER stress responses, and limiting inflammatory cascades (31,52). Several previous experimental studies have demonstrated that QRC protects against DOX-induced hepatic and renal toxicity by reducing oxidative stress and associated tissue damage in animal models (53-56). In line with this evidence, the observed renoprotective and hepatoprotective effects of QRC in our study may be, at least in part, attributed to its strong antioxidant properties, which likely mitigate DOX-induced oxidative and inflammatory tissue injury (Figure 9) (53-56).

Conclusion

These findings suggest that QRC interrupts the self-perpetuating cycle of ROS accumulation, ER stress, and DOX-induced inflammation. By restoring SIRT1 signaling and reinforcing antioxidant defenses, QRC preserves cellular homeostasis and limits cardiomyocyte injury. This integrated mechanism provides a coherent explanation for the observed cardioprotective effects of QRC in DOX-induced cardiotoxicity.

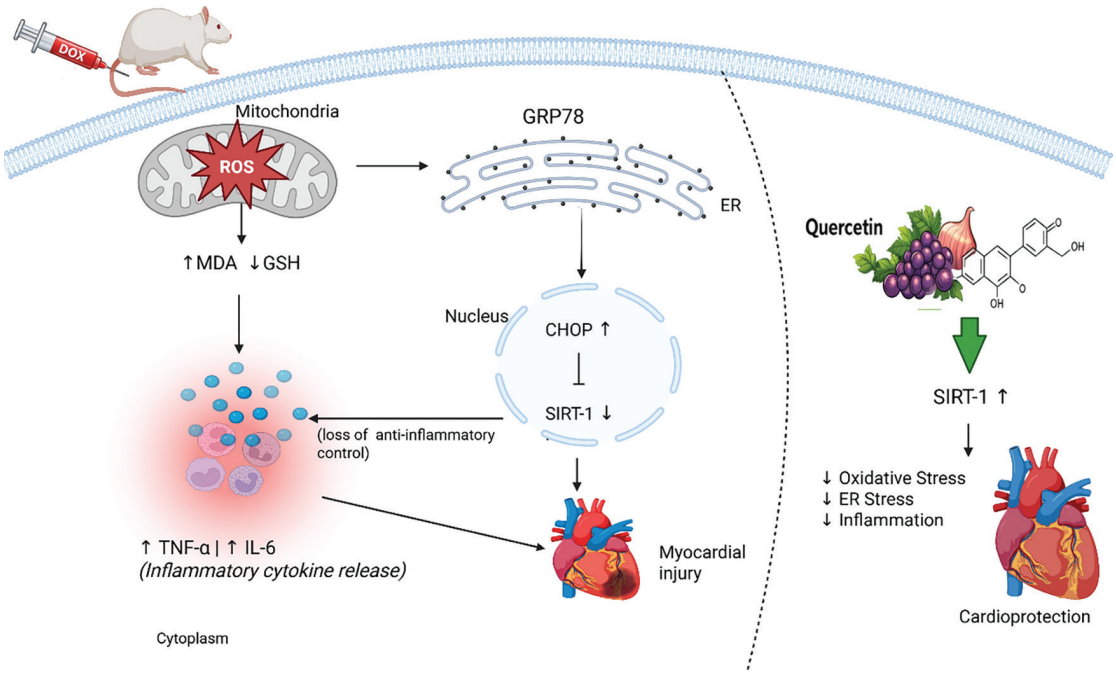

Figure 9. Graphical abstract

TNF: Tumor necrosis factor, MDA: Malondialdehyde, IL: Interleukin, ER: Endoplasmic reticulum, GSH: Glutathione, ROS: Reactive oxygen species

Ethics

Ethics Committee Approval: All procedures were approved by the Local Animal Experiments Ethics Committee of Tokat Gaziosmanpaşa University (approval no: 2019-HADYEK-15, date: 09.06.2019).

Informed Consent: Not applicable. This study is an experimental animal study.

Footnotes

Authorship Contributions

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

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ORIGINAL RESEARCH

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Morphometric MRI Changes After Posterior Fossa Decompression in Chiari Type I Malformation

Posterior Fossa Dekompresyonu Sonrası Chiari Tip I Malformasyonunda Morfometrik MRG Değişiklikleri

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Abstract

Objective: Chiari type I malformation (CM1) involves herniation of the cerebellar tonsils through the foramen magnum and altered cerebrospinal fluid (CSF) dynamics. Morphometric magnetic resonance imaging (MRI) measurements can objectively assess anatomical and physiological changes after posterior fossa decompression surgery (PFDS). This study evaluated postoperative morphometric alterations in CM1 and their implications for CSF flow.

Method: This retrospective study included 23 adult patients who underwent PFDS for CM1 between 2015 and 2024. Preoperative and postoperative mid-sagittal MRI images were analyzed to measure tonsillar ectopia (TE), displacement of the iter (DOI), and mammillopontine distance (MPD). Boogard's angle (BooA) was used as an anatomical reference for postoperative evaluation. Paired t-tests were used for comparison of morphometric parameters, with $p<0.05$ considered statistically significant.

Results: The mean age of patients was 34.0±8.7 years; 19 (82.6%) were female. The mean TE significantly decreased from 10.9±2.8 mm preoperatively to 6.9±2.5 mm postoperatively ($p=0.0003$). DOI also showed a significant reduction from 4.2±0.9 mm to 3.9±0.8 mm ($p=0.048$). No significant change was observed in MPD (6.2±0.7 mm vs. 6.1±0.7 mm, $p=0.324$).

Conclusion: PFDS effectively reduces tonsillar descent in CM1, confirming the anatomical decompression of the posterior fossa. The modest reduction in DOI suggests potential improvement in CSF flow, while stable MPD values indicate limited brainstem displacement. Larger prospective studies incorporating dynamic CSF

Öz

Amaç: Chiari tip I malformasyonu (CM1), serebellar tonsillerin foramen magnumdan aşağı herniasyonu ve buna bağlı beyin omurilik sıvısı (BOS) dinamiklerinde bozulma ile karakterizedir. Morfometrik manyetik rezonans görüntüleme (MRG) ölçümleri, posterior fossa dekompresyon cerrahisi (PFDC) sonrasında oluşan anatomik ve fizyolojik değişiklikleri nesnel olarak değerlendirmeye olanak sağlar. Bu çalışmada, CM1 hastalarında PFDC sonrası morfometrik değişikliklerin ve BOS akımı üzerindeki olası etkilerinin değerlendirilmesi amaçlandı.

Yöntem: Bu retrospektif çalışmaya, 2015-2024 yılları arasında CM1 nedeniyle PFDC uygulanan 23 erişkin hasta dahil edildi. Ameliyat öncesi ve sonrası orta sagital MRG kesitlerinde tonsiller ektopi (TE), iter deplasmanı (DOI) ve mamillopontin mesafe (MPD) ölçüldü. Postoperatif değerlendirmede anatomik referans olarak Boogard açısı (BooA) kullanıldı. Morfometrik parametrelerin karşılaştırılmasında eşleştirilmiş t-testi kullanıldı ve $p<0,05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: Hastaların ortalama yaşı 34,0±8,7 yıl olup, 19'u (%82,6) kadın ve 4'ü (%17,4) erkekti. Ortalama TE değeri ameliyat öncesi 10,9±2,8 mm iken ameliyat sonrası 6,9±2,5 mm'ye geriledi ($p=0,0003$). DOI değeri de 4,2±0,9 mm'den 3,9±0,8 mm'ye azaldı ($p=0,048$). MPD'de ise anlamlı bir değişiklik saptanmadı (6,2±0,7 mm vs. 6,1±0,7 mm, $p=0,324$).

Sonuç: PFDC, CM1 hastalarında serebellar tonsil ektopisini anlamlı biçimde azaltarak posterior fossada etkili anatomik dekompresyon sağlar. DOI'deki hafif düşüş BOS akımında kısmi iyileşmeyi

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Abstract

flow analysis are warranted to better define radiological predictors of surgical success.

Keywords: Cerebrospinal fluid dynamics, Chiari type I malformation, morphometry, posterior fossa decompression, tonsillar ectopia

Öz

düşündürürken, MPD'nin değişmemesi beyin sapı pozisyonunun büyük ölçüde sabit kaldığını göstermektedir. Dinamik BOS akım analizini de içeren daha geniş prospektif çalışmalar, cerrahi başarının radyolojik belirteçlerini daha net tanımlayabilir.

Anahtar kelimeler: Beyin omurilik sıvısı dinamikleri, Chiari tip I malformasyonu, morfometri, posterior fossa dekompresyonu, tonsiller ektopi

Introduction

Chiari type I malformation (CM1) is a congenital condition defined by herniation of the cerebellar tonsils through the foramen magnum, usually associated with a small posterior cranial fossa and disturbed cerebrospinal fluid (CSF) circulation. Patients may present with occipital headache, neck pain, or disequilibrium due to altered CSF flow at the craniocervical junction. In recent years, magnetic resonance imaging (MRI)–based morphometric measurements have gained importance for both diagnostic and prognostic assessment (1-4).

Key morphometric parameters include the mammillopontine distance (MPD), displacement of the iter (DOI), and Boogard angle (BooA), which together describe the spatial relationship of the brainstem, cerebellum, and cranial base. Because the clivus, basion, and opisthion are stable osseous landmarks, BooA remains constant and can serve as a reliable reference point, particularly when postoperative imaging limits direct visualization of the foramen magnum (5,6).

Morphometric analysis also assists in distinguishing CM1 from other conditions presenting with tonsillar ectopia (TE), such as spontaneous intracranial hypotension, which may appear similar on MRI. Parameters like the DOI and MPD are particularly useful in differentiating congenital tonsillar descent from secondary sagging due to CSF volume loss (4,5,7,8). Thus, precise morphometric assessment supports both accurate diagnosis and appropriate surgical selection.

Posterior fossa decompression is the standard treatment for symptomatic CM1, aiming to restore CSF circulation and relieve neural compression at the foramen magnum. However, how decompression alters morphometric indices remains unclear. Defining these radiological changes may help clarify the pathophysiology of CM1 and provide objective markers of surgical success (4,9-11).

This study aimed to evaluate how posterior fossa decompression affects key morphometric parameters, TE, DOI, and MPD in patients with CM1. We hypothesized that decompression would significantly reduce tonsillar descent and modify morphometric indices reflecting improved CSF flow.

Materials and Methods

Ethical Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of İstanbul University, İstanbul Faculty of Medicine (decision number: 23, date: 14.11.2025) prior to data collection. As this research involved retrospective analysis of existing medical records and imaging studies, the requirement for informed consent was waived by the ethics committee. All patient data were anonymized to ensure confidentiality and privacy.

Study Design

This retrospective study was conducted at İstanbul University, İstanbul Faculty of Medicine, between 2015 and 2024. Demographic data, clinical presentations, neuroradiological imaging, surgical details, and postoperative findings were retrospectively reviewed from medical records.

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) age ≥18 years; (2) cerebellar TE >5 mm below the foramen magnum on MRI; (3) diagnosis of CM1; (4) treatment with posterior fossa decompression surgery (PFDS); and (5) availability of adequate pre- and postoperative MRI scans suitable for morphometric analysis.

Exclusion criteria included previous cranial or cervical surgery, associated craniovertebral anomalies such as atlantoaxial dislocation or basilar invagination, and lack of postoperative imaging or consent.

Patient Selection and Statistical Plan

A total of 39 patients who underwent surgery for CM1 were screened. Sixteen were excluded due to incomplete or low-quality postoperative imaging, leaving 23 patients for final analysis. Quantitative variables were expressed

as mean ± standard deviation (SD). Three separate paired t-tests were performed to compare preoperative and postoperative TE, DOI, and MPD values. Because three related paired comparisons were conducted, the issue of multiple comparisons was considered. However, no formal correction (e.g., Bonferroni adjustment) was applied, and unadjusted p-values are reported. A p-value <0.05 was considered statistically significant. DOI and MPD analyses should therefore be interpreted as exploratory.

No a priori power or sample size calculation was performed for this study. The final sample size was determined by the number of eligible patients who met the inclusion criteria during the study period and had complete and adequate pre- and postoperative MRI data available for morphometric analysis. As this was a retrospective single-center study, the cohort size was determined by available data rather than a predefined statistical estimate.

Image Analysis

Based on the median sagittal plane, TE, MPD, DOI, and BooA were obtained. All measurements were obtained on sagittal MRI. TE was defined as the maximum projection of the tonsils below the McRae line, which is drawn between the opisthion and the basion (Figure 1) (12). MPD was defined as the distance between the inferior aspect of the mamillary bodies and the superior aspect of the pons (Figure 1) (13). DOI was determined by measuring a line along the plane of the incisura and measuring the distance to this line to the aperture of the cerebral aqueduct. DOI refers to the displacement of the third ventricular aperture of the cerebral aqueduct from the plane of the incisura; as the value becomes negative, the part below the incisura increases (Figure 2) (13,14). BooA is an angle that is used to determine the McRae line after posterior fossa decompression surgery. In the preoperative MRI, in addition to the line drawn from the basion to the opisthion, Wackenheim's clivus canal line is drawn from the clivus to the basion. The angle calculated at the intersection of the two lines is the BooA. Postoperatively, a virtual McRae line can be created by drawing a horizontal line at the BooA along the Wackenheim line passing through the basion (Figure 3). Thanks to BooA, TE after the posterior fossa decompression surgery can be measured.

All morphometric measurements (TE, DOI, MPD, and BooA) were independently performed on the same mid-sagittal MRI slice by two observers blinded to the timing of imaging (preoperative vs. postoperative). Interobserver reliability was assessed using the intraclass correlation coefficient (ICC; two-way random-effects model, absolute agreement). Excellent agreement was observed for TE [ICC =0.92; 95% confidence interval (CI) 0.83-0.96], DOI (ICC =0.88; 95% CI 0.76-0.94), and MPD (ICC =0.90; 95% CI 0.80-0.95). Discrepant measurements (>1 mm for TE/MPD or >0.5 mm for DOI) were resolved by consensus review.

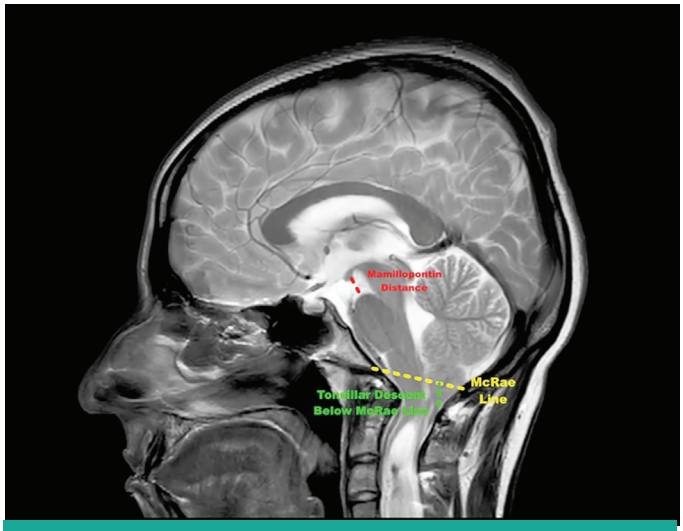

Figure 1. Measurement of tonsillar ectopia (TE) and mammillopontine distance (MPD) on mid-sagittal magnetic resonance imaging. The McRae line is drawn between the basion and opisthion. TE is defined as the maximum vertical distance of the cerebellar tonsils below this line. MPD is measured between the inferior margin of the mammillary bodies and the superior surface of the pons

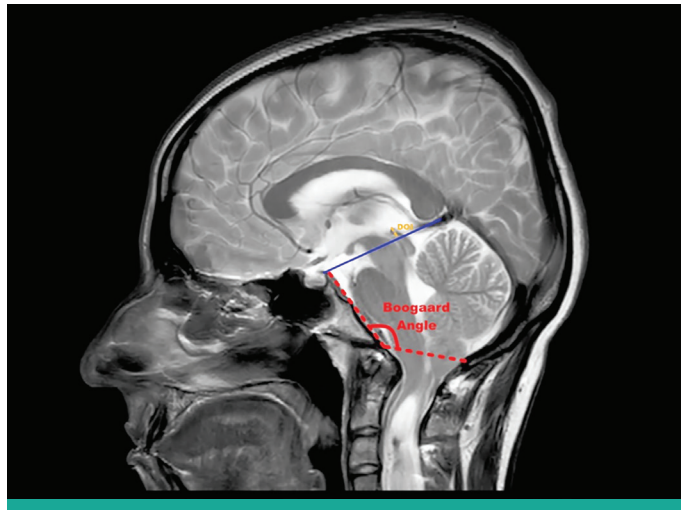

Figure 2. Measurement of Boogard's angle (BooA) and displacement of the iter (DOI) on mid-sagittal magnetic resonance imaging. BooA is formed by the intersection of Wackenheim's clivus canal line and the basion-opisthion line. DOI is determined by drawing a reference line along the plane of the tentorial incisura and measuring the perpendicular distance from this line to the cerebral aqueduct opening, representing the vertical displacement of the midbrain relative to the incisural plane

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean ± SD. The Shapiro-Wilk test was used to assess the normality of data distribution. Preoperative and postoperative morphometric measurements were compared using paired t-tests. Interobserver reliability was evaluated using ICC with 95% CIs. A p-value <0.05 was considered statistically significant.

Results

A total of 23 patients who met the inclusion criteria were analyzed. The mean age was 34.0±8.7 years, and most were female (n=19, 82.6%), while 4 (17.4%) were male (Table 1). The mean preoperative TE was 10.9±2.8 mm, the MPD was 6.2±0.7 mm, and the DOI was 4.2±0.9 mm. Postoperatively, these values were 6.9±2.5 mm, 6.1±0.7 mm, and 3.9±0.8 mm, respectively (Table 2). TE decreased by a mean of 4.0 mm (95% CI -5.1 to -2.9; p=0.0003). DOI showed a small mean decrease of 0.3 mm (95% CI -0.60 to -0.00; p=0.048). In contrast, MPD demonstrated no significant change (mean difference -0.05 mm; 95% CI -0.15 to 0.05; p=0.324). Interobserver agreement was excellent across morphometric measurements (ICC range 0.88-0.92).

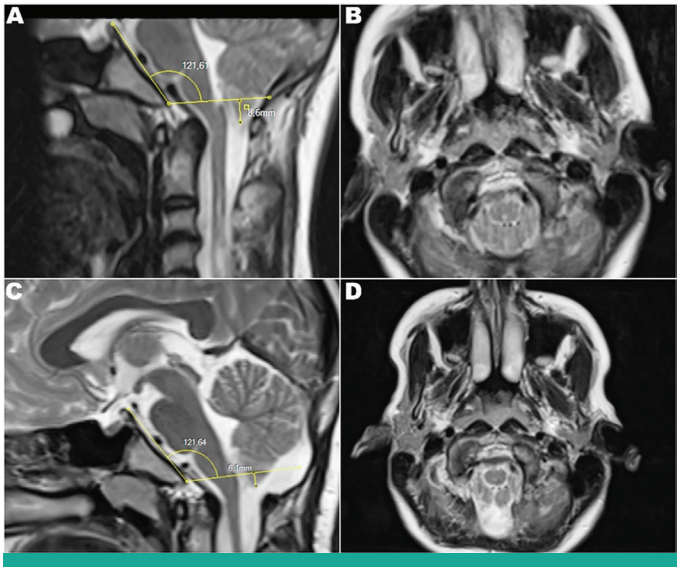

Figure 3. Postoperative reconstruction of the McRae line using Boogard's angle (BooA). After posterior fossa decompression, when the opisthion is no longer identifiable, a virtual McRae line can be reconstructed by projecting a horizontal line at the level of the BooA along Wackenheim's clivus canal line passing through the basion. This allows standardized measurement of tonsillar ectopia on postoperative magnetic resonance imaging

Statistical analysis demonstrated a significant postoperative reduction in TE compared with preoperative measurements (p<0.02). DOI showed a small decrease postoperatively (p=0.048, unadjusted). Given that three paired comparisons were performed and no correction for multiple testing was applied, this finding should be interpreted with caution. In contrast, the change in MPD was not statistically significant (p=0.324). No postoperative complications, CSF leakage, or wound infections were noted during follow-up. The reduction in TE was consistent across both male and female patients, with no significant sex-related difference in morphometric change. Postoperatively, most patients reported subjective improvement in headache and neck pain during routine clinical follow-up, consistent with expected symptomatic benefit after PFDS. Given the retrospective design, formal symptom scoring was not uniformly available and therefore was not included in statistical correlation analyses.

Discussion

CM1 is defined by herniation of the cerebellar tonsils through the foramen magnum, leading to disturbed CSF circulation and compression of posterior fossa structures. Although its pathophysiology has been extensively described, differentiating CM1 from conditions such as spontaneous intracranial hypotension remains clinically challenging because of overlapping radiological features. Previous reports have shown that up to one-third of patients with spontaneous intracranial hypotension were initially misdiagnosed as having CM1, resulting in delayed treatment and unnecessary surgery (12).

Morphometric parameters measured on MRI, such as TE, DOI, and MPD, have been proposed as objective markers to evaluate posterior fossa morphology and CSF dynamics (13,14). Among these, TE provides a direct anatomical indicator of neural descent, while DOI and MPD are

Table 1. Demographic characteristics of patients with Chiari type I malformation who underwent posterior fossa decompression surgery

Variable	n (%)/mean ± SD
Total patients included	39
Excluded (no postoperative imaging)	16
Patients analyzed	23
Female	19 (82.6%)
Male	4 (17.4%)
Mean age (years)	34.0±8.7

Data are expressed as the number of patients (n) and percentage (%) or mean ± standard deviation (SD), as appropriate

Table 2. Comparison of preoperative and postoperative morphometric measurements in patients with Chiari type I malformation

Parameter	Preoperative (mean ± SD)	Postoperative (mean ± SD)	Mean change (mm)	p-value
Tonsillar descent below McRae line (mm)	10.9±2.8	6.9±2.5	-4.0 (95% CI -5.1 to -2.9)	0.0003
DOI length (mm)	4.2±0.9	3.9±0.8	-0.3 (95% CI -0.60 to -0.00)	0.048
Mamillopontine distance (mm)	6.2±0.7	6.1±0.7	-0.05 (95% CI -0.15 to 0.05)	0.324 NS

Data are presented as mean ± standard deviation (SD). Statistical analysis was performed using paired t-tests comparing pre- and postoperative values. p<0.05 was considered statistically significant; NS: Not significant, DOI: Displacement of the iter, CI: Confidence interval

thought to reflect the effect of altered intracranial pressure and brainstem position.

In the present study, TE significantly decreased following posterior fossa decompression surgery (PFDS), confirming that surgical decompression effectively corrects the anatomical descent of the cerebellar tonsils. This finding is consistent with previous studies demonstrating radiological reversal of tonsillar herniation after PFDS and correlating this with clinical improvement (4,9,11,15). The significant but modest reduction in DOI observed here may indicate partial restoration of normal CSF pathways at the level of the incisura. However, the absence of a significant change in MPD suggests that the brainstem and mammillary body position remain relatively stable postoperatively, implying that decompression primarily affects the posterior fossa and foramen magnum region rather than midbrain alignment. Although clinical outcome measures were not formally analyzed, the observed reduction in TE and DOI may provide anatomical context for the symptomatic improvement commonly reported after decompression surgery. Future prospective studies incorporating standardized symptom scoring could further clarify whether the magnitude of morphometric change directly correlates with clinical improvement.

Our results contribute to the growing evidence that morphometric measurements can complement clinical assessment in postoperative follow-up of CM1 patients. Quantitative evaluation using BooA-based reconstruction of the McRae line also proved useful for standardizing TE measurement when the posterior fossa is surgically altered. This method allows consistent comparison between preoperative and postoperative MRIs, addressing one of the common limitations in morphometric CM1 research.

Study Limitations

The study has several limitations. First, the sample size was relatively small and derived from a single center, which may limit the generalizability of the findings. Importantly, no a priori power analysis was conducted, and the final cohort size was determined by the availability of eligible retrospective cases with complete imaging data. As a result, the study may have been underpowered to detect smaller effect sizes. This is particularly relevant for parameters demonstrating borderline statistical significance, such as the DOI, where limited statistical power may have influenced the robustness of the observed associations. Additionally, CSF flow was not directly measured with cine-MRI or invasive pressure monitoring; therefore, interpreting DOI as a surrogate for CSF dynamics remains indirect. Nevertheless, measurements were performed using standardized imaging planes, and interobserver agreement was excellent based on ICC analysis, supporting the reliability of the morphometric outcomes. The lack of correction for multiple comparisons increases the risk of type I error, particularly for the borderline DOI finding (p=0.048).

Future studies with larger cohorts and incorporation of dynamic CSF flow imaging or volumetric posterior fossa analysis could further clarify the radiological correlates of clinical improvement after PFDS. Longitudinal analyses may also help identify which morphometric changes best predict symptomatic relief or recurrence in CM1. These morphometric parameters may ultimately serve as objective imaging biomarkers in evaluating surgical outcomes and guiding postoperative management in CM1 patients.

Conclusion

Posterior fossa decompression surgery (PFDS) effectively reduces cerebellar TE in patients with CM1, confirming the anatomical success of decompression. The modest postoperative decrease in DOI may reflect partial restoration of CSF flow, whereas the stable MPD suggests limited impact on brainstem position. Future prospective studies integrating morphometric parameters with dynamic CSF flow assessment using cine MRI may improve the ability to correlate anatomical decompression with physiological restoration and clinical outcomes. Combining structural morphometry with cine MRI-based CSF flow metrics could

provide a more comprehensive postoperative imaging framework and enhance the translational value of MRI in CM1.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of İstanbul University, İstanbul Faculty of Medicine (decision number: 23, date: 14.11.2025) prior to data collection.

Informed Consent: This research involved retrospective analysis of existing medical records and imaging studies, the requirement for informed consent was waived by the ethics committee. All patient data were anonymized to ensure confidentiality and privacy.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: D.D.B., C.İ.G., Concept: D.D.B., S.Ö., F.K., T.C.Ü., İ.D., P.A.S., A.A., Y.A., A.S., Design: C.İ.G., S.Ö., T.C.Ü., İ.D., P.A.S., A.A., Y.A., A.S., Data Collection or Processing: D.D.B., C.İ.G., S.Ö., T.C.Ü., İ.D., P.A.S., Y.A., A.S., Analysis or Interpretation: D.D.B., C.İ.G., S.Ö., F.K., A.A., Y.A., A.S., Literature Search: C.İ.G., F.K., P.A.S., Writing: D.D.B., C.İ.G., S.Ö., F.K.

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ORIGINAL RESEARCH

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Lesion Size Predicts Survival After Single-stage Core Decompression with Autologous Iliac Cancellous Bone Graft and Demineralized Bone Matrix in Pre-collapse and Selected Early-collapse Stages Osteonecrosis of the Femoral Head

Erken Evre Femur Başı Osteonekrozunda Otolog İliyak Krest Kansellöz Greft ve Demineralize Kemik Matrisi ile Tek Aşamalı Core Dekompresyon Sonrası Sağkalımda Lezyon Boyutunun Belirleyici Rolü

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Abstract

Objective: This study evaluated the mid- to long-term outcomes of single-stage core decompression augmented with autologous iliac crest cancellous bone graft and demineralized bone matrix (DBM) in patients with pre-collapse and selected early-collapse stages osteonecrosis of the femoral head (ONFH). It also aimed to identify predictors of treatment failure, particularly lesion size.

Method: A retrospective review was conducted on 42 patients (50 hips) with ONFH treated between January 2011 and November 2024. Inclusion criteria were Ficat stage I-III disease managed with biologically augmented core decompression. Patients over 65 years or with prior hip surgery, vascular pathology, septic arthritis, or osteomyelitis were excluded. Lesion size was evaluated preoperatively using the modified Kerboul method on MRI. The primary endpoint was conversion to total hip arthroplasty (THA), regarded as treatment failure. THA-free survival was assessed using Kaplan-Meier estimates, with group comparisons via log-rank test. Cox regression identified predictors of THA.

Results: Over a mean follow-up of 56.7 months, 15 hips (30%) progressed to THA. THA-free survival rates were 95.9% at 12 months,

Öz

Amaç: Bu çalışmada, femur başı osteonekrozu (FBON) kollaps öncesi ve seçilmiş erken kollaps evrelerindeki hastalarda, otolog iliak krest kansellöz kemik grefti ve demineralize kemik matrisi (DKM) ile desteklenmiş tek aşamalı kor dekompresyon uygulamasının orta ve uzun vadeli klinik ve radyolojik sonuçları değerlendirilmiş; özellikle lezyon boyutuna odaklanarak tedavi başarısızlığını öngören faktörler araştırılmıştır.

Yöntem: Ocak 2011-Kasım 2024 tarihleri arasında tek merkezde Ficat evre I–III FBON tanısı ile biyolojik olarak desteklenmiş tek aşamalı kor dekompresyon uygulanan 42 hasta (50 kalça) retrospektif olarak incelendi. Altmış beş yaş üzerindeki hastalar ile daha önce kalça cerrahisi geçirmiş, vasküler hastalığı, septik artriti veya osteomiyeliti olan bireyler dışlandı. Ameliyat öncesi lezyon boyutu, manyetik rezonans görüntüleme üzerinden modifiye Kerboul yöntemiyle değerlendirildi. Birincil sonuç ölçütü, total kalça artroplastisine (TKA) geçiş olup, bu durum tedavi başarısızlığı olarak kabul edildi. TKA'sız sağkalım Kaplan-Meier yöntemiyle analiz edildi; grup farkları log-rank testi ile değerlendirildi. Cox regresyon modeliyle TKA riskini öngören faktörler belirlendi.

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Abstract

82.0% at 24 months, and 62.6% at 60 months. Survival differed significantly by modified Kerboul category (p=0.024), with lower rates in intermediate and large lesions. No statistically significant difference was observed across Ficat stages (p=0.066). In multivariate Cox analysis, lesion size remained an independent predictor of failure [intermediate vs. small: hazard ratio (HR) 5.74; large vs. small: HR 14.20].

Conclusion: Single-stage core decompression with autologous bone graft and DBM is a safe, effective joint-preserving option in pre-collapse and selected early-collapse stages ONFH. Lesion size, more than radiographic stage, predicted failure, highlighting the need for quantitative assessment in treatment planning.

Keywords: Autologous bone grafting, core decompression, demineralized bone matrix, femoral head, hip joint preservation, osteonecrosis

Öz

Bulgular: Ortalama 56,7 aylık takipte 15 kalça (%30) TKA'ya dönüştü. TKA'sız sağkalım oranları 12 ayda %95,9, 24 ayda %82,0 ve 60 ayda %62,6 idi. Modifiye Kerboul kategorilerine göre sağkalım anlamlı olarak farklılık gösterdi (p=0,024); orta ve büyük lezyonlarda oranlar düşüktü. Ficat evreleri arasında anlamlı fark saptanmadı (p=0,066). Çok değişkenli analizde, lezyon boyutu bağımsız bir başarısızlık belirleyicisi olarak kaldı [orta vs. küçük: tehlike oranı (HR) 5,74; büyük vs. küçük: HR 14,20].

Sonuç: Otolog kemik grefti ve DKM ile desteklenmiş tek aşamalı kor dekompresyon, FBON'un erken evresi için güvenli ve etkili bir tedavi seçeneğidir. Radyolojik evreden ziyade lezyon boyutu, tedavi başarısını öngörmede daha belirleyicidir. Bu bulgu, preoperatif planlamada kantitatif lezyon değerlendirmesinin önemini vurgulamaktadır.

Anahtar kelimeler: Core dekompresyon, demineralize kemik matrisi, femur başı, kalça eklemi koruma, osteonekroz, otojen kemik grefti

Introduction

Osteonecrosis of the femoral head (ONFH) is a progressive and debilitating condition characterized by disruption of blood supply to the femoral head, ultimately leading to subchondral bone collapse and secondary osteoarthritis. ONFH, which most commonly affects young and middle-aged adults, imposes a significant socio-economic burden owing to the early loss of hip function and the potential need for total hip arthroplasty (THA) at a relatively young age (1,2). Therefore, early intervention aimed at preserving the native femoral head is critical for improving long-term outcomes (3).

Core decompression is an important technique for managing early stage ONFH. Among joint-preserving surgical techniques, core decompression remains the most widely utilized method in early-stage osteonecrosis. By alleviating intraosseous pressure and improving blood flow, core decompression aims to halt disease progression (4,5). However, clinical outcomes following core decompression alone can be unpredictable, especially in lesions of substantial size or in advanced stages. In response, various augmentation techniques have been proposed to enhance the biological environment within the femoral head and support its structural integrity (6-8).

Autologous cancellous bone grafting from the iliac crest provides osteoconductive and osteoinductive properties that can stimulate new bone formation within the necrotic area (9,10). Similarly, the application of demineralized bone matrix (DBM), which is rich in growth factors, offers an additional biologically active scaffold to promote healing (11-13). Combining core decompression with autologous cancellous bone grafting and DBM application may synergistically improve outcomes by addressing both mechanical support and biological stimulation.

This study aimed to evaluate the clinical and radiological outcomes of patients with pre-collapse and selected early-collapse stages femoral head osteonecrosis treated with core decompression augmented with autologous iliac crest cancellous bone graft and DBM in a single-stage procedure. We hypothesized that this combined approach could enhance femoral head preservation and delay or prevent the need for total hip replacement.

Materials and Methods

This retrospective single-center study included all patients who underwent single-stage core decompression augmented with autologous iliac crest cancellous bone graft and DBM for pre-collapse and selected early-collapse stages femoral head osteonecrosis. This study adhered to the strengthening the reporting of observational studies in epidemiology guidelines for reporting observational research.

After obtaining institutional review board approval, patients were retrospectively identified from the institutional database. A total of 42 patients (50 hips) who underwent single-stage core decompression augmented with autologous iliac crest cancellous bone graft and DBM between January 1, 2011, and November 1, 2024 were included. The inclusion criteria comprised patients diagnosed with ONFH at Ficat stages I, II, or III who were

treated using this single-stage joint-preserving procedure at our institution. Patients older than 65 years, those with a history of hip surgery, documented vascular disease, or a history of septic arthritis or osteomyelitis were excluded from the study. The patient selection process, exclusion criteria, and final study cohort are shown in Figure 1.

There were 38 men (45 hips) and 4 women (5 hips), of whom 8 (19%) had bilateral ONFH. Overall, 23 and 27 hips were on the right and left sides, respectively. The mean age of the patients was 43.9±9.5 years (range, 22-62 years) at the time of surgery. Minimum follow-up was one year. The mean follow-up was 56.7 months (range 12-168 months).

The diagnosis of ONFH was established by anteroposterior radiography and conventional magnetic resonance imaging (MRI). The hip stage was categorized according to the Ficat classification system. There were 11 (22%) cases of stage I, 21 (42%) cases of stage II, and 18 (36%) cases of stage III.

Preoperative radiographs were reviewed to determine the modified Kerboul classification for each hip joint. The combined necrotic angle was measured on MRI using mid-sagittal and mid-coronal images, following the methodology described by Ha et al. (14), who evaluated the relationship between the combined necrotic angle and the risk of subsequent femoral head collapse. During postoperative follow-up, the development of femoral head collapse was recorded, along with the time to collapse. Additionally, whether patients subsequently underwent THA following the procedure was documented. For those who required THA, the interval between the index procedure and arthroplasty was noted.

The study was approved by the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (date: 26/07/2024, no: 2024/07/05/058). Although the study was retrospective, patients were contacted during follow-up and informed consent was obtained for the use of their clinical data.

Surgical Procedure

The procedure was performed with the patient in the supine position on a radiolucent traction table under spinal or general anesthesia. A 4-5-cm longitudinal incision was made over the iliac crest, followed by subperiosteal dissection to expose the crest. A cortical window was created to access the cancellous bone, from which approximately 20 cc of cancellous bone chips were harvested using curettes.

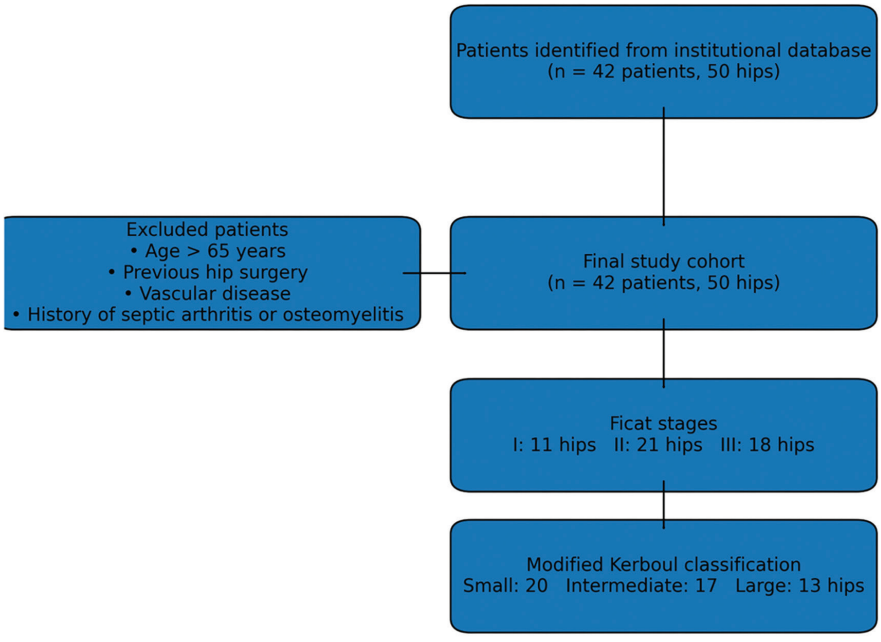

Figure 1. Flow diagram illustrating patient selection, exclusion criteria, and final study cohort.
The diagram summarizes patient identification, exclusions, and classification of hips according to the Ficat stage and the modified Kerboul classification

After graft collection, the cortical lid was repositioned and secured with bone wax, and the donor site was closed in layers.

Attention was directed to the proximal femur. Under fluoroscopic guidance, a 4-cm longitudinal incision was made at the level of the greater trochanter. The subcutaneous tissue, fascia lata, and vastus lateralis were dissected to expose the lateral cortex of the femur. Using anteroposterior, lateral, and oblique fluoroscopic views, a Kirschner wire was advanced toward the necrotic lesion to serve as the guide. Over this guidewire, and with a soft-tissue protector in place, a 9-mm cannulated drill was used to perform core decompression under fluoroscopy. Drilling was stopped approximately 5 mm from the endosteal surface of the femoral head. The necrotic area was then thoroughly debrided using angled and sharp curettes, with fluoroscopy aiding in confirming the adequacy of debridement (Figure 2).

Following debridement, the tract was irrigated and aspirated using a cannula system. DBM was then injected into the debrided cavity through the cannula. The harvested autologous iliac crest cancellous bone graft was then placed into the cavity until the defect was fully filled. The procedure was completed with a layered closure of the soft tissue.

All patients received routine antibiotic prophylaxis with a single preoperative intravenous 2 g cefazolin dose. Patients with a known β-lactam allergy received 1 g of vancomycin. Thromboprophylaxis was initiated the evening before surgery with a subcutaneous injection of low-molecular-weight heparin and continued once daily for six weeks postoperatively.

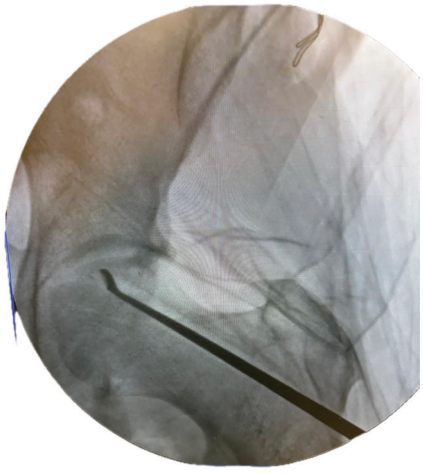

Figure 2. Intraoperative fluoroscopic image demonstrating the debridement of the necrotic area within the femoral head through the core decompression tract. A curette is advanced under fluoroscopic guidance to thoroughly remove necrotic tissue before graft placement

Postoperative Rehabilitation

Postoperative mobilization began on the first postoperative day. The rehabilitation protocol was structured as follows:

Weeks 0-6 (non-weight-bearing phase): Patients ambulated with two crutches without weight bearing on the operated extremity. Passive and active-assisted range of motion exercises of the hip were initiated immediately to prevent stiffness. Isometric quadriceps and gluteal strengthening exercises were encouraged.

Weeks 6-12 (partial weight-bearing phase): After radiographic confirmation of stability, gradual partial weight bearing was initiated using crutches. Strengthening exercises were progressively advanced, and patients were encouraged to increase hip abductor and core stability exercises.

After 12 weeks (full weight-bearing phase): Patients were allowed to progress to full weight bearing as tolerated. Functional strengthening and gait normalization exercises were continued. Return to low-impact daily activities was permitted after three months, whereas high-impact sports were discouraged.

Statistical Analysis

All analyses were performed on a hip basis. Continuous data are reported as mean with standard deviation or as median with interquartile range, while categorical data are presented as frequencies and percentages. The primary endpoint was conversion to THA, which was defined as treatment failure. Hips without THA were censored during the last follow-up.

Kaplan-Meier analysis was used to estimate THA-free survival, and group comparisons were performed using the log-rank test. The time to event was calculated from the index procedure to THA or censoring.

Associations between clinical variables and THA risk were assessed using Cox proportional hazard models. The Ficat stage was analyzed as stages 1-2 versus stage 3 because of the absence of events in stage 1 hips. In the analysis, the small modified Kerboul group and Ficat stages I and II were

used as reference categories. Hazard ratios were reported along with 95% confidence intervals, and statistical significance was defined as a p-value below 0.05.

Results

A total of 50 hips from 42 patients were analyzed. Table 1 summarizes the baseline demographic and clinical characteristics of the cohort. During follow-up, 15 hips (30.0%) underwent conversion to THA. The median time-to-event/censoring was 36.5 months [interquartile range (IQR), 22.0-79.8; range, 6-168]. Among the failures, the median time to THA was 24.0 months (IQR, 19.5-35.5; range, 6-60).

Kaplan-Meier estimates of THA-free survival were 95.9% at 12 months, 82.0% at 24 months, and 62.6% at 60 months; the median THA-free survival was not reached in the overall cohort. THA-free survival differed across the modified Kerboul categories (log-rank, p=0.024), with lower survival in the intermediate and large necrosis groups. In contrast, survival comparisons across Ficat stages showed a trend without statistical significance (log-rank p=0.066), and dichotomized analysis (Ficat 1-2 vs. 3) similarly did not reach significance (p=0.107). The Kaplan-Meier survival curves stratified by the Ficat stage and modified Kerboul classification are shown in Figure 3.

In the univariable Cox models, the modified Kerboul category was associated with an increased risk of THA (intermediate vs. small: HR 5.33, p=0.037; large vs. small: HR 6.87, p=0.019). In a multivariable model including age, dichotomized Ficat stage, and modified Kerboul category,

Table 1. Baseline demographic and clinical characteristics of the study cohort (hip-based analysis)

Variable	Value
Hips, n	50
Patients, n	42
Age, years, mean ± SD (range)	43.9±9.5 (22–62)
Sex (patients), n (%)	
Male	38 (90.5)
Female	4 (9.5)
Side, n (%)	
Right	23 (46.0)
Left	27 (54.0)
Bilateral involvement, n (%)	8 patients (19.0)
Ficat stage, n (%)	
Stage I	11 (22.0)
Stage II	21 (42.0)
Stage III	18 (36.0)
Modified Kerboul classification, n (%)	
Small	20 (40.0)
Intermediate	17 (34.0)
Large	13 (26.0)
Follow-up duration, months	
Mean ± SD	56.0±44.6
Median (IQR)	36.5 (22.0-79.8)
Range	12-168

Values are presented on a hip basis unless otherwise stated. Sex and bilateral involvement are reported on a patient basis. Follow-up duration represents time to total hip arthroplasty or last clinical follow-up.
SD: Standard deviation, IQR: Interquartile range

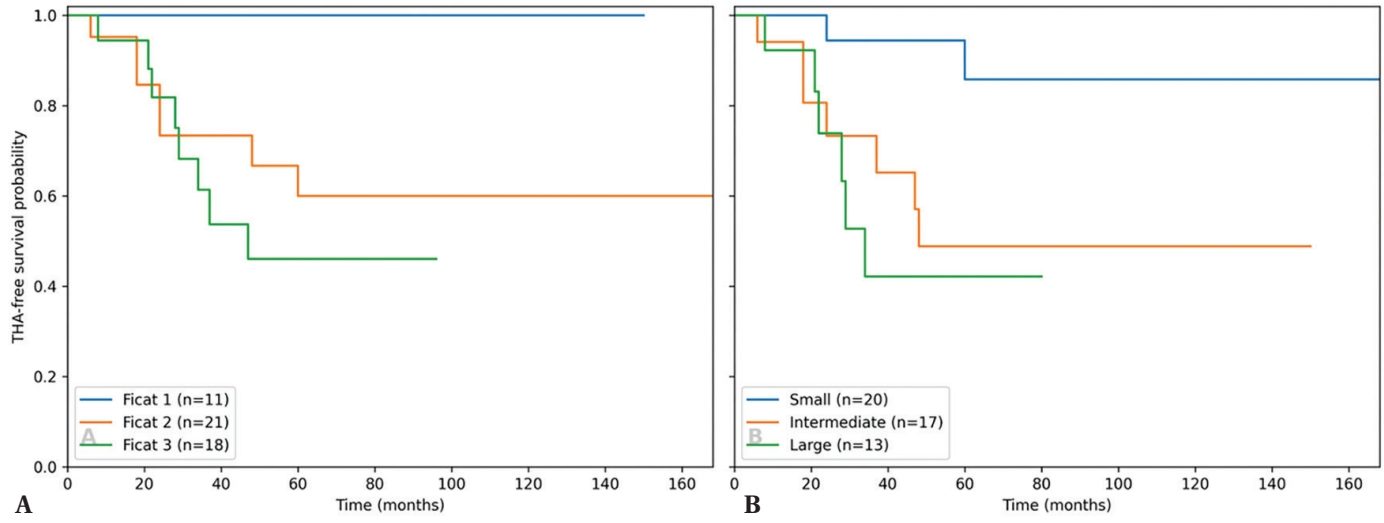

Figure 3. Kaplan-Meier estimates of THA-free survival. (A) Survival curves stratified by the Ficat stage. (B) Survival curves stratified by the modified Kerboul classification. Conversion to total hip arthroplasty was defined as the event. Hips without THA were censored at the last follow-up

THA: Total hip arthroplasty

Table 2. Hip-based survival and risk of conversion to total hip arthroplasty after core decompression with iliac cancellous autograft and DBM

Variable	Hips, n	THA, n (%)	Univariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
Overall cohort	50	15 (30.0)	–	–	–	–
Ficat stage						
Ficat 1	11	0 (0.0)	Reference	–	Reference	–
Ficat 2	21	7 (33.3)	–	–	–	–
Ficat 3	18	8 (44.4)	–	–	–	–
Ficat (1-2 vs. 3)	–	–	2.25 (0.81-6.24)	0.118	2.01 (0.70-5.78)	0.193
Modified Kerboul						
Small	20	2 (10.0)	Reference	–	Reference	–
Intermediate	17	7 (41.2)	5.33 (1.10-25.67)	0.037	5.74 (1.09-30.20)	0.039
Large	13	6 (46.2)	6.87 (1.38-34.23)	0.019	14.20 (1.39-144.8)	0.026
Age (per year)	–	–	1.02 (0.97-1.08)	0.412	1.01 (0.95-1.07)	0.721

Analyses were performed on a hip basis, with each hip considered an independent unit. Failure was defined as conversion to total hip arthroplasty (THA). Hips without THA were censored at the last clinical or radiographic follow-up. Hazard ratios (HRs) were calculated using Cox proportional hazards models. Reference categories were Ficat stage 1 and small modified Kerboul classification. Multivariable Cox regression model included age, dichotomized Ficat stage (1-2 vs. 3), and modified Kerboul classification. Kaplan-Meier analysis demonstrated overall THA-free survival rates of 95.9% at 12 months, 82.0% at 24 months, and 62.6% at 60 months; median survival was not reached, CI: Confidence interval, DBM: Demineralized bone matrix

the Kerboul category remained independently associated with THA (intermediate vs. small: HR 5.74, p=0.039; large vs. small: HR 14.20, p=0.026). The hip-based THA-free survival and Cox regression results are presented in Table 2.

Discussion

The present study evaluated the mid- to long-term outcomes of single-stage core decompression augmented with autologous iliac crest cancellous bone graft and DBM in patients with pre-collapse and selected early-collapse stages ONFH. The principal findings of this study are as follows. First, the overall THA-free survival rate of approximately 70% at a mean follow-up of nearly five years supports the effectiveness of this biologically augmented joint-preserving strategy. Second, lesion size assessed using the modified Kerboul classification emerged as a strong and

independent predictor of failure, whereas the Ficat stage showed only a non-significant association with conversion to THA. Third, patients with small necrotic lesions derived the greatest benefit from this approach, highlighting the importance of careful selection.

Our results demonstrate that single-stage core decompression augmented with autologous cancellous iliac crest bone graft and DBM can achieve favorable joint preservation outcomes in early-stage ONFH. At the mid-term follow-up, approximately 70% of the treated hips remained free of conversion to THA. This THA-free survival rate aligns with the success range reported for core decompression in pre-collapse ONFH. Historical series and meta-analyses have shown roughly 60-65% of hips avoid arthroplasty after core decompression alone in Ficat stage I-II disease (15,16). The slight improvement in the survivorship of our cohort (approaching 70%) is consistent with the known benefits of biological augmentation. In a large review of 32 studies (2441 hips), adding autologous bone graft or bone marrow cells to core decompression significantly increased success rates compared to decompression alone (16). Similarly, a 2024 meta-analysis of 15 studies (954 hips) confirmed that core decompression combined with regenerative therapy yields better outcomes than decompression alone (pooled risk ratio ~0.55 for disease progression), with the most pronounced benefit seen when bone marrow aspirate concentrate (BMAC) was used (17). Thus, our THA-free survival findings are consistent with current evidence that biologically augmented decompression is an effective joint preserving strategy for appropriately selected Ficat I-III-stage ONFH.

Our study supports the consensus that the size of the necrotic lesion is a critical prognostic factor, often outweighing the nominal stage of the disease in predicting outcomes (18). We observed markedly better results in hips with small necrotic lesions, whereas larger lesions had a higher risk of collapse and subsequent THA. Notably, the modified Kerboul combined necrotic angle was strongly predictive of treatment success in our cohort, whereas the Ficat stage (I vs. II) was not statistically significant. This finding underscores the clinical relevance of quantifying lesion size and location for accurate prognostication. It is well established that the extent of necrosis drives the likelihood of femoral head collapse and should be a major determinant in management (18). Our findings align with Boontanapibul et al. (19), who showed that core decompression success is strongly influenced by lesion size based on the modified Kerboul angle. In their study, lesions ≥250° had high failure rates despite BMAC use, while lesions <250° showed significantly better outcomes. Notably, BMAC improved 3-year survival in smaller lesions, but its benefit diminished in larger necrotic areas (19). These data, together with our findings, highlight that the modified Kerboul classification is more informative than the Ficat stage for early disease: A Ficat stage II lesion can have a wide prognostic spectrum depending on its size and location. In practical terms, a small stage II lesion may remain intact under joint-preserving treatment, whereas a large stage II lesion (e.g., a Kerboul angle >250°) is likely to fail despite intervention. Our lack of outcome difference between Ficat I and II hips is consistent with other studies focused on precollapse disease (20) and suggests that within early stages, lesion volume is the dominant driver of outcome. In contrast, once collapse occurs (Ficat III), the success rates of head-sparing procedures drop precipitously (21). This reinforces that while Ficat staging distinguishes precollapse vs. collapsed disease, it is the quantitative lesion assessment (e.g., combined necrotic angle or volume) that refines risk stratification among precollapse hips.

When comparing our augmented core decompression results with other treatment modalities and adjuncts, several points emerge. First, core decompression without any graft or biological adjunct has shown only moderate long-term efficacy in early ONFH. Mont et al. (22) reported that roughly 36% of hips continued to progress after core decompression alone, and a comprehensive meta-analysis documented an overall 65% success rate for core decompression in early stage ONFH (16). Our 70% THA-free survival is at least as good as, if not slightly better than, these outcomes for isolated core decompression, which we attribute to the added osteogenic stimulus and structural support from the autologous iliac crest bone graft and DBM. Our approach is analogous to the so-called “light bulb” decompression and grafting techniques, and recent studies using autograft alone have reported comparable mid-term results. For example, Ansari et al. (20) observed a 5-year collapse-free survival of 68.2% after core decompression with a trochanteric bone graft, with only 9% of hips requiring arthroplasty by 5 years. They also noted that smaller lesions (combined angle <200°) had a much lower collapse rate (~17%) than larger lesions (20). These similarities suggest that our single-center findings are generalizable: augmented decompression yields approximately 65-75% survival at 5 years in early ONFH, particularly when necrotic involvement is limited to the femoral head.

Second, the use of cell-based regenerative adjuncts, such as BMAC or cultured stem cells, appears to confer additional benefits beyond what morselized grafts alone can provide. Numerous studies have shown improved outcomes when BMAC is injected into the decompression tract. In the classic trial by Gangji et al. (23) and subsequent long-term follow-ups by Hernigou et al. (24), BMAC significantly delayed or prevented femoral head collapse compared to core decompression alone (21). Remarkably, Hernigou's 25-year data showed that 72% of hips treated with core decompression plus concentrated bone marrow grafting were still intact, whereas 76% of hips treated with core decompression alone collapsed over time (21,24). More recent evidence continues to favor BMAC; a systematic review reported that adding bone marrow concentrate roughly halved the risk of ONFH progression or THA conversion relative to decompression alone (17). Our study did not utilize BMAC; however, by combining autologous iliac crest cancellous bone graft (which contains osteoblast progenitors) with DBM (rich in bone growth factors), we aimed to simulate a pro-regenerative environment. The biological rationale for combining autologous cancellous bone graft with DBM is supported by both experimental and clinical evidence (25,26). Autologous cancellous bone provides osteogenic cells and an osteoconductive scaffold, while DBM contributes osteoinductive growth factors that may enhance local bone regeneration. The 70% joint survival we achieved is comparable to the ~72% 5-year survivorship reported in controlled trials of core decompression with BMAC (24), albeit direct comparisons should be made with caution. It is worth noting that not all cell-based therapies have shown success; for instance, a recent randomized trial of autologous expanded osteoblast implantation found no significant benefit over standard core decompression (27). This suggests that the type of biological augmentation matters; concentrated marrow (with its mix of mesenchymal stem cells, hematopoietic cells, and growth factors) appears more efficacious than isolated *ex vivo*-expanded cell populations (28). The complex cellular and cytokine milieu in BMAC, including MSCs and supportive macrophages, likely orchestrates a more robust repair response (29,30). The use of fresh autograft and DBM is a practical alternative that provides both osteogenic cells and an osteoconductive scaffold. Our outcomes confirm that this approach can achieve meaningful joint preservation, consistent with the outcomes of cell therapies.

Wang et al. (26) employed a similar approach using single-stage core decompression augmented with fresh cancellous autograft and DBM in patients with ONFH. However, their surgical technique differed notably, utilizing the Watson-Jones approach with anterior capsulotomy and a 1.5 cm osteotomy at the femoral head-neck junction to access the lesion. This method involves direct violation of the joint capsule and risks compromising femoral head vascularity due to potential injury to the retinacular vessels. In contrast, our approach allows access to the necrotic area via a lateral cortical window, avoiding capsular violation and femoral neck osteotomy. This technique may offer a safer alternative that reduces the risk of compromising femoral head vascularity.

Study Limitations

This study had several limitations. First, its retrospective design and single-center nature may affect the generalizability of our findings. Second, the relatively small sample size also limited the inclusion of variables in the multivariate analyses. Third, the use of a hip-based analysis, although common in osteonecrosis research, may have introduced bias in patients with bilateral involvement. Additionally, clinical outcome scores were not consistently recorded and could not be evaluated as part of the analysis. Finally, the absence of a control group treated with core decompression alone limits direct comparison of the added value of biological augmentation.

Nonetheless, the findings of this study offer meaningful clinical insights. The results suggest that patient selection based on lesion size, as determined by the modified Kerboul classification, is crucial when considering core decompression augmented with biological grafting. Patients with small necrotic lesions appear to benefit most from this approach, whereas those with larger lesions remain at a higher risk of eventual conversion to THA.

Conclusion

Single-stage core decompression with autologous iliac crest cancellous bone graft and DBM is a safe, effective joint-preserving strategy for pre-collapse and selected early-collapse stages osteonecrosis of the femoral head. Results show favorable mid-term outcomes, particularly in small necrotic lesions, with lesion size being more prognostic than radiographic staging. The modified Kerboul classification predicted treatment success and may guide preoperative planning. While biologic augmentation

showed encouraging results, future studies must compare augmentation strategies and include functional outcomes to improve patient selection and joint preservation.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (date: 26/07/2024, no: 2024/07/05/058).

Informed Consent: Participants were informed in detail, and verbal and written consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.F.D., S.B., A.A., M.U., O.B., E.C.B., M.A.G., Concept: M.F.D., M.A.G., Design: M.F.D., A.A., M.U., Data Collection or Processing: S.B., O.B., E.C.B., Analysis or Interpretation: M.F.D., S.B., A.A., E.C.B., Literature Search: M.F.D., M.U., O.B., Writing: M.F.D., S.B., M.A.G.

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

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CASE REPORT

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Nephrocalcinosis: A Case Report

Nefrokalsiniz: Olgu Sunumu

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Abstract

Nephrocalcinosis is characterized by increased calcium deposition within the renal parenchyma, most commonly affecting the renal medulla and less frequently the cortex, and may result in progressive renal dysfunction. It is often detected incidentally through imaging modalities such as abdominal radiography, ultrasonography, or computed tomography (CT). We report the case of an 18-year-old female with a history of recurrent nephrolithiasis and growth retardation who presented with acute left flank pain, gross hematuria, and mild dehydration. Laboratory evaluation revealed hypercalciuria, hyperchloremic metabolic acidosis with a normal anion gap, and inappropriately alkaline urine. Imaging studies demonstrated bilateral medullary nephrocalcinosis and a 17-mm calculus at the left ureteropelvic junction, resulting in grade 3 hydronephrosis. Non-contrast CT confirmed the diagnosis and excluded infectious or obstructive complications. The ureteral stone was successfully removed via ureteroscopy without complications. Based on clinical and laboratory findings, a diagnosis of distal renal tubular acidosis (dRTA) was established, and alkali therapy with sodium bicarbonate and potassium citrate was initiated. Nephrocalcinosis is frequently associated with dRTA, a disorder characterized by impaired urinary acidification leading to alkaline urine in the presence of hyperchloremic metabolic acidosis. Early recognition is crucial to prevent recurrent nephrolithiasis and long-term renal impairment.

Keywords: Distal renal tubular acidosis, hematuria, nephrocalcinosis, nephrolithiasis

Öz

Nefrokalsinoz, böbrek parankiminde, en sık böbrek medullasını ve daha az sıklıkla korteksi etkileyen ve ilerleyici böbrek fonksiyon bozukluğuna yol açabilen artmış kalsiyum birikimi ile karakterizedir. Genellikle karın radyografisi, ultrasonografi veya bilgisayar tomografisi (BT) gibi görüntüleme yöntemleriyle tesadüfen tespit edilir. Tekrarlayan nefrolitiyazis ve büyüme geriliği öyküsü olan 18 yaşında bir kadın hastanın akut sol yan ağrısı, makroskopik hematüri ve hafif dehidratasyon ile başvurduğu bir olgu sunulmuştur. Laboratuvar değerlendirmesinde hiperkalsiüri, normal anyon açıklığı ile hiperklorik metabolik asidoz ve uygunsuz derecede alkali idrar saptandı. Görüntüleme çalışmaları, bilateral medüller nefrokalsinoz ve sol üreteropelvik kavşakta 17 mm'lik bir taş olduğunu ve bunun sonucunda 3. derece hidronefroz oluştuğunu gösterdi. Kontrastsız BT, tanıyı doğruladı ve enfeksiyon veya obstrüktif komplikasyonları ekarte etti. Üreter taşı, üreteroskopi yoluyla komplikasyonsuz bir şekilde başarıyla çıkarıldı. Klinik ve laboratuvar bulgularına dayanarak distal renal tübüler asidoz (dRTA) tanısı konuldu ve sodyum bikarbonat ve potasyum sitrat ile alkali tedaviye başlandı. Nefrokalsinoz, sıklıkla hiperklorik metabolik asidoz varlığında idrar asitliğinin bozulması ve alkali idrar oluşumu ile karakterize bir bozukluk olan dRTA ile ilişkilidir. Tekrarlayan nefrolitiyazis ve uzun süreli böbrek yetmezliğini önlemek için erken teşhis çok önemlidir.

Anahtar kelimeler: Böbrek, hematüri, nefrokalsinozis, nefrolitiyazis

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Introduction

Nephrocalcinosis is characterized by an intense increase in calcium content in the kidneys. It can be effective at the molecular level or vary from microscopic to macroscopic levels and ultimately leads to progressive renal impairment (1). It predominantly affects the renal medulla, although the cortex may be involved less frequently. In the context of hypercalciuria, the increased concentration and supersaturation of urine lead to the accumulation of calcium crystals within the renal parenchyma (2).

Incidental diagnoses are frequently encountered in patients. Key imaging modalities for diagnosis include abdominal scanning, kidney ultrasonography, and computed tomography (3). Nephrocalcinosis is commonly regarded as a manifestation of a systemic disorder, thus requiring a thorough evaluation to ascertain its underlying causes (3). The differential diagnosis encompasses conditions such as primary hyperparathyroidism, medullary sponge kidney, sarcoidosis, vitamin D intoxication, distal renal tubular acidosis (dRTA), and various inherited tubulopathies. In alignment with clinical suspicion, the initial laboratory assessment should encompass serum levels of calcium and phosphate, parathyroid hormone, vitamin D, as well as urinalysis and urine electrolytes (4).

This case report details an 18-year-old female patient diagnosed with nephrocalcinosis, for whom written informed consent was procured prior to the preparation of the case presentation.

Case Report

The family of the patient presented an 18-year-old female to the pediatric emergency department of the hospital. She had a documented history of growth retardation, with a height of 148 cm (<3rd percentile) and a weight of 38 kg (<3rd percentile) according to age- and sex-matched reference values. She had a history of recurrent kidney stones. Patient's complaints were sudden, severe pain in the left flank and gross hematuria that developed over the preceding 12 hours.

Upon admission, vital signs were appropriate for late adolescence. Body temperature was 36.3 °C, heart rate was 104 bpm, blood pressure was 110/60 mmHg, and respiratory rate was 30 breaths/min. Physical examination revealed a mildly distressed patient who appeared slightly dehydrated but otherwise non-toxic. Palpation of the left flank produced tenderness, while the midline spine was non-tender. Abdominal assessment demonstrated localized tenderness, with rebound and guarding noted in the left lower quadrant of the abdomen. No abnormalities were observed in the remaining systems.

The patient's blood tests, peripheral blood smear and urinalysis results were summarized in Table 1.

Arterial blood gas analysis demonstrated metabolic acidosis with a normal anion gap (pH: 7.21, HCO_3^-: 15.7 mmol/L, pCO_2: 41.3 mmHg). The calculated serum anion gap was 9 mEq/L. Urinary pH was persistently alkaline (pH: 8.0), and the urine anion gap was positive, supporting impaired renal acid excretion. Urinary calcium excretion was elevated at 4.9 mg/kg/day. Urine culture was negative, and inflammatory markers normalized during follow-up, excluding urinary tract infection.

An anteroposterior abdominal radiograph was obtained as part of the initial evaluation to assess for radiographic signs suggestive of an acute abdomen and to exclude gross abdominal pathology (e.g, appendicitis, complicated acute cholecystitis, ectopic pregnancy, diabetic ketoacidosis, sickle cell crisis, noncomplicated hepatobiliary disease and non-complicated acute cholecystitis, gallstones, viral gastroenteritis/viral syndrome, Henoch-Schönlein purpura, constipation, mononucleosis) (Figure 1).

Ultrasonography revealed the presence of bilateral medullary nephrocalcinosis, characterized by calcification in the medullary regions of both kidneys, in addition to calyceal stones with an average diameter of 1 centimeter.

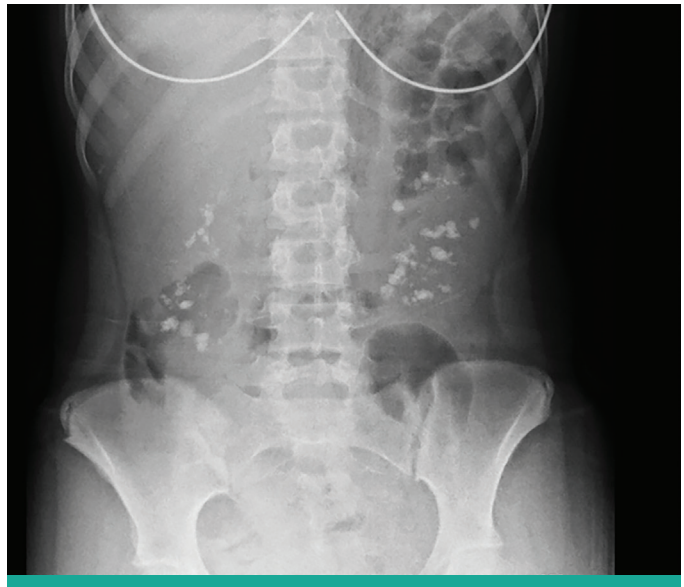

Figure 1. Anteroposterior abdominal radiograph taken at the patient's initial presentation (medullary nephrocalcification in the right and left renal fossae)

Table 1. The patient's blood tests, peripheral blood smear and urinalysis results

Test category	Test name	Result	Unit	Pediatric reference range	Observation
Blood tests	Hemoglobin	11.8	g/dL	11.5-15.5	Within range
	WBC	7.66	x10^9/L	4.0-10.5	Within range
	Platelets	355	x10^9/L	150-450	Within range
	Urea	8.3	mmol/L	2.5-7.1	Slightly high
	Creatinine	58	µmol/L	27-88	Within range
	Uric acid	155	µmol/L	120-330	Within range
	CRP	105	mg/L	<10	Significantly high
	Sodium	138	mmol/L	135-145	Within range
	Chloride	113	mmol/L	98-107	High
	Potassium	3.9	mmol/L	3.5-5.0	Within range
	Phosphorus	1.26	mmol/L	1.29-2.26	Slightly low
	Calcium	2.10	mmol/L	2.12-2.62	Slightly low
	Magnesium	0.95	mmol/L	0.7-0.9	Slightly high
	ALP	80	U/L	130-560 (during growth)	Low
Peripheral blood smear	PNL	62.5	%	25-60	Slightly high
	Lymphocytes	27.1	%	30-65	Slightly low
Urinalysis	Appearnce	Turbid	-	Clear	Abnormal
	Color	Red	-	Yellow	Abnormal
	pH	8.0	-	5.0-8.0	Alkaline
	Nitrite	Negative	-	Negative	Normal
	Density	1010	-	1003-1030	Normal
	Protein	+++	Dipstick	Negative	Positive
	Glucose	Negative	-	Negative	Normal
	Ketone	Negative	-	Negative	Normal

WBC: White blood cell, CRP: C-reactive protein, PNL: Percutaneous nephrolithotomy, ALP: Alkaline phosphatase

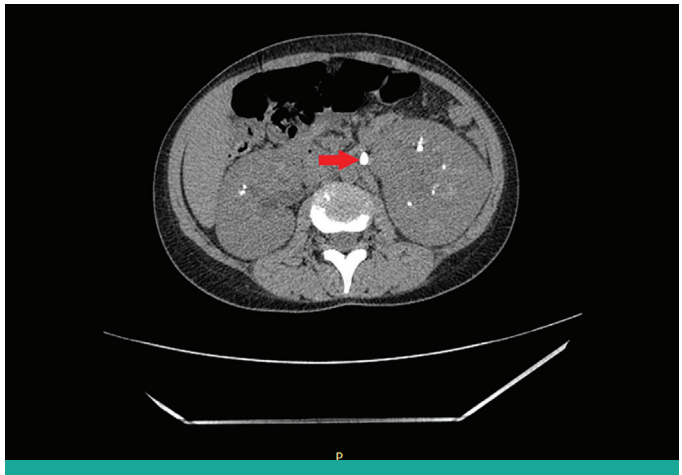

Figure 2. Calcification in the renal medulla together with mixed nephrocalcinosis and proximal left ureteral stone (red arrow)

At the left uteropelvic junction, a stone sitting proximally to the ureter with a diameter of 17 mm is observed, grade 3 hydronephrosis is observed in the left kidney.

Non-contrast CT excluded pyelonephritis, abscess formation, or other infectious complications and confirmed mild left-sided hydroureter. The findings indicated the presence of medullary nephrocalcinosis, a 17 mm calculus located in the proximal left ureter, and mild hydroureter on the left side (Figure 2). The patient underwent ureteroscopic stone extraction without perioperative complications. Post-procedural follow-up demonstrated resolution of pain and hematuria.

Following initiation of alkali therapy, the patient showed improvement in metabolic acidosis, normalization of serum bicarbonate levels, and remained clinically stable without recurrence of hematuria or flank pain during follow-up.

As a result, the case was characterized by inappropriately alkaline urine in the setting of hyperchloremic normal anion gap metabolic acidosis and growth retardation. Based on these findings, a diagnosis of dRTA was established, and

oral sodium bicarbonate (3 mEq/kg/day) and potassium citrate therapy were initiated.

Discussion

Nephrocalcinosis has a multifactorial etiology. It can arise secondary to dRTA but may also result from hypercalcemia, hyperoxaluria, or exposure to certain medications such as furosemide, vitamin D analogues, amphotericin B, ifosfamide, and lithium. In some instances, however, nephrocalcinosis remains idiopathic (5).

dRTA is defined by the presence of persistently alkaline urine, even in the context of hypokalemic, hyperchloremic metabolic acidosis (6). This pathology arises from a primary defect in the urinary acidification process, specifically the impaired excretion of protons in the collecting ducts (7). The type A intercalated cells within the connecting tubules and collecting ducts exhibit insufficient proton excretion as ammonium, which is essential for the elimination of ammonia, the acidification of urine, and the production of new bicarbonate (8,9).

The net acid excretion is quantified by the total of urinary ammonium and titratable acidity, with bicarbonate being subtracted from this sum (10). In clinical practice, urinary phosphate often serves as an indicator of titratable acidity, while urinary bicarbonate is typically disregarded if the urine pH is below 6.5. The function of type A intercalated cells, along with overall acid excretion, generally increases in response to systemic acidosis (11).

Patients diagnosed with dRTA frequently exhibit signs of hyperchloremic metabolic acidosis with a normal anion gap, often accompanied by hypokalemia. In pediatric and adolescent populations, dRTA may present as growth retardation, failure to thrive, kidney stones, rickets, or nephrocalcinosis, which are often the initial manifestations of the condition. Furthermore, polyuria may arise due to impaired urine concentration resulting from hypercalciuria, hypokalemia, or nephrocalcinosis (12-14). Based on the presence of hyperchloremic normal anion gap metabolic acidosis, persistently alkaline urine, positive urine anion gap, hypercalciuria, nephrocalcinosis, and growth retardation, dRTA was diagnosed.

During childhood, nephrocalcinosis usually presents in the medullary rather than cortical region (15). dRTA is often associated with significant hypercalciuria, predisposing to kidney stones, bone demineralization, nephrocalcinosis, and potentially progressing to chronic kidney disease requiring dialysis in adolescence or early adulthood (16). The patient exhibited nephrocalcinosis, ureteral calculi, hyperchloremic metabolic acidosis characterized by a normal anion gap, recurrent episodes of dehydration suggestive of polyuria, and growth retardation.

Conclusion

dRTA is a rare metabolic disorder that can lead to serious clinical complications. It should be included in the pediatric differential diagnosis showing marked growth retardation, tubular dysfunction, polyuria, refractory rickets, and hypokalemic metabolic acidosis.

A continuum appears to exist linking recurrent nephrolithiasis, nephrocalcinosis, and distal renal tubular acidosis. Diagnosis is established through clinical suspicion supported by characteristic laboratory findings. Clinicians are advised to pursue further evaluation in children with recurrent urinary tract infections, renal stone formation, or growth retardation due to diagnostic challenges at early stages.

dRTA should be considered in adolescents presenting with recurrent nephrolithiasis, nephrocalcinosis, growth retardation, and hyperchloremic metabolic acidosis.Early diagnosis and appropriate alkali therapy are essential to prevent long-term renal damage.

Ethics

Informed Consent: This case report details an 18-year-old female patient diagnosed with nephrocalcinosis, for whom written informed consent was procured prior to the preparation of the case presentation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.A., E.N.A.Ö., P.E., Concept: D.A., E.N.A.Ö., P.E., K.Ö., Design: D.A., E.N.A.Ö., P.E., K.Ö., Data Collection or Processing: D.A., E.N.A.Ö., P.E., Analysis or Interpretation: D.A., K.Ö., Literature Search: D.A., E.N.A.Ö., P.E., K.Ö., Writing: D.A., K.Ö.

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

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