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Original Article INTERNAL MEDICINE

Real-world immunosuppressive treatment patterns and disease progression in systemic sclerosis-associated interstitial lung disease

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ABSTRACT

OBJECTIVE: Interstitial lung disease (ILD) is a frequent and prognostically important manifestation of systemic sclerosis (SSc), with a substantial proportion of patients developing progressive pulmonary fibrosis (PPF) despite immunosuppressive treatment. The objective of the study was to compare real-world lung function trajectories and the occurrence of progressive PPF among patients with SSc-ILD receiving commonly used immunosuppressive therapies.

METHODS: We conducted a retrospective single-center cohort study of adult patients with SSc-ILD receiving immunosuppressive therapy, assessing longitudinal changes in pulmonary function and PPF according to international guideline-based criteria.

RESULTS: Among 80 patients with SSc-ILD, mycophenolate mofetil (MMF) was the most frequently used immunosuppressive agent across both first-line and subsequent treatment lines. Despite its extensive use, MMF was associated with relatively low rates of progressive PPF (18.2% in first-line and 25% in second/third-line use) and largely stable forced vital capacity over time, with only modest decline in diffusing capacity for carbon monoxide. Cyclophosphamide (CYC) showed transient improvements in lung function at 1 year, followed by stabilization. In contrast, first-line azathioprine (AZA) use was associated with the highest PPF proportion (55.6%).

CONCLUSION: In this real-world SSc-ILD cohort, MMF emerged as the most frequently used backbone therapy after the scleroderma lung study II, with generally stable lung function trajectories observed during follow-up. Higher proportions of progressive PPF were observed among AZA-treated patients, whereas CYC was mainly used as an induction therapy in selected cases. Rituximab, administered alone or in combination with MMF, was more frequently used in patients with progressive or treatment-refractory disease and was associated with relatively low progression proportions in this cohort. These findings reflect treatment patterns and clinical trajectories observed in routine clinical practice rather than comparative treatment efficacy.

Keywords: Interstitial lung disease; progressive pulmonary fibrosis; systemic sclerosis; treatment.

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Systemic sclerosis (SSc) is an autoimmune disease characterized by microvascular dysfunction, immune activation, and progressive fibrosis of the skin and internal organs [1]. Pulmonary involvement is common and clinically important. The presence of interstitial lung disease (ILD) can be detected on high-resolution computed

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tomography (HRCT) in approximately 70–80% of patients, and 30–40% of these patients subsequently develop clinically significant disease [2–4]. ILD is considered an important cause of morbidity and mortality, contributing to approximately 20–40% of cases of SSc-related mortality [5]. Early development of ILD, often within the 1st few years of disease onset, is associated with a greater likelihood of progression and poorer long-term outcomes [6].

A subset of patients experience progressive pulmonary fibrosis (PPF), defined by functional decline, radiographic progression, or the worsening of respiratory symptoms despite treatment [7]. Recent observational cohorts report PPF in approximately 20–30% of individuals with SSc-ILD, although estimates vary depending on baseline severity, disease duration, and treatment exposure [8]. As progression exerts a considerable effect on symptoms, lung function, and survival, the identification of therapeutic approaches that may help stabilize the disease course remains a central aspect of clinical care.

The cornerstone of treatment for SSc-ILD is immunosuppressive therapy. Cyclophosphamide (CYC) was the first agent evaluated in randomized controlled trials and demonstrated modest improvements in forced vital capacity (FVC). However, its long-term use is limited by toxicity [9]. Mycophenolate mofetil (MMF) subsequently emerged as the preferred first-line option in international recommendations, due to its comparable efficacy and a more favorable safety profile. Notwithstanding, a proportion of patients continue to demonstrate a decline in response to MMF or CYC, necessitating the exploration of alternative therapeutic modalities [10].

Other immunosuppressive agents, such as azathioprine (AZA) and methotrexate (MTX), remain in use in selected situations, although evidence supporting their effectiveness in ILD is limited. Biologic therapies such as rituximab (RTX) and tocilizumab (TCZ) have demonstrated favorable outcomes in specific patient groups [11, 12]. Still, results across studies have been heterogeneous, and their place in routine practice continues to evolve. Current guidelines generally endorse MMF as initial therapy and suggest considering CYC, RTX, or TCZ in patients with progressive disease or intolerance to first-line treatment [10, 13].

Although clinical trials provide essential information on efficacy, real-world data are required to understand treatment performance across a broader, more heterogeneous patient population encountered in practice. Comparative evidence on commonly used immunosuppressive regimens in everyday care remains limited, particularly regarding longitudinal changes in FVC and diffusing capacity for carbon monoxide (DLCO) and the frequency of PPF.

Highlight key points

- In this real-world SSc-ILD cohort, MMF was the most frequently used immunosuppressive therapy and was associated with sustained lung function stability and low rates of progressive PPF across treatment lines.
- CYC provided modest short-term improvement followed by stabilization, consistent with its role as an induction rather than maintenance strategy.
- RTX, alone or combined with MMF, showed the lowest progression rates, supporting its use as an effective escalation option in progressive or treatment-refractory SSc-ILD.

In this retrospective cohort study, we examine real-life outcomes in patients with SSc-ILD receiving immunosuppressive therapies frequently used in routine practice, including MMF, CYC, AZA, MTX, RTX, and TCZ. The longitudinal spirometric trajectories and the occurrence of PPF are evaluated across treatment groups. Because a substantial proportion of our cohort received MMF and preliminary observations suggested variability in progression patterns across regimens, this analysis aims to provide complementary real-world information relevant to contemporary management of SSc-ILD.

MATERIALS AND METHODS

Study Design and Patients

This retrospective, single-center cohort study was conducted at the Department of Rheumatology, Gazi University Hospital (Ankara, Turkiye). This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for this study was obtained from the Ethics Committee of Gazi University on October 22, 2024. Patients aged ≥18 who fulfilled the 1980 classification criteria for SSc [14] and the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for SSc [15] and were followed between January 2010 and July 2025 were screened for eligibility. A total of 124 patients with SSc-ILD confirmed by HRCT were screened, of whom 88 receiving immunosuppressive therapy were eligible for inclusion. Eight patients were excluded from the study because the initiation dates of their immunosuppressive treatment could not be verified.

Demographic, Clinical, and Laboratory Features

Demographic data and disease duration (calculated from the time of first non-Raynaud's symptom) were recorded for all patients. The disease subset was classified as diffuse or limited cutaneous SSc according to the criteria established by LeRoy et al. [16]. The presence of esophageal involvement was considered to be evident in patients with a documented history of gastroesophageal reflux disease and/or dysphagia. The term "scleroderma renal crisis" was defined as new-onset acute kidney injury with hypertension, not attributable to other causes. Digital ischemic complications included the presence of digital ulcers, pitting scars, cases of auto-amputation, and instances of pulp atrophy. Serological profiles, including relevant autoantibodies, were collected from patient records.

Data on immunosuppressive therapies used to manage SSc-ILD were systematically recorded, including the specific agents administered and the treatment line in which each was initiated. The distribution and sequencing of immunosuppressive regimens across treatment lines were visualized using a Sankey diagram. For all patients, pulmonary function measurements – FVC and DLCO – were documented, when applicable, at three time points: Before treatment initiation, at the 1st year of therapy, and at the most recent available assessment.

The progressive PPF was defined in accordance with the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association clinical practice guidelines employed in this study. As the presence of at least two of the following three criteria occurred within the past year: (i) Either an absolute decline in FVC >5% is predicted, or an absolute decline in DLCO >10% is predicted; (ii) worsening respiratory symptoms; radiological evidence of disease progression [17]. Using this definition, progression events were evaluated and documented for each immunosuppressive agent, based on whether patients experienced PPF during therapy.

Statistical Analysis

Descriptive statistics were used to summarize patients' characteristics. Categorical variables were presented as absolute frequencies and percentages. Continuous and normally distributed variables were expressed as mean (±standard deviation [SD]), and constant and not normally distributed variables as median (and interquartile range). The normality of continuous variables was evaluated using the Shapiro–Wilk test and confirmed by visual inspection of histogram plots.

For each immunosuppressive agent, longitudinal pulmonary function data were collected, and FVC% predicted, and DLCO % predicted values were recorded – when available – at three predefined time points: Baseline (before treatment initiation), the 1st year of therapy, and the last available follow-up measurement. Changes in FVC and DLCO across these time points were visualized separately for MMF, AZA, CYC, and RTX using box-and-whisker plots with overlaid jittered individual data points to illustrate both central tendency and within-group variability.

PPF events were quantified for each immunosuppressive agent and treatment line. For each treatment course, the proportion of patients meeting the predefined PPF criteria was calculated, and progression frequencies were expressed as percentages. These analyses were descriptive; no inferential statistical testing was performed between drug groups, as the objective was to characterize the distribution of PPF rates across therapeutic categories rather than to compare their efficacy. The resulting proportions of progression and non-progression were visualized using horizontal bar charts.

Notched box-and-whisker plots and horizontal bar charts were generated using R software (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria) with RStudio interface. Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics software (version 31.0; IBM Corp., Armonk, NY, USA) with $p<0.05$ considered significant.

RESULTS

Clinical Characteristics of SSc Patients

The study comprised 80 patients with SSc-ILD, with a mean age of 54.55 years (±12.6) and a mean age at SSc onset of 45.43 years (±13.67). The majority of these patients were female, and 70% of them had been diagnosed with diffuse cutaneous SSc. At baseline, HRCT evaluation revealed that fibrotic non-specific interstitial pneumonia (NSIP) was the predominant radiological pattern, observed in 37 patients (46.3%), followed by cellular NSIP in 29 patients (36.3%). A usual interstitial pneumonia (UIP)-like pattern was identified in 13 patients (16.3%), while organizing pneumonia (OP) was uncommon (1 patient, 1.3%). Baseline pulmonary function tests demonstrated a mean FVC of 83.16% predict-

ed and a mean DLCO of 63.9% predicted, indicating a moderately reduced diffusing capacity despite preserved lung volumes at study entry. Baseline characteristics of the SSc-ILD cohort were given in Table 1.

As shown in Figure 1, the distribution of first-, second, and third-line immunosuppressive therapies is illustrated in 80 patients with SSc-ILD. Initial treatment regimens comprised MMF (n=33), CYC (n=36), AZA (n=9), and MTX (n=2). During the follow-up period, 51 patients received MMF as second-line therapy, followed by AZA (n=12), CYC (n=2), RTX (n=4), TCZ (n=2), and RTX+MMF (n=5). In the third-line setting, MMF remained the most frequently used agent (n=54), while additional transitions included AZA (n=9), RTX+MMF (n=6), RTX (n=4), TCZ (n=2), TCZ+MMF (n=1), and CYC (n=2). The Sankey diagram in Figure 1 illustrates the treatment flows across lines of therapy and the number of patients transitioning between each regimen.

In our first-line treatment cohort of patients with SSc-ILD, a clear shift in therapeutic strategy was observed over time, reflecting the impact of landmark clinical trials. Before the scleroderma lung study (SLS) II (n=30), CYC was the predominant initial therapy, prescribed in 18 patients (60%), followed by AZA in 7 (23.3%), MMF in 4 (13.3%), and MTX in 1 (3.3%). In contrast, after the SLS II (n=50), MMF emerged as the most frequently used first-line agent, initiated in 29 patients (58%), while CYC was used in 18 (36%), AZA in 2 (4%), and MTX in 1 (2%). Overall, these findings demonstrate a paradigm shift from CYC-based induction toward preferential use of MMF as first-line therapy in SSc-ILD, consistent with evolving evidence supporting comparable efficacy with improved tolerability.

Figure 2 summarizes the changes in FVC% and DLCO% at baseline, 1-year, and last follow-up across treatment groups. In the MMF group, FVC% remained relatively stable over time, while DLCO% showed a modest decline. Patients treated with AZA exhibited higher FVC% values at 1 year, with DLCO% remaining within a similar range across visits. In the CYC group, both FVC% and DLCO% showed slight increases at 1 year, followed by stable values at the last follow-up. RTX-treated patients demonstrated higher FVC% and DLCO% values at 1 year compared with baseline, with modest reductions thereafter.

Given that MMF was the most frequently used immunosuppressive agent in the cohort, a subgroup analysis was performed by separating patients into first-line and second/third-line MMF users (Fig. 3). In first-line MMF users, median FVC% values were 88.5% at baseline, 90.1% at 1 year, and 83.7% at the last visit, while median DLCO% values were 68.3%, 69.6%, and 64.0%, respectively. Among patients receiving MMF as second- or third-line therapy, median FVC% values were 81.5% at baseline, 81.3% at 1 year, and 79.2% at the last visit; corresponding DLCO% values were 64.4%, 60.1%, and 57.8%. These plots display individual measurements together with group medians across time points.

Table 1. Baseline demographic, clinical, serological, and pulmonary characteristics of patients with systemic sclerosis-associated interstitial lung disease included in the study (n=80)

Feature	Value
Age, years, mean (SD)	54.55±12.6
Age at SSc onset, years, mean (SD)	45.43±13.67
Sex, female, (%)	93.8
Diffuse SSc, (%)	70
Anti-topoisomerase 1 antibody, (%)	72.5
Anti-centromere antibody, (%)	2.5
Clinical involvements (ever) (%)	
Raynaud's phenomenon	96.3
Digital ulcers	41.3
Telangiectasia	58.8
Arthralgia	75
Muscle weakness	33.8
Esophageal dysphagia	43.8
Pulmonary hypertension	6.25
Scleroderma renal crisis	3.8
Pulmonary characteristics	
Baseline HRCT patterns (%)	
Cellular NSIP	36.3
Fibrotic NSIP	46.3
UIP	16.3
OP	1.3
Baseline FVC% predicted, mean (SD)	83.16±14.59
Baseline DLCO % predicted, mean (SD)	63.9±15.11

Data are presented as mean±SD or number (percentage), as appropriate. Clinical involvements indicate features documented at baseline. HRCT patterns were classified as cellular NSIP, fibrotic NSIP, UIP, or OP. FVC and DLCO are expressed as percentages of predicted values. SD: Standard deviation; SSc: Systemic sclerosis; HRCT: High-resolution computed tomography; NSIP: Non-specific interstitial pneumonia; UIP: Usual interstitial pneumonia; OP: Organizing pneumonia; FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide.

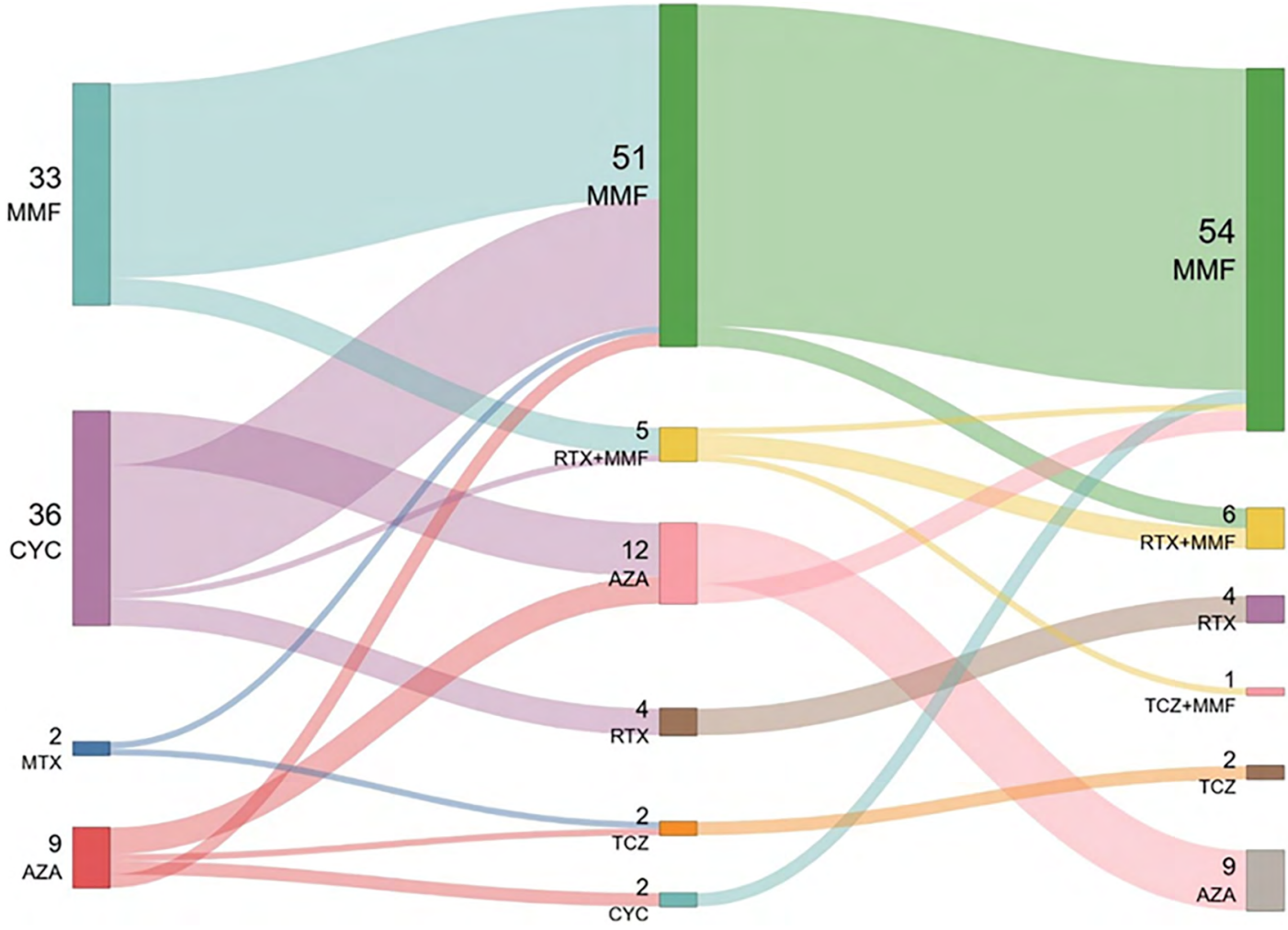

FIGURE 1. Sankey diagram illustrating treatment lines and patient transitions between immunosuppressive regimens in SSc-ILD. The left, middle, and right columns represent first-, second-, and third-line treatment regimens, respectively, in patients with systemic SSc-ILD. Each flow represents the transition of patients from one treatment line to the next. The width of each flow is proportional to the number of patients transitioning between regimens, while the numbers displayed within each box indicate the total number of patients (n) receiving that therapy at each line. Different colors represent individual therapeutic agents or combination regimens.

MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; AZA: Azathioprine, MTX: Methotrexate; RTX: Rituximab; TCZ: Tocilizumab; SSc-ILD: Sclerosis-associated interstitial lung disease.

A total of 12 patients received RTX, either alone or in combination with MMF, as second- or third-line therapy. The mean baseline FVC and DLCO values were 79.2%±13.27 and 56.5%±16.83 of predicted, respectively. HRCT patterns included cellular NSIP in 33.3%, fibrotic NSIP in 41.7%, and a UIP-like pattern in 25% of patients. All patients had previously received at least one conventional immunosuppressive therapy (MMF or CYC) before RTX initiation. RTX was mainly introduced due to progressive PPF in MMF-treated patients or after completion of CYC therapy because of concerns regarding cumulative toxicity; in some cases, fertility considerations also contributed to the transition from CYC to RTX.

The median follow-up duration under each treatment regimen was also assessed. Among all patients receiving MMF at any treatment line, the median follow-up duration was 42.5 months, while it was 28.2 months in the subgroup of 29 patients who initiated MMF as first-line therapy and continued without switching. The median duration of CYC exposure was 11.1 months. Among patients receiving AZA at any treatment line, the median

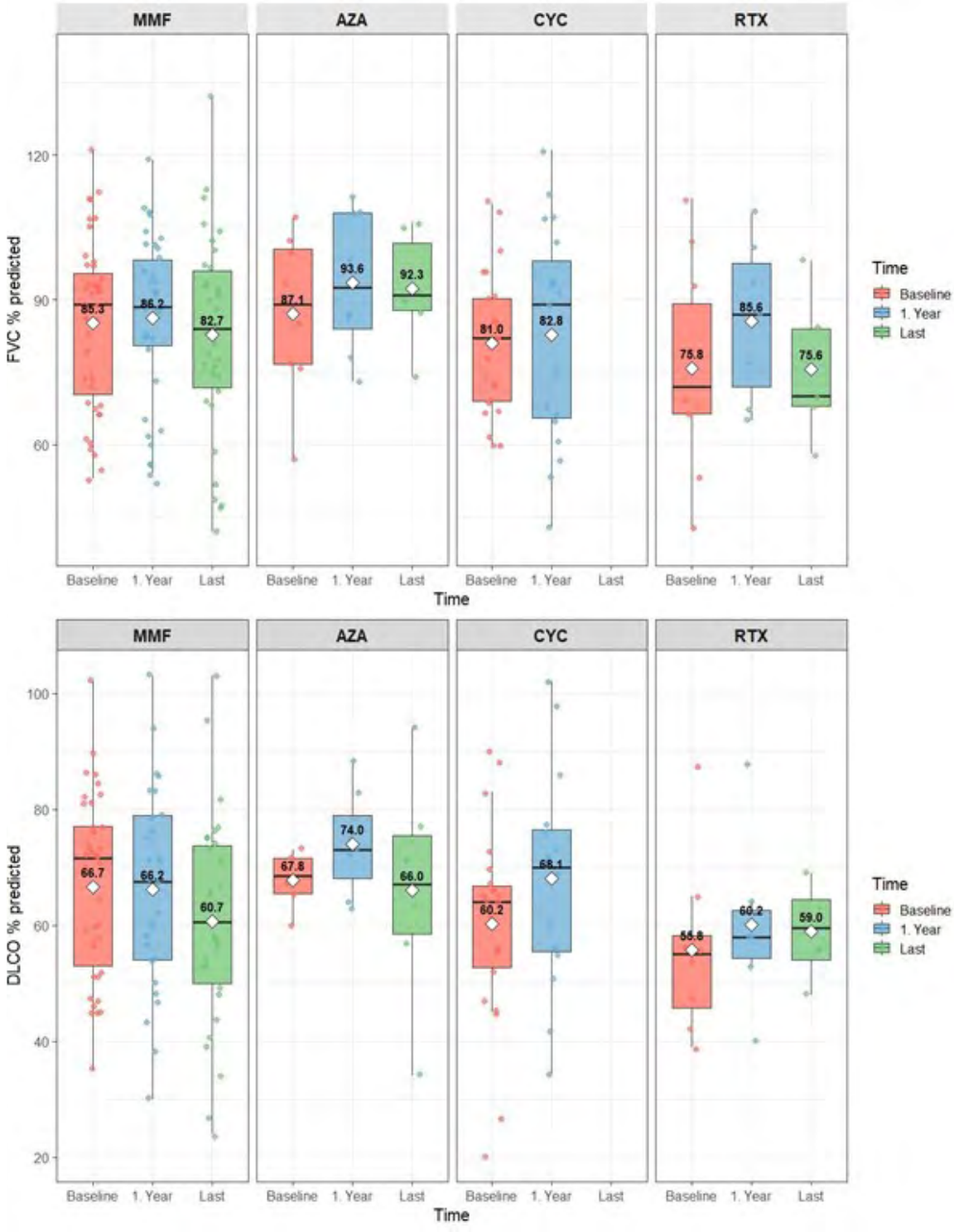

FIGURE 2. Longitudinal changes in FVC% predicted and DLCO% predicted across treatment groups. Changes in (FVC% predicted) and (DLCO% predicted) are shown at baseline, 1-year follow-up, and the last available follow-up visit across treatment groups (MMF, AZA, CYC, and RTX). Upper panels illustrate FVC% predicted, whereas lower panels show DLCO% predicted. Individual patient measurements are represented by dots, while the central markers represent group mean values at each time point. These plots illustrate the longitudinal trajectories of pulmonary function parameters during follow-up in patients receiving different immunosuppressive therapies.

MMF: Mycophenolate mofetil; AZA: Azathioprine; CYC: Cyclophosphamide; RTX: Rituximab; FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide.

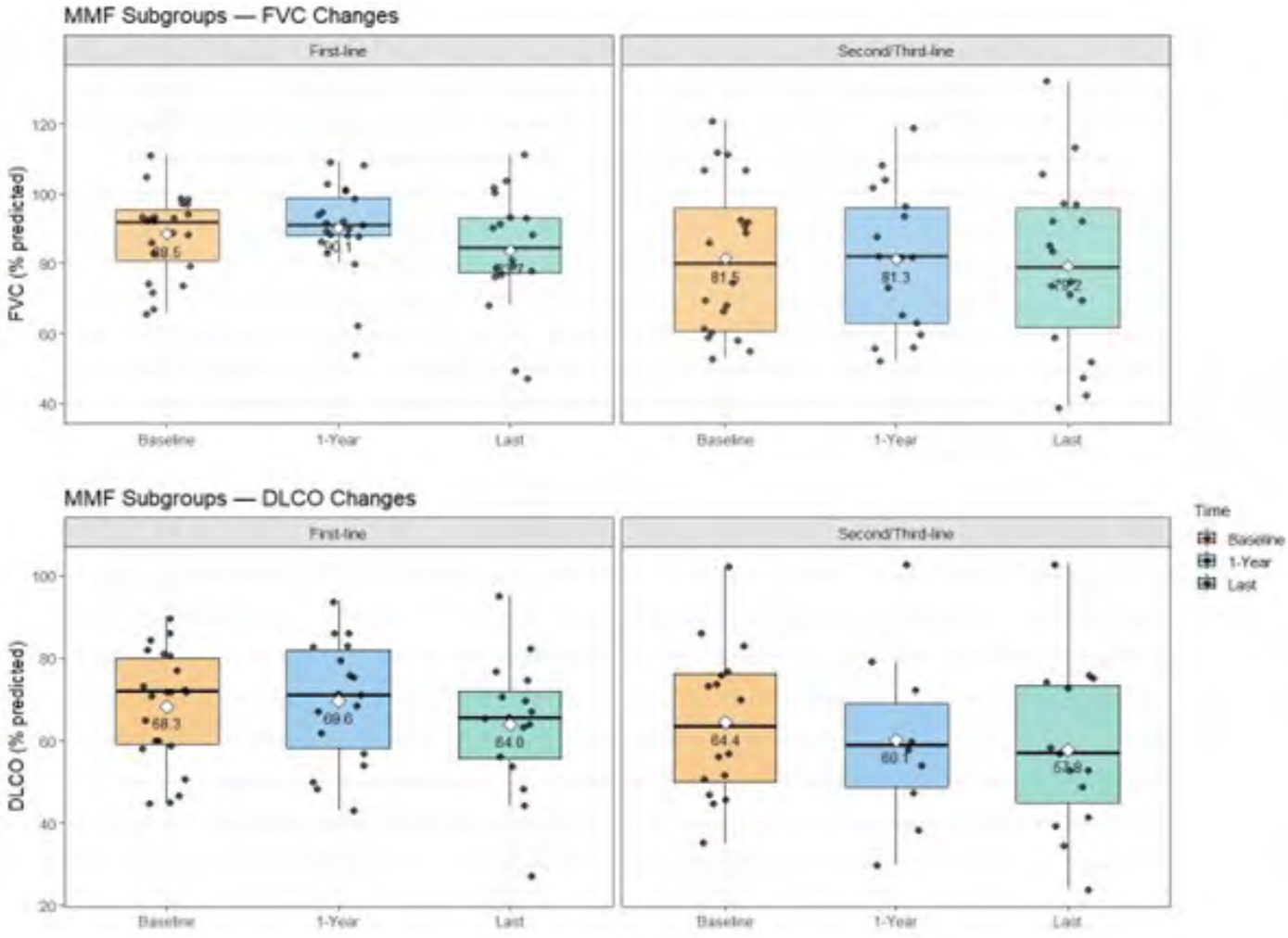

FIGURE 3. Longitudinal changes in FVC% predicted and DLCO% predicted in MMF-treated patients stratified by treatment line. Changes in FVC% predicted (upper panels), and DLCO% predicted (lower panels) are shown at baseline, 1-year follow-up, and the last available follow-up visit in patients treated with MMF. Patients are stratified according to whether MMF was used as first-line therapy or as second- or third-line therapy. Individual patient measurements are displayed as dots, while central markers represent group mean values at each time point, illustrating longitudinal pulmonary function trajectories according to treatment sequencing.

MMF: Mycophenolate mofetil; FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide.

follow-up duration was 64 months, whereas it was 28.4 months in the RTX-treated subgroup.

As shown in Figure 4, the proportion of patients who developed progressive PPF varied across treatment groups. Among first-line AZA users, 55.6% met progression criteria, compared with 37.5% among second-line AZA users. Progression occurred in 21.1% of patients treated with CYC, 18.2% of first-line MMF users, and 25% of those receiving MMF as second- or third-line therapy. In patients treated with RTX (with or without MMF), progression was observed in 14.3%. When treatment groups were compared, no statistically significant differences in PPF rates were observed; however, patients receiving AZA had higher PPF proportions than those in the other treatment groups. The corresponding non-progression rates for each group are shown in the stacked bar plot.

In addition to immunosuppressive therapies, three patients in the cohort received antifibrotic therapy (nintedanib) during follow-up as adjunctive treatment alongside immunosuppressive regimens.

DISCUSSION

This well-defined SSc-ILD cohort provides insight into ILD-directed treatment strategies and progression patterns in routine clinical practice. Most patients received

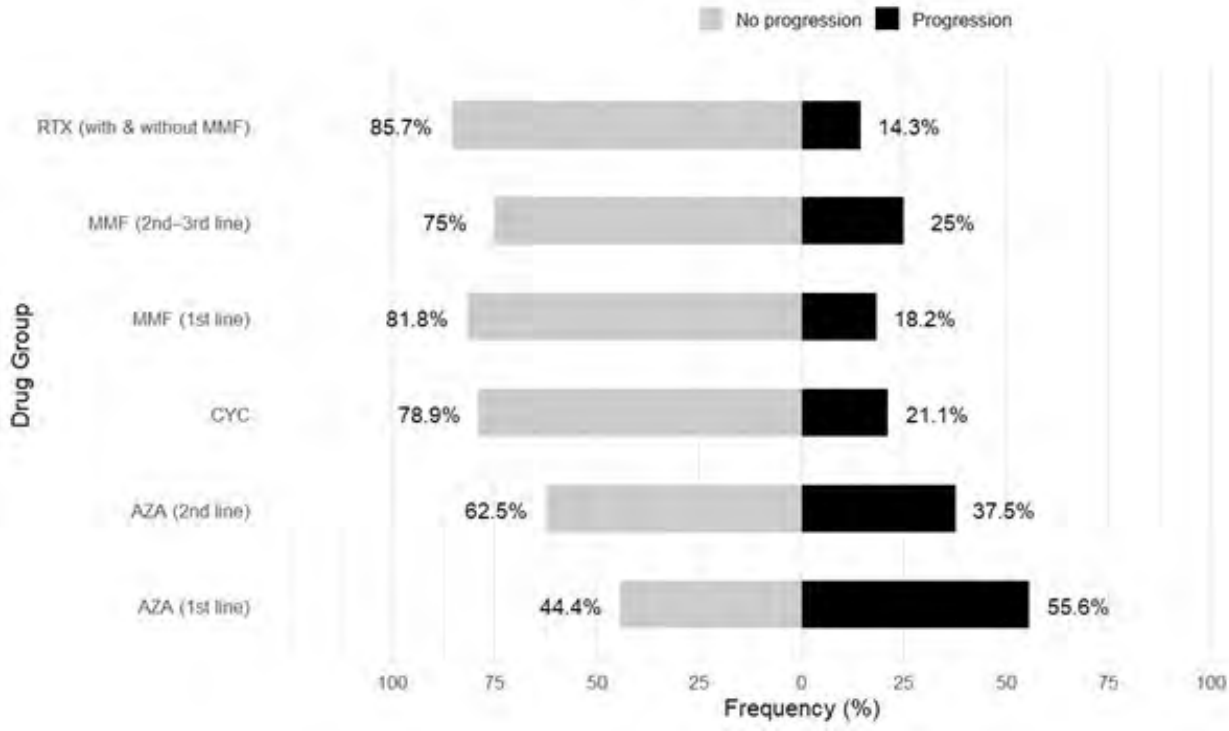

Figure 4. Distribution of PPF and non-progression across treatment groups. Stacked bar charts illustrate the proportion of patients who developed PPF and those without progression during follow-up across different treatment groups. Percentages represent the relative frequency of progression within each treatment group. Progression status was determined according to the predefined study criteria for PPF, based on longitudinal clinical and pulmonary function assessments during follow-up.

RTX: Rituximab; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; AZA: Azathioprine; PPF: Progressive pulmonary fibrosis.

MMF or CYC as first-line therapy, with MMF also remaining the most used agent in second and third lines. Patients treated with MMF frequently demonstrated a relatively stable disease course during follow-up. In this cohort, the proportion of progression among MMF-treated patients appeared lower than that observed in some other treatment groups; however, these observations should be interpreted as descriptive findings rather than evidence of comparative treatment efficacy. In patients with progressive PPF, RTX was used as an escalation therapy in selected cases, reflecting its emerging role as a therapeutic option in clinical practice.

SSc-ILD is a significant contributing factor to the morbidity and mortality associated with SSc, accounting for almost one-third of deaths related to the disease [1, 18]. It also represents an important cause of functional decline, impaired quality of life, and healthcare utilization [19]. Early radiographic involvement is common, and although lung function may appear relatively preserved at diagnosis [20], a substantial proportion of patients experience progression over time, often despite immunosuppressive therapy. Real-world data are essential to capture the heterogeneity of treatment practices, longitudinal trajectories of lung function, and the frequency of PPF across commonly used regimens – particularly because clinical trials typically include highly selected patient populations. In this context, the present study provides a comprehensive real-life evaluation of immunosuppressive therapies used for SSc-ILD over 15 years in a tertiary rheumatology Centre, detailing longitudinal changes in FVC and DLCO and quantifying PPF across therapeutic categories.

As in previous cohorts, the majority of patients were female and anti-topoisomerase I-positive [3], with fibrotic NSIP as the predominant HRCT pattern [21]. These features align with established SSc-ILD risk factors and reflect a patient population at meaningful risk for disease progression. Immunosuppressive use was common, as expected for a cohort enriched with fibrotic ILD. MMF and CYC were the most frequently administered first-line agents, whereas transitions to MMF or biologic therapies occurred more often in treatment-refractory cases [22]. This distribution parallels contem-

porary treatment paradigms, where MMF has replaced CYC as the preferred initial therapy due to its more favorable safety profile and comparable efficacy.

MMF has emerged as the cornerstone of SSc-ILD management. Evidence from randomized controlled trials – including SLS II – confirmed that MMF improves FVC similarly to CYC, but with markedly lower rates of leukopenia, thrombocytopenia, and treatment discontinuation [23]. Accordingly, both the 2023 ACR/CHEST guideline and EULAR recommendations strongly endorse MMF as a first-line agent for SSc-ILD [10, 24]. Real-world analyses, including Japanese claims data, also demonstrate increasing MMF utilization and sustained long-term treatment rates, reinforcing its tolerability in routine practice [25]. Our findings reflect this shift in clinical practice. In our cohort, MMF accounted for the highest proportion of first-line therapy, and longitudinal FVC and DLCO values generally remained stable among patients receiving MMF, particularly among those who initiated treatment earlier in the disease course. In addition, the proportion of PPF among MMF users was lower than or comparable to that observed in other treatment groups, and notably much lower than that observed in AZA-treated patients. These observations are consistent with current guideline recommendations that position MMF as a preferred first-line therapy for SSc-ILD. In this real-world cohort, lung function trajectories among MMF-treated patients were generally stable during follow-up.

In contrast, AZA, despite historical use in SSc, is no longer recommended for the treatment of ILD. Evidence supporting AZA in PPF is limited, and several observational studies suggest inferior performance compared with MMF or CYC [10]. In our cohort, AZA-treated patients demonstrated a relatively higher proportion of PPF compared with other treatment groups. Given the limited evidence supporting the use of AZA in SSc-ILD, the relatively higher progression rates observed in AZA-treated patients in this cohort may reflect differences in treatment selection, disease characteristics, or historical prescribing practices before the widespread adoption of MMF. These findings further reinforce the international trend of decreasing utilization of AZA for SSc-ILD.

CYC remains an evidence-based therapeutic option and has demonstrated benefits on FVC in randomized trials [9]. However, its use is constrained by cumulative toxicity and is appropriate for induction rather than maintenance. In our cohort, patients receiving CYC demonstrated modest increases in lung function parameters at 1 year, while PPF occurred in approximately 21% of patients during follow-up. These findings are broadly consistent with prior observations that CYC is often used as an induction therapy in patients with more aggressive disease phenotypes.

In recent years, biologic therapies, particularly RTX and TCZ, have become increasingly prominent in the management of SSc-ILD [10, 24]. RTX has demonstrated consistent enhancement in FVC across open-label studies, meta-analyses, and comparative trials, including RECITAL and DESIRES [26, 27]. TCZ has been shown to have a significant effect on stabilizing lung function in early diffuse SSc cohorts and is now FDA-approved for SSc-ILD [28]. An important development has been the emergence of evidence supporting combination therapy, particularly MMF plus RTX, which targets complementary immune pathways and has demonstrated encouraging results in preliminary trials (EVER-ILD) and multicenter observational cohorts (MycRiSSc) [29, 30]. These analyses suggest that combination therapy may offer superior improvement in FVC, particularly in patients with SSc-ILD. The findings of our study are in concordance with these results. RTX, whether administered alone or in combination with MMF, exhibited the lowest PPF proportions (14.3%) in the present cohort, despite its utilization predominantly in patients with more severe or treatment-refractory disease. This pattern may indicate a potential association between RTX use and relatively lower progression proportions in this cohort; however, causal inferences cannot be drawn from this observational analysis. These findings are consistent with current guideline recommendations that consider RTX a reasonable escalation or adjunctive option in patients with progressive SSc-ILD. Although our cohort was not powered to evaluate formal comparative efficacy, the observed pattern – low progression despite uses in advanced disease – reinforces the emerging role of B-cell-directed therapy.

The differences observed in the median follow-up duration across treatment groups likely reflect changes in therapeutic strategies and prescribing patterns over time rather than intrinsic differences between the agents. The relatively longer follow-up duration observed in patients receiving AZA probably reflects earlier treatment practices, in which AZA was frequently used as maintenance therapy following CYC induction. In contrast, the shorter follow-up duration under MMF therapy may be explained by the increasing adoption of MMF as first-line therapy after the publication of the SLS II, resulting in

a higher proportion of more recently diagnosed patients receiving MMF. The relatively shorter duration of CYC exposure is consistent with its use primarily as an induction therapy rather than a long-term maintenance agent. Similarly, RTX was generally introduced later in the disease course, often in patients with progressive or treatment-refractory disease, which likely contributed to the shorter observed follow-up duration in this subgroup.

Overall, the treatment patterns observed in this study broadly reflect contemporary clinical practice in SSc-ILD management. MMF was the most commonly used backbone therapy in this cohort, whereas AZA-treated patients exhibited relatively higher progression proportions. CYC was primarily used as an induction therapy in selected patients, and RTX-based approaches were more frequently used in cases with progressive or treatment-refractory disease. The PPF distribution across treatment groups in our cohort – particularly the relatively lower rates in MMF and RTX users – aligns with current guidelines and underscores the potential of early, appropriately selected immunosuppression to modify the trajectory of SSc-ILD.

Because this study was retrospective and descriptive in nature, the findings should not be interpreted as evidence of comparative treatment efficacy between therapeutic agents. Instead, the results reflect treatment patterns and clinical trajectories observed in a real-world cohort of patients with SSc-ILD. These observations should therefore be considered hypothesis-generating and may help inform future prospective comparative studies.

Our study has certain limitations, including its retrospective design, the absence of comparative statistical testing, and potential confounding by indication, in which more severe patients are more likely to receive biologic or combination therapies. Nonetheless, the cohort captures long-term, real-world treatment pathways, incorporates serial spirometric and radiological assessments, and reflects contemporary practice across multiple therapeutic eras. Importantly, the consistency of our findings with emerging guideline-based recommendations enhances the value of this data for informing clinical decision-making.

CONCLUSION

Our real-world analysis highlights the frequent use of MMF in SSc-ILD management, the relatively higher progression proportions observed among AZA-treated patients, the continued use of CYC as an induction option in selected cases, and the emerging role of RTX-based approaches, particularly in patients with progressive disease. The relatively lower proportions of PPF observed among MMF- and RTX-treated patients in this cohort are consistent with contemporary guideline-based treatment strategies and highlight the heterogeneity of treatment approaches and outcomes in real-world SSc-ILD care.

Ethics Committee Approval: The Gazi University Ethics Committee granted approval for this study (date: 22.10.2024, number: 17).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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

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REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685–99. [CrossRef]
2. Schurawitzki H, Stiglbauer R, Graninger W, Herold C, Pölzleitner D, Burghuber OC, et al. Interstitial lung disease in progressive systemic sclerosis: high-resolution CT versus radiography. Radiology 1990;176:755–9. [CrossRef]
3. Jung E, Suh CH, Kim HA, Jung JY. Clinical characteristics of systemic sclerosis with interstitial lung disease. arch rheumatol 2018;33:322–7. [CrossRef]
4. Steen VD, Conte C, Owens GR, Medsger TA Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994;37:1283–9. [CrossRef]
5. Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum 2014;44:208–19. [CrossRef]
6. Jaeger VK, Wirz EG, Allanore Y, Rossbach P, Riemekasten G, Hachulla E, et al. Incidences and Risk Factors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal EUSTAR Study. PLoS One 2016;11:e0163894. [CrossRef]
7. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718–27. [CrossRef]
8. Roeser A, Brillet PY, Tran Ba S, Caux F, Dhote R, Nunes H, et al. The importance of considering progression speed in systemic sclerosis-associated interstitial lung diseases: application of 2022 and 2024 clinical practice guidelines for progressive pulmonary fibrosis, a retrospective cohort study. Respir Res 2025;26:305. [CrossRef]

9. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66. [CrossRef]
10. Johnson SR, Bernstein EJ, Bolster MB, Chung JH, Danoff SK, George MD, et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases. Arthritis Care Res (Hoboken) 2024;76:1051–69. [CrossRef]
11. Goswami RP, Ray A, Chatterjee M, Mukherjee A, Sircar G, Ghosh P. Rituximab in the treatment of systemic sclerosis-related interstitial lung disease: a systematic review and meta-analysis. Rheumatology (Oxford) 2021;60:557–67. [CrossRef]
12. Goldman NR, Nihtyanova SI, Beesley CF, Wells AU, Denton CP, Renzoni EA, et al. Tocilizumab and rituximab for systemic sclerosis interstitial lung disease: a real-world cohort analysis. Rheumatology (Oxford) 2025;64(SI):SI184–9. [CrossRef]
13. Antoniou KM, Distler O, Gheorghiu AM, Moor CC, Vikse J, Bizymi N, et al. ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease developed by the task force for connective tissue disease-associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR) Endorsed by the European Reference Network on rare respiratory diseases (ERN-LUNG). Ann Rheum Dis 2026;85:22–60. [CrossRef]
14. Masi AT. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581–90. [CrossRef]
15. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747–55. [CrossRef]
16. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-205.
17. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic pulmonary fibrosis (an Update) and progressive pulmonary fibrosis in adults: an official ats/ers/jrs/alat clinical practice guideline. Am J Respir Crit Care Med 2022;205:e18–e47. [CrossRef]
18. Strickland G, Pauling J, Cavill C, Shaddick G, McHugh N. Mortality in systemic sclerosis-a single centre study from the UK. Clin Rheumatol 2013;32:1533–9. [CrossRef]
19. Lumetti F, Barone L, Alfieri C, Silva M, Serra V, Delsante G, et al. Quality of life and functional disability in patients with interstitial lung disease related to Systemic Sclerosis. Acta Biomed 2015;86:142–8.
20. Suliman YA, Dobrota R, Huscher D, Nguyen-Kim TD, Maurer B, Jordan S, et al. Brief Report: Pulmonary Function Tests: High Rate of False-Negative Results in the Early Detection and Screening of Scleroderma-Related Interstitial Lung Disease. Arthritis Rheumatol 2015;67:3256–61. [CrossRef]
21. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002;165:1581–6. [CrossRef]
22. Macklin M, Bauer Ventura I, Khanna D. Therapeutic Choices in Systemic Sclerosis-Associated Interstitial Lung Disease, a Survey of 2 International Research Groups. J Clin Rheumatol 2025;31:284–7. [CrossRef]
23. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708–19. [CrossRef]
24. Del Galdo F, Lescoat A, Conaghan PG, Bertoldo E, Čolić J, Santiago T, et al. EULAR recommendations for the treatment of systemic sclerosis: 2023 update. Ann Rheum Dis 2025;84:29–40. [CrossRef]
25. Funatogawa T, Mii K, Kojima K, Aoki Y, Matsubara Y, Hoshiba M. Real-world treatment for systemic sclerosis and systemic sclerosis-associated interstitial lung disease: information from a Japanese hospital claims database. Mod Rheumatol 2025;36:39–48. [CrossRef]
26. Maher TM, Tudor VA, Saunders P, Gibbons MA, Fletcher SV, Denton CP, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. Lancet Respir Med 2023;11:45–54. [CrossRef]
27. Ebata S, Yoshizaki A, Oba K, Kashiwabara K, Ueda K, Uemura Y, et al. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): open-label extension of a double-blind, investigators-initiated, randomised, placebo-controlled trial. Lancet Rheumatol 2022;4(8):e546-e555. [CrossRef]
28. Roofeh D, Lin CJF, Goldin J, Kim GH, Furst DE, Denton CP, et al. Tocilizumab prevents progression of early systemic sclerosis-associated interstitial lung disease. Arthritis Rheumatol 2021;73:1301–10. [CrossRef]
29. Mankikian J, Caille A, Reynaud-Gaubert M, Agier MS, Bermudez J, Bonniaud P, et al. Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial. Eur Respir J 2023;61:2202071. [CrossRef]
30. Barde F, Chevalier K, Decker P, Merin M, Nicolas A, Lescoat A, et al. Evaluation of the mycophenolate mofetil-rituximab combination in systemic sclerosis: a French retrospective multicenter study (MycRiSSc). J Autoimmun 2025;157:103492. [CrossRef]

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Original Article Ophthalmology

Structural and microvascular alterations in clinically unaffected fellow eyes of patients with acute central serous chorioretinopathy: An OCT and OCTA study

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ABSTRACT

OBJECTIVE: This study aimed to investigate potential subclinical structural and microvascular changes in the clinically unaffected fellow eyes of patients with acute central serous chorioretinopathy (aCSC) and to compare these findings with age- and sex-matched healthy controls.

METHODS: In this retrospective study, the fellow eyes of 33 aCSC patients and one randomly selected eye from 40 healthy controls were analyzed. Central macular thickness (CMT), retinal nerve fiber layer thickness (RNFLT), and subfoveal choroidal thickness (SFCT) were measured using optical coherence tomography (OCT). OCT angiography was performed to assess vessel density (VD) in the superficial capillary plexus (SCP), deep capillary plexus (DCP), choriocapillaris plexus (CCP), and peripapillary capillary plexus (PPCP), as well as the foveal avascular zone.

RESULTS: No differences were observed in mean CMT or RNFLT between fellow eyes of aCSC patients (faCSC) and controls; however, superior and inferior macular quadrants were significantly thicker in faCSC eyes (p=0.005 and p=0.007, respectively). SFCT was markedly increased in faCSC eyes compared to controls (333.2±93.16 μm vs. 239.8±34.27 μm; p<0.001). While SCP and DCP VDs did not differ significantly, CCP VD was elevated in the foveal, superior, inferior, and temporal regions of faCSC eyes (p<0.001–p=0.005). PPCP VD was also higher in the superior and temporal quadrants (p=0.02 and p=0.01).

CONCLUSION: Clinically, faCSC patients demonstrate increased SFCT, regional macular thickening, and elevated VD in both CCP and PPCP. These findings indicate that CSC is not exclusively a localized retinal disorder but may involve systemic and bilateral choroidal changes. Early subclinical alterations in the fellow eye highlight the importance of careful monitoring for timely intervention and prevention of disease progression.

Keywords: Acute central serous chorioretinopathy; optical coherence tomography; optical coherence tomography angiography; vascular density.

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Central serous chorioretinopathy (CSC) is a retinal disorder characterized by the presence of serous subretinal fluid (SRF) in the macula. This condition is associated with the impaired function of the retinal pigment epithelium (RPE) and disruptions in choroidal circulation [1]. Epidemiological studies report a male predominance, with a male-to-female ratio ranging from 2.6:1 to 6:1, and an annual incidence of approximately

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9.9/100,000 in men [2]. CSC has become the fourth most common vision-threatening retinal disease, highlighting the importance of its diagnosis and follow-up, with the increasing incidence reported in recent years [1].

Acute CSC (aCSC) constitutes about 70–80% of all instances and generally manifests with mild to moderate visual impairments, including central scotoma, metamorphopsia, and micropsia [3, 4]. Although SRF resolves spontaneously within a few months in most patients, a subset may experience recurrent episodes, chronicity, or persistent RPE alterations, leading to lasting visual deficits. aCSC most commonly affects one eye; however, bilateral involvement has been reported in up to 35% of cases, with higher rates observed in chronic or recurrent disease [5]. Therefore, evaluation of the clinically unaffected fellow eye is essential to identify subclinical structural changes and to assess the risk of bilateral involvement.

Both systemic and ocular factors contribute to the development of aCSC. Systemic risk factors include corticosteroid use, hypertension, type A personality traits, sleep disturbances, and psychological stress. In addition, endogenous hypercortisolism and exogenous steroid exposure have been strongly linked to disease onset [6]. From an ocular perspective, pachychoroid spectrum features associated with increased choroidal vascular permeability, RPE dysfunction, and local steroid exposure are considered key contributors to the pathogenesis of CSC [6].

In this study, we aimed to perform a comparative evaluation of posterior segment findings in the fellow eyes of patients with aCSC and in healthy controls, focusing on both neurostructural and microvascular parameters.

Highlight key points

- The fellow eyes of acute CSC patients show increased subfoveal choroidal thickness.
- Regional macular thickening is observed, particularly in the superior and inferior quadrants.
- Choriocapillaris and peripapillary vessel densities are elevated, indicating early microvascular alterations.
- These findings suggest that CSC involves bilateral and systemic choroidal changes, not just localized retinal pathology.

MATERIALS AND METHODS

This retrospective study was conducted at the Ophthalmology Clinic of Kartal Dr. Lutfi Kirdar City Hospital between September 2021 and December 2025. The research adhered to the guidelines of the Declaration of Helsinki and received approval from the local ethics committee (2026/010.99/25/66).

Since the study was retrospective, obtaining written informed consent from participants was not necessary.

The study included participants who were 18 years or older and had been diagnosed with aCSC, characterized by the presence of SRF for <6 months. The diagnosis was established using optical coherence tomography (OCT) (swept-source OCT [SS-OCT], Topcon, Japan), fundus autofluorescence imaging, and fluorescein angiography (FA) (Canon, Japan). The control group was composed of healthy individuals, matched by age and sex, who visited the ophthalmology clinic for routine examinations, refractive error assessments, or pre-employment screenings, and who exhibited normal results in both anterior and posterior segment examinations. The analysis included the clinically unaffected fellow eyes of patients with aCSC (faCSC) and one randomly chosen eye from each control participant.

Exclusion criteria comprised the presence of systemic autoimmune or inflammatory diseases, malignancy, hematologic disorders, renal or hepatic insufficiency, and a history of cardiovascular or cerebrovascular disease, as well as acute or chronic infections. In addition, patients who had previously received medical or laser treatment for CSC, those using corticosteroids or immunosuppressive agents, and individuals with ocular pathologies such as uveitis, retinal vasculitis, choroidal neovascularization, glaucoma, optic disc anomalies, or a history of ocular trauma or surgery were excluded. Cases with inadequate image quality or an OCT/OCT angiography (OCTA) signal strength index below 50 were also excluded from the analysis.

Data retrieved from medical records included best-corrected visual acuity (BCVA) measured with a Snellen chart, intraocular pressure measured by Goldmann applanation tonometry, pachymetry, and findings from slit-lamp examination of the anterior and posterior segments. OCT parameters included central macular thickness (CMT), retinal nerve fiber layer thickness (RNFLT), and subfoveal choroidal thickness (SFCT). OCTA measurements included superficial and deep macular vessel density (VD) and foveal avascular zone (FAZ), and choriocapillaris plexus (CCP) and peripapillary capillary plexus (PPCP) VD metrics. Data were collected on various demographic and clinical aspects, such as the patient's age, gender, laterality of involvement, the presence of any systemic conditions, and the use of additional medications.

Optic Coherence Tomography and Optic Coherence Tomography Angiography

CMT, peripapillary RNFLT, and SFCT were measured in all participants using a SS-OCT device by an experienced technician. CMT measurements were obtained from the foveal (1 mm) and parafoveal (3 mm) regions in accordance with the early treatment diabetic retinopathy study protocol. Peripapillary RNFLT was automatically calculated within a 3.45 mm diameter circular scan centered on the optic disc and analyzed in four quadrants (superior, inferior, temporal, and nasal). SFCT was manually measured on a horizontal B-scan as the distance from the Bruch's membrane to the inner scleral border at the fovea. Only images with a signal quality of ≥7 were included in the analysis.

OCTA images were acquired from a 6×6 mm^2 macular scan area. The superficial capillary plexus (SCP) and deep capillary plexus (DCP) were automatically segmented using the Topcon IMAGEnet software. VD was defined as the proportion of vascular area within the segmented region, calculated between 2.6 μm and 15.6 μm for the SCP, and between 15.6 μm and 70.2 μm for the DCP. The device automatically quantified capillary density in five regions (foveal, superior, inferior, temporal, and nasal) using two concentric circular zones with diameters of 1 mm and 3 mm centered on the fovea. The FAZ area was manually delineated by the same investigator.

CCP VD was measured in the slab extending from the Bruch's membrane to a depth of 20.2 μm. In addition, PPCP VD was assessed within a 4.5×4.5 mm^2 rectangular scan area centered on the optic nerve head and analyzed across four quadrants. Only OCTA images with a signal strength index of ≥45 and without motion artifacts or segmentation errors were included in the study.

Statistical Analysis

Data analysis was conducted using the jamovi statistical software package (The jamovi Project, Sydney, Australia). To evaluate the normality of continuous variables, both visual methods (such as histograms and Q–Q plots) and analytical tests were employed. Variables that followed a normal distribution were expressed as mean±standard deviation. For group comparisons, the independent samples t-test was utilized for continuous variables with a normal distribution, while the Mann–Whitney U test was used for those not meeting the normality assumption. Categorical variables were analyzed using the Chi-square test. A two-tailed $p<0.05$ was deemed statistically significant for all tests.

Table 1. Demographic and clinic features of all study participants

	Fellow eyes of aCSC patients (n=33)	Healthy controls (n=40)	p
Age	49.27±9.80	51.20±6.52	0.34
Gender (male) (%)	66.7	67.5	0.72
BCVA (LogMAR)	0±0	0±0	-
IOP (mmHg)	17.56±5.35	16.97±7.65	0.64

aCSC: Acute central serous chorioretinopathy; BCVA: Best- corrected visual acuity; IOP: Intraocular pressure.

RESULTS

The study included the clinically unaffected fellow eyes of 33 patients with aCSC and one randomly selected eye from 40 healthy control subjects. The mean age was 49.27±9.80 years in the aCSC group and 51.20±6.52 years in the control group ($p=0.34$). No pathological findings were detected in the anterior or posterior segment examinations of any participant, and BCVA was 0±0 logMAR in both groups. The demographic and clinical characteristics of all participants are presented in Table 1.

The analysis of posterior segment parameters revealed that CMT was 250.45±31.00 μm in the faCSC group and 252±25.26 μm in the healthy control group, with no statistically significant difference between groups ($p=0.81$). However, macular thickness in the superior and inferior quadrants was significantly greater in the faCSC group ($p=0.005$ and $p=0.007$, respectively). There were no significant differences between the groups in terms of mean or quadrant-specific RNFLT values (all $p>0.05$). SFCT was significantly higher in the faCSC group (333.2±93.16 μm) compared to the control group (239.8±34.27 μm) ($p<0.001$) (Table 2).

Regarding macular VD parameters, no significant differences were observed between the groups in either the SCP or DCP. In contrast, VD in the CCP layer was significantly higher in the faCSC group at the foveal, superior, inferior, and temporal regions ($p<0.001$, $p<0.001$, $p<0.001$, and $p=0.005$, respectively). Evaluation of PPCP VD demonstrated higher values in the superior and temporal quadrants in the faCSC group ($p=0.02$ and $p=0.01$, respectively) (Table 3).

TABLE 2. The posterior segment parameters obtained by OCT in all participants

Parameters	Fellow eyes of aCSC patients	Healthy controls	p
CMT (µm)	250.45±31	252±25.26	0.81
MT, superior quadrant (µm)	312.85±19.18	302.73±19.08	0.05
MT, inferior quadrant (µm)	310.03±20.36	301.05±22.88	0.07
MT, temporal quadrant (µm)	301±19.99	301.5±14.59	0.73
MT, nasal quadrant (µm)	313.03±18.04	301.7±15.4	0.73
Average RNFLT (µm)	105.97±10	104.1±12.03	0.88
RNFLT, superior quadrant (µm)	131.85±16.8	129.1±21.6	0.54
RNFLT, inferior quadrant (µm)	135.7±15.7	131.8±21.2	0.38
RNFLT, temporal quadrant (µm)	73.2±10.5	71.1±11.83	0.41
RNFLT, nasal quadrant (µm)	78.1±12.6	77.0±10.3	0.31
SFCT (µm)	333.2±93.16	239.8±34.27	<0.001

aCSC: Acute central serous chorioretinopathy; CMT: Central macular thickness; MT: Macular thickness; RNFLT: Retinal nerve fiber layer thickness; SFCT: Subfoveal choroidal thickness; OCT: Optical coherence tomography.

DISCUSSION

CSC is often considered a unilateral and self-limiting condition; however, structural and vascular alterations have also been reported in the clinically unaffected fellow eye [7]. Previous studies have demonstrated that fluorescein leakage can be detected in eyes deemed clinically normal on FA, accompanied by increased choroidal thickness (CT), enlarged choroidal vessel diameter, and reduced choriocapillaris blood flow. These findings suggest that CSC may develop on a background of bilateral and systemic choroidal dysfunction [8, 9]. This study aimed to investigate potential subclinical changes in the faCSC and to determine whether structural or vascular alterations are present. The results of this study indicated that macular thickness, particularly in the superior and inferior quadrants, was greater in the faCSC patients. SFCT was also significantly increased in these eyes. VD in the CCP was higher in the foveal, superior, inferior, and temporal regions, and PPCP VD was elevated in the superior and temporal quadrants of the faCSC eyes.

Studies on macular thickness in CSC have shown variable structural outcomes depending on disease stage. In chronic CSC, central subfoveal thickness (CST), ganglion cell complex (GCC; ganglion cell layer+inner plexiform layer), and macular volume are reduced compared to healthy controls, with thinning correlating with disease duration and visual acuity loss [10]. In a CSC, thinning is more pronounced in the outer retinal layers, particularly the photoreceptor outer segments, whereas inner retinal layers and CST are less affected compared to the chronic stage [10]. Longitudinal studies have demonstrated that, over a 6-month follow-up, GCC and peripapillary RNFLT did not differ significantly between affected eyes, fellow eyes, and healthy controls; however, degenerative thinning of the outer retina could develop after SRF resolution [11]. In line with these findings, our study observed no significant differences in CMT or RNFLT between fellow and healthy eyes, but regional thickening in the superior and inferior macular quadrants was evident. These observations suggest that early changes in choroidal vascular dynamics and possible inflammatory processes may lead to localized macular thickening in the initial phase of the disease, which may later transition to thinning as the disease progresses.

Previous studies have reported that asymptomatic fellow eyes of patients with CSC may exhibit various choroidal alterations [12, 13]. These changes include asymmetric venous drainage patterns, the presence of intervortex venous anastomoses, increased choroidal vascular permeability, and enlarged choroidal vessels, commonly referred to as pachyvessels [14]. In addition, intervortex venous anastomoses are more frequently observed in watershed regions of fellow eyes, and certain anatomical features, such as increased scleral thickness, may predispose these eyes to choroidal congestion [12, 15, 16]. Xiao et al. [17] demonstrated that

Table 3. Macular, choriocapillaris, and peripapillary capillary plexus vascular densities in all participants

Parameters	Fellow eyes of aCSC patients	Healthy controls	p
SCP VD (%)			
Foveal	17.92±4.47	18.69±3.63	0.41
Superior	40.06±5.17	39.9±3.67	0.76
Inferior	39.14±4.32	38.39±4.22	0.45
Temporal	41.79±3.39	40.82±3.97	0.26
Nasal	40.19±3.62	39.76±3.96	0.71
DCP VD (%)			
Foveal	16.66±4.45	17.09±3.99	0.59
Superior	43.04±6.27	43.47±4.06	0.72
Inferior	41.57±5.37	50.57±6.42	0.43
Temporal	44.02±3.96	43.11±4.12	0.34
Nasal	42.83±4.32	42.25±4.69	0.67
FAZ (μm^2)			
Superficial	312.47±11.66	313.16±122.12	0.65
Deep	330.57±125.3	333±117.9	0.95
CCP VD (%)			
Foveal	53.47±3.65	45.42±3.98	<0.001
Superior	50.67±3.57	47.77±2.68	<0.001
Inferior	51.08±2.47	48.39±3.74	<0.001
Temporal	52.58±2.51	50.76±2.85	0.005
Nasal	52.35±2.37	51.58±2.07	0.14
PPCP VD (%)			
Superior	49.94±2.92	47.36±2.73	0.02
Inferior	50.4±3.65	49.83±3.78	0.44
Temporal	45.9±2.68	43.8±4.17	0.01
Nasal	43.66±4.75	43.66±4.41	0.73

aCSC: Acute central serous chorioretinopathy; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; VD: Vessel density; FAZ: Foveal avascular zone; CCP: Choriocapillary plexus; PPCP: Peripapillary capillary plexus.

treatment-naïve aCSC patients exhibited significantly higher choroidal vascularity index, CT, choroidal vessel volume, and stromal volume in both affected and fellow eyes compared to healthy controls. These findings place CSC within the pachychoroid spectrum and highlight its association with systemic factors. Consistently, in our study, SFCT and VD in the CCP across the foveal, superior, inferior, and temporal quadrants were significantly increased in faCSC eyes. These findings align with existing literature and substantiate the notion that CSC should not be regarded solely as a localized retinal pathology, but rather as a disorder characterized by systemic and bilateral involvement.

Regarding peripapillary microvasculature, no prior studies have specifically evaluated fellow eyes in aCSC. Kizildag Ozbay et al. [18] have shown reduced PPCP VD in the small-vessel disc area in eyes with persistent SRF with chronic CSC, linking these changes to chronic neural and vascular retinal damage. Demirel et al. [15] reported that intervortex vein anastomoses in the horizontal watershed zone were observed in 75.4% of CSC eyes, 61.5% of fellow eyes, and 36.4% of healthy age-matched controls. While these intervortex anastomoses may represent a normal anatomical variation in healthy eyes, the authors noted that both the frequency and the caliber of these connections were significantly greater in eyes with CSC as well as in their fellow eyes [15]. In our study, PPCP VD was increased in the superior and temporal quadrants of aCSC fellow eyes. Some studies have also suggested that dysregulation of the autonomic nervous system in CSC may lead to outer retinal hyperperfusion, which could increase oxidative stress [19, 20]. Thus, the observed increase in PPCP VD may reflect either disease-related anatomical variations or early-stage vascular dysregulation and hyperperfusion responses.

This research faces some limitations, such as its retrospective and cross-sectional nature, along with a relatively limited sample size. Furthermore, OCTA measurements are device- and algorithm-dependent, which may limit generalizability. Nonetheless, the detailed OCTA analysis focused on fellow eyes represents a major strength of our study.

CONCLUSION

The fellow eyes of patients with aCSC exhibit increased SFCT, regional macular thickening, and alterations in CCP and PPCP VD. These findings strongly support the concept that CSC is not solely a localized retinal pathology but may reflect bilateral and systemic choroidal vascular dysfunction. Even in the initial stages of the disease, there can be subtle structural and microvascular changes that might lead to further developments over time. Therefore, careful monitoring of both the affected and fellow eyes is critical for early diagnosis, risk assessment, and prevention of potential disease progression. Larger, prospective, and long-term studies are needed to clarify the clinical implications of these subclinical changes.

Ethics Committee Approval: The Kartal Dr. Lutfi Kirdar City Hospital Ethics Committee granted approval for this study (date: 24.02.2026, number: 2026/010.99/25/66).

Informed Consent: Since the study was retrospective, obtaining written informed consent from participants was not necessary.

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

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Authorship Contributions: Concept – UK, GA; Design – UK, GA; Supervision – DCY, UK; Data collection and/or processing – DCY, GA, OFB; Analysis and/or interpretation – NB, OFB; Literature review – DCY, UK, GA; Writing – UK, GA; Critical review – NB, OFB.

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REFERENCES

1. Khan AH, Lotery AJ. Central Serous Chorioretinopathy: Epidemiology, Genetics and Clinical Features. Annu Rev Vis Sci 2024;10:477–505. [CrossRef]
2. Kitzmann AS, Pulido JS, Diehl NN, Hodge DO, Burke JP. The incidence of central serous chorioretinopathy in Olmsted County, Minnesota, 1980-2002. Ophthalmology 2008;115:169–73. [CrossRef]
3. Berger L, Bühler V, Yzer S. Central serous chorioretinopathy - an overview. Klin Monbl Augenheilkd 2021;238:971–9. [CrossRef]
4. Nicholson BP, Ali Idris AM, Bakri SJ. Central Serous Chorioretinopathy: Clinical Characteristics Associated with Visual Outcomes. Semin Ophthalmol 2018;33:804–7. [CrossRef]
5. Singh SR, Parameswarappa DC, Arora S, Maltsev DS, Sahoo NK, Kulikov AN, et al. Imaging characteristics of bilateral CSCR cases:12 months follow up. Eye (Lond) 2023;37:97–102. [CrossRef]
6. Liu B, Deng T, Zhang J. Rısk factors for central serous chorıoretınopathy: a systematic review and meta-analysis retina. 2016;36:9–19. [CrossRef]
7. Ersoz MG, Arf Karacorlu S, Hocaoglu M, Sayman Muslubas I, Karacorlu M. Patient characteristics and risk factors for central serous chorioretinopathy: an analysis of 811 patients. Br J Ophthalmol 2019;103:725–9. [CrossRef]
8. Bujarborua D, Chatterjee S, Choudhury A, Bori G, Sarma AK. Fluorescein angiographic features of asymptomatic eyes in central serous chorioretinopathy. Retina 2005;25:422–9. [CrossRef]
9. Goktas A. Correlation of subretinal fluid volume with choroidal thickness and macular volume in acute central serous chorioretinopathy. Eye (Lond) 2014;28:1431–6. [CrossRef]
10. Gawęcki M, Grzybowski A. Ganglion cell loss in the course of central serous chorioretinopathy. Ophthalmol Ther 2023;12:517–33. [CrossRef]
11. Kim DI, Bae KW, Jang K, Hwang DD. Longitudinal changes in the ganglion cell complex thickness in acute central serous chorioretinopathy using spectral-domain optical coherence tomography. Sci Rep 2024;14:821. [CrossRef]
12. Parameswarappa DC, Arora S, Singh SR, Sahoo NK, Maltsev DS, Kulikov AN, et al. Influence of fellow eye on the diagnosis and classification of central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol 2022;260:1147–52. [CrossRef]
13. Valsecchi N, Sadeghi E, Davis E, Ibrahim MN, Hasan N, Bollepalli SC, et al. Three-dimensional choroidal vessels assessment in fellow eyes of patients with central serous chorioretinopathy. Transl Vis Sci Technol 2025;14:10. [CrossRef]
14. Pauleikhoff LJB, Diederen RMH, Chang-Wolf JM, Moll AC, Schlingemann RO, van Dijk EHC, et al. Choroidal vascular changes on ultrawidefield ındocyanine green angiography in central serous chorioretinopathy: CERTAIN study report 1. Ophthalmol Retina 2024;8:254–63. [CrossRef]
15. Demirel S, Ayaz RE, Yanık Ö, Batıoğlu F, Özmert E, Iovino C, et al. Quantitative assessment of intervortex anastomosis in central serous chorioretinopathy and fellow eyes: Does the size of anastomotic vessels matter for the diagnosis? Graefes Arch Clin Exp Ophthalmol 2024;262:3509–17. [CrossRef]
16. Aichi T, Terao N, Imanaga N, Sawaguchi S, Wakugawa S, Miyara Y, et al. Scleral thıckness ın the fellow eyes of patıents wıth unılateral central serous chorıoretınopathy. Retina 2023;43:1573–8. [CrossRef]
17. Xiao B, Yan M, Song YP, Ye Y, Huang Z. Quantitative assessment of choroidal parameters and retinal thickness in central serous chorioretinopathy using ultra-widefield swept-source optical coherence tomography: a cross-sectional study. BMC Ophthalmol 2024;24:176. [CrossRef]
18. Kızıldağ Özbay E, Sabancı Ş, Küçük MF, Erol MK. Quantitative Changes in Vascular and Neural Fibers Induced by Subretinal Fluid Excluding the Peripapillary Region in Patients with Chronic Central Serous Chorioretinopathy. Diagnostics (Basel) 2025;15:174. [CrossRef]
19. Penas S, Castro P, Pereira G, Oliveira AM, Carneiro AM, Rocha-Sousa A, et al. Cerebral neurovascular coupling ımpairment in central serous chorioretinopathy. Ophthalmic Res 2022;65:446–54. [CrossRef]
20. Cardillo Piccolino F, Lupidi M, Cagini C, Fruttini D, Nicolò M, Eandi CM, et al. Choroidal vascular reactivity in central serous chorioretinopathy. Invest Ophthalmol Vis Sci 2018;59:3897–05. [CrossRef]

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Original Article General Surgery

Evaluation of the relationship between combined scores derived from pre-operative routine parameters and weight loss following sleeve gastrectomy: A retrospective cohort study

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ABSTRACT

OBJECTIVE: This study aimed to investigate whether pre-operative composite indices derived from routine laboratory parameters, namely the fibrosis-4 (FIB-4) index, the aspartate aminotransferase-to-platelet ratio index (APRI), and the homeostatic model assessment of insulin resistance (HOMA-IR), were associated with post-operative percentage of excess weight loss (%EWL) after laparoscopic sleeve gastrectomy (LSG).

METHODS: This retrospective cohort study included 91 adults who underwent LSG at a tertiary referral center. Pre-operative FIB-4, APRI, and HOMA-IR values were calculated from routinely obtained clinical and biochemical parameters. The primary endpoint was %EWL during post-operative follow-up. Patients were also classified as successful (%EWL ≥50%) or suboptimal (%EWL <50%) responders. Comparative analyses, correlation analyses, and multivariable linear regression were performed.

RESULTS: The cohort had a mean age of 39.2±10.0 years and was predominantly female (80.2%). Mean baseline body mass index (BMI) was 45.1±6.3 kg/m^2. Mean post-operative %EWL was 51.0±20.2%, whereas total weight loss reached 26.5±8.4%. Marked post-operative metabolic improvement was observed, including significant declines in HOMA-IR, fasting glucose, triglycerides, alanine aminotransferase, and glycated hemoglobin. However, neither FIB-4 nor APRI nor HOMA-IR demonstrated a significant linear association with %EWL, and none remained an independent predictor in the regression model adjusted for age and baseline BMI. In subgroup analyses, the suboptimal weight loss group had a significantly higher baseline BMI and a borderline-higher triglyceride level.

CONCLUSION: Pre-operative FIB-4, APRI, and HOMA-IR appear valuable for metabolic and hepatic phenotyping before surgery, but they do not provide sufficient standalone prognostic discrimination for early post-operative %EWL after LSG. Baseline adiposity may remain more informative than these composite indices for identifying patients at risk of suboptimal relative weight loss.

Keywords: Aspartate aminotransferase-to-platelet ratio index; bariatric surgery; excess weight loss; fibrosis-4; homeostatic model assessment of insulin resistance; obesity; sleeve gastrectomy; weight loss prediction.

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Obesity is a chronic, relapsing, multisystem disease that is tightly linked to cardiometabolic morbidity, impaired quality of life, and premature mortality [1]. Among patients with severe obesity, laparoscopic sleeve gastrectomy (LSG) has become one of the most frequently performed bariatric procedures because it

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provides substantial weight reduction together with meaningful metabolic improvement [2]. Nevertheless, post-operative outcomes remain heterogeneous, and identifying patients who are likely to achieve suboptimal relative weight loss continues to be an important issue for pre-operative counseling and risk stratification.

The hepatic-metabolic phenotype of bariatric candidates is particularly relevant in this context. What was historically termed non-alcoholic fatty liver disease is now framed within the updated metabolic dysfunction-associated steatotic liver disease (MASLD) nomenclature, which better reflects the metabolic basis of disease and is supported by multisociety consensus [3, 4]. In patients with obesity, insulin resistance, hypertriglyceridemia, steatosis, and fibrotic remodeling frequently coexist; therefore, inexpensive composite markers derived from routine laboratory tests are attractive for perioperative assessment.

Among these markers, the fibrosis-4 (FIB-4) index and the aspartate aminotransferase-to-platelet ratio index (APRI) are widely used as non-invasive tools for FIB risk estimation, whereas homeostatic model assessment of insulin resistance (HOMA-IR) remains one of the most established surrogate measures of insulin resistance [5–7]. Although these scores were originally developed for diagnostic or staging purposes rather than prognostic modeling after bariatric surgery, they may theoretically capture the baseline metabolic burden that shapes post-operative adaptation. If a higher hepatic or insulin-resistant burden reflects metabolic rigidity, these indices could be associated with poorer weight loss efficiency. Conversely, if surgery exerts a strong metabolic reset that overrides baseline derangement, its prognostic contribution may be limited.

Recent evidence suggests that this relationship is likely more complex than a simple one-to-one association. Systematic evidence indicates that MASLD presence alone does not consistently worsen short-term weight loss outcomes after bariatric surgery. However, certain subgroups, particularly patients with more advanced steatohepatitic phenotypes, may show less favorable trajectories after sleeve gastrectomy [8]. Similarly, studies evaluating post-operative FIB indices have shown that not all liver-related composite scores move in parallel after surgery; in particular, APRI may improve while FIB-4 may remain unchanged or even become less informative in the post-operative setting [9]. These observations raise the possibility that pre-operative composite indices may characterize baseline phenotype without necessarily predicting early %EWL.

Highlight key points

- Preoperative FIB-4, APRI, and HOMA-IR were not independent predictors of %EWL after sleeve gastrectomy.
- Sleeve gastrectomy produced marked improvements in glycemic, lipid, and hepatic parameters.
- Higher baseline BMI was associated with suboptimal postoperative relative weight loss.
- Composite metabolic-hepatic scores may aid phenotyping rather than weight-loss prediction.

Accordingly, the present study aimed to evaluate the relationship between pre-operative FIB-4, APRI, and HOMA-IR values and post-operative percentage of excess weight loss (%EWL) after LSG in a tertiary-care cohort. We additionally sought to compare baseline clinical and biochemical characteristics between patients with successful and suboptimal post-operative weight loss in order to identify more clinically informative pre-operative signals.

MATERIALS AND METHODS

Study Design and Ethical Approval

This retrospective cohort study was conducted at the Department of General Surgery, Ankara Etlik City Hospital, Turkiye. The study protocol was approved by the Institutional Ethics Committee of Ankara Etlik City Hospital (AESH-BADEK2-2026-072) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Study Population

A total of 91 adult patients who underwent LSG between 2023 and 2024 were included. Eligibility criteria were age between 18 and 65 years, body mass index (BMI) ≥40 kg/m^2 or BMI ≥35 kg/m^2 in the presence of obesity-related comorbidities, and availability of complete perioperative and follow-up data. Patients with known primary liver disease, excessive alcohol consumption, or prior bariatric surgery were excluded.

Pre-operative Variables and Composite Indices

Routine pre-operative biochemical and hematological data were used to calculate three composite indices:

1. FIB-4: (Age×AST)/(Platelets×√Plat)
2. APRI: [(AST/upper limit of normal)/Platelets]×100
3. HOMA-IR: (Fasting glucose×fasting insulin)/405

Outcome Definitions

The primary outcome was %EWL, calculated using an ideal BMI of 25 kg/m^2. Weight loss success was defined a priori as %EWL ≥50%. Patients were therefore categorized as either the successful or suboptimal weight loss group.

Statistical Analysis

Data analysis was performed using Python 3.11. Continuous variables were summarized as mean±standard deviation. Pre-operative and post-operative measurements were compared with paired analyses. Group comparisons between successful and suboptimal weight loss categories were performed using independent-sample tests. Correlation analyses examined linear associations between %EWL and the composite scores. A multivariable linear regression model adjusted for age and baseline BMI was used to assess whether FIB-4, APRI, or HOMA-IR independently predicted post-operative %EWL.

RESULTS

Cohort Characteristics and Overall Weight Loss Response

Ninety-one patients were included in the final analysis. The mean age was 39.2±10.0 years, and women constituted 80.2% of the cohort. Mean pre-operative body weight was 118.9±19.6 kg, and mean BMI was 45.1±6.3 kg/m^2. At post-operative follow-up, mean body weight decreased to 87.4±14.2 kg. Mean %EWL reached 51.0±20.2%, whereas mean total weight loss percentage (%TWL) was 26.5±8.4%.

The study workflow and patient selection framework are summarized in Figure 1.

Post-operative Metabolic and Hepatic Improvement

Substantial biochemical improvement was observed after LSG. HOMA-IR declined from 6.92±5.08 to 2.78±1.48, corresponding to a 59.8% reduction. Fasting glucose decreased from 108.67±44.14 to 89.07±10.93 mg/dL, triglycerides from 164.05±81.37 to 110.51±45.40 mg/dL, hemoglobin A1c (HbA1c) from 5.64±0.86% to 5.19±0.48%, and alanine aminotransferase (ALT) from 29.74±19.53 to 19.57±12.40 U/L. These changes are detailed in Table 1 and visually summarized in Figure 2.

Relationship Between Pre-operative Composite Scores and %EWL

The mean pre-operative FIB-4 index was 0.57±0.24, and the mean APRI score was 0.25±0.15, both corresponding overall to a low-risk profile for advanced FIB. Correlation analysis showed no statistically significant linear association between %EWL and FIB-4 (r=0.013, p=0.900), APRI (r=0.077, p=0.468), or HOMA-IR (r=-0.043, p=0.683). These effect estimates are presented in Figure 3.

In the multivariable model adjusted for age and baseline BMI, none of the three composite scores emerged as an independent predictor of post-operative %EWL.

Subgroup Analysis According to Weight Loss Success

Patients were then stratified according to post-operative %EWL. The suboptimal group (%EWL <50%) had a significantly higher baseline BMI than the successful group (45.61±6.49 vs 42.47±5.10 kg/m^2, p=0.013). Baseline triglyceride levels were also higher in the suboptimal group (179.58±78.62 vs 146.72±81.79 mg/dL), with borderline statistical significance (p=0.054). In contrast, pre-operative HOMA-IR, FIB-4, and APRI values were comparable between groups. Detailed comparisons are shown in Table 2, whereas the principal between-group differences are illustrated in Figure 4.

DISCUSSION

The present study shows that while LSG was associated with marked early post-operative metabolic improvement, pre-operative FIB-4, APRI, and HOMA-IR did not meaningfully predict relative weight loss success as measured by %EWL. This distinction has clinically important. A score may be valuable for phenotyping baseline disease severity and still lack sufficient prognostic resolution for a post-operative endpoint driven by multiple biological and behavioral pathways. In our cohort, the composite indices captured baseline hepatic and insulin-resistant burden, yet they did not discriminate which patients would achieve superior early %EWL.

The overall metabolic response observed here was substantial. The nearly 60% fall in HOMA-IR, together with reductions in triglycerides, fasting glucose, HbA1c, and ALT, is consistent with the concept that sleeve gastrectomy induces a broad endocrine-metabolic reprogramming rather than merely a restrictive reduction in caloric intake [2, 10]. Contemporary hepatology literature further suggests

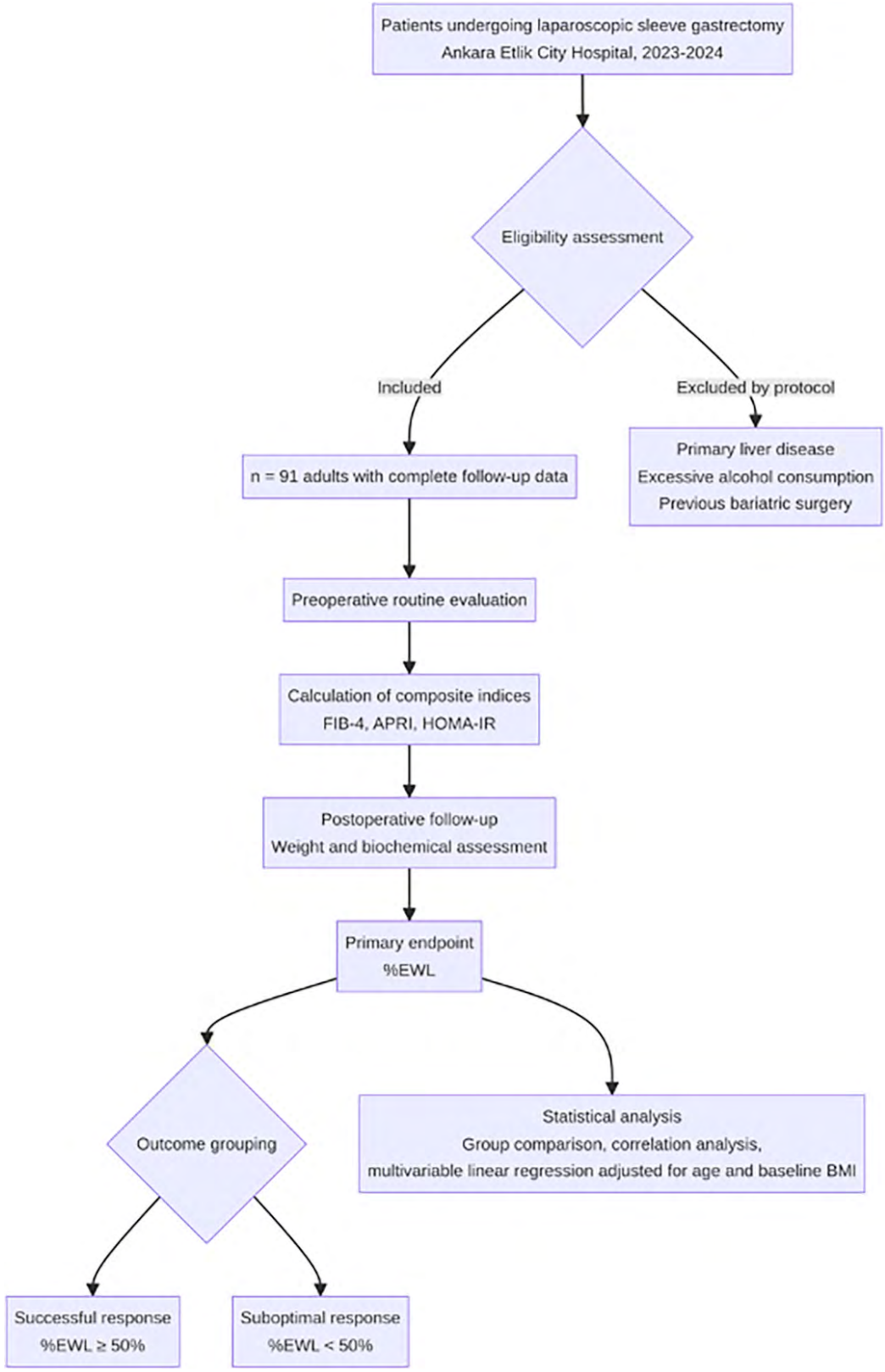

FIGURE 1. Study flowchart summarizing cohort assembly, eligibility, exclusions by criterion, score calculation, and analytic grouping according to post-operative percentage of excess weight loss.

FIB-4: Fibrosis-4; APRI: Aminotransferase-to-platelet ratio index; HOMA-IR: Homeostatic model assessment of insulin resistance; %EWL: Percentage of excess weight loss.

Table 1. Evolution of major metabolic and hepatic parameters after laparoscopic sleeve gastrectomy

Parameters	Pre-operative	Post-operative	Change (%)	p
Homeostatic model assessment of insulin resistance	6.92±5.08	2.78±1.48	-59.8	<0.001
Triglycerides (mg/dL)	164.05±81.37	110.51±45.40	-32.6	<0.001
Hemoglobin A1c (%)	5.64±0.86	5.19±0.48	-8.0	<0.001
Alanine aminotransferase (U/L)	29.74±19.53	19.57±12.40	-34.2	<0.001
Glucose (mg/dL)	108.67±44.14	89.07±10.93	-18.0	<0.001

Table 2. Pre-operative comparison of successful and suboptimal weight loss groups

Parameters	Successful (%EWL ≥50)	Suboptimal (%EWL <50)	p
Baseline body mass index (kg/m^2)	42.47±5.10	45.61±6.49	0.013
Triglycerides (mg/dL)	146.72±81.79	179.58±78.62	0.054
Homeostatic model assessment of insulin resistance	6.73±3.45	7.09±6.22	0.738
Fibrosis-4 index	0.57±0.28	0.57±0.19	0.913
Aspartate aminotransferase-to-platelet ratio index score	0.26±0.19	0.23±0.10	0.239

%EWL: Percentage of excess weight loss.

that bariatric surgery improves steatosis and downstream liver injury through integrated effects on incretin signaling, bile acid pathways, gut-liver crosstalk, and insulin sensitivity [10]. Within such a framework, it is biologically plausible that baseline composite indices become less powerful as standalone predictors because the intervention itself exerts a strong and relatively global metabolic reset.

Our findings are also congruent with recent evidence indicating that MASLD status alone does not uniformly determine short-term post-operative weight loss. In a recent systematic review and meta-analysis, Sabench and colleagues found no consistent difference in 12-month BMI change, EWL, or TWL between patients with MASLD and those with normal liver status after bariatric surgery. However, more advanced inflammatory phenotypes showed signals toward less favorable outcomes in selected sleeve gastrectomy subgroups [8]. This broader literature supports the interpretation that baseline hepatic involvement may modulate outcome heterogeneity only under specific circumstances and is unlikely to be fully represented by FIB-4 or APRI alone.

The present data further suggest that baseline adiposity burden may be more informative than the studied composite scores when %EWL is the endpoint of interest. Patients with suboptimal weight loss had significantly higher pre-operative BMI. This finding is mechanistically coherent because %EWL is a relative metric anchored to excess body weight rather than to absolute kilograms lost. Individuals entering surgery with greater excess adiposity may still lose substantial absolute weight but appear less successful when outcomes are expressed as %EWL. This nuance should be emphasized during patient counseling and supports the complementary use of %TWL, absolute weight change, and BMI trajectory alongside %EWL when interpreting surgical response [2, 11].

The borderline association between higher baseline triglycerides and suboptimal %EWL also deserves attention. Although this difference did not reach formal statistical significance in our cohort, it is biologically plausible and directionally consistent with emerging evidence that triglyceride-rich metabolic phenotypes may reflect greater visceral adiposity, more pronounced insulin resistance, and less favorable post-operative weight-loss efficiency [12, 13]. Recent predictive modeling studies after sleeve gastrectomy likewise identify triglycerides among potentially relevant pre-operative variables, but also emphasize that useful prediction generally requires multivariable integration of anthropometric, metabolic, nutritional, and behavioral domains rather than reliance on a single routine score [13].

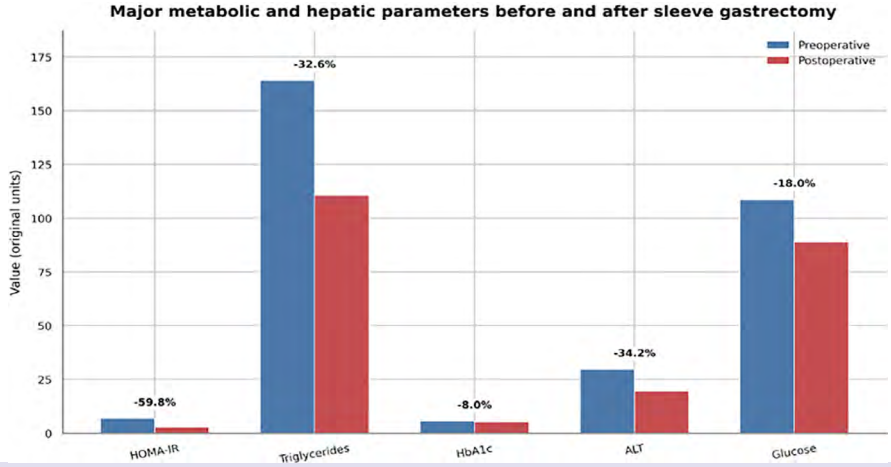

FIGURE 2. Pre-operative versus post-operative relative changes in major metabolic and hepatic parameters after laparoscopic sleeve gastrectomy.

HOMA-IR: Homeostatic model assessment of insulin resistance; HbA1c: Hemoglobin A1c; ALT: Alanine aminotransferase.

A particularly notable observation is the neutral prognostic performance of FIB-4 and APRI despite their established value in non-invasive liver risk assessment. This may partly reflect the distribution of our cohort, in which the mean pre-operative values were overall within low-risk ranges. When advanced FIB burden is uncommon, the discriminatory range of FIB scores is inevitably narrowed. In addition, the post-operative behavior of these markers may differ according to how each formula incorporates age, transaminases, and platelet count. Alexander et al. [9] recently reported that after sleeve gastrectomy, APRI may improve, whereas FIB-4 may remain unchanged or even worsen numerically, underscoring that these indices are not interchangeable and should not automatically be assumed to mirror post-operative metabolic success. Our results extend that idea by suggesting that even in the pre-operative setting, these scores may be better viewed as contextual clinical descriptors than as reliable standalone predictors of %EWL.

The absence of a predictive relationship for HOMA-IR should not be interpreted as evidence that insulin resistance is clinically unimportant. Rather, it may indicate that severe pre-operative insulin resistance is not necessarily an obstacle to early post-operative metabolic benefit after LSG. Bariatric surgery has repeatedly been shown to improve glycemic control and insulin sensitivity even in patients with marked baseline metabolic dysfunction [2, 10, 11]. Therefore, the practical implication is not that HOMA-IR lacks clinical value, but that its principal utility may lie in metabolic characterization and longitudinal assessment rather than in isolated prediction of early relative weight loss.

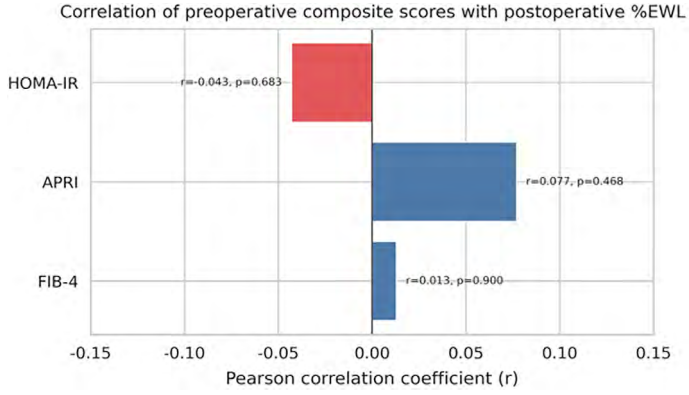

FIGURE 3. Correlation summary plot showing Pearson correlation coefficients and p-values for the association between pre-operative fibrosis-4, aspartate aminotransferase-to-platelet ratio index, and homeostatic model assessment of insulin resistance and post-operative percentage of excess weight loss.

%EWL: Percentage of excess weight loss.

Several limitations should be acknowledged. First, the retrospective single-center design introduces inherent risks of selection bias and residual confounding. Second, the sample size was modest, which limits statistical power, especially for subgroup analyses and for detecting small predictive effects. Third, the follow-up window represents the dynamic early post-operative period; longer observation may reveal different associations, particularly with regard to weight regain, late plateau, or evolving liver-related trajectories. Fourth, because the analysis was restricted to routine composite indices, potentially influential domains such as eating behavior, psychiatric profile, physical activ-

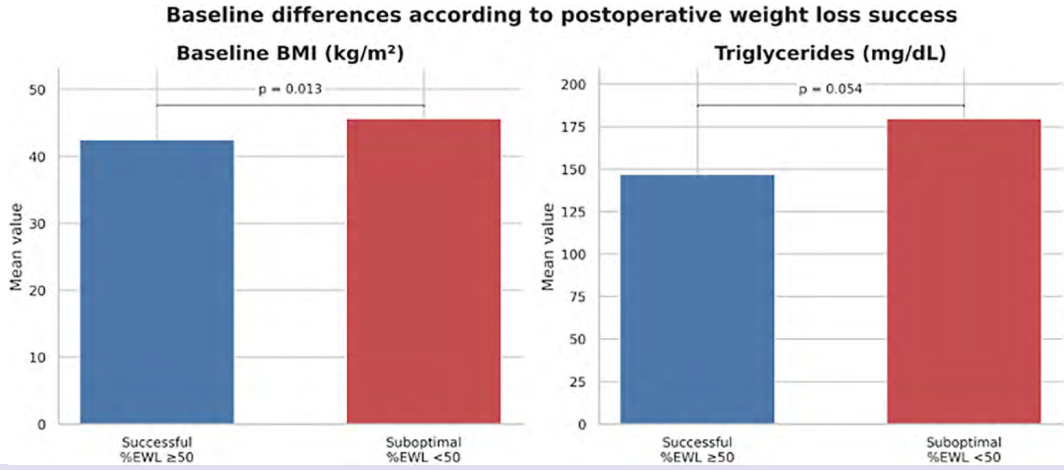

FIGURE 4. Group comparison plot for baseline body mass index and triglyceride values in patients with successful (percentage of excess weight loss [%EWL] ≥50%) and suboptimal (%EWL <50%) post-operative weight loss.

BMI: Body mass index.

ity, body composition, and adherence to post-operative follow-up could not be incorporated into the model.

Despite these limitations, the study has practical relevance. It addresses a clinically accessible question using markers that are inexpensive, routinely available, and often already present in pre-operative workups. The findings argue against overinterpreting low-cost composite hepatic-metabolic scores as deterministic predictors of early weight loss success after LSG. Instead, a broader pre-operative assessment framework that integrates baseline BMI, lipid-metabolic profile, behavioral factors, and possibly more advanced body-composition or liver phenotyping tools may be more useful for individualized prognostication.

Conclusion

LSG produced substantial early improvements in weight, glycemic regulation, lipid metabolism, and liver-associated biochemical markers in this retrospective cohort. However, pre-operative FIB-4, APRI, and HOMA-IR values were not independently associated with post-operative %EWL and did not distinguish successful from suboptimal responders as standalone indices. Higher baseline BMI emerged as the more clinically informative signal for suboptimal relative weight loss, while elevated triglycerides showed a borderline association that merits confirmation in larger cohorts. Future prospective studies with larger samples, longer follow-up, and multidimensional phenotyping should develop integrated predictive models rather than relying on isolated routine composite scores.

Ethics Committee Approval: The Ankara Etlik City Hospital Hospital Ethics Committee granted approval for this study (date: 27.01.2026, number: AESH-BADEK2-2026-072).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The author declare that there is no conflict of interest

Financial Disclosure: The authors declared that this study received no financial support.

Use of AI for Writing Assistance: The authors declare that no artificial intelligence (AI) tools or large language models were used in the preparation of this manuscript.

Authorship Contributions: Concept – DK; Design – DK, GD; Supervision – DK; Fundings – GD, DK; Materials – DK; Data collection and/or processing – GD; Analysis and/or interpretation – DK; Literature review – DK; Writing – DK; Critical review – DK, GD.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Kopelman PG. Obesity as a medical problem. Nature 2000;404:635–43. [CrossRef]
2. Angrisani L, Santonicola A, Iovino P, Vitiello A, Zundel N, Buchwald H, et al. Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014. Obes Surg 2017;27:2279–89. [CrossRef]
3. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79:1542–56. [CrossRef]
4. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;81:492–542.
5. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict signif-

icant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317–25. [CrossRef]
6. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518–26. [CrossRef]
7. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9. [CrossRef]
8. Sabench F, Rusu EC, Clavero-Mestres H, Arredondo-Prats V, Veciana-Molins M, Muñiz-Piera S, et al. Metabolic-Associated Fatty Liver Disease and Weight Loss After Bariatric Surgery: A Systematic Review and Meta-Analysis. Obes Surg 2024;34:4459–71. [CrossRef]
9. Alexander H, Falk R, Utz S, Felix D, Aladdin AD, Hermann K, et al. Comparison of different liver fibrosis scores following sleeve gastrectomy. Langenbecks Arch Surg 2025;410:29. [CrossRef]
10. Liu H, Lefere S, Guillot A, Zheng MH, Tacke F. Bariatric surgery for metabolic dysfunction-associated steatotic liver disease (MASLD): Current knowledge of mechanisms. Hepatology. 2025 May 30. doi: 10.1097/HEP.0000000000001417. [Epub ahead of print] [CrossRef]
11. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, et al. Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes. N Engl J Med 2014;370:2002–13. [CrossRef]
12. Huang X, Li G, Xu B, Zhang J, Wang X, Cheng X, et al. Lower Baseline Serum Triglyceride Levels Are Associated With Higher Decrease in Body Mass Index After Laparoscopy Sleeve Gastrectomy Among Obese Patients. Front Endocrinol (Lausanne) 2021;12:633856. [CrossRef]
13. Casas Domínguez M, Herrena Montano I, López Gómez JJ, Ramos Bachiller B, de Luis Román DA, Díez IT. Predicting Weight Loss Success After Gastric Sleeve Surgery: A Machine Learning-Based Approach. Nutrients 2025;17:1391. [CrossRef]

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ORIGINAL ARTICLE INTERNAL MEDICINE

Association of serum 25-hydroxyvitamin D levels with fatigue severity in adults: A cross-sectional study

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ABSTRACT

OBJECTIVE: The objective of the study is to evaluate the association between serum 25-hydroxyvitamin D (25[OH]D) levels and fatigue severity.

METHODS: This single-center, cross-sectional study included 228 participants aged 18–65 years who completed the fatigue severity scale (FSS) questionnaire. Individuals who had received vitamin supplementation within the previous 3 months, had known chronic disease, used regular medication, or had a history of antidepressant/anxiolytic use for depression/anxiety were excluded. Serum 25(OH)D, hemoglobin, ferritin, iron, magnesium, vitamin B12, and folate values were retrieved from the hospital information system. The Mann–Whitney U-test was used for comparisons between genders, and the Spearman correlation test was used for relationships between FSS and biochemical parameters. P<0.05 was considered statistically significant.

RESULTS: A total of 228 participants (57 males and 171 females) were included in the study. Most variables were not normally distributed; therefore, non-parametric analyses were performed. Spearman correlation analysis demonstrated a weak but significant negative correlation between FSS scores and both hemoglobin (p=0.003) and ferritin levels (p=0.001). No significant correlations were found between FSS and vitamin D, vitamin B12, folate, magnesium, or serum iron levels (p>0.05). In group comparisons based on fatigue severity, ferritin levels were significantly lower in the high-fatigue group compared to the low-fatigue group (p<0.001). Hemoglobin levels were also lower in the high-fatigue group (p=0.043). In contrast, vitamin B12 levels were significantly higher in the high-fatigue group (p=0.032). No significant differences were observed between groups in terms of vitamin D, folate, magnesium, or serum iron levels (p>0.05).

CONCLUSION: Serum 25(OH)D levels were not associated with fatigue severity. The observed relationship between fatigue severity and hematological markers (hemoglobin and ferritin) suggests that these parameters should be considered in the clinical evaluation of fatigue.

Keywords: Endocrinology; family medicine; internal medicine; public medicine.

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Vitamin D is a steroid hormone primarily involved in calcium–phosphorus homeostasis and bone mineralization. In 1967, the metabolism of vitamin D was elucidated for the first time, and vitamin D was subsequently defined as a steroid hormone responsible for maintaining calcium and phosphorus homeostasis and regulating bone mineralization [1]. More than 80% of vitamin D in the human body is synthesized in the epidermis from 7-dehydrocholesterol as a prehormone under the influence of ultraviolet radiation from sunlight. In addition, vitamin D can be obtained through dietary intake from animal (vitamin D_3, cholecalciferol) and plant (vitamin

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D_2, ergosterol) sources, after which it is converted to its biologically active forms in the liver and kidneys [2]. Recent studies have demonstrated the presence of vitamin D receptors in nearly all tissues, suggesting that vitamin D is not limited to calcium–phosphorus metabolism and bone turnover but also plays a role in multiple biological systems, including malignancies, autoimmune, rheumatologic, neurologic, cardiovascular, psychiatric disorders, and diabetes mellitus [3–9].

Fatigue is a common and clinically important complaint, often described as a lack of energy, tiredness, exhaustion, and weakness, and it may substantially impair occupational performance and social functioning. While it can occur as a consequence of physical or mental activity, fatigue may also arise from a wide range of organic conditions, including infections, psychiatric disorders, rheumatologic diseases, malignancies, anemia, and medication use [10]. Accordingly, it is a symptom frequently encountered across multiple medical specialties during a comprehensive clinical history. Fatigue is also among the most common reasons for presentation to internal medicine outpatient clinics. Because fatigue is subjective and has a broad differential diagnosis, its evaluation and management can be challenging and often necessitate extensive clinical assessment and laboratory testing, resulting in a considerable burden in terms of workload and healthcare resource utilization [11].

The pathophysiology of fatigue has not been fully elucidated. It is generally hypothesized to involve multiple mechanisms, including elevated circulating pro-inflammatory cytokines that may trigger oxidative stress and disrupt glial function (astrocytes and microglia), activation of the hypothalamic–pituitary axis leading to increased cortisol levels, and alterations in serotonergic and melatonergic pathways that adversely affect sleep quality [12–14].

Fatigue may lead to a persistent sense of sleep deprivation, diffuse myalgias, and impaired attention. Consequently, quality of life can be substantially reduced, and individuals may experience difficulty performing even routine daily activities. Nevertheless, fatigue is a highly subjective complaint; therefore, its assessment commonly relies on standardized questionnaire-based instruments developed for general or specific populations. Among the most frequently used tools are the Fatigue Severity Scale (FSS) and the Fatigue Impact Scale (FIS). The Turkish version of the FSS was adapted by Armutlu et al. in 2007 [15, 16].

Highlight key points

- Fatigue severity was not associated with serum 25-hydroxyvitamin D [25(OH)D] levels in this cross-sectional cohort.
- Fatigue severity showed a significant negative correlation with hemoglobin and ferritin, even in non-anemic individuals.
- These findings suggest that subclinical iron deficiency may contribute to fatigue, independent of overt anemia.
- Vitamin D supplementation alone may have limited clinical impact on fatigue in the absence of other contributing factors.
- A multidimensional and holistic evaluation is essential in patients presenting with fatigue.

Although psychological factors are often considered the most common contributors to fatigue, a broad range of other etiologies should also be considered, including chronic fatigue syndrome, infections, malignancies, medication use, malnutrition, nutritional deficiencies, dehydration, pregnancy, and various systemic diseases [11]. In this study, we aimed to evaluate the association between serum 25-hydroxyvitamin D [25(OH)D] levels and fatigue severity as assessed by the FSS.

MATERIALS AND METHODS

Study Design and Ethical Approval

This study was designed as a single-center, cross-sectional study conducted in the Internal Medicine Outpatient Clinic of Ümraniye Training and Research Hospital. The study protocol was approved by the Ethics Committee on 10 July 2025 (Approval No.: 237). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Population

Based on the power analysis, a total of 228 participants aged 18–65 years who completed the FSS questionnaire were included in the study. Individuals who had received vitamin replacement/supplementation within the preceding 3 months, had a known chronic disease, used regular medication, or had a history of pharmacologic treatment for depression or anxiety were excluded. Data collection and laboratory sampling were performed between September 2025 and November 2025 (autumn season).

Individuals with previously diagnosed anemia under active treatment were also excluded. Anemia was defined according to World Health Organization criteria as hemoglobin levels <13 g/dL in men and <12 g/dL in women.

Table 1. Demographic and laboratory characteristics according to sex

Variables (unit)	Men (n=57)	Women (n=171)
Age (years)	33.37±9.79 (18.00–56.00)	33.42±10.39 (17.00–58.00)
FSS score (points)	37.63±15.62 (9.00–63.00)	43.37±14.12 (9.00–63.00)
25(OH)D (ng/mL)	17.67±7.77 (4.99–49.60)	15.26±9.58 (3.00–75.80)
Vitamin B12 (pg/mL)	309.95±98.53 (148.00–545.00)	313.28±130.74 (100.00–834.00)
Folate (ng/mL)	6.58±2.43 (3.10–13.60)	7.19±3.55 (1.70–20.00)
Hemoglobin (g/dL)	15.48±1.33 (11.30–17.70)	12.77±1.32 (7.20–16.30)
Ferritin (ng/mL)	111.03±106.78 (7.47–591.70)	31.56±31.73 (3.13–279.10)
Iron (µg/dL)	99.46±36.20 (16.00–176.00)	78.17±39.01 (9.60–182.00)

Data are presented as median (interquartile range, 25th–75th percentile). 25(OH)D: 25-hydroxyvitamin D; FSS: Fatigue Severity Scale.

Clinical and Laboratory Assessment

Serum levels of vitamin B12, folate, ferritin, hemoglobin, iron, magnesium, and (25[OH]D) were retrospectively retrieved from the hospital information system.

Fatigue Assessment

Fatigue severity was assessed using the FSS, which has demonstrated validity and reliability in the Turkish population [17, 18]. The FSS is a 9-item instrument, with each item rated on a 7-point Likert scale ranging from 1 ("strongly disagree") to 7 ("strongly agree"), designed to measure subjective fatigue severity. In this study, the total FSS score was calculated on a scale of 9–63, with higher scores indicating greater fatigue severity. Following data verification, no missing item responses were identified, and the minimum observed FSS total score was corrected to 9.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean±standard deviation and minimum–maximum values and categorical variables as numbers and percentages. Normality of continuous variables was assessed using the Shapiro–Wilk test. Because the variables did not meet the assumption of normality, non-parametric statistical methods were applied. Sex-based comparisons were conducted using the Mann–Whitney U test. Associations between FSS scores and biochemical parameters were examined using Spearman's correlation test. P<0.05 was considered statistically significant.

Descriptive statistics were presented as mean±standard deviation for readability, whereas inferential analyses were performed using non-parametric methods due to non-normal data distribution.

RESULTS

The study included a total of 228 participants, comprising 57 males and 171 females. The mean age was 33.37±9.79 years in males and 33.42±10.39 years in females. The mean FSS score was 37.63±15.62 in males and 43.37±14.12 in females.

In descriptive analyses, mean vitamin D levels were 17.67±7.77 ng/mL in males and 15.26±9.58 ng/mL in females. Mean vitamin B12 levels were 309.95±98.53 pg/mL in males and 313.28±130.74 pg/mL in females, while folate levels were 6.58±2.43 ng/mL and 7.19±3.55 ng/mL, respectively. Hemoglobin levels were 15.48±1.33 g/dL in males and 12.77±1.32 g/dL in females. Ferritin levels were markedly higher in males (111.03±106.78 ng/mL) compared to females (31.56±31.73 ng/mL). Serum iron levels were 99.46±36.20 µg/dL in males and 78.17±39.01 µg/dL in females. Descriptive statistics are summarized in Table 1.

Normality analysis using the Shapiro–Wilk test demonstrated that most variables deviated significantly from normal distribution (p<0.05 for all variables except magnesium), and therefore, non-parametric tests were applied in subsequent analyses.

Spearman correlation analysis revealed a weak but statistically significant negative correlation between FSS scores and hemoglobin levels (r=-0.197, p=0.003), as

well as ferritin levels (r=-0.215, p=0.001). No significant correlations were observed between FSS and vitamin D (p=0.712), vitamin B12 (p=0.329), folate (p=0.587), magnesium (p=0.352), or serum iron levels (p=0.078). Correlation analysis data are summarized in Table 2.

Participants were divided into two groups according to the mean FSS item score. A mean FSS score of <4 was considered low fatigue, whereas a score of ≥4 was considered high fatigue. Comparative analysis using the Mann–Whitney U test showed that ferritin levels were significantly lower in the high-fatigue group compared to the low-fatigue group (44.09±67.98 vs. 65.26±69.11 ng/mL, p<0.001). Similarly, hemoglobin levels were significantly lower in the high-fatigue group (13.25±1.80 vs. 13.81±1.67 g/dL, p=0.043). Vitamin B12 levels were significantly higher in the high-fatigue group compared to the low-fatigue group (324.97±129.93 vs. 288.82±106.44 pg/mL, p=0.032).

No statistically significant differences were found between the low- and high-fatigue groups in terms of vitamin D (p=0.658), folate (p=0.258), magnesium (p=0.997), or serum iron levels (p=0.405).

A mean FSS item score of ≥4 was accepted as indicative of clinically significant fatigue, consistent with previous studies using the FSS.

Table 2. Spearman correlation analysis between FSS and biochemical parameters

Variables	ρ	p
FSS–hemoglobin (g/dL)	-0.20	0.003
FSS–ferritin (ng/mL)	-0.22	0.001
FSS–25(OH)D (ng/mL)	-0.03	0.712
FSS–vitamin B12 (pg/mL)	0.07	0.329
FSS–folate (ng/mL)	-0.04	0.587
FSS–magnesium (mg/dL)	-0.06	0.352
FSS–iron (µg/dL)	-0.12	0.078

Spearman's rank correlation coefficient (ρ) was used. A p<0.05 was considered statistically significant. FSS: Fatigue severity scale; 25(OH)D: 25-hydroxyvitamin D. TSH values were not included in the final analyses because complete laboratory data were unavailable for all participants.

DISCUSSION

Fatigue is a specific yet multidimensional symptom characterized by marked tiredness during daily activities, reduced energy to sustain routine tasks, and decreased performance. It is among the most common reasons for presentation to internal medicine and family medicine outpatient clinics, and its etiology is influenced by numerous factors, including hematologic, endocrine, metabolic, and psychosocial contributors [19, 20]. In a study by Dağ et al. [21] including 174 patients with iron deficiency anemia presenting to an internal medicine outpatient clinic, fatigue severity – assessed using a Visual Analog Scale for fatigue – was reported to be high (mean score, 6.2/10). Similarly, our study demonstrated significant associations between fatigue severity and hemoglobin and ferritin levels. However, because the primary aim of the present study was to evaluate the relationship between serum 25(OH)D levels and fatigue, participants with anemia were excluded to minimize the impact of overt hematologic disorders on the results [21]. Notably, the associations between fatigue and hemoglobin/ferritin persisted despite exclusion of anemic individuals, suggesting that fatigue may be related not only to overt anemia but also to reduced iron stores or subclinical states such as functional/early iron deficiency [22, 23]. Consistent with this interpretation, several studies in non-anemic individuals with low ferritin have reported that iron supplementation is associated with improvement in subjective fatigue outcomes, indirectly supporting our findings [22, 23].

In our study, no statistically significant association was found between serum 25(OH)D levels and fatigue severity. The literature on this topic remains inconsistent. Roy et al. [24]evaluated 174 patients presenting to an internal medicine outpatient clinic with fatigue and reported vitamin D deficiency in the vast majority; moreover, patient-reported fatigue decreased markedly after vitamin D supplementation. However, such findings may be influenced by selection bias and the subjective nature of post-supplementation assessment and may also reflect concurrent lifestyle changes and placebo effects. In a study by Knutsen et al. [25] including 572 patients of diverse ethnic backgrounds presenting with myalgia, fatigue, and headache, headache was reported to be more prominent than fatigue among those with low vitamin D levels, highlighting heterogeneity in symptom patterns. Conversely, a large-scale study conducted in the United Kingdom between 2006 and 2010 involving approximately 500,000 individuals did not demonstrate a meaningful association between vitamin D levels and self-reported fatigue and suggested that interventions aimed at increasing vitamin D levels are unlikely to have clinically significant effects on fatigue symptoms [26]. Differences

across studies may be attributable to variable control of confounding factors that can simultaneously contribute to both fatigue and low vitamin D status, such as obesity, physical inactivity, reduced sunlight exposure, dietary habits, sleep disturbances, and psychological conditions. In this context, the lack of comprehensive assessment of these potential confounders in the present study may have contributed to the absence of an observed vitamin D–fatigue association.

Although data collection was performed within a relatively limited seasonal period (autumn), future multicenter, prospective studies incorporating broader seasonal variation and detailed lifestyle variables may clarify the vitamin D–fatigue relationship more reliably. In addition, randomized controlled trials would provide higher-level evidence regarding the potential effect of vitamin D replacement on fatigue symptoms.

Study Limitations

This study has several limitations. First, its cross-sectional design precludes causal inference between vitamin D levels and fatigue severity. Second, the study was conducted at a single center with a predominantly female population, which may limit generalizability. Third, potential confounding variables including body mass index, physical activity, sleep quality, sunlight exposure, dietary habits, and inflammatory markers were not comprehensively evaluated. Finally, multivariable regression analyses adjusting for possible confounders such as age and sex were not performed.

Conclusion

In this study, no statistically significant association was found between serum 25(OH)D levels and FSS scores. In contrast, fatigue severity was associated with hematological parameters, particularly hemoglobin and ferritin. Given that fatigue is a multifactorial and subjective symptom, a comprehensive clinical evaluation of individuals presenting with fatigue should consider not only vitamin D status but also hematologic factors and other potentially contributing metabolic, psychological, and lifestyle-related determinants.

Ethics Committee Approval: This study was approved by The Ethics Committee of University of Health Sciences, Umraniye Training and Research Hospital on 10 July 2025 (Approval No: 237).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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REFERENCES

1. Jones G. 100 YEARS OF VITAMIN D: Historical aspects of vitamin D. Endocr Connect 2022;11:e210594. [CrossRef]
2. Lips P. Vitamin D physiology. Prog Biophys Mol Biol 2006;92:4-8. [CrossRef]
3. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol 2014;21:319-s29. [CrossRef]
4. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503-11. [CrossRef]
5. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J Clin Pract 2003;57:258-61. [CrossRef]
6. Griffin MD, Xing N, Kumar R. Vitamin D and its analogs as regulators of immune activation and antigen presentation. Annu Rev Nutr 2003;23:117-45. [CrossRef]
7. Yang L, Yun P, Li F. Association between vitamin D serum levels and thyroid cancer: a meta-analysis. Front Endocrinol (Lausanne) 2025;16:1602844. [CrossRef]
8. Valipour G, Saneei P, Esmaillzadeh A. Serum vitamin D levels in relation to schizophrenia: a systematic review and meta-analysis of observational studies. J Clin Endocrinol Metab 2014;99:3863-72. [CrossRef]
9. Plantone D, Primiano G, Manco C, Locci S, Servidei S, De Stefano N. Vitamin D in Neurological Diseases. Int J Mol Sci 2022;24:87. [CrossRef]
10. Rosenthal TC, Majeroni BA, Pretorius R, Malik K. Fatigue: an overview. Am Fam Physician 2008;78:1173-9.
11. Stadje R, Dornieden K, Baum E, Becker A, Biroga T, Bösner S, et al. The differential diagnosis of tiredness: a systematic review. BMC Fam Pract 2016;17:147. [CrossRef]
12. Morris G, Berk M, Walder K, Maes M. Central pathways causing fatigue in neuro-inflammatory and autoimmune illnesses. BMC Med 2015;13:28. [CrossRef]
13. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332:1351-62. [CrossRef]
14. Karshikoff B, Sundelin T, Lasselin J. Role of inflammation in human fatigue: relevance of multidimensional assessments and potential neuronal mechanisms. Front Immunol 2017;8:21. [CrossRef]
15. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis 1994;18(Suppl 1):S79-83. [CrossRef]
16. Armutlu K, Keser I, Korkmaz N, Akbiyik DI, Sümbüloğlu V, Güney Z, et al. Psychometric study of Turkish version of Fatigue Impact Scale in multiple sclerosis patients. J Neurol Sci 2007;255:64-8. [CrossRef]

17. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-3. [CrossRef]
18. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. Sleep 2008;31:1601-7. [CrossRef]
19. Cornuz J, Guessous I, Favrat B. Fatigue: a practical approach to diagnosis in primary care. CMAJ 2006;174:765-7. [CrossRef]
20. Murtagh J. Fatigue--a general diagnostic approach. Aust Fam Physician 2003;32:873-6.
21. Dağ A, Kıyak E. Demir eksikliği anemisi hastalarında yorgunluğun değerlendirilmesi. İnönü Üniversitesi Sağlık Hizmetleri Meslek Yüksekokulu Dergisi 2021;9:594-603. [CrossRef]
22. Pratt JJ, Khan KS. Non-anaemic iron deficiency - a disease looking for recognition of diagnosis: a systematic review. Eur J Haematol 2016;96:618-28. [CrossRef]
23. NIH. Hurrie D, Graham J, Rimmer E, Abousetta A, Bernstein C, Houston D, et al. Efficacy of iron replacement therapy on fatigue and work capacity in non-anemic adults with iron depletion: a systematic review of randomized controlled trials. PROSPERO. Available at: https://www.crd.york.ac.uk/PROSPERO/view/CRD42014007085. Accessed February 15, 2026.
24. Roy S, Sherman A, Monari-Sparks MJ, Schweiker O, Hunter K. Correction of low vitamin D improves fatigue: effect of correction of low vitamin D in fatigue study (EViDiF Study). N Am J Med Sci 2014;6:396-402. [CrossRef]
25. Knutsen KV, Brekke M, Gjelstad S, Lagerløv P. Vitamin D status in patients with musculoskeletal pain, fatigue and headache: a cross-sectional descriptive study in a multi-ethnic general practice in Norway. Scand J Prim Health Care 2010;28:166-71. [CrossRef]
26. Havdahl A, Mitchell R, Paternoster L, Davey Smith G. Investigating causality in the association between vitamin D status and self-reported tiredness. Sci Rep 2019;9:2880. [CrossRef]

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Original Article ORTHOPEDICS

Clinical and functional outcomes of open reduction and internal fixation for scapular fractures using the modified Judet approach

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ABSTRACT

OBJECTIVE: Displaced scapular fractures are uncommon injuries, and the optimal surgical approach remains controversial. Muscle-preserving techniques may improve post-operative shoulder function by minimizing soft-tissue damage. The purpose of the study was to evaluate the clinical and functional outcomes of open reduction and internal fixation (ORIF) using a muscle-preserving modified Judet approach in displaced scapular fractures and to assess the effect of surgical timing on post-operative shoulder function.

METHODS: This retrospective study included 12 adult patients who underwent ORIF for displaced scapular fractures between 2015 and 2024 with a minimum follow-up of 12 months. Fractures were classified according to the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association system and treated using the modified Judet approach. Functional outcomes were evaluated using the Constant-Murley, Disabilities of the Arm, Shoulder, and Hand (DASH), and University of California, Los Angeles (UCLA) scores, and shoulder range of motion was compared with the contralateral side.

RESULTS: Mean patient age was 35.3±15.0 years, and mean follow-up was 41.6±37.5 months. Fracture union was achieved in all patients at a mean of 7.5±1.7 weeks. No infections, neurovascular injuries, malunion, or infraspinatus atrophy occurred. Final shoulder motion reached 97% forward flexion, 89% abduction, 93% external rotation, and 90.9% internal rotation compared with the contralateral side. Mean constant, DASH, and UCLA scores were 84.0±8.6, 6.1±8.8, and 31.9±3.4, respectively. All patients returned to work at a mean of 4.7±2.3 months.

CONCLUSION: ORIF using a muscle-preserving modified Judet approach provides reliable union, low complication rates, and satisfactory functional recovery in displaced scapular fractures.

Keywords: Modified Judet approach; open reduction internal fixation; orthopedic trauma; scapular fracture; shoulder function; surgical timing.

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The scapula occupies a central position in the biomechanical linkage between the upper extremity and the trunk and plays a fundamental role in coordinating the shoulder's multiplanar movements. Scapular fractures are uncommon injuries, accounting for <1% of all fractures and approximately 3–5% of shoulder girdle injuries [1–4]. Due to the substantial muscular envelope and the intrinsic strength of the bone, these

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fractures most often result from high-energy trauma [3, 5, 6]. Motor vehicle collisions and falls from height are the most frequently reported mechanisms, and associated thoracic or skeletal injuries are present in 80–95% of cases [4, 5]. Consequently, a comprehensive, multidisciplinary approach is essential for accurate diagnosis and appropriate treatment planning.

Minimally displaced fractures generally yield satisfactory outcomes with short-term immobilization followed by early rehabilitation, whereas surgical management is recommended in the presence of significant displacement [5, 7]. Inadequate treatment of displaced fractures may lead to chronic pain, restricted shoulder range of motion, scapulothoracic dyskinesis, and rotator cuff dysfunction, resulting in substantial functional impairment [8].

The literature addressing the surgical treatment of scapular fractures largely consists of small case series with limited sample sizes. In series reported by Cofield (10 cases) [9], Mayo (27 cases) [10], and Schandelmaier (22 cases) [11], surgical management of displaced fractures resulted in satisfactory functional outcomes in the majority of patients. Current evidence indicates that both operative and non-operative treatments may result in favorable outcomes, depending on fracture pattern, and optimal management should be tailored to individual patient characteristics [12, 13].

Nevertheless, a universal consensus regarding surgical indications for scapular fractures has not yet been established. Commonly accepted criteria include an intra-articular step-off ≥4 mm, medial or lateral displacement >20 mm, angular deformity ≥40–45°, shortening >20–25 mm, and a glenopolar angle (GPA) ≤22°. In addition, fractures associated with disruption of the superior shoulder suspensory complex (SSSC) with ≥10 mm displacement, or concomitant acromion or coracoid fractures, are generally considered candidates for surgical intervention [14–16].

Open reduction and internal fixation (ORIF) of scapular fractures is technically demanding because of the scapula's complex three-dimensional anatomy, limited surgical exposure, and close proximity to critical neurovascular structures [17, 18]. In this context, the modified Judet approach has emerged as a favorable surgical option, providing adequate exposure of the lateral column and glenoid neck while minimizing soft-tissue disruption [19–21]. Various fixation devices have been described in the literature, including locking compression plates, reconstruction plates, T-plates, distal radius or humeral plates, and microplates [19].

Highlight key points

- ORIF using the muscle-preserving modified Judet approach achieved 100% fracture union with a mean healing time of 7.5 weeks.
- The procedure resulted in excellent functional outcomes, with high Constant–Murley and UCLA scores and low DASH and VAS scores.
- Postoperative shoulder range of motion reached near-symmetrical levels (89–97%) compared with the contralateral side.
- The complication rate was minimal, with no infections, neurovascular injuries, or muscle atrophy observed.
- Earlier surgical intervention showed a trend toward better functional outcomes, although not statistically significant.

Recent studies have reported high union rates and satisfactory functional outcomes following surgical fixation of scapular fractures. In line with these findings, recent literature has increasingly supported the surgical management of displaced scapular fractures, demonstrating favorable functional outcomes and low complication rates following ORIF using muscle-preserving techniques [3, 8]. Cole et al. [15] reported a 100% union rate and near-normal shoulder range of motion in fractures involving the scapular body and glenoid neck. Jaikish and Sambandam reported a mean Constant-Murley score of 80 after plate fixation of displaced extra-articular fractures [19], while Vidović et al. [14] documented a mean Constant-Murley score of 93 with low complication rates. Nonetheless, potential complications, including infection, implant irritation, and neurovascular injury, should not be overlooked [5].

Despite increasing interest in the surgical management of scapular fractures, the current literature remains limited to small retrospective series with heterogeneous patient populations, fracture patterns, and outcome measures. In particular, studies specifically evaluating the clinical and functional outcomes of ORIF using a muscle-preserving modified Judet approach are scarce. Furthermore, the effect of surgical timing on post-operative shoulder function has not been clearly established. Therefore, the aim of this study was to evaluate the clinical and functional outcomes of ORIF performed using a muscle-preserving modified Judet approach in displaced scapular fractures and to investigate the effect of surgical timing on post-operative shoulder function.

MATERIALS AND METHODS

This retrospective study included 12 patients who underwent ORIF for scapular fractures between 2015 and 2024. Patients aged ≥18 years with displaced fractures of the scapular body and/or neck who were treated surgically and completed a minimum of 12 months of clinical and radiological follow-up were included. Patients with pathological fractures or those who underwent simultaneous ipsilateral humeral or clavicular surgery were excluded. This study was approved by the institutional ethics committee (approval date: November 18, 2025; approval number: E-54132726-000-295097595). The requirement for informed consent was waived due to the retrospective nature of the study. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Diagnosis was established using anteroposterior, scapular Y-lateral, and axillary radiographs in all patients. Fracture configurations were evaluated using three-dimensional computed tomography scans in all patients to allow detailed assessment of fracture morphology. Fractures were classified according to the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) scapular fracture classification system. Surgical indications were determined based on widely accepted criteria in the literature, including an intra-articular step-off ≥4 mm, medial or lateral displacement >20 mm, angular deformity ≥40–45°, GPA ≤22°, and double disruptions of the SSSC with ≥10 mm displacement [14, 15].

All surgical procedures were performed under general anesthesia following prophylactic antibiotic administration. Patients were positioned in a semi-prone position with the ipsilateral upper extremity left free to facilitate fluoroscopic imaging and manipulation of the scapula, and a support pad was placed beneath the anterior chest wall. A modified posterior Judet approach (boomerang incision) was used in all cases.

The skin incision was initiated at the posterior corner of the acromion, extended medially along the scapular spine, and continued inferiorly toward the inferior angle of the scapula. Sharp dissection was carried down to the fascia of the deltoid and infraspinatus muscles. Without detaching the deltoid muscle from the scapular spine, the posterior border of the deltoid was elevated and retracted anteriorly, thereby exposing the infraspinatus muscle. The infraspinatus was then elevated subperiosteally from the infraspinatus fossa and retracted laterally. The suprascapular nerve and artery passing through the posterosuperior aspect of the glenoid were carefully identified, dissected, and protected.

Gentle lateral retraction of the lateral portions of the infraspinatus and teres minor muscles allowed adequate exposure of the lateral border of the scapula. In selected cases, the posterior capsule was cautiously opened to assess the articular surface. Fracture fragments were mobilized and reduced, enabling restoration of the glenoid articular surface and indirect reduction of fractures extending to the glenoid neck. Reduction was facilitated using temporary Kirschner wires placed along the lateral border of the scapula, glenoid neck, or scapular spine, and stabilized when necessary with small pointed reduction forceps.

Plates were precontoured and applied to the intact lateral border of the scapula and secured in this region. This technique facilitated maintenance of reduction and allowed controlled compression of the short glenoid neck fragment. Buttress fixation of the lateral border was achieved using 2.5–3.0 mm locking scapular plates, dynamic compression plates, and/or periarticular screws. Boomerang plates were preferred for fractures involving the scapular body. In fracture patterns involving displacement of the scapular spine or medial border, direct reduction and stabilization were achieved through the same surgical approach using tubular or reconstruction plates (Fig. 1, 2).

At the conclusion of the procedure, the posterior joint capsule and infraspinatus fascia were anatomically repaired. To prevent dead space formation, the infraspinatus muscle was sutured to the plates positioned on the scapular body and subsequently reattached to the medial border of the scapula together with the fascia. The deltoid muscle was returned to its native anatomical position; repair of the deltoid fascia was not required. After achieving meticulous hemostasis, a drain was placed at an appropriate level to reduce the risk of post-operative seroma formation. The surgical layers were closed in accordance with anatomical planes, and a sterile dressing was applied.

In cases of scapular fractures associated with concomitant acromion, coracoid, and/or glenoid fractures, all associated fractures were anatomically reduced and stabilized with appropriate internal fixation devices during the same surgical session.

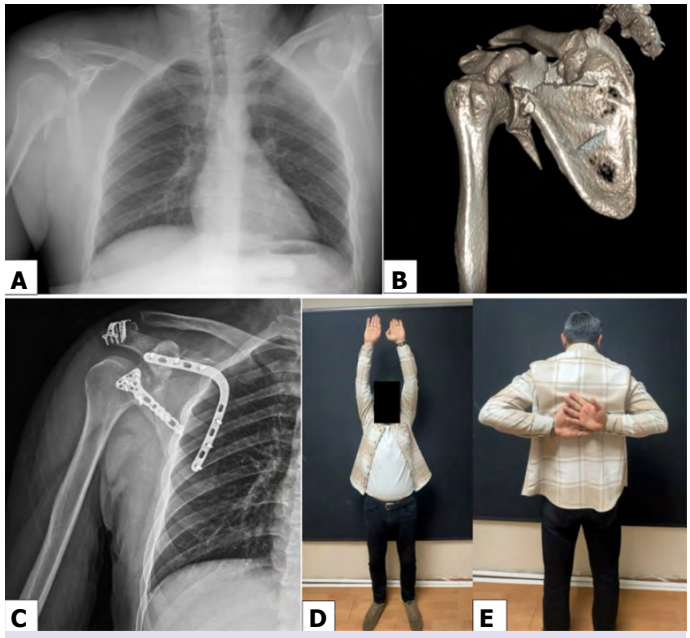

FIGURE 1. Representative case of a patient with a displaced scapular fracture treated with open reduction and internal fixation using the modified Judet approach. **(A)** Pre-operative radiograph demonstrating the fracture pattern. **(B)** Three-dimensional computed tomography reconstruction showing fracture configuration and glenoid involvement. **(C)** Post-operative radiograph demonstrating anatomical reduction and stable fixation. **(D)** Clinical photograph demonstrating satisfactory forward elevation. **(E)** Clinical photograph demonstrating internal rotation at final follow-up.

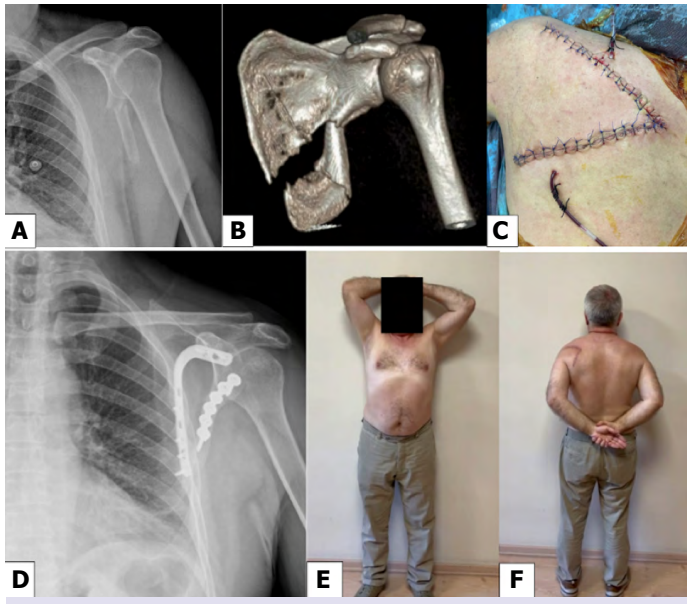

FIGURE 2. Representative case of a complex displaced scapular fracture treated with open reduction and internal fixation using the modified Judet approach. **(A)** Pre-operative radiograph demonstrating fracture displacement. **(B)** Three-dimensional computed tomography reconstruction showing fracture configuration and involvement of the scapular body. **(C)** Intraoperative photograph demonstrating the modified Judet approach and surgical exposure. **(D)** Post-operative radiograph showing anatomical reduction and stable fixation. **(E)** Clinical photograph demonstrating satisfactory forward elevation. **(F)** Clinical photograph demonstrating internal rotation at final follow-up.

Postoperatively, patients were provided with a simple shoulder sling, and immediate elbow range-of-motion exercises were permitted. Pendulum exercises were initiated at the 4th post-operative week. After the 6th week, active shoulder range-of-motion exercises and a supervised physical therapy program were commenced. Resistance and strengthening exercises were allowed beginning at the 3rd post-operative month. This rehabilitation protocol was applied uniformly to all patients, and no modifications were required due to associated injuries.

Functional outcomes were assessed using the Constant-Murley score [22], Disabilities of the Arm, Shoulder and Hand (DASH) score [23], and the University of California, Los Angeles (UCLA) shoulder score [24]. Shoulder range of motion was evaluated using goniometric measurements of forward flexion, abduction, and internal and external rotation. All range-of-motion measurements and functional outcome assessments were obtained at the final follow-up visit for each patient. Clinical evaluation included assessment of post-operative infraspinatus muscle atrophy, pain level, development of complications, time to return to work, and overall functional recovery. Surgical timing was recorded as the interval between injury and operation, and its relationship with post-operative functional outcomes was analyzed. Clinical evaluations were performed by an independent orthopedic surgeon who was not involved in the surgical procedures and was blinded to the study design and patient information to minimize potential assessment bias.

Radiological evaluations were independently performed by two orthopedic and traumatology surgeons who were not involved in the study. Fracture union status and time to union, as well as the presence of secondary arthrosis, were assessed. Union was defined as painless functional loading and evidence of callus formation on biplanar radiographs.

Table 1. Demographic and clinical characteristics of the patients

Variables	Value
Number of patients	12
Age (years)	35.3±15.0
Sex (male / female)	11 (91.7%) / 1 (8.3%)
Body mass index (kg/m²)	28.7±2.9
Smoking status (yes / no)	6 (50%) / 6 (50%)
Follow-up duration (months)	41.6±37.5
Affected side (right / left)	2 (16.7%) / 10 (83.3%)
Dominant hand (right / left)	12 (100%) / 0 (0%)
Trauma mechanism (high / low energy)	9 (75%) / 3 (25%)
Time from injury to surgery (days)	8.1±5.6
Associated injuries (yes/no)	4 (33.3%) / 8 (67.7%)

Values are presented as mean±standard deviation or number of patients.

Table 2. Radiological and functional outcomes

Outcome measure	Result
Fracture union rate	12 (100%)
Union time (weeks)	7.5±1.7
Return-to-work rate	12 (100%)
Time to return to work (months)	4.7±2.3
Complication (yes / no)	Implant irritation: 1 (8.3%) / 11 (91.7%)
UCLA score	31.9±3.4
Constant–Murley score	84.0±8.6
DASH score	6.1±8.8
VAS pain score	1.33±1.62

UCLA: University of California at Los Angeles Shoulder Score; DASH:Disabilities of the Arm, Shoulder and Hand questionnaire; VAS: Visual Analog Scale.

Statistical Analysis

Statistical analyses were conducted using IBM Statistical Package for the Social Sciences Statistics software (version 26.0; IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data are presented as mean±standard deviation, whereas non-normally distributed data are reported as median (minimum–maximum). Categorical variables are expressed as frequencies and percentages. Comparisons of continuous variables between the injured and contralateral shoulders were performed using the paired t-test. A $p<0.05$ was considered statistically significant for all analyses.

RESULTS

A total of 12 patients were included in the study. The mean age was 35.3±15.0 years. Fractures were located on the right side in 16.7% of patients (n=2) and on the left side in 83.3% (n=10); the dominant extremity was the right side in all patients (100%). Eleven patients (91.7%) were male, and one (8.3%) was female. The mean body mass index was 28.7±2.9 kg/m^2. Six patients (50%) were smokers, and six (50%) were non-smokers. No patient had additional comorbidities such as hypertension, diabetes mellitus, or osteoporosis. The mean follow-up duration was 41.6±37.5 months, with a median follow-up of 19 months (range, 12–108 months) (Table 1).

The mechanism of injury was high-energy trauma in nine patients (75%) and low-energy trauma in three patients (25%). One patient (8.3%) sustained an open fracture. The mean time from injury to surgery was 8.1±5.6 days. All patients were treated surgically using the modified Judet approach (Table 1).

According to the AO/OTA classification, scapular body fractures (14B2) were present in 75% of cases (n=8), and scapular neck fractures (14B1) were identified in 25% (n=4). Five patients had associated coracoid fractures (14A1), and three patients had associated acromion fractures (14A2). All patients (100%) had concomitant glenoid rim fractures (14F1.3), of which 41.7% were classified as 14F1.3P, 33.3% as 14F1.3I, and 25.0% as 14F1.3E.

One patient (8.3%) developed implant irritation as a post-operative complication; the implant was electively removed approximately 1 year after surgery, following confirmed fracture union. No patient demonstrated infraspinatus muscle atrophy or post-operative neurovascular injury at final follow-up. Fracture union was achieved in all patients (100%), with a mean time to union of 7.5±1.7 weeks. All patients returned to work, with a mean return-to-work time of 4.7±2.3 months (Table 2).

Associated injuries were observed in four patients (33.3%), including L2–L3–L4 transverse process fractures (n=1), a left coronoid fracture (n=1), a metacarpal fracture (n=1), and right upper lobe pulmonary contusion (n=1). No additional injuries were identified in eight patients (66.7%) (Table 1).

TABLE 3. Comparison of active range of motion between the affected and contralateral shoulders

Motion	Affected side	Contralateral side	p	Effect size (Cohen's dz)
Forward flexion (°)	167.5c 15.4	172.5±13.6	0.339[a]	N/A
Abduction (°)	150.0±42.2	168.8±20.4	0.148[a]	N/A
External rotation (°)	78.8±17.1	85.0±7.4	0.340[a]	N/A
Internal rotation (°)	75.0±22.5	82.5±10.3	0.221[a]	N/A

N/A: Not applicable; a: Paired t-test; Bolded p values indicate statistical significance.

TABLE 4. Functional outcomes according to surgical timing (median split)

Outcome measure	Early surgery (≤8 days, n=6)	Late surgery (>8 days, n=6)
Constant score	**86.2**	**81.8**
DASH score	5.7	6.5
UCLA score	**32.7**	**31.2**
VAS pain score	1.2	1.5

UCLA: University of California at Los Angeles Shoulder Score; DASH:Disabilities of the Arm, Shoulder and Hand questionnaire; VAS: Visual Analog Scale.

At final follow-up, mean forward flexion of the injured shoulder was 167.5±15.4°, compared with 172.5±13.6° in the contralateral shoulder. Forward flexion of the injured shoulder reached approximately 97% of the contralateral side, with no statistically significant difference between sides (p=0.339). Mean abduction was 150.0±42.2° on the injured side and 168.8±20.4° on the contralateral side; injured-side abduction reached approximately 89% of the contralateral shoulder, with no significant difference (p=0.148). Mean external rotation was 78.8±17.1° on the injured side and 85.0±7.4° on the contralateral side, corresponding to approximately 93% of the contralateral value, without a statistically significant difference (p=0.340). Mean internal rotation was 75.0±22.5° on the injured side and 82.5±10.3° on the contralateral side; injured-side internal rotation reached approximately 90.9% of the contralateral shoulder, with no significant difference between sides (p=0.221) (Table 3).

At final follow-up, the mean visual analog scale pain score was 1.33±1.62 (median: 0.5; range: 0–4), and no pain was reported in half of the patients. The mean UCLA shoulder score was 31.9±3.4 (median: 32; range: 27–35), the mean DASH score was 6.1±8.8 (median: 1.15; range: 0–22.7), and the mean Constant-Murley score was 84.0±8.6 (median: 86; range: 72–95) (Table 2).

Surgical timing showed a trend toward influencing functional recovery. Patients treated within the first 8 days had slightly higher constant and UCLA scores compared with those treated later, although these differences did not reach statistical significance and therefore should be interpreted with caution (Table 4).

DISCUSSION

In recent years, the surgical management of scapular fractures has been increasingly favored because it provides more predictable clinical and functional outcomes. The present study contributes to the existing literature in several important aspects. First, it specifically evaluates the clinical and functional outcomes of a muscle-preserving modified Judet approach, which has been relatively underreported. Second, a comprehensive assessment including both radiological and functional outcomes was performed using validated scoring systems. Third, the potential influence of surgical timing on post-operative functional recovery was analyzed, which remains a less clearly defined factor in current literature. These findings provide additional insight into the role of surgical technique and timing in optimizing outcomes for displaced scapular fractures.

Although conservative treatment has historically been the mainstay, fractures with significant displacement are frequently associated with restricted shoulder range of motion, persistent pain, and functional impairment. Disruption of anatomical alignment compromises shoulder girdle biomechanics by reducing rotator cuff efficiency, impairing scapulothoracic rhythm, and predisposing to impingement and secondary degenerative changes [1]. In particular, scapular neck fractures may result in altered glenoid orientation and distur-

bance of the optimal length–tension relationship of the surrounding musculature, thereby diminishing rotator cuff strength and lever-arm mechanics and leading to substantial functional deficits [25]. Ada and Miller demonstrated shoulder elevation weakness, subacromial pain, and motion limitation in patients with displaced scapular neck fractures [1]. Furthermore, the systematic review by Zlowodzki et al. [26] reported poor functional outcomes, radiographic deformity, and persistent pain in a subset of conservatively treated extra-articular fractures, underscoring the importance of surgical intervention in appropriately selected cases. Similarly, Kannan et al. [27] emphasized that surgical fixation yields superior clinical outcomes in markedly displaced and comminuted fractures, particularly in scapular neck fractures with displacement >10 mm, where post-operative functional gains are more pronounced.

Contemporary surgical series have consistently demonstrated high union rates and satisfactory functional recovery following operative fixation of scapular fractures [28, 29]. However, the absence of a clear consensus on surgical indications and the lack of standardized reporting of radiographic parameters, such as displacement, angulation, and the GPA, limit the applicability of available evidence to clinical decision-making [26, 28]. This heterogeneity, particularly in small case series, complicates the interpretation and comparison of outcomes across studies.

Scapular fractures typically result from high-energy trauma and are frequently associated with concomitant injuries. Rib fractures are the most commonly reported associated injuries in the literature and may increase the risk of pulmonary complications [3, 30]. In the series by Vidović et al., [14] rib fractures constituted the most frequent associated injury, consistent with this expectation. Moreover, potentially severe neurovascular injuries, including brachial plexus and subclavian artery damage, may occur, emphasizing the importance of thorough clinical evaluation and appropriate imaging [19]. Although some studies have reported an increasing incidence of scapular fractures related to low-energy trauma in elderly women, high-energy mechanisms remain predominant in patients referred to tertiary trauma centers [28]. In the present study, 75% of injuries resulted from high-energy mechanisms. Although associated injuries were identified in one-third of the patients, they did not adversely affect surgical outcomes or functional recovery. Stabilization of concomitant acromion, coracoid, and glenoid fractures during the same surgical session may have contributed to restoration of shoulder girdle stability and preservation of functional outcomes.

Functional outcomes following scapular fractures vary widely in the literature for both surgical and conservative management. Vidović et al. [14] reported high Constant-Murley scores (93.5±8.9) after surgical treatment; while Bartoníček and Frič and Porcellini et al. [29, 31] also documented satisfactory post-operative Constant-Murley scores. Schroder et al. [28] demonstrated a 100% union rate and favorable functional outcomes with low DASH scores. In contrast, results of conservative treatment are more heterogeneous: Schofer et al. [30] reported a mean Constant-Murley score of 79, Bozkurt et al. [32] 78.8, and van Noort and van Kampen 90 [33]. Rajfer et al. [34] and Darwish [20] reported good functional outcomes with low DASH scores following non-operative treatment. In the present study, a mean Constant-Murley score of 84.0±8.6 and a mean DASH score of 6.1±8.8 indicate that patients were able to return to daily activities with minimal functional limitation. These findings support the notion that surgical fixation of displaced scapular fractures, when performed with appropriate indications, facilitates meaningful functional recovery.

From a technical standpoint, the classic Judet approach may require substantial retraction of the infraspinatus muscle to access the scapular neck and infraglenoid region, which has been associated with post-operative infraspinatus atrophy and external rotation weakness [31, 35, 36]. The modified Judet approach aims to preserve muscle integrity by minimizing infraspinatus dissection. Porcellini et al. [31] reported reduced infraspinatus hypotrophy and external rotation deficits with the modified technique. Jaikish and Sambandam [19] similarly reported no post-operative loss of muscle strength, even in cases requiring medial column fixation, provided that meticulous muscle repair was performed. In the present study, no patient demonstrated post-operative infraspinatus hypotrophy or clinically significant external rotation weakness. These findings suggest that the soft-tissue–sparing nature of the modified Judet approach, combined with careful rotator cuff repair, contributes positively to functional recovery.

Reported complication rates following surgical treatment of scapular fractures are generally low. Kiritsis et al. [5] reported an early post-operative complication rate of 2.0% and a surgical site infection rate of 0.8%. Bauer et al. [37] and Cole et al. [38] reported no short-term complications in their respective series of 20 and 6 patients.

Similarly, Vidović et al. [14] observed no post-operative infections in a series of 14 patients. In contrast, Lantry et al. [39] reported an infection rate of 4.2% in a systematic review, and Rollo et al. [40] reported surgical site infection and reoperation rates of 5% in a 20-patient series. In the present study, implant irritation occurred in only one patient (8.3%) and was managed with elective implant removal after fracture union. No surgical site infections, neurovascular injuries, or major complications requiring reoperation were observed. These low complication rates indicate that safe and reliable surgical outcomes can be achieved in scapular fractures with appropriate technique and meticulous soft-tissue handling.

Regarding shoulder range of motion, several studies have reported no significant differences between the injured and contralateral shoulders following surgical treatment [19, 20, 28]. However, many reports present absolute values without direct statistical comparison to the uninjured side. In the present study, shoulder range of motion was assessed comparatively, demonstrating that forward flexion, abduction, internal rotation, and external rotation of the injured shoulder reached 97%, 89%, 90.9%, and 93% of the contralateral side, respectively, with no statistically significant differences. This finding is clinically relevant, as it demonstrates that surgical treatment can effectively restore shoulder function to near-symmetrical levels.

ORIF performed through the muscle-sparing modified Judet approach was associated with successful fracture union, satisfactory functional recovery, and preservation of shoulder range of motion in patients with displaced scapular fractures. Although a trend toward better functional outcomes was observed in patients who underwent earlier surgery, this finding did not reach statistical significance and should be interpreted with caution. Further studies with larger patient cohorts are required to better clarify the potential influence of surgical timing on post-operative outcomes.

This study has several limitations. Its retrospective design and relatively small sample size (n=12) may limit both the statistical power and the generalizability of the findings. The absence of a control group precluded direct comparison between surgical and conservative treatment modalities. In addition, heterogeneity in fracture patterns and the presence of associated injuries may have influenced the outcomes. Therefore, the results should be interpreted with caution, and larger multicenter studies are needed to validate the present findings.

Conclusion

In conclusion, the present study suggests that ORIF performed via the modified Judet approach is associated with high union rates, a low complication profile, and satisfactory clinical and functional outcomes in displaced scapular fractures. Post-operative shoulder range of motion closely approximated that of the contralateral side, and functional scores were comparable to those reported in previous case series. Although these findings are encouraging, they should be interpreted in light of the retrospective design, small sample size, and absence of a comparative group. Further studies with larger cohorts and comparative designs are needed to confirm the effectiveness of this approach and to better define its role in the management of displaced scapular fractures.

Ethics Committee Approval: This study was approved by The Institutional Review Board of Umraniye Training and Research Hospital, University of Health Sciences (date: 18.11.2025, IRB No: E-54132726-000-295097595).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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REFERENCES

1. Ada JR, Miller ME. Scapular fractures. Analysis of 113 cases. Clin Orthop Relat Res 1991;269:174-80. [CrossRef]
2. Goss TP. Scapular Fractures and Dislocations: Diagnosis and Treatment. J Am Acad Orthop Surg 1995;3:22-33. [CrossRef]
3. Tatro JM, Schroder LK, Molitor BA, Parker ED, Cole PA. Injury mechanism, epidemiology, and Hospital trends of scapula fractures: A 10-year retrospective study of the National Trauma Data Bank. Injury 2019;50:376-81. [CrossRef]
4. Vander Voort W, Wilkinson B, Bedard N, Hendrickson N, Willey M. The operative treatment of scapula fractures: an analysis of 10,097 patients. Iowa Orthop J 2022;42:213-6.
5. Kiritsis NR, Reiter CR, Satalich JR, Protzuk O, O'Neill CN, Vanderbeck JL. Risk factors and incidence of short-term complications following open reduction and internal fixation of scapula fractures. Eur J Orthop Surg Traumatol 2024;34:3163-9. [CrossRef]
6. Cole PA, Gauger EM, Schroder LK. Management of scapular fractures. J Am Acad Orthop Surg 2012;20:130-41. [CrossRef]

7. Hardegger FH, Simpson LA, Weber BG. The operative treatment of scapular fractures. J Bone Joint Surg Br 1984;66:725-31. [CrossRef]
8. Pires RE, Giordano V, de Souza FSM, Labronici PJ. Current challenges and controversies in the management of scapular fractures: a review. Patient Saf Surg 2021;15:6. [CrossRef]
9. Kavanagh BF, Bradway JK, Cofield RH. Open reduction and internal fixation of displaced intra-articular fractures of the glenoid fossa. J Bone Joint Surg Am 1993;75:479-84. [CrossRef]
10. Mayo KA, Benirschke SK, Mast JW. Displaced fractures of the glenoid fossa. Results of open reduction and internal fixation. Clin Orthop Relat Res 1998;347:122-30. [CrossRef]
11. Schandelmaier P, Blauth M, Schneider C, Krettek C. Fractures of the glenoid treated by operation. A 5- to 23-year follow-up of 22 cases. J Bone Joint Surg Br 2002;84:173-7. [CrossRef]
12. Lehmann LJ, Schmalzl J. Scapulafrakturen [Scapular fractures]. Unfallchirurgie (Heidelb) 2024;127:69-78. [Article in German] [CrossRef]
13. Schmidt V, Mukka S, Bergdahl C, Ekholm C, Brüggemann A, Wolf O. Epidemiology, treatment, and mortality of 3973 scapula fractures from the Swedish fracture register. J Shoulder Elbow Surg 2025;34:e47-e56. [CrossRef]
14. Vidović D, Benčić I, Ćuti T, Bakota B, Bekić M, Dobrić I, et al. Surgical treatment of scapular fractures: Results and complications. Injury 2021;52(Suppl 5):S38-S43. [CrossRef]
15. Cole PA, Gauger EM, Herrera DA, Anavian J, Tarkin IS. Radiographic follow-up of 84 operatively treated scapula neck and body fractures. Injury 2012;43:327-33. [CrossRef]
16. Limb D. Scapula fractures: a review. EFORT Open Rev 2021;6:518-25. [CrossRef]
17. da Costa MP, Braga AC, Geremias RA, Tenor Junior AC, Ribeiro FR, Brasil Filho R. Anatomy of the scapula applied to the posterior surgical approach: safety parameters during access to the lateral angle. Rev Bras Ortop (Sao Paulo) 2019;54:587-90. [CrossRef]
18. Villatte G, Antoni M, Girard M, Marcheix PS. Articular and extra-articular scapula fracture. Orthop Traumatol Surg Res 2026;112:104438. [CrossRef]
19. Jaikish S, Sambandam B. Functional outcome of open reduction and internal fixation of displaced extra-articular scapula fractures. Indian J Orthop 2020;55:708-13. [CrossRef]
20. Darwish AE. Long-term outcome of open reduction and internal fixation of scapular fractures. The Egyptian Orthopaedic Journal 2022;57:205-8. [CrossRef]
21. Konda SR, Solasz SJ, Ganta A. Operative fixation of extra-articular scapula body fracture through a modified judet approach. J Orthop Trauma 2022;36(Suppl 3):S3-S4. [CrossRef]
22. Constant CR, Gerber C, Emery RJ, Søjbjerg JO, Gohlke F, Boileau P. A review of the Constant score: modifications and guidelines for its use. J Shoulder Elbow Surg 2008;17:355-61. [CrossRef]
23. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med 1996;29:602-8. [CrossRef]
24. Amstutz HC, Sew Hoy AL, Clarke IC. UCLA anatomic total shoulder arthroplasty. Clin Orthop Relat Res 1981;155:7-20. [CrossRef]
25. Chadwick EK, van Noort A, van der Helm FC. Biomechanical analysis of scapular neck malunion--a simulation study. Clin Biomech (Bristol) 2004;19:906-12. [CrossRef]
26. Zlowodzki M, Bhandari M, Zelle BA, Kregor PJ, Cole PA. Treatment of scapula fractures: systematic review of 520 fractures in 22 case series. J Orthop Trauma 2006;20:230-3. [CrossRef]
27. Kannan S, Singh HP, Pandey R. A systematic review of management of scapular fractures. Acta Orthop Belg 2018;84:497-508.
28. Schroder LK, Gauger EM, Gilbertson JA, Cole PA. Functional outcomes after operative management of extra-articular glenoid neck and scapular body fractures. J Bone Joint Surg Am 2016;98:1623-30. [CrossRef]
29. Bartoníček J, Frič V. Scapular body fractures: results of operative treatment. Int Orthop 2011;35:747-53. [CrossRef]
30. Schofer MD, Sehrt AC, Timmesfeld N, Störmer S, Kortmann HR. Fractures of the scapula: long-term results after conservative treatment. Arch Orthop Trauma Surg 2009;129:1511-9. [CrossRef]
31. Porcellini G, Palladini P, Congia S, Palmas A, Merolla G, Capone A. Functional outcomes and clinical strength assessment after infraspinatus-sparing surgical approach to scapular fracture: Does it really make a difference? J Orthop Traumatol 2018;19:15. [CrossRef]
32. Bozkurt M, Can F, Kirdemir V, Erden Z, Demirkale I, Başbozkurt M. Conservative treatment of scapular neck fracture: the effect of stability and glenopolar angle on clinical outcome. Injury 2005;36:1176-81. [CrossRef]
33. van Noort A, van Kampen A. Fractures of the scapula surgical neck: outcome after conservative treatment in 13 cases. Arch Orthop Trauma Surg 2005;125:696-700. [CrossRef]
34. Rajfer RA, Salopek T, Mosier BA, Miller MC, Altman GT. Long-term functional outcomes of nonoperatively treated highly displaced scapular body and neck fractures. Orthopedics 2020;43:e177-81. [CrossRef]
35. Harmer LS, Phelps KD, Crickard CV, Sample KM, Andrews EB, Hamid N, et al. A Comparison of exposure between the classic and modified judet approaches to the scapula. J Orthop Trauma 2016;30:235-9. [CrossRef]
36. Noguchi T, Mautner JF, Duncan SFM. Dorsal plate fixation of scapular fracture. J Hand Surg Am 2017;42:843.e1-e5. [CrossRef]
37. Bauer G, Fleischmann W, Dussler E. Displaced scapular fractures: indication and long-term results of open reduction and internal fixation. Arch Orthop Trauma Surg 1995;114:215-9. [CrossRef]
38. Cole PA Jr, Jacobson AR, Cole PA Sr. Open reduction and internal fixation of scapula fractures in a geriatric series. Geriatr Orthop Surg Rehabil 2015;6:180-5. [CrossRef]
39. Lantry JM, Roberts CS, Giannoudis PV. Operative treatment of scapular fractures: a systematic review. Injury 2008;39:271-83. [CrossRef]
40. Rollo G, Huri G, Meccariello L, Familiari F, Çetik RM, Cataldi C, et al. Scapular body fractures: Short-term results of surgical management with extended indications. Injury 2021;52:481-6. [CrossRef]

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Original Article PHYSICAL MEDICINE & REHABILITATION

Clinical outcomes following a home-based dual-task telerehabilitation program in Parkinson's disease

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ABSTRACT

OBJECTIVE: To examine changes in motor and non-motor clinical outcomes following participation in a home-based telerehabilitation program incorporating motor-cognitive dual-task exercises in individuals with Parkinson's disease (PD).

METHODS: This retrospective cohort study analyzed prospectively recorded clinical data obtained from a government-supported telerehabilitation service implemented at a tertiary physical medicine and rehabilitation center in Istanbul, Türkiye. The study included 60 participants with mild-to-moderate PD (Hoehn and Yahr stages 1–3) who completed a 6-week intervention consisting of 30 supervised sessions (60 min/session, 5 days/week). The program combined motor exercises, cognitive tasks, and integrated dual-task activities delivered through synchronous video-based supervision. Clinical assessments included balance (Berg Balance Scale, Mini-BESTest), balance confidence (Activities-specific Balance Confidence Scale), mobility (Timed Up and Go test), manual dexterity (Nine-Hole Peg Test), quality of life (PD Questionnaire-39), depressive symptoms (Beck Depression Inventory), and self-reported urinary/fecal incontinence.

RESULTS: Post-intervention analyses demonstrated statistically significant improvements in all evaluated outcomes (all $p<0.001$). Participants showed better balance, mobility, and hand dexterity, accompanied by increased balance confidence and improved gait-related performance. Quality-of-life scores improved, while depressive symptom severity decreased following the intervention. The proportion of participants reporting urinary incontinence declined from 40% to 23%, whereas fecal incontinence decreased from 12% to 2%. Effect size analyses demonstrated moderate-to-large improvements across the primary and key secondary outcomes, with the largest effects observed for depressive symptoms, quality of life, and balance-related performance. No intervention-related adverse events were identified during the study period.

CONCLUSION: Participation in a remotely supervised, dual-task–based telerehabilitation program was associated with favorable changes across multiple clinical domains in individuals with PD. The findings suggest that home-based telerehabilitation may represent a feasible and clinically relevant rehabilitation approach within routine practice. Given the retrospective nature of the study and the lack of a control group, the observed findings should be considered preliminary. Prospective randomized controlled trials are needed to confirm these findings and evaluate their long-term clinical significance.

Keywords: Dual-task training; Parkinson's disease; quality of life; remote rehabilitation; telerehabilitation.

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Parkinson's disease (PD) is a chronic and progressive neurodegenerative condition associated with the loss of dopaminergic neurons within the substantia nigra and related basal ganglia dysfunction [1–3]. The disease

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is characterized not only by motor manifestations, such as tremor, rigidity, bradykinesia, and postural instability, but also by a broad spectrum of non-motor manifestations, including cognitive decline, depressive symptoms, and autonomic disturbances [4]. Together, these impairments negatively affect daily functioning, social participation, and overall quality of life, while also increasing long-term healthcare needs.

Exercise-based rehabilitation has become an important component of contemporary PD management. Previous research has demonstrated that structured rehabilitation interventions may contribute to improvements in motor performance, functional mobility, and neuroplastic adaptation while helping to reduce disability progression [5–7]. Among emerging rehabilitation approaches, motor-cognitive dual-task training has received growing attention because it combines simultaneous cognitive and motor demands that resemble everyday functional activities. Earlier studies have suggested that dual-task interventions may positively influence gait performance, postural control, and executive functioning in individuals with PD [8]. This approach may be particularly relevant for PD-related gait and balance impairments, which often worsen during cognitively demanding situations and may consequently increase fall risk.

At the same time, developments in digital health technologies have expanded the use of telerehabilitation within neurological rehabilitation practice. Telerehabilitation provides opportunities for remotely supervised exercise, individualized treatment planning, and ongoing patient monitoring, potentially reducing barriers associated with transportation difficulties, geographical limitations, and restricted access to specialized rehabilitation services [9–11]. Evidence from systematic reviews and clinical investigations suggests that remotely delivered rehabilitation may improve functional outcomes, treatment adherence, and patient satisfaction in neurological disorders, including PD [12–15]. In addition, technology-assisted approaches, such as virtual reality applications and telehealth-based multidisciplinary interventions have demonstrated encouraging findings regarding balance, gait, and health-related quality of life [16, 17].

Nevertheless, several limitations remain within the present literature. A substantial proportion of telerehabilitation studies in PD have concentrated predominantly on motor outcomes, while relatively fewer investigations have examined broader clinical dimensions, such as manual dexterity, emotional status, and autonomic symptoms. Furthermore, although dual-task rehabilitation has shown beneficial effects under controlled experimental conditions, evidence regarding its implementation within structured home-based telerehabilitation models remains limited. Another important limitation is the scarcity of real-world clinical data evaluating routine telerehabilitation service delivery, particularly in healthcare systems with middle-income resource settings [18].

Highlight key points

- A structured home-based telerehabilitation program incorporating motor–cognitive dual-task training led to significant improvements in both motor and non-motor outcomes in Parkinson's disease.
- Multidimensional gains were observed across balance, mobility, dexterity, quality of life and depressive symptoms, indicating broad clinical impact.
- Real-time supervised telerehabilitation was feasible and safe, with high adherence and no adverse events reported.
- Improvements in autonomic symptoms, including urinary and fecal incontinence, suggest potential benefits beyond traditional rehabilitation targets.
- These findings support telerehabilitation as a scalable, clinically applicable model of care, although controlled trials are needed to confirm effectiveness.

A clearer understanding of these issues is important for evaluating the practical integration of telerehabilitation into routine PD management. Therefore, the present study examined clinical changes associated with a structured home-based telerehabilitation program integrating motor-cognitive dual-task exercises in individuals with PD. The intervention was delivered within an established real-world rehabilitation service and evaluated using multidimensional clinical outcomes related to balance, mobility, dexterity, psychosocial status, and autonomic function [19].

It was hypothesized that participation in this remotely supervised multidimensional rehabilitation program would be associated with favorable changes in both motor and non-motor clinical parameters.

MATERIALS AND METHODS

Study Design

The present investigation was conducted as a retrospective cohort study using anonymized clinical data that had been prospectively recorded during the implementation of a structured telerehabilitation service program. The program was carried out within the scope of a government-supported telerehabilitation initiative at a tertiary

physical medicine and rehabilitation center in Türkiye. Throughout routine clinical service delivery, all rehabilitation sessions together with baseline and post-intervention evaluations were systematically documented according to a pre-defined clinical project framework [20].

Ethical Considerations

Approval for the retrospective evaluation of the dataset was granted by the relevant Scientific Research Ethics Committee (protocol no: 2024/8-43). Study procedures were performed in accordance with the ethical principles outlined in the Declaration of Helsinki. Before participation in the telerehabilitation program, all individuals provided written informed consent permitting both participation in the rehabilitation process and the scientific use of anonymized clinical data obtained during routine care.

Participants

Clinical records of individuals diagnosed with PD who participated consecutively in the telerehabilitation program were reviewed retrospectively. Eligibility criteria included a diagnosis established according to the UK PD Society Brain Bank criteria, disease severity corresponding to Hoehn and Yahr stages 1–3, and preserved cognitive capacity evaluated using the PD-Cognitive Rating Scale (PD-CRS). A PD-CRS score >80 was accepted as indicating the absence of clinically significant cognitive impairment. The PD-CRS was preferred because of its reported utility in identifying PD-related cortical and subcortical cognitive dysfunction [21].

Participants with PD-CRS scores ≤80 were not included in the analysis. Additional eligibility requirements included adequate communication skills, the ability to understand and follow exercise instructions and sufficient technological competence to participate in remotely supervised sessions independently or with caregiver assistance when necessary.

Exclusion criteria consisted of advanced PD (Hoehn and Yahr stages IV–V), medical conditions limiting safe exercise participation, concomitant neurological or psychiatric disorders likely to affect cognitive performance, severe sensory impairments, and inability to engage in video-based rehabilitation sessions.

Only individuals who completed the entire 6-week telerehabilitation protocol comprising 30 sessions were included in the final analysis. No statistical imputation procedure was applied for missing observations.

Intervention

Participants underwent an individualized home-based telerehabilitation program lasting 6 weeks and consisting of 30 treatment sessions delivered 5 days/week. Each session lasted approximately 60 min. Rehabilitation sessions were conducted synchronously through a secure video communication platform under the supervision of physiotherapists experienced in neurological rehabilitation and PD management.

The intervention protocol followed a structured session format. Sessions began with preparatory exercises involving stretching and joint range-of-motion activities, followed by motor rehabilitation components targeting balance, gait performance, and coordination. Cognitive tasks focusing on attention, memory, and executive functioning were also incorporated into the program. These elements were combined within a motor-cognitive dual-task framework requiring participants to perform cognitive and motor activities simultaneously to simulate daily-life functional demands. Each session ended with cool-down exercises.

The rehabilitation program was individualized by gradually modifying exercise difficulty and task complexity according to each participant's clinical performance and tolerance level. Sessions were completed within the participants' home environments using computers or tablet devices. Caregiver support was provided only when required for technical assistance or session setup. To enhance safety, therapists continuously monitored participants throughout the sessions and environmental precautions were recommended before program initiation. No falls, adverse events, or intervention-related safety problems were documented during the study period.

The participant selection and follow-up process are summarized in Figure 1.

Outcome Measures

Clinical evaluations were performed before initiation of the telerehabilitation program and immediately after completion of the intervention. Standardized and validated assessment tools were used to examine multiple clinical dimensions relevant to PD.

The primary outcome of the study was postural balance, assessed using the Berg Balance Scale (BBS). Balance was designated as the primary endpoint because impairments in postural control are strongly associated with falls, functional dependency, and deterioration in quality of life among individuals with PD.

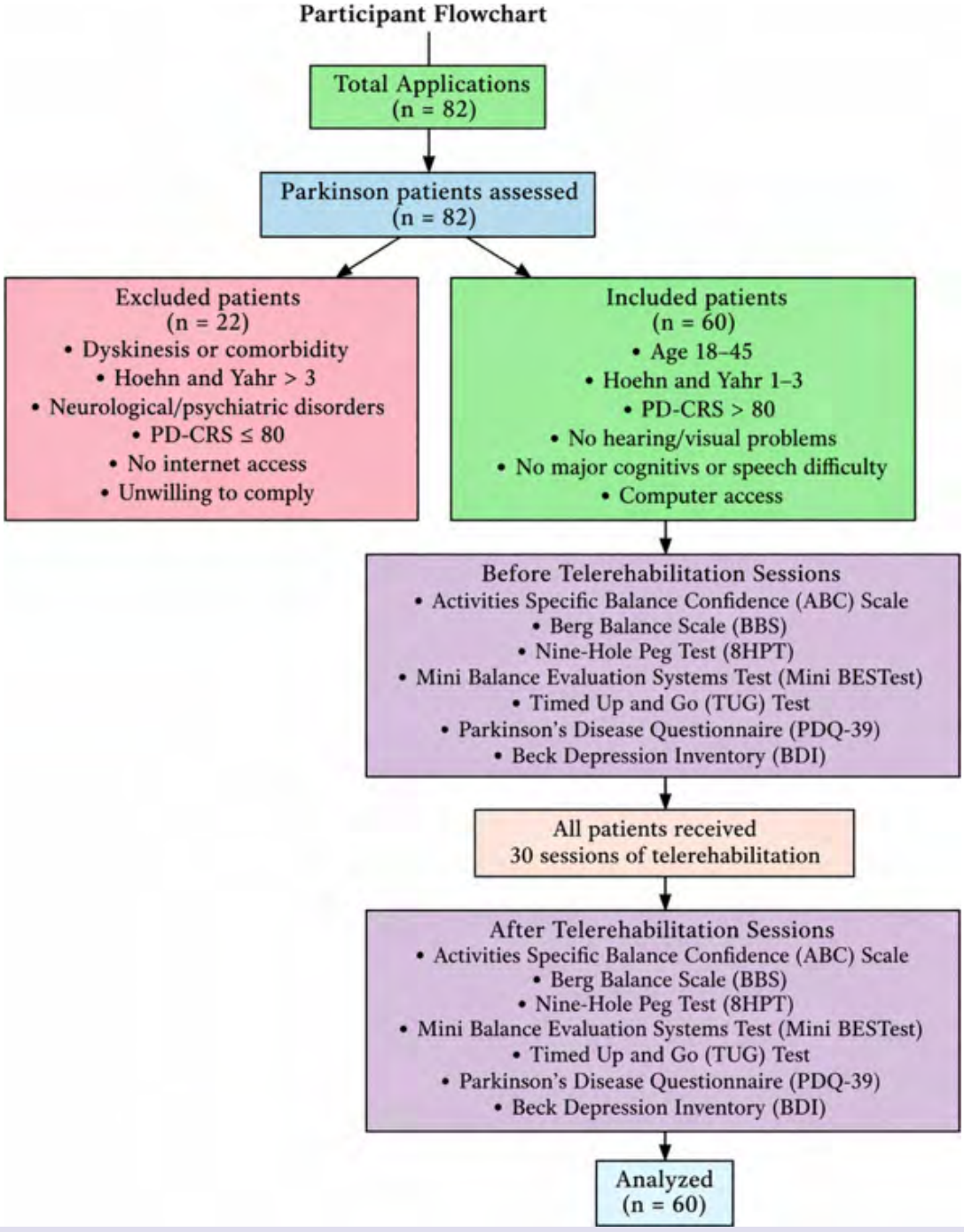

Figure 1. Participant flowchart.
PD-CRS: Parkinson's Disease-Cognitive Rating Scale.

Secondary outcomes included dynamic balance measured by the Mini-BESTest, balance confidence evaluated using the Activities-specific Balance Confidence (ABC) Scale, functional mobility assessed with the Timed Up and Go (TUG) test, and upper-extremity dexterity examined through the Nine-Hole Peg Test (9HPT). Health-related quality of life was evaluated using the PD Questionnaire-39 (PDQ-39), while depressive symptoms were measured with the Beck Depression Inventory (BDI). Self-reported urinary and fecal incontinence data were also recorded [22–29].

The selected assessment tools were intended to provide a multidimensional evaluation of clinically relevant motor, functional, and psychosocial outcomes associated with PD.

Table 1. Demographic characteristics of participants

Variables	Percentage (n=60)
Sex	
Male	68.3
Female	31.7
Age (mean±SD: 67.60±10.05)	
<65 years	36.7
≥65 years	63.3
Comorbidities	
Diabetes	23.3
Hypertension	51.7
Coronary heart disease	18.3
Others (arrhythmia, etc.)	16.7
Urinary incontinence	40.0
Fecal incontinence	11.7

Participants could have more than one comorbidity; therefore, percentages do not sum to 100%. SD: Standard deviation.

This comprehensive assessment strategy was adopted to capture potential intervention-related changes across several domains of daily functioning and aligns with contemporary neurorehabilitation approaches emphasizing integrated evaluation of motor and non-motor manifestations.

Sample Size

The required sample size was calculated using G*Power software with reference to previously published rehabilitation studies evaluating balance-related outcomes in individuals with PD [30, 31]. Based on the assumption of a large treatment effect, at least 42 participants were needed to provide 95% statistical power with a two-sided alpha level of 0.05. A total of 60 participants met the study criteria and completed the intervention, exceeding the minimum calculated requirement and supporting sufficient statistical power for analyses related to the primary outcome measure.

Statistical Analysis

All statistical procedures were conducted using the Statistical Package for the Social Sciences software version 20.0. Distribution characteristics of continuous variables were examined with the Kolmogorov-Smirnov test to determine normality assumptions [32, 33]. For comparisons between pre- and post-intervention measurements, paired-sample t-tests were used for variables demonstrating normal distribution, whereas the Wilcoxon signed-rank test was preferred for non-normally distributed variables. Categorical variables were evaluated using the McNemar test [34, 35].

Continuous data are reported as mean±standard deviation, while categorical variables are presented as frequencies and percentages.

All statistical analyses were conducted using two-tailed testing procedures and p-values below 0.05 were considered statistically significant unless otherwise specified by correction procedures. Because multiple outcome comparisons were performed, a Bonferroni adjustment was applied in secondary and item-based analyses to reduce the probability of Type I error. Accordingly, the adjusted statistical significance threshold was set at $\alpha=0.003$ for these analyses.

In addition to significance testing, effect size calculations were performed to support the interpretation of the magnitude of observed changes. Cohen's d values were calculated for parametric analyses and r effect sizes were calculated for non-parametric analyses. For non-parametric analyses, the effect size (r) was calculated by dividing the standardized test statistic (Z) by the square root of the number of observations (N). Effect sizes were interpreted according to Cohen's criteria, whereby values of 0.10, 0.30, and 0.50 represent small, moderate, and large effects, respectively [36].

RESULTS

Sixty participants diagnosed with PD completed the telerehabilitation program and were included in the final analysis. Baseline demographic and clinical characteristics are summarized in Table 1. Most participants were older adults aged 65 years or above, and hypertension represented the most commonly reported accompanying medical condition.

A reduction in self-reported urinary and fecal incontinence was identified after completion of the intervention among participants who reported these symptoms at baseline (Table 2). The prevalence of urinary incontinence declined from 40% before treatment to 23% after the intervention, whereas fecal incontinence decreased from 12% to 2%. Although mechanistic explanations were beyond the scope of the present study, these findings may suggest favorable changes in autonomic symptom-related complaints.

Table 2. Comparison of participants' urinary and fecal incontinence status before and after telerehabilitation

Variables	Before telerehabilitation n=60 (%)	After telerehabilitation n=60 (%)	p
Urinary incontinence			0.002*
Yes	40.0	23.3	
No	60.0	76.7	
Fecal incontinence			0.031*
Yes	11.7	1.7	
No	88.3	98.3	

*: P<0.05, McNemar test was used to assess within-subject changes in binary variables.

Table 3. Activity-specific balance confidence scale: Comparison of pre-and post-telerehabilitation scores

Variable	Before telerehabilitation Mean±SD	After telerehabilitation Mean±SD	p
Walking around the house	80.00±19.83	90.00±13.04	<0.001*
Climbing up and down stairs	60.00±25.34	80.00±17.95	<0.001*
Bending down to get slippers from the bottom of a cupboard	60.00±22.80	80.00±18.08	<0.001*
Reaching for a small box on a shelf at eye level	70.00±24.11	80.00±18.90	<0.001*
Standing on tiptoe to reach for something above your head	60.00±25.60	80.00±21.56	<0.001*
Climbing on a chair to reach something	40.00±26.83	60.00±26.45	<0.001*
Sweeping the floor	60.00±30.21	80.00±24.21	<0.001*
Walking out the door into the street	70.00±25.32	80.00±18.32	<0.001*
Getting in and out of a car	60.00±23.97	80.00±19.33	<0.001*
Walking through a parking lot to a shopping mall	60.00±24.03	80.00±21.66	<0.001*
Walking up and down a slope	50.00±24.49	70.00±21.85	<0.001*
Walking through a crowded shopping mall	55.00±27.09	70.00±24.95	<0.001*
Bumping into people while walking in a mall	55.00±28.04	70.00±23.92	<0.001*
Going up/down an escalator while holding the handrail	60.00±26.61	70.00±23.97	<0.001*
Going up/down an escalator without holding the handrail due to carrying something	40.00±28.17	60.00±28.09	<0.001*
Walking on a slippery sidewalk	20.00±22.78	40.00±24.49	<0.001*
Total	860.00±322.16	1160.00±266.56	<0.001*

Wilcoxon signed-rank test; Bonferroni-corrected significance level α=0.003; all p<0.001 remained significant*; SD: Standard deviation

Perceived balance confidence demonstrated significant improvement following the telerehabilitation program. ABC scale scores increased significantly both in individual item analyses and in overall total scores (all p<0.001), reflecting greater confidence during daily functional activities (Table 3).

Objective clinical assessments also demonstrated statistically significant post-intervention improvements. Scores obtained from the BBS and Mini-BESTest indicated enhanced postural and dynamic balance performance across evaluated domains (all p<0.001). Functional mobility outcomes assessed using the TUG test showed reductions

TABLE 4. Clinical and functional outcomes before and after telerehabilitation

Outcome measures	Before telerehabilitation Mean±SD	After telerehabilitation Mean±SD	p
Balance assessment			
Berg balance scale	47.00±12.15	53.00±9.72	<0.001*
Dexterity (nine-hole peg test)			
Completion time (right hand)	32.15±10.84	28.65±10.27	<0.001*
Completion time (left hand)	33.70±15.37	31.55±14.45	<0.001*
Mini-BESTest scores subscale			
Anticipatory postural adjustments	4.00±1.59	5.00±1.24	<0.001*
Reactive postural control	4.00±1.52	5.00±1.19	<0.001*
Sensory orientation	4.00±1.74	6.00±1.25	<0.001*
Dynamic gait	7.00±2.19	9.00±2.07	<0.001*
Timed up and go test			
Step count	24.00±13.57	20.00±9.30	<0.001*
Duration (sec)	15.00±8.94	13.00±6.79	<0.001*
Speed (m/s)	1.55±0.33	1.74±0.30	<0.001*
Quality of life and mental health			
Parkinson's disease questionnaire	46.00±24.24	31.50±21.93	<0.001*
Beck depression inventory	17.00±6.44	8.50±3.89	<0.001*

Wilcoxon signed-rank test; timed up and go speed analyzed with paired t-test. Bonferroni-corrected significance threshold α=0.003. All significant results appear as p<0.001*. SD: Standard deviation.

in completion time and number of steps, together with increased gait speed (all p<0.001). Manual dexterity performance improved bilaterally, as demonstrated by shorter completion times on the 9HPT (p<0.001) (Table 4).

Patient-reported outcomes showed similarly positive changes. PDQ-39 scores decreased significantly after the intervention, indicating improvement in health-related quality of life. In parallel, BDI scores demonstrated a significant reduction in depressive symptom severity (p<0.001) (Table 4).

Effect size analyses demonstrated moderate-to-large magnitudes of change across the primary and key secondary outcomes. The largest effects were observed for depressive symptoms (BDI, r=0.72), health-related quality of life (PDQ-39, r=0.67), sensory orientation (Mini-BESTest, r=0.63), and dynamic gait performance (Mini-BESTest, r=0.61). Balance performance (BBS, r=0.58), anticipatory postural adjustments (r=0.55), and reactive postural control (r=0.52) also demonstrated large effects, whereas mobility and dexterity outcomes showed moderate effect sizes (r=0.39–0.60) (Table 4).

Collectively, the findings demonstrated consistent favorable changes across motor, functional, and psychosocial domains following participation in the telerehabilitation program.

DISCUSSION

The present study examined clinical changes associated with a structured home-based telerehabilitation program integrating motor-cognitive dual-task exercises in individuals with PD. Following the intervention, favorable changes were identified across several clinical domains, including balance performance, functional mobility, manual dexterity, quality of life, and depressive symptoms. Collectively, these findings suggest that remotely supervised multidimensional rehabilitation may represent a clinically relevant supportive approach for individuals living with PD within routine rehabilitation settings. The observed changes were further supported by moderate-to-large effect sizes across the primary and key secondary outcomes, suggesting that the magnitude

of the improvements may be clinically meaningful in addition to being statistically significant.

An important aspect of the present study is that the intervention was implemented within an established real-world clinical service model rather than under highly controlled experimental conditions. Although previous investigations have reported beneficial effects of telerehabilitation in PD, many studies have been conducted within tightly controlled research environments or have focused on limited outcome domains [14, 15]. In contrast, the present study reflects outcomes obtained during routine clinical implementation, which may provide additional insight into the practical applicability and translational potential of telerehabilitation in daily rehabilitation practice. This distinction may be clinically meaningful because interventions demonstrating efficacy in experimental settings may not always produce comparable results under real-life healthcare conditions.

The improvements observed in balance and mobility outcomes are clinically relevant given the substantial impact of gait impairment and postural instability on disability and fall risk in PD [37]. Improvements in BBS and Mini-BESTest scores observed in the present study are consistent with previous rehabilitation studies reporting beneficial effects of exercise-based interventions on postural control [14, 31]. One possible explanation for these findings may be the incorporation of motor-cognitive dual-task activities within the rehabilitation protocol. Simultaneous engagement of cognitive processing and motor execution may facilitate more effective motor planning and attentional control during functional activities. Previous studies have suggested that dual-task rehabilitation may contribute to improvements in gait automaticity and adaptive motor responses in individuals with PD [18, 38].

Another notable finding was the increase in balance confidence following the intervention. Reduced confidence during mobility-related activities and fear of falling frequently contribute to activity restriction and decreased social participation in PD. Therefore, improvements in ABC scores may reflect not only enhanced physical performance but also greater perceived functional security during everyday activities. Increased confidence may, in turn, support higher participation in social and physical activities, potentially contributing to broader functional benefits.

The observed improvements in manual dexterity further support the multidimensional nature of the intervention effects. Impairments in fine motor control and coordination commonly interfere with daily living activities in individuals with PD [39]. The integration of upper-extremity exercises into cognitively demanding task conditions may have promoted task-oriented motor learning and repetitive functional practice, thereby contributing to better dexterity performance after the intervention period.

In addition to motor outcomes, the intervention was associated with improvements in psychosocial measures, including quality of life and depressive symptoms. Non-motor manifestations, particularly depression, substantially influence disease burden and patient well-being in PD [40]. Earlier research has indicated that rehabilitation and exercise participation may positively affect mood, emotional status, and social engagement. Potential mechanisms proposed in the literature include increased physical activity, enhanced self-efficacy, and greater participation in meaningful activities [19]. The present findings appear to support the broader psychosocial value of telerehabilitation interventions beyond purely physical rehabilitation outcomes.

A reduction in urinary and fecal incontinence symptoms was also observed among participants reporting these complaints at baseline. Autonomic dysfunction is a common non-motor feature of PD and may significantly reduce quality of life [41]. Although the present study was not designed to identify mechanistic explanations for these changes, improvements in overall mobility, neuromuscular coordination, and functional control may have contributed indirectly to these findings. Nevertheless, these observations should be interpreted cautiously because autonomic outcomes were based on self-reported data and were not assessed using specialized urological or gastrointestinal measures.

From a practical perspective, the findings of this study support the feasibility of delivering remotely supervised rehabilitation to individuals with PD in a home environment. Continuous therapist supervision during synchronous sessions may have contributed to treatment adherence and safe participation throughout the intervention process. No falls or intervention-related adverse events were documented during the study period. These observations are consistent with previous reports suggesting that telerehabilitation may represent a safe and accessible rehabilitation strategy for neurological populations [15]. In healthcare systems where access to specialized rehabilitation services is limited, remotely delivered rehabilitation may help improve continuity and accessibility of care.

Several limitations should be acknowledged when interpreting the present findings. The retrospective design and absence of a comparator group restrict the ability to establish causal relationships between the intervention and observed outcomes. In addition, inclusion of only participants who completed the program may have introduced selection bias and may potentially overestimate treatment-related improvements. Behavioral changes related to increased clinical attention during participation cannot be excluded. Furthermore, the lack of long-term follow-up prevents evaluation of the persistence and sustainability of post-intervention improvements over time.

Accordingly, the findings of the present study should be considered preliminary and hypothesis-generating rather than definitive evidence of efficacy. Future prospective randomized controlled studies incorporating larger samples, comparison groups, and long-term follow-up assessments are needed to further clarify the effectiveness, sustainability, and clinical utility of dual-task-based telerehabilitation interventions in PD.

Conclusion

A structured home-based telerehabilitation program integrating motor-cognitive dual-task training was associated with significant improvements in balance, mobility, manual dexterity, balance confidence, quality of life, depressive symptoms, and self-reported autonomic symptoms in individuals with mild-to-moderate Parkinson's disease. The intervention was delivered safely within a real-world clinical service, with high treatment adherence and no reported adverse events, supporting the feasibility of remotely supervised rehabilitation in routine practice. Although the retrospective design and lack of a control group preclude causal inference, these findings suggest that dual-task telerehabilitation may represent a practical and clinically relevant rehabilitation strategy for individuals with Parkinson's disease. Future well-designed randomized controlled trials with larger samples and long-term follow-up are warranted to confirm these findings and establish the long-term effectiveness of this approach.

Ethics Committee Approval: This study was approved by the Scientific Research Ethics Committee of University of Health Sciences, Erenkoy Mental and Neurological Diseases Training and Research Hospital (protocol no: 2024/8-43).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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

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REFERENCES

1. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79:368-76. [CrossRef]
2. Belvisi D, Pellicciari R, Fabbrini G, Tinazzi M, Berardelli A, Defazio G. Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: What do prospective studies suggest? Neurobiol Dis 2020;134:104671. [CrossRef]
3. Hanağası HA. Epidemiology and environmental factors in Parkinson's disease. In: Elibol B, editor. Hareket Bozuklukları. Ankara; 2011.
4. Chaudhuri KR, Healy DG, Schapira AH; National Institute for Clinical Excellence. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006;5:235-45. [CrossRef]
5. Hüseyinoğlu N, Çelik B. Rehabilitation of Parkinson's disease. In: Oğuz H, Çakırbay H, Yanık B, editors. Tıbbi Rehabilitasyon. 3rd ed. İstanbul: Nobel Tıp Kitabevleri; 2015. p. 497-504.
6. Lau YS, Patki G, Das-Panja K, Le WD, Ahmad SO. Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration. Eur J Neurosci 2011;33:1264-74. [CrossRef]
7. Hirsch MA, Farley BG. Exercise and neuroplasticity in persons living with Parkinson's disease. Eur J Phys Rehabil Med 2009;45:215-29.
8. Jessop RT, Horowicz C, Dibble LE. Motor learning and Parkinson disease: Refinement of movement velocity and endpoint excursion in a limits of stability balance task. Neurorehabil Neural Repair 2006;20:459-67. [CrossRef]
9. Öztekin Ö, Bilir Kaya B. Telerehabilitation. In: Bilir Kaya B, editor. A multidisciplinary perspective on telerehabilitation: Clinical, technological and health management approaches. 1st ed. Ankara: Nobel Tıp Kitabevleri Ltd. Şti.; 2025. p. 1-16.
10. Cottrell MA, Russell TG. Telehealth for musculoskeletal physiotherapy. Musculoskelet Sci Pract 2020;48:102193. [CrossRef]

11. Kesiktaş FN, Bilir Kaya B. Telerehabilitation. In: Ayhan FF, Demirbağ Kabayel D, editors. COVID-19 Pandemic and Physical Medicine and Rehabilitation. 1st ed. Ankara: Türkiye Klinikleri; 2020. p. 89-93.
12. Shaw MT, Best P, Frontario A, Charvet LE. Telerehabilitation benefits patients with multiple sclerosis in an urban setting. J Telemed Telecare 2021;27:39-45. [CrossRef]
13. Bilir Kaya B, Güngör Ketenci P, Öztekin Ö, Memişoğlu K. The impact of motion capture camera-supported telerehabilitation gamification on upper extremity functions and quality of life in stroke and cerebral palsy patients. Turk J Phys Med Rehabil 2025;71:157-66. [CrossRef]
14. Vellata C, Belli S, Balsamo F, Giordano A, Colombo R, Maggioni G. Effectiveness of telerehabilitation on motor impairments, non-motor symptoms and compliance in patients with parkinson's disease: a systematic review. Front Neurol 2021;12:627999. [CrossRef]
15. Bianchini E, Onelli C, Morabito C, Alborghetti M, Rinaldi D, Anibaldi P, et al. Feasibility, safety, and effectiveness of telerehabilitation in mild-to-moderate parkinson's disease. Front Neurol 2022;13:909197. [CrossRef]
16. Gandolfi M, Geroin C, Dimitrova E, Boldrini P, Waldner A, Bonadiman S, et al. Virtual reality telerehabilitation for postural instability in parkinson's disease: a multicenter, single-blind, randomized, controlled trial. Biomed Res Int 2017;2017:7962826. [CrossRef]
17. García-Bustillo A, Olivares-Gil A, Garrido-Labrador JL, Ramírez-Sanz JM, Arnaiz-González A, Valiñas-Sieiro F, et al. Feasibility and efficacy of a multidisciplinary home-telehealth intervention program to reduce falls and improve quality of life in Parkinson's disease: First results. Mov Disord 2022; 235.
18. Yang YR, Cheng SJ, Lee YJ, Liu YC, Wang RY. Cognitive and motor dual task gait training exerted specific training effects on dual task gait performance in individuals with Parkinson's disease: A randomized controlled pilot study. PLoS One 2019;14:e0218180. [CrossRef]
19. Nascimento CMC, Teixeira CVL, Gobbi LTB, Gobbi S, Stella F. A controlled clinical trial on the effects of a physical activity program on cognition and depressive symptoms in oldest-old people with mild cognitive impairment. Braz J Phy. Ther 2012;16: 197-204. [CrossRef]
20. İstanbul İl Sağlık Müdürlüğü. İstanbul'da teknoloji odaklı, sürdürülebilir telerehabilitasyon hizmeti üretme ve nitelikli iş gücü yetiştirme projesi (İSTER). (reference number TR10/21/YEP/0039). Available from: https://istanbulism.saglik.gov.tr/TR-288250/istanbulda-teknoloji-odakli-surdurulebilir-telerehabilitasyon-hizmeti-uretme-ve-nitelikli-is-gucu-yetistirme-projesi.html. Accessed Jun 16, 2026.
21. Pagonabarraga J, Kulisevsky J, Llebaria G, García-Sánchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. Mov Disord 2008;23:998-1005. [CrossRef]
22. Qutubuddin AA, Pegg PO, Cifu DX, Brown R, McNamee S, Carne W. Validating the Berg Balance Scale for patients with Parkinson's disease: a key to rehabilitation evaluation. Arch Phys Med Rehabil 2005;86:789-92. [CrossRef]
23. Oxford Grice K, Vogel KA, Le V, Mitchell A, Muniz S, Vollmer MA. Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. Am J Occup Ther 2003;57:570-3. [CrossRef]
24. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. J Rehabil Med 2010;42:323-31. [CrossRef]
25. da Silva BA, Faria CDCM, Santos MP, Swarowsky A. Assessing timed up and go in parkinson's disease: reliability and validity of timed up and go assessment of biomechanical strategies. J Rehabil Med 2017;49:723-31. [CrossRef]
26. Nocera JR, Stegemöller EL, Malaty IA, Okun MS, Marsiske M, Hass CJ, et al. Using the Timed Up & Go test in a clinical setting to predict falling in Parkinson's disease. Arch Phys Med Rehabil 2013;94:1300-5. [CrossRef]
27. Matsui H, Udaka F, Miyoshi T, Hara N, Tamaura A, Oda M, et al. Three-dimensional stereotactic surface projection study of freezing of gait and brain perfusion image in Parkinson's disease. Mov Disord 2005;20:1272-7. [CrossRef]
28. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res 1995;4:241-8. [CrossRef]
29. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71. [CrossRef]
30. Cousineau D. Approximating the distribution of Cohen's dp in within-subject designs. Quant Methods Psychol 2020;16:418-21. [CrossRef]
31. Lorenzo-García P, Cavero-Redondo I, Núñez de Arenas-Arroyo S, Guzmán-Pavón MJ, Priego-Jiménez S, Álvarez-Bueno C. Effects of physical exercise interventions on balance, postural stability and general mobility in Parkinson's disease: a network meta-analysis. J Rehabil Med 2024;56:jrm10329. [CrossRef]
32. Rosenthal R, Rosnow RL. Essentials of behavioral research: methods and data analysis. 3rd ed. New York: McGraw-Hill; 2008.
33. Bland JM, Altman DG. Multiple significance tests: The Bonferroni method. BMJ 1995;310:170. [CrossRef]
34. Kirkwood BR, Sterne JAC. Essential medical statistics. 2nd ed. Oxford: Blackwell Science; 2003.
35. Mcnemar Q. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika 1947;12:153-7. [CrossRef]
36. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988.
37. Dibble LE, Addison O, Papa E. The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum. J Neurol Phys Ther 2009;33:14-26. [CrossRef]
38. Mirelman A, Rochester L, Maidan I, Del Din S, Alcock L, Nieuwhof F, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. Lancet 2016;388:1170-82. [CrossRef]
39. Proud EL, Bilney B, Miller KJ, Morris ME, McGinley JL. Measuring hand dexterity in people with parkinson's disease: reliability of pegboard tests. Am J Occup Ther 2019;73:7304205050p1-8. [CrossRef]
40. Troeung L, Egan SJ, Gasson N. A meta-analysis of randomised placebo-controlled treatment trials for depression and anxiety in Parkinson's disease. PLoS One 2013;8:e79510. [CrossRef]
41. Jia C, Cui X, Yoshimura N, Mao W, Xu E, Wang Q, Ou T. Assessment and Management of Urinary Dysfunction in 187 Patients with Parkinson's Disease. J Parkinsons Dis 2020;10:993-1001. [CrossRef]

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Original Article General Surgery

Diagnostic and predictive value of the hemoglobin-albumin-lymphocyte-platelet score in thyroid nodules: A retrospective analysis of 521 patients

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ABSTRACT

OBJECTIVE: The hemoglobin-albumin-lymphocyte-platelet (HALP) score, an integrated immunonutritional index, has shown significant prognostic value in several aggressive solid tumors. However, its role in the diagnostic workup and predictive stratification of thyroid cancer remains underexplored. This study aimed to comprehensively evaluate the diagnostic efficacy of the pre-operative HALP score and its association with lymph node metastasis (LNM) in patients undergoing thyroidectomy.

METHODS: We retrospectively reviewed 521 consecutive patients who underwent thyroid surgery between 2022 and 2024. Pre-operative laboratory parameters, including thyroid-stimulating hormone (TSH), fT4, albumin, and complete blood count, were recorded. The HALP score was calculated as (Hemoglobin×Albumin×Lymphocytes)/Platelets. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis in combination with multivariate logistic regression. A subgroup analysis was performed for malignant cases to evaluate predictors of LNM.

RESULTS: Of the cohort, 210 (40.3%) patients had malignant pathology. While serum TSH ($p<0.001$) and fT4 ($p=0.043$) were significantly higher in the malignant group, the HALP score demonstrated no significant difference (50.8±17.9 vs. 51.2±18.4, $p=0.694$). ROC analysis yielded an area under the curve of 0.510 for the HALP score, indicating a lack of discriminative power. In multivariate analysis, only Bethesda categories V (odds ratio [OR]: 17.48) and VI (OR: 104.29) were independent predictors of malignancy. For LNM, younger age ($p=0.005$), higher TSH ($p=0.036$), and lymphovascular invasion ($p<0.001$) were significant predictors, whereas the HALP score showed no predictive value ($p=0.919$).

CONCLUSION: The pre-operative HALP score does not serve as a reliable diagnostic or predictive biomarker for thyroid malignancy or LNM. Pre-operative stratification should remain focused on cytopathology and established clinical-ultrasonographic risk factors.

Keywords: Biomarkers; hemoglobin-albumin-lymphocyte-platelet score; inflammation markers; lymph node metastasis; thyroid cancer; thyroid nodule.

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Among endocrine cancers, thyroid malignancies are the most frequently encountered, with papillary thyroid carcinoma (PTC) representing the predominant histological subtype [1, 2]. Despite its generally favorable prognosis, the management of thyroid nodules remains a clinical challenge, particularly in the context of "overdiagnosis" and the need for accurate risk stratification to guide surgical extent [3, 4]. While fine-needle aspiration (FNA) remains the gold standard, its limitations in indeterminate categories (Bethesda III and IV) have spurred the search for novel, cost-effective biomarkers [5, 6].

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Interactions between systemic inflammation, nutritional status, and the tumor microenvironment play a key role in cancer progression [7, 8]. Inflammation-related hematological markers, including the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio (PLR), have been widely investigated as indicators of this relationship [9, 10]. Recently, the hemoglobin-albumin-lymphocyte-platelet (HALP) score has emerged as a more comprehensive index, integrating both inflammatory (lymphocytes, platelets) and nutritional (hemoglobin, albumin) components [11, 12]. High HALP scores have been associated with better survival in gastric, colorectal, and renal cell carcinomas [13, 14].

However, the biological behavior of thyroid cancer differs significantly from these aggressive solid tumors. Thyroid malignancies, especially PTC, often exhibit an indolent clinical course and may not elicit a systemic inflammatory response of sufficient magnitude to alter peripheral blood indices [15, 16]. This study seeks to provide a comprehensive evaluation of the HALP score's diagnostic utility in a large, single-center thyroidectomy cohort, while exploring its relationship with lymph node metastasis (LNM) – a key determinant of surgical management and recurrence risk [17, 18].

Highlight key points

- HALP score showed no diagnostic value in thyroid nodules
- No association was found between HALP score and LNM
- Cytopathological classification remains the strongest predictor of malignancy
- Inflammation-based indices may be less useful in indolent malignancies.

MATERIALS AND METHODS

Study Design and Population

This retrospective cohort study was conducted at the Department of General Surgery, Ankara Etlik City Hospital, Turkey. We reviewed the medical records of all patients who underwent thyroidectomy (total, lobectomy, or hemithyroidectomy) between October 2022 and November 2024. The study protocol was approved by the Institutional Ethics Committee of Ankara Etlik City Hospital (AESH-BADEK-2024-1088, approval date: November 27, 2024) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Inclusion criteria were patients aged ≥18 years with complete pre-operative laboratory and histopathological data.

Data Collection and Variables

Demographic data (age, sex), pre-operative laboratory parameters (serum albumin, fT3, fT4, thyroid-stimulating hormone [TSH], white blood cell, hemoglobin, lymphocyte count, platelet count), and ultrasonographic findings (nodule size, echogenicity, composition, microcalcification, TIRADS category) were retrieved from the electronic medical records system. Pre-operative fine needle aspiration biopsy results were classified according to the Bethesda System.

The HALP score was calculated using the following formula:

HALP=(Hemoglobin [g/dL]×Albumin [g/dL]×Lymphocyte count [/L])/Platelet count [/L]

The PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. Histopathological data included the final diagnosis (benign vs. malignant), pathological subtype, lymphovascular invasion (LVI), and lymph node status.

Statistical Analysis

All statistical analyses were conducted using Jamovi software (version 2.7). The distribution of continuous variables was evaluated with the Shapiro-Wilk test. Depending on normality, data were presented as mean±standard deviation or median with interquartile range. Group comparisons were carried out using the Mann–Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables. The discriminative performance of continuous parameters was evaluated using receiver operating characteristic (ROC) curve analysis.

To determine factors independently associated with malignancy, both univariate and multivariate logistic regression analyses were conducted. Variables showing a potential association in univariate analysis ($p<0.10$), together with clinically meaningful factors, were entered into the multivariate model. Statistical significance was defined as $p<0.05$.

RESULTS

Patient Characteristics

A total of 521 patients were included in the study. The mean age was 48.78±12.73 years, and 79.1% (n=412)

Table 1. Clinical and laboratory characteristics of patients according to final pathological diagnosis

Parameter	Benign (n=311)	Malignant (n=210)	p
Age (years)	49.2±12.5	48.1±13.1	0.342
Thyroid-stimulating hormone (mIU/L)	1.06 (0.5–2.1)	1.43 (0.8–3.2)	<0.001
fT4 (ng/dL)	1.16±0.15	1.20±0.18	0.043
Albumin (g/dL)	4.3±0.4	4.3±0.3	0.812
Hemoglobin-albumin-lymphocyte-platelet score	51.2±18.4	50.8±17.9	0.694
Nodule size (mm)	32.0 (20–45)	18.5 (12–28)	<0.001

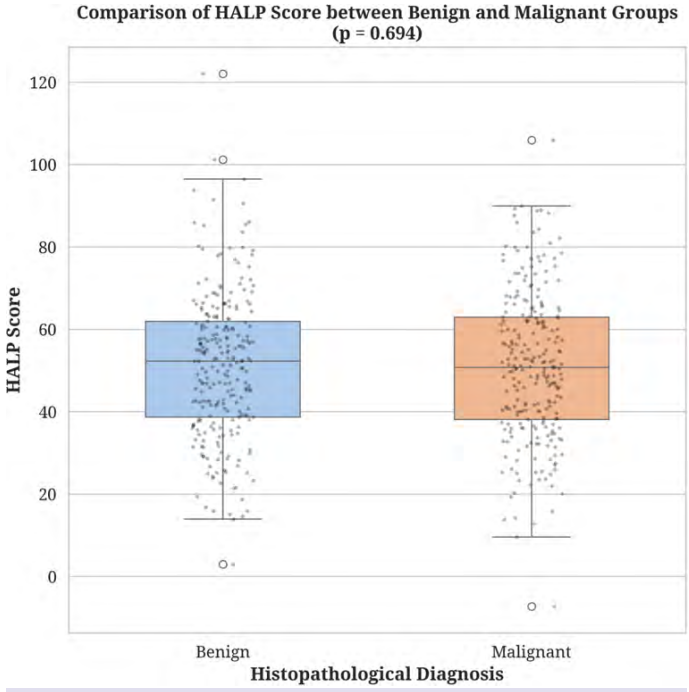

Figure 1. Comparison of hemoglobin-albumin-lymphocyte-platelet score between benign and malignant groups.

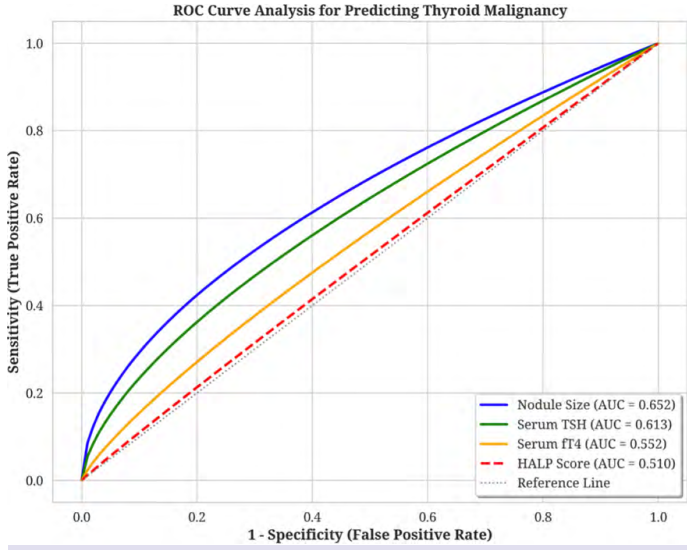

Figure 2. Receiver operating characteristic curve analysis for predicting thyroid malignancy.

were female. Based on final pathology, 311 (59.7%) patients had benign and 210 (40.3%) had malignant thyroid pathology. The clinical and laboratory characteristics stratified by diagnosis are summarized in Table 1.

Serum TSH and fT4 levels were significantly higher in the malignant group compared with the benign group (p<0.001 and p=0.043, respectively). In contrast, the HALP score did not differ between benign and malignant cases (50.8±17.9 vs. 51.2±18.4, p=0.694). The distribution of HALP scores between benign and malignant groups is illustrated in Figure 1, demonstrating a substantial overlap between the two groups.

ROC Analysis

ROC curve analysis was used to determine the ability of continuous variables to differentiate between malignant and benign thyroid conditions. Among the analyzed parameters, nodule size demonstrated the highest discriminative ability (area under the curve [AUC]=0.652), followed by serum TSH (AUC=0.613) and serum fT4 (AUC=0.552). In contrast, the HALP score showed minimal diagnostic performance (AUC=0.510). The comparative ROC curves of these variables are presented in Figure 2.

Predictors of Malignancy

In univariate analyses, serum TSH, fT4 levels, and nodule size were significantly associated with thyroid malignancy. However, in the multivariate logistic regression model, only Bethesda category V (odds ratio [OR]=17.48, 95% confidence interval [CI] 4.91–62.25,

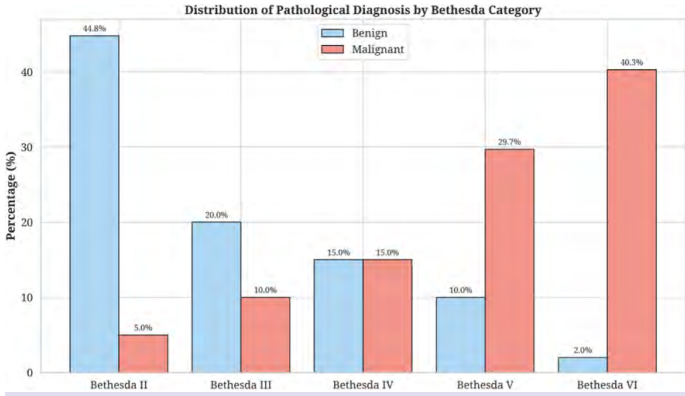

FIGURE 3. Distribution of pathological diagnosis by Bethesda category.

p<0.001) and Bethesda category VI (OR=104.29, 95% CI 21.86–497.43, p<0.001) remained independent predictors of malignancy.

The distribution of pathological outcomes according to Bethesda cytology categories is shown in Figure 3, which demonstrates the progressively increasing malignancy rate across higher Bethesda categories.

Subgroup Analysis for LNM

Among the 175 malignant cases with available nodal data, LNM was identified in 26 patients (14.9%). Younger age (p=0.005), higher TSH levels (p=0.036), and LVI (p<0.001) were significantly associated with nodal metastasis, whereas the HALP score showed no predictive value (p=0.919). Patients with LNM were significantly younger (40.69±15.45 vs. 49.23±12.72 years, p=0.005) and had higher TSH levels (median: 2.19 vs. 1.37 mIU/L, p=0.036). LVI was the strongest predictor of LNM (50.0% vs. 7.1%, p<0.001). The HALP score showed no association with LNM status (p=0.919).

DISCUSSION

The present study evaluated the diagnostic and predictive value of the pre-operative HALP score in patients undergoing thyroidectomy. The main finding of this study is that the HALP score does not provide meaningful diagnostic or predictive information for thyroid malignancy or LNM. In contrast, cytopathological classification using the Bethesda system remained the strongest predictor of malignancy, highlighting the continued central role of FNA cytology in the evaluation of thyroid nodules [5, 6]. It should be noted that our study population consisted exclusively of surgically treated patients, representing a selected cohort with a higher pretest probability of malignancy. Therefore, the findings may not be fully generalizable to all patients with thyroid nodules, particularly those managed conservatively. This limitation should be considered when interpreting the diagnostic performance of the HALP score.

The HALP score has gained attention as a combined immunonutritional marker that captures both systemic inflammatory activity and overall nutritional status. Previous studies have demonstrated its prognostic significance in several aggressive solid malignancies, including gastric, colorectal, and bladder cancers, where higher HALP scores have been associated with improved survival outcomes [11–14]. The biological rationale underlying this association is that cancer-related systemic inflammation may alter circulating lymphocytes and platelets while also affecting nutritional parameters such as hemoglobin and albumin [7, 8, 19, 20].

However, our findings suggest that the clinical utility of composite immunonutritional indices such as the HALP score may be strongly dependent on tumor biology. Unlike aggressive tumors, differentiated thyroid carcinoma – particularly PTC – generally follows an indolent clinical course and does not induce a sufficiently pronounced systemic inflammatory or nutritional response to influence composite hematologic indices [1, 21, 22]. This may partly explain why inflammation-based biomarkers that perform well in aggressive malignancies fail to demonstrate diagnostic value in thyroid cancer.

We also observed a significant relationship between serum TSH levels and the presence of thyroid malignancy. Elevated TSH levels have been repeatedly linked to an increased risk of differentiated thyroid cancer in previous studies [23–26]. TSH acts as a growth factor for thyroid follicular cells and may stimulate tumor proliferation through activation of TSH receptors. Consistent with this concept, we observed significantly higher TSH levels in patients with malignant pathology. However, TSH did not remain an independent predictor in multivariate analysis after adjustment for cytological findings, indicating that biochemical markers should be interpreted as supportive factors rather than substitutes for cytopathological evaluation.

Our results also reinforce the dominant role of the Bethesda system in pre-operative risk stratification. In the multivariate model, only Bethesda categories V and VI remained independently associated with malignancy, demonstrating markedly elevated ORs. This finding is

consistent with the well-established diagnostic performance of the Bethesda system and its widespread adoption in current thyroid nodule management guidelines [5, 6]. Although numerous hematologic and inflammatory indices have been investigated as potential adjunctive markers, their diagnostic performance generally remains inferior to cytological classification.

In the subgroup analysis of malignant cases, LNM was detected in 14.9% of patients. Younger age and LVI were significantly associated with nodal metastasis. Previous studies have also reported that younger patients with PTC tend to present more frequently with lymph node metastases despite overall favorable survival outcomes [17, 27]. This phenomenon may reflect age-related differences in tumor biology or the immune microenvironment [28]. In contrast, the HALP score was not associated with LNM in our cohort, suggesting that metastatic behavior in thyroid cancer is primarily influenced by local tumor characteristics rather than systemic immunonutritional status.

This study has some limitations. First, its retrospective design may introduce inherent bias. Second, the study population consisted only of surgically treated patients, which may limit the generalizability of the findings. In addition, the relatively small number of LNM events should be considered when interpreting subgroup analyses.

Taken together, these findings indicate that systemic composite indices such as the HALP score have limited applicability in the diagnostic evaluation of thyroid nodules. While such markers may provide prognostic information in aggressive malignancies, their clinical utility appears substantially reduced in indolent cancers such as differentiated thyroid carcinoma. Accordingly, the HALP score does not provide meaningful diagnostic or predictive value in thyroid nodules, emphasizing that inflammation-based composite indices may not be suitable for indolent malignancies such as differentiated thyroid cancer.

Conclusion

The pre-operative HALP score does not provide meaningful diagnostic or predictive value for thyroid malignancy or lymph node metastasis in patients undergoing thyroidectomy. Cytopathological evaluation using the Bethesda system remains the cornerstone of pre-operative risk stratification. These findings suggest that the clinical utility of the HALP score is limited in differentiated thyroid carcinoma, and prospective multicenter studies are warranted to further validate its role.

Ethics Committee Approval: This study was approved by The Institutional Ethics Committee of Ankara Etlik City Hospital (AESH-BADEK-2024-1088, approval date: November 27, 2024).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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

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Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Authorship Contributions: Concept – GD; Design – GD; Supervision – GD, DK; Resource – GD, SS; Materials – DK, MHC; Data collection and/or processing – GD, MSS; Analysis and/or interpretation – GD, DK, SS; Literature review – GD, DK; Writing – GD, DK; Critical review – GD, DK.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133. [CrossRef]
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12-49. [CrossRef]
3. Hoang JK, Nguyen XV, Davies L. Overdiagnosis of thyroid cancer: answers to five key questions. Acad Radiol 2015;22:1024-9. [CrossRef]
4. Boucai L, Zafereo M, Cabanillas ME. Thyroid cancer: A Review. JAMA 2024;331:425-35. [CrossRef]
5. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017;27:1341-6. [CrossRef]
6. Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, Cooper DS. The diagnosis and management of thyroid nodules: a review. JAMA 2018;319:914-24. [CrossRef]
7. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74. [CrossRef]
8. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883-99. [CrossRef]
9. Ozmen S, Timur O, Calik I, Altinkaynak K, Simsek E, Gozcu H, et al. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) may be superior to C-reactive protein (CRP) for predicting the occurrence of differentiated thyroid cancer. Endocr Regul 2017;51:131-6. [CrossRef]
10. Zhang Z, Xia F, Wang W, Huang Y, Li X. The systemic immune-inflammation index-based model is an effective biomarker on predicting central lymph node metastasis in clinically nodal-negative papillary thyroid carcinoma. Gland Surg 2021;10:1368-73. [CrossRef]
11. Chen XL, Xue L, Wang W, Chen HN, Zhang WH, Liu K, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. Oncotarget 2015;6:41370-82. [CrossRef]
12. Fu J, Yue X, Zou Y, Zhang J, Wang X, Zhang D. Association of hemoglobin, albumin, lymphocyte, and platelet score with risk of all-cause and cause-specific mortality among cancer survivors: NHANES 1999-2018. Front Oncol 2024;14:1402217. [CrossRef]

13. Yalav O, Topal U, Unal AG, Eray IC. Prognostic significance of preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in patients undergoing curative resection for colorectal cancer. Ann Ital Chir 2021;92:283-92.
14. Peng D, Zhang CJ, Gong YQ, Hao H, Guan B, Li XS, et al. Prognostic significance of HALP (hemoglobin, albumin, lymphocyte and platelet) in patients with bladder cancer after radical cystectomy. Sci Rep 2018;8:794. [CrossRef]
15. Gambardella C, Mongardini FM, Paolicelli M, Bentivoglio D, Cozzolino G, Ruggiero R, et al. Role of inflammatory biomarkers (NLR, LMR, PLR) in the prognostication of malignancy in indeterminate thyroid nodules. Int J Mol Sci 2023;24:6466. [CrossRef]
16. Cunha LL, Marcello MA, Ward LS. The role of the inflammatory microenvironment in thyroid carcinogenesis. Endocr Relat Cancer 2014;21:R85-R103. [CrossRef]
17. Asimakopoulos P, Shaha AR, Nixon IJ, Shah JP, Randolph GW, Angelos P, et al. Management of the neck in well-differentiated thyroid cancer. Curr Oncol Rep 2020;23:1. [CrossRef]
18. Zhang W, Zhu J, Zhang Y, Sun L, Wang K, Dong Y, et al. Personalized prediction of lymph node metastasis in papillary thyroid microcarcinoma: a nomogram and web calculator. Sci Rep 2025;15:45288. [CrossRef]
19. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436-44. [CrossRef]
20. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev 2013;39:534-40. [CrossRef]
21. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014 Oct 23;159(3):676-90.
22. Fagin JA, Wells SA Jr. Biologic and clinical perspectives on thyroid cancer. N Engl J Med 2016;375:1054-67. [CrossRef]
23. Zheng J, Li C, Lu W, Wang C, Ai Z. Quantitative assessment of preoperative serum thyrotropin level and thyroid cancer. Oncotarget 2016;7:34918-29. [CrossRef]
24. Haymart MR, Repplinger DJ, Leverson GE, Elson DF, Sippel RS, Jaume JC, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. J Clin Endocrinol Metab 2008;93:809-14. [CrossRef]
25. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab 2006;91:4295-301. [CrossRef]
26. Ito Y, Kihara M, Takamura Y, Kobayashi K, Miya A, Hirokawa M, et al. Prognosis and prognostic factors of papillary thyroid carcinoma in patients under 20 years. Endocr J 2012;59:539-45. [CrossRef]
27. Adam MA, Pura J, Goffredo P, Dinan MA, Reed SD, Scheri RP, et al. Presence and Number of Lymph Node Metastases Are Associated With Compromised Survival for Patients Younger Than Age 45 Years With Papillary Thyroid Cancer. J Clin Oncol 2015;33:2370-5. [CrossRef]
28. Liddy DD, Zhang Z, Shirlekar K, He Z, Herremans KM, Han S, et al. Impact of age on genomic alterations and the tumor immune microenvironment in papillary thyroid cancer. Endocr Relat Cancer 2024;31:e230341. [CrossRef]

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Original Article GASTROENTEROLOGY

Maternal nutritional knowledge and child anthropometric outcomes in preschool children: A cross-sectional study

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ABSTRACT

OBJECTIVE: This study aimed to evaluate the nutritional knowledge levels of mothers of children aged 4–6 years attending pediatric outpatient clinics, analyze knowledge levels according to maternal age, education, and income, and investigate their relationship with children's anthropometric measurements.

METHODS: This cross-sectional study included 282 mothers of preschool-aged children who attended a pediatric outpatient clinic. Nutritional knowledge was assessed using the Nutritional Knowledge Level Scale for Adults, comprising Basic Nutritional Knowledge (BNK) and food preference (FP) subscales. Mothers also rated Nutrition-Health Awareness (NHA) and Dietary Adequacy Self-Assessment (DAS) on a 0–10 visual scale. Children's height-for-age (HAZ) and weight-for-age (WAZ) z-scores were calculated. Multiple linear regression and correlation analyses were performed.

RESULTS: The median maternal age was 34 (interquartile range [IQR]: 29.25–40) years. Median BNK and FP scores were 58 (IQR: 51–69) and 35 (IQR: 30–40), respectively. Educational attainment was the strongest independent predictor of BNK ($p=0.006$) and DAS ($p=0.033$). Household income independently predicted FP ($p=0.022$) and NHA ($p=0.026$) after adjusting for age and education. Younger maternal age was associated with higher BNK scores. No statistically significant associations were found between maternal nutritional knowledge variables and children's HAZ or WAZ scores (all $p>0.05$).

CONCLUSION: Most mothers demonstrated adequate BNK; however, this did not consistently translate into FP competence or healthy dietary self-perception. Maternal nutritional knowledge was not directly associated with children's growth outcomes in this cohort, suggesting the pathway from knowledge to child growth is indirect and multifactorial. Nutrition interventions should move beyond knowledge transfer to address practical dietary skills and socioeconomic determinants of eating behavior.

Keywords: Child anthropometry, mothers, nutritional knowledge, preschool children.

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The nutritional status during early childhood is influenced by a complex interplay of genetic, environmental, socioeconomic, and behavioral factors. Among these, parental influence, particularly that of the mother, plays a pivotal role in shaping children's eating behaviors and food preferences (FP) [1]. Mothers typically serve as primary caregivers responsible for food selection, preparation, and feeding practices within the household.

Parts of this study were presented as a poster at the 58th Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN 2026); 2026; Lille, France.

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Consequently, maternal nutritional knowledge has been identified as a key determinant of children's dietary quality and nutrition [2]. The preschool period, spanning 4–6 years of age, represents a critical window for establishing dietary habits and growth trajectories that often persist into adulthood [3].

Despite the recognized importance of maternal nutritional knowledge, studies investigating both maternal nutritional knowledge and its relationship with anthropometric measurements in Turkish preschool children are limited. Most existing studies have focused on school-aged children or adolescents, leaving a gap in the literature regarding younger age groups [4]. Furthermore, validated tools for assessing nutritional knowledge in Turkish adults, such as the Nutritional Knowledge Level Scale for Adults (NKLSA; Turkish: Yetişkinler İçin Beslenme Bilgi Düzeyi Ölçeği), have only recently become available, enabling more reliable evaluations of parental knowledge [5].

Understanding the association between maternal nutritional knowledge and children's growth parameters is essential for designing effective nutrition education programs and public health intervention strategies. Such insights can help healthcare professionals identify at-risk populations and tailor counseling strategies to improve maternal knowledge and child health outcomes.

Highlight key points

- Most mothers demonstrated adequate basic nutritional knowledge, but this did not consistently translate into food preference competence or healthy dietary self-perception.
- Educational attainment was the strongest predictor of Basic Nutritional Knowledge (BNK) and Dietary Adequacy Self-Assessment (DAS).
- Household income independently predicted Food Preference (FP) and Nutrition-Health Awareness (NHA), suggesting material living conditions shape dietary behavior beyond formal education.
- No significant associations were found between maternal nutritional knowledge variables and children's height-for-age or weight-for-age Z-scores in this sample.
- Nutrition interventions should move beyond knowledge transfer to address practical dietary skills, behavioral self-efficacy, and socioeconomic determinants of eating behavior.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study included 282 mothers of children aged 4–6 years who attended the pediatric outpatient clinics of our hospital between April 15, 2026, and May 31, 2026. Eligible participants were recruited consecutively during routine outpatient visits. Mothers who agreed to participate voluntarily and could complete the questionnaire independently were included. Children with chronic diseases, genetic syndromes, endocrine disorders, or conditions affecting growth and nutrition were excluded.

Data Collection

The sociodemographic characteristics of the mothers, including age, educational status, and family income, were recorded using a structured data collection form. Nutritional knowledge was evaluated using the NKLSA, a validated questionnaire developed to assess nutrition-related knowledge and FP [5].

The questionnaire consisted of two sections:

- Section A: Basic nutrition and food-health knowledge (20 items)
- Section B: FP behaviors (12 items).

Each item was rated on a 5-point Likert scale ranging from "strongly disagree" to "strongly agree." Higher scores indicate higher levels of nutritional knowledge and healthier FP. Participants also rated the relationship between nutrition and health (Nutrition-Health Awareness [NHA]) and the adequacy of their FP (dietary adequacy self-assessment [DAS]) using visual scales ranging from 0 to 10. Basic Nutritional Knowledge (BNK) scores (maximum 80) were categorized as defined by the scale developers [5]: Poor (<45), fair (45–55), good (56–65), and very good (>65). FP scores (maximum 48) were categorized as follows: Poor (<30), fair (30–36), good (37–42), and very good (>42). The NKLSA has previously demonstrated acceptable internal consistency in its validation study, with Cronbach's alpha coefficients of 0.72 for the BNK subscale and 0.70 for the FP subscale.

Anthropometric Measurements

Anthropometric measurements of the children were performed by trained healthcare professionals according to standard procedures. Body weight was measured using a calibrated digital scale with the child wearing light clothing and no shoes. Height was measured using a stadiometer with the child standing upright in the Frankfort plane. Weight-for-age (WAZ) and height-for-age (HAZ) *z*-scores were calculated according to World Health Organization reference standards.

Table 1. Descriptive statistics of participants (n=282)

Variables	Median (IQR)	Min–Max
Continuous variables		
Age (years)	34 (29.25–40)	25–46
Basic nutritional knowledge score (max. 80)	58 (51–69)	34–76
Food preference score (max. 48)	35 (30–40)	9–48
Nutrition-health awareness score (0–10)	7 (5–8)	3–10
Dietary adequacy self-assessment score (0–10)	6.5 (5–8)	2–10
Monthly household income (TL)	50.000 (35.000–60.000)	20.000–120.000
Categorical variables	Percentage	
Education level		
Low (primary/middle school)	18.4	
Middle (high school)	44.0	
High (university/postgraduate)	37.6	
Age group		
≤29 years	25.2	
30–39 years	47.1	
≥40 years	27.7	
Child anthropometric measures		
Height-for-age Z-score	0.08 (-0.57–0.69)	-2.02–2.20
Weight-for-age Z-score	0.07 (-0.62–0.64)	-2.71–2.47

IQR: Interquartile range; Min: Minimum; Max: Maximum.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee (Approval No: 2026/0165, Date: April 09, 2026). Written informed consent was obtained from all mothers before enrollment. This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Continuous variables are expressed as median (interquartile range [IQR]) and minimum–maximum values, whereas categorical variables are presented as numbers and percentages. The normality of the distribution was assessed using the Kolmogorov–Smirnov test. Comparisons between groups were performed using Student's t-test or Mann–Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. Post hoc pairwise comparisons following significant Kruskal-Wallis tests were conducted using Mann–Whitney U tests with Bonferroni correction. Correlations between maternal nutritional knowledge scores and children's anthropometric measurements were evaluated using Pearson's or Spearman's correlation analyses. Household income was entered into regression models in units of 1,000 TL to yield interpretable coefficients. A $p<0.05$ was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences Statistics (version 25.0; IBM Corp., Armonk, NY, USA). Post hoc power analysis was conducted using G*Power version 3.1. Based on the observed effect sizes of the regression models ($R^2=0.030–0.089$), a sample size of 282 participants, three predictors, and a significance level of $\alpha=0.05$, the achieved statistical power ranged from 0.80 to 0.99, indicating adequate power to detect small-to-moderate effects.

RESULTS

Sample Characteristics

A total of 282 mothers of preschool-aged children participated in the study. The median age was 34 (IQR: 29.25–40) years, and the majority held a high school diploma (44.0%). Median BNK and FP scores were 58

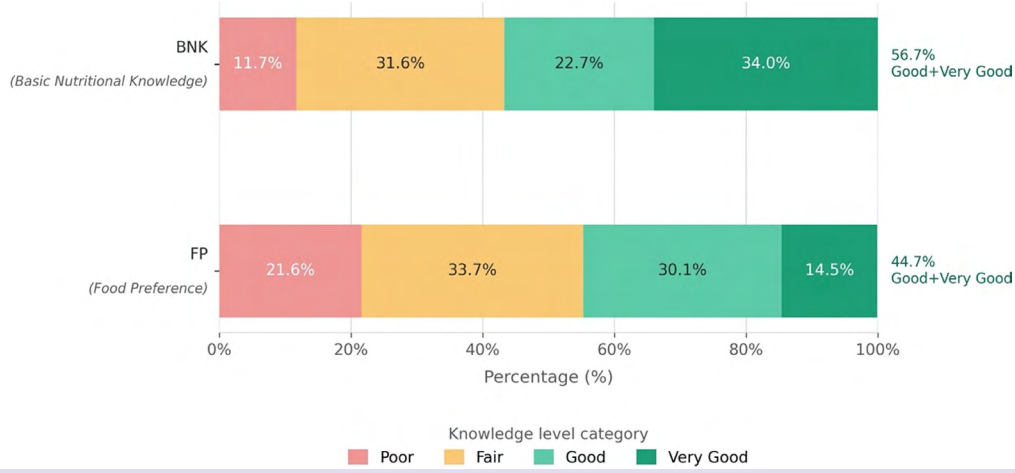

Figure 1. Distribution of nutrition knowledge level categories among mothers of preschool children (n=282). BNK: Basic Nutritional Knowledge (max. 80); FP: Food preference (max. 48). Cut-off criteria – BNK: <45 poor, 45–55 fair, 56–65 good, >65 very good; FP: <30 poor, 30–36 fair, 37–42 good, >42 very good.

Table 2. Correlations among maternal and child variables (n=282)

Variables	Age	Education	BNK	FP	NHA	DAS	HAZ	WAZ
Age	—	-0.036	-0.218***	-0.095	-0.007	-0.033	-0.011	-0.033
Education	-0.036	—	0.173**	0.074	0.125*	0.147*	-0.010	-0.042
BNK	-0.218***	0.173**	—	0.243***	0.099	0.231***	0.047	-0.047
FP	-0.095	0.074	0.243***	—	0.180**	0.205***	-0.104	-0.062
NHA	-0.007	0.125*	0.099	0.180**	—	0.154**	-0.063	0.036
DAS	-0.033	0.147*	0.231***	0.205***	0.154**	—	0.078	0.026
HAZ	-0.011	-0.010	0.047	-0.104	-0.063	0.078	—	-0.074
WAZ	-0.033	-0.042	-0.047	-0.062	0.036	0.026	-0.074	—

BNK: Basic nutritional knowledge; FP: Food preference; NHA: Nutrition-health awareness; DAS: Dietary adequacy self-assessment; HAZ: Height-for-age Z-score; WAZ: Weight-for-age Z-score. Education: 3-level (1=Low, 2=Middle, 3=High). Pearson correlation coefficients. *: P<0.05; **: P<0.01; ***: P<0.001.

(IQR: 51–69) and 35 (IQR: 30–40), respectively, with self-reported NHA and DAS medians of 7 (IQR: 5–8) and 6.5 (IQR: 5–8) on a 0–10 scale (Table 1). When categorized by knowledge level, 56.7% of mothers scored in the "good" or "very good" categories on the BNK scale, compared to 44.7% on the FP scale. The distribution of nutrition knowledge levels is presented in Figure 1.

Correlational Analyses

Pearson correlation analyses revealed that age was negatively associated with BNK ($r=-0.218$, $p<0.001$), whereas education level was positively correlated with BNK ($r=0.173$, $p<0.01$) and DAS ($r=0.147$, $p<0.05$). BNK, FP, NHA, and DAS were significantly and positively intercorrelated (Table 2). No significant correlations were observed between any maternal nutritional knowledge variable and children's HAZ or WAZ (all $p>0.05$).

Multiple Linear Regression Analyses

Age, education level, and household income were entered as predictors in the four models. Education level was a significant independent predictor of BNK ($B=3.009$, $p=0.006$) and DAS ($B=0.373$, $p=0.033$). Household income was the only significant predictor of FP ($B=0.056$, $p=0.022$) and NHA ($B=0.014$, $p=0.026$). Age was a significant independent predictor only for BNK ($B=-0.395$, $p<0.001$). The explained variance ranged from 3.0% to 8.9% (Table 3).

TABLE 3. Multiple linear regression analysis results

Variables	B	SE	t	p	Significance
Model 1: Dependent variable=Basic nutritional knowledge (BNK)					
Constant	67.606	4.664	14.497	<0.001	***
Age	-0.395	0.102	-3.857	<0.001	***
Education	3.009	1.081	2.783	0.006	**
Income (per 1,000 TL)	0.021	0.041	0.520	0.603	NS
R^2=0.089, Adj. R^2=0.078, F(3, 278)=8.028, p<0.001, n=282					
Model 2: Dependent variable=Food preference (FP)					
Constant	33.150	2.764	11.992	<0.001	***
Age	-0.074	0.061	-1.214	0.226	NS
Education	0.748	0.641	1.168	0.244	NS
Income (per 1,000 TL)	0.056	0.024	2.302	0.022	*
R^2=0.036, Adj. R^2=0.024, F(3, 278)=3.038, p=0.030, n=282					
Model 3: Dependent variable=Nutrition-health awareness (NHA)					
Constant	5.595	0.703	7.959	<0.001	***
Age	-0.002	0.015	-0.136	0.892	NS
Education	0.275	0.163	1.689	0.092	NS
Income (per 1,000 TL)	0.014	0.006	2.246	0.026	*
R^2=0.036, Adj. R^2=0.025, F(3, 278)=3.092, p=0.028, n=282					
Model 4: Dependent variable=Dietary adequacy self-assessment (DAS)					
Constant	5.566	0.751	7.413	<0.001	***
Age	-0.007	0.017	-0.423	0.673	NS
Education	0.373	0.174	2.143	0.033	*
Income (per 1,000 TL)	0.010	0.007	1.541	0.125	NS
R^2=0.030, Adj. R^2=0.021, F(3, 278)=2.744, p=0.041, n=282					

B: Unstandardized coefficient; SE: Standard error; NS: Not significant (p≥0.05). Education=3-level (Low=1, Middle=2, High=3). Income=approximate monthly household income, entered per 1,000 TL. *: P<0.05; **: P<0.01; ***: P<0.001.

Comparisons by Demographic and Anthropometric Groups

Kruskal-Wallis analyses revealed significant differences in BNK scores by maternal age group (H=10.994, p=0.004) and by education level (H=8.594, p=0.014). Bonferroni-corrected post hoc comparisons for age groups indicated that mothers aged ≤29 years scored significantly higher than those aged ≥40 years (p=0.011), and mothers aged 30–39 years also scored significantly higher than those aged ≥40 years (p=0.014); no significant difference was observed between the two younger groups (p=1.000). Post hoc comparisons for education groups showed that mothers with low educational attainment scored significantly lower than those with high attainment (p=0.010); no significant difference was found between middle and high education groups (p=0.999). No significant differences in FP scores were observed by education level (H=2.934, p=0.231). Child anthropometric indicators (HAZ and WAZ groups) were not associated with maternal nutritional knowledge scores (all p>0.05).

DISCUSSION

This study examined nutritional knowledge, FP behavior, and self-perceived dietary behaviors among 282 mothers of preschool-aged children, and their associations with maternal sociodemographic characteristics and children's anthropometric growth outcomes. Overall, findings revealed that while most mothers demonstrated

adequate BNK, this did not consistently translate into FP competence or positive dietary self-perception. Educational attainment was the strongest predictor of BNK and DAS, whereas household income independently predicted FP and NHA. Maternal nutrition knowledge showed no significant association with children's HAZ or WAZ scores.

Regarding knowledge distribution, 56.7% of mothers scored in the "good" or "very good" categories on the BNK scale, compared with 44.7% on the FP scale. This discrepancy is clinically meaningful because, while the BNK reflects the factual recall of nutritional principles, the FP requires their application to real-world food selection, which is a more cognitively demanding task [6, 7]. One finding that stands out is that mothers with poor BNK scores still gave themselves relatively high dietary adequacy ratings (median 6.0 out of 10). This suggests that many mothers overestimate how well they eat, which is a practical concern - someone who believes their diet is already good is unlikely to seek help or engage with nutrition programs [8, 9].

Mothers with higher education levels scored better on BNK and dietary self-assessment. This is well-established in the literature: education improves health literacy and helps people make better use of nutrition information in daily life [10, 11]. When we compared groups, mothers with low education scored significantly lower on BNK than those with high education ($p=0.010$), but there was no meaningful difference between the middle and high education groups. This hints at a threshold effect - getting through secondary school may be enough to pick up most basic nutrition knowledge, but the jump from low to any higher level of education is where the biggest gap lies. That said, even well-educated mothers did not always report healthier dietary habits, which shows that knowledge alone is not enough to change behavior [12, 13]. Nutrition programs for less-educated mothers should focus on simple, practical guidance rather than theory, while programs for more educated mothers might be better focused on helping them act on what they already know.

An interesting finding was that household income - not education - predicted FP scores and NHA. After accounting for age and education, mothers in higher-income households reported healthier FP. This is not surprising: families with more money have better access to a variety of foods, nutrition information, and health-promoting environments [14, 15]. Basic factual knowledge about nutrition seems to come mainly from schooling, but the ability to actually eat well appears to depend more on what a family can afford. This finding reinforces the idea that nutrition interventions need to go beyond education alone and also address the practical, economic barriers that shape what people eat [16, 17].

Younger mothers scored higher on BNK. Mothers aged 29 or under scored significantly higher than those aged 40 or over, and so did those in the 30–39 age group. This finding may reflect generational differences in exposure to nutrition education and health information sources [18, 19]. Interestingly, age had no effect on FP or self-assessed dietary adequacy, suggesting that this generational gap is specific to factual knowledge rather than actual eating behavior or self-perception.

We found no significant association between any of the maternal nutritional knowledge measures and children's HAZ or WAZ scores. This is consistent with findings from other urban settings, where severe undernutrition is rare, and a single factor like maternal knowledge is unlikely to directly determine child growth [12, 20]. The children in our sample were growing normally on average, which means there was little room to detect a knowledge-growth relationship even if one existed. By contrast, in lower-income settings where undernutrition is more common, studies more often find a direct link between maternal knowledge and child anthropometric outcomes [17, 21].

The absence of a significant association should not be interpreted to mean that maternal nutritional knowledge is irrelevant to child health. Rather, it underscores that the pathway from knowledge to growth is indirect and mediated by actual feeding practices, dietary diversity, household food security, and healthcare utilization - variables not assessed in this study [17, 22, 23]. Future studies should incorporate objective dietary intake measures and household food security assessments to more fully characterize how maternal knowledge influences the growth trajectories of children in urban Turkish settings.

Study Limitations

The present study had some limitations that should be noted when interpreting the findings. The cross-sectional design precludes causal inference; longitudinal studies are needed to establish whether improvements in maternal knowledge lead to better child growth outcomes over time. Self-reported dietary behavior mea-

sures are susceptible to social desirability bias, which may account for the inflated self-assessment scores observed among mothers with objectively poor nutritional knowledge. Actual objective dietary intake was not assessed; therefore, the functional pathway between knowledge, dietary behavior, and child growth cannot be established from the present data. Additional limitations include a lack of household food security evaluation and the relatively short recruitment period. The sample was drawn from a single urban pediatric outpatient setting, which limits generalizability of the findings to rural or lower-income populations.

Conclusion

This study demonstrates that while most mothers of preschool-aged children in an urban Turkish sample possess adequate BNK, this knowledge does not consistently translate into FP competence or healthy dietary self-perception. Educational attainment is the most robust determinant of BNK and dietary self-assessment, whereas household income exerts a selective influence on FP and NHA beyond formal education. The absence of significant knowledge-growth associations reflects the indirect and complex nature of this pathway. These findings highlight the need for nutrition interventions that move beyond knowledge transfer to address practical dietary skills, behavioral self-efficacy, and the social determinants of eating behavior, with content tailored to the educational level and socioeconomic context of the target population. Future research should employ longitudinal designs and objective dietary assessment tools to characterize the mechanisms through which maternal nutritional knowledge shapes child growth.

Ethics Committee Approval: This study was approved by The Ethics Committee of Goztepe Prof. Dr. Suleyman Yalcin City Hospital (Approval No: 2026/0165, Date: 09.04.2026).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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REFERENCES

1. Scaglioni S, De Cosmi V, Ciappolino V, Parazzini F, Brambilla P, Agostoni C. Factors influencing children's eating behaviours. Nutrients 2018;10:706. [CrossRef]
2. Forh G, Apprey C, Frimpomaa Agyapong NA. Nutritional knowledge and practices of mothers/caregivers and its impact on the nutritional status of children 6-59 months in Sefwi Wiawso Municipality, Western-North Region, Ghana. Heliyon 2022;8:e12330. [CrossRef]
3. Kostecka M, Kostecka-Jarecka J, Kowal M, Jackowska I. Dietary habits and choices of 4-to-6-year-olds: do children have a preference for sweet taste? Children (Basel) 2021;8:774. [CrossRef]
4. Ghabashi MA, Babateen AM, Zagzoog AM, Aljaadi AM. The impact of nutritional knowledge of mothers on their children's nutritional knowledge and weight status. Healthcare (Basel) 2025;13:2226. [CrossRef]
5. Batmaz H. Yetişkinler için beslenme bilgi düzeyi ölçeği geliştirilmesi ve geçerlik-güvenirlik çalışması [master's thesis]. İstanbul: Marmara University, Institute of Health Sciences; 2018. [in Turkish]
6. Debela BL, Demmler KM, Rischke R, Qaim M. Maternal nutrition knowledge and child nutritional outcomes in urban Kenya. Appetite 2017;116:518-26. [CrossRef]
7. Appoh LY, Krekling S. Maternal nutritional knowledge and child nutritional status in the Volta region of Ghana. Matern Child Nutr 2005;1:100-10. [CrossRef]
8. Matsumoto M, Hatamoto Y, Masumoto A, Sakamoto A, Ikemoto S. Mothers' nutrition knowledge is unlikely to be related to adolescents' habitual nutrient intake inadequacy in Japan: a cross-sectional study of Japanese junior high school students. Nutrients 2020;12:2801. [CrossRef]
9. Wawrzyniak A, Traczyk I. Nutrition-related knowledge and nutrition-related practice among polish adolescents-a cross-sectional study. Nutrients 2024;16:1611. [CrossRef]
10. Burchi F. Child nutrition in Mozambique in 2003: the role of mother's schooling and nutrition knowledge. Econ Hum Biol 2010;8:331-45. [CrossRef]
11. Gebremichael B, Beletew Abate B, Tesfaye T. Mothers had inadequate knowledge towards key essential nutrition action messages in mainly rural Northeast Ethiopia. J Nutr Sci 2021;10:e19. [CrossRef]
12. Meriç ÇS, Demirci KŞ, Yılmaz HÖ. Maternal food and nutrition literacy and its association with growth indicators in children and adolescents: a cross-sectional study in Türkiye. BMC Pediatr 2026;26:198. [CrossRef]
13. Arslanbaş C, Okburan G. Does mother's nutritional knowledge level affect anthropometric measurements of 0-2 year old infants? Ecol Food Nutr 2025;64:20-37. [CrossRef]
14. Alristina AD, Laili RD, Nagy É, Feith HJ. The importance of socioeconomic factors associated with maternal nutrition knowledge and undernutrition among children under five. Nutrients 2025;17:3355. [CrossRef]
15. Azak M, Gözen D. The impact of web-based education provided to parents on the nutritional risk of preschoolers: A quasi-experimental study. Matern Child Nutr 2025;21:e13735. [CrossRef]

16. Inayati DA, Scherbaum V, Purwestri RC, Wirawan NN, Suryantan J, Hartono S, et al. Improved nutrition knowledge and practice through intensive nutrition education: a study among caregivers of mildly wasted children on Nias Island, Indonesia. Food Nutr Bull 2012;33:117-27. [CrossRef]
17. Saaka M, Wemah K, Kizito F, Hoeschle-Zeledon I. Effect of nutrition behaviour change communication delivered through radio on mothers' nutritional knowledge, child feeding practices and growth. J Nutr Sci 2021;10:e44. [CrossRef]
18. Muluye SD, Lemma TB, Diddana TZ. Effects of nutrition education on improving knowledge and practice of complementary feeding of mothers with 6- to 23-month-old children in daycare centers in Hawassa Town, Southern Ethiopia: an institution-based randomized control trial. J Nutr Metab 2020;2020:6571583. [CrossRef]
19. Angeles-Agdeppa I, Monville-Oro E, Gonsalves JF, Capanzana MV. Integrated school based nutrition programme improved the knowledge of mother and schoolchildren. Matern Child Nutr 2019;15(Suppl 3):e12794. [CrossRef]
20. Rezaeizadeh G, Mansournia MA, Keshtkar A, Farahani Z, Zarepour F, Sharafkhah M, et al. Maternal education and its influence on child growth and nutritional status during the first two years of life: a systematic review and meta-analysis. EClinicalMedicine 2024;71:102574. [CrossRef]
21. Fadare O, Amare M, Mavrotas G, Akerele D, Ogunniyi A. Mother's nutrition-related knowledge and child nutrition outcomes: Empirical evidence from Nigeria. PLoS One 2019;14:e0212775. [CrossRef]
22. Kossinna C, Lau CL, Mayr HL, Wilkinson SA, Young AM, Meloncelli N, et al. Application of the Knowledge-to-Action framework in translating nutrition and dietetic knowledge into practice: A systematic review. Nutr Clin Pract 2025;40:1276-300. [CrossRef]
23. Andersen CT, Chopra PK, Dave N, Hariprasad D, Kak M, Pandey R, et al. Maternal and child nutrition services associated with nutritional knowledge and practices, India. Bull World Health Organ 2024;102:9-21. [CrossRef]

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Original Article NEUROSURGERY

Experimental sciatic nerve neuropathy caused by diclofenac sodium in rats

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ABSTRACT

OBJECTIVE: Our aim in this study is to investigate the total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) values of diclofenac sodium, which is a non-steroidal anti-inflammatory analgesic, after sciatic nerve injury, to examine the histopathological changes in the sciatic nerve, and to examine the results and enable important changes in treatment. It is one of the rare studies conducted histopathologically on post-injection sciatic nerve damage of diclofenac sodium, and the parameters of our biochemical approach have not been evaluated before in the literature.

METHODS: study was divided into 5 main groups as control, sham, trauma, isotonic fluid, and diclofenac sodium. Sham, trauma, isotonic fluid, and diclofenac sodium groups were divided into four subgroups as early stage (day 1, day 3) and late stage (day 7 and day 14). Subjects in each group were evaluated daily by neurological examination according to the Tarlov scale. In all groups except the control group, the sciatic nerve was exposed through appropriate surgical procedures. TAS, TOS, and OSI were run on blood samples biochemically. Nerve tissue samples were evaluated histopathologically and immunohistochemically.

RESULTS: There was a significant difference in pairwise comparison of the groups in terms of CASPASE-3 values. A statistically significant difference was found between the groups in terms of myelin thickness and axon diameter. A statistically significant difference was found between the groups in terms of nerve diameter values.

CONCLUSION: Our study demonstrates that intramuscular injections of diclofenac sodium have potential harmful effects. We recommend that alternative methods of using diclofenac sodium intramuscularly be preferred whenever possible due to the potential complications associated with this drug, that healthcare professionals receive necessary training on intramuscular administration, that the procedures be performed more carefully, and that patients be informed about these complications.

Keywords: Diclofenac sodium; injection; neuropathy; sciatic.

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Post-injection sciatic nerve damage is a serious health problem with socioeconomic and medicolegal dimensions in both developed and developing societies [1–3]. The general incidence is estimated to be around 2%. Affected patients may experience temporary and permanent neuropathic pain, sensory and motor deficits, and associated gait disturbances [4–6].

Injury after injection may vary depending on the neurotoxicity of the drug, the dose and rate of administration, and needle-related characteristics such as diameter and length [7]. Possible mechanisms of injury include chemical damage, neuronal ischemia, direct needle injury, compression injury, and constriction due to scarring. Free radicals and cytokines released as a result of some of the ischemic and inflammatory changes that occur after injury cause calcium ions to enter the cell. This leads to the activation of proteolysis sites [8]. Repairment after injury is a complex process involving changes in Schwann cells, activation of macrophages, and rearrangement of vascular structures [9, 10].

The aim of this study is to demonstrate histopathologically and biochemically the damage caused by diclofenac sodium, which induces nerve damage through oxidative stress and apoptosis mechanisms [11, 12]. To this end, our study used biochemical, histopathological, and functional approaches. In the biochemical approach, we evaluated total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) parameters. The parameters in our biochemical approach have not been evaluated in previous studies of sciatic nerve injury after injection in the literature.

Highlight key points

- Peripheral nerve injury is a common complication after intramuscular injection and can be prevented with training.
- Post-injection damage may vary depending on the neurotoxicity of the given drug, dose and rate of administration, and needle-related characteristics such as diameter and length.
- This is the first study conducted in this context.
- Post-injection sciatic nerve damages importance as a health problem with socioeconomic and medicolegal dimensions.
- It was shown that TOS and OSI values increased and TAS values decreased after diclofenac sodium injection.

MATERIALS AND METHODS

Experimental Model

Ethics committee approval was obtained from the local ethics committee. During the study, the study was conducted in accordance with the Declaration of Helsinki.

The use of experimental animals was carried out in accordance with local ethical guidelines. The study was divided into 5 main groups: Control, sham, trauma, isotonic fluid, and diclofenac sodium. The sham, trauma, isotonic fluid, and diclofenac sodium groups were divided into four subgroups: Early stage (day 1 and day 3) and late stage (day 7 and day 14). In our study, a total of 119 Wister albino rats (250–300 mg, male) were used, including the control and 7 rats in each subgroup, taking into account the statistical significance of any wastage that might occur. In all groups except the control group, the sciatic nerve was exposed through appropriate surgical procedures. In the sham groups, only the sciatic nerve was observed. Trauma groups underwent dry needling injury. Isotonic groups received 0.5 mL of intraneural isotonic solution. Diclofenac groups received 0.2 mg/kg/0.5 mL of diclofenac sodium intraneurally. The skin was then closed with 3/0 Prolene. We had to take blood and tissue samples on 1, 3, 7, and 14 days. Xylazine (30 mg/kg) and ketamine hydrochloride (200 mg/kg) were administered intraperitoneally for anesthesia.

Biochemical Evaluation

Sample Collection

Blood samples were collected from the rats intracardially into a yellow-capped gel biochemistry tube (BD Vacutainer SST II Advance). After allowing 20 min for clotting to occur, the samples were centrifuged for 10 min at 1500× g, and the supernatants were separated, aliquoted, and stored at -80°C until the day of the study for biochemical analysis.

Measurement of total Serum Antioxidant Status

The 2,2'-azinobis (3-ethylbenzothiazolin-6-sulfonate) (ABTS) reagent is radicalized with hydrogen peroxide in the presence of a buffer solution, while the pH of the environment is kept constant. The characteristic color (a color between dark green and dark blue) produced by the radical cation appears when the antioxidants in the sample are added to the medium, neutralizing the existing ABTS radicals. Therefore, the total amount of antioxidants in the serum is proportional to the color intensity of the solution. TAS values were expressed as mmol Trolox/L.

Measurement of TOS in Serum

When the oxidative species in the sample dissolve the compound $Fe_2\ SO_4$ in water, they release Fe_2^+. Oxidants present in the serum allow the Fe_2^+ to be oxidized to Fe_3^+. The ferric ion forms a colored complex with the X-orange reagent in an acidic environment. The intensity of the color, measured spectrophotometrically, is proportional to the total amount of oxidant molecules in the sample. TOS levels were expressed as μmol H_2O_2/L.

Calculation of the OSI

The OSI was calculated according to the following formula. OSI=TOS (μmol H_2O_2/L)/(TAS (mmol Trolox/L)×100) OSI was expressed as an arbitrary unit.

Histopathological Evaluation

Histomorphological Study

After the tissues were fixed in 10% formaldehyde solution for 48 h, 3 mm thick sections were cut perpendicular to the long axis of the nerve fiber and embedded vertically in paraffin. Sections of 4 microns were cut from each sample. After staining with toluidine blue, quantitative morphometric analyses were performed using a computerized image analysis program (Olympus BX51 microscope and DP2-BSW image analysis system). Immersion oil was used for measurements at high magnification (×1000). 15 nerve fibers were examined in each nerve section. Nerve diameter and axon diameter were measured. In addition, the ratio of axon diameter to nerve diameter (myelinated axon), the G-ratio, was calculated for each nerve fiber.

Immunohistochemical Study

Immunohistochemical staining was performed according to the protocol of the study entitled Effects of Dexamethasone on Bupivacaine-Induced Peripheral Nerve Injection Injury by Comez et al. [13].

Tonsil tissue was used as a positive control for anti-CASPASE 3 and S100, and schwannoma tissue was used as a positive control. All immunohistochemically stained specimens were examined blindly by the pathologist under a bright-field light microscope (Olympus BX53). To evaluate the percentage of CASPASE-3 positive cells, the percentage of positive nuclear staining with anti-CASPASE-3 was recorded in the nerve section of each rat. Brown positive cytoplasmic staining with S100 was observed in myelinated fibers as opposed to demyelinated fibers. The percentage of positive staining with S100 was determined using a four-point grading system as mild (+), moderate (++), severe (+++), and very severe (++++), according to the method of Bostan et al. [14]. Immunohistochemical staining was performed on the study groups and control cases at the same session.

Functional Analysis

Subjects in each group were assessed daily by neurological examination according to the modified Tarlov scale. On the Tarlov scale, Grade 0: Complete plegia, Grade 1: Marked hind limb movement but no weight bearing, Grade 2: Frequent or strong hind limb movement, marked hind limb movement not resulting in weight bearing or locomotion, Grade 3: Hind limbs support body weight but there is no normal walking, Grade 4: There is a slight loss of walking, Grade 5: It is judged as normal walking [15].

Statistical Analysis

The suitability of continuous variables included in the study was evaluated through graphical analysis and the application of the Shapiro–Wilk test. The results demonstrated that the continuous variables were not normally distributed, with the exception of TAS and G-ratio. Mean±standard deviation values were used in the presentation of descriptive statistics. Kruskal–Wallis non-parametric analysis of variance (ANOVA) was used to compare TOS, OSI, axon diameter, nerve diameter, myelin thickness, myelin number, Tarlov score, CASPASE-3, and S100 values between groups. Analysis results are presented with Bonferroni correction for pairwise comparisons. One-way ANOVA test was used to compare TAS and G-ratio values according to groups. When a difference was found as a result of the one-way ANOVA test, *post hoc* pairwise comparisons were performed to determine the different groups, and the analysis results were presented with Bonferroni correction. IBM Statistical Package for the Social Sciences Statistics 21.0 was used for statistical analyses and calculations. The level of statistical significance was accepted as $p<0.05$.

RESULTS

Biochemical Results

In the paired comparison of sham and control groups, a statistically significant increase in TOS was found only in the early sham group ($p=0.033$), while no significant difference was found in TAS and OSI. In the paired compar-

Table 1. Biochemical results of day 1 groups

Biochemical parameters	Control Mean±SD	Sham-1 Mean±SD	Isotonic-1 Mean±SD	Trauma-1 Mean±SD	Diclofenac-1 Mean±SD	Test statistic	
						χ^2; F	p
TAS	1.14±0.17	1.03±0.25	0.97±0.26	0.94±0.24	0.95±0.39	F=0.623	0.650
TOS	8.11±3.26	15.03±2.98	13.73±3.49	20.34±5.27	17.39±4.80	χ^2=17.652	**0.001***
OSI	0.73±0.34	1.52±0.43	1.48±0.53	2.45±1.39	2.04±0.88	χ^2=16.835	**0.002***

TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative Stress Index; F: One-way analysis of variance; χ^2: Kruskal–Wallis test statistic; SD: Standard deviation; *: P<0.05 statistical significant value.

Table 2. Biochemical results of day 3 groups

Biochemical parameters	Control Mean±SD	Sham-2 Mean±SD	Isotonic-2 Mean±SD	Trauma-2 Mean±SD	Diclofenac-2 Mean±SD	Test statistic	
						χ^2; F	p
TAS	1.14±0.17	1.01±0.20	1.01±0.24	0.98±0.39	0.95±0.22	F=0.535	0.711
TOS	8.11±3.26	10.82±8.20	11.59±4.46	16.26±3.64	15.02±2.84	χ^2=12.813	**0.012***
OSI	0.73±0.34	1.17±0.96	1.16±0.45	1.89±0.85	1.63±0.32	χ^2=11.852	**0.018***

TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative Stress Index; F: One-way analysis of variance; χ^2: Kruskal–Wallis test statistic; SD: Standard deviation; *: P<0.05 statistical significant value.

ison of trauma and control groups, statistically significant increases in TOS (p<0.001, p=0.015) and OSI (p=0.001, p=0.017) were found in the early trauma group compared to the control group. In the paired comparison between isotonic groups and the control group, no statistically significant difference was found in TAS, TOS, and OSI values. In the pairwise comparison of diclofenac groups with the control group, statistically significant increases in TOS (p=0.011, p=0.021) and OSI (p=0.005, p=0.017) were found in the early diclofenac groups compared to the control group. However, a significant decrease in TOS (p=0.012, p=0.023) and OSI (p=0.008, p=0.025) was observed in the late diclofenac group compared to the early diclofenac groups. In the pairwise comparison of the control and early groups (Table 1, 2), a significant increase in TOS (p=0.001, p=0.017) and OSI (p=0.002, p=0.009) values was observed in the trauma and diclofenac groups compared to the control group. In the pairwise comparison of the control and late-stage groups, a significant increase in TOS (p=0.042, p=0.006) and OSI (p=0.013, p=0.042) values was observed between the control and trauma groups. However, a greater decrease in TOS (p=0.006) was observed in the late-stage diclofenac group compared to the trauma group.

Histomorphological Results

In our study, axon diameter, nerve diameter, G-ratio, myelin thickness, and myelin count were evaluated as histological parameters. In the pairwise comparison of the control and sham groups, a statistically significant decrease in myelin thickness (p=0.015, p=0.048, and p=0.037) and myelin count (p=0.007, p=0.034, and p=0.005) was observed in the sham group compared to the control group in both the early and late periods. In the pairwise comparison of the trauma and control groups, a significant decrease in nerve diameter (p=0.004) and myelin thickness (p=0.001) was observed in the trauma group compared to the control group in the early period. A significant decrease in myelin count was observed as the days progressed (Fig. 1A). In the pairwise comparison between the isotonic groups and the control group, a significant decrease in axon diameter was observed in the early period (p=0.017) and a significant increase in the late period (p=0.021) compared to the control group. A significant decrease in myelin thickness (p=0.009) was observed in the early period compared to the control group, while myelin count decreased in both the early and late periods (p<0.001, p=0.014) (Fig. 1B). A significant

TABLE 3. Histomorphological results of day 1 groups

Measured parameter	Control Mean±SD	Sham-1 Mean±SD	Isotonic-1 Mean±SD	Trauma-1 Mean±SD	Diclofenac-1 Mean±SD	Test statistic	
						χ^2; F	p
Axon diameter	2688.17±678.16	2513.57±667.95	2160.00±467.27	1963.88±478.04	3013.60±828.77	χ^2=6.215	0.184
Nerve diameter	6469.51±916.96	5556.00±712.91	4860.63±541.15	5050.86±594.02	5338.08±417.52	χ^2=12.675	**0.013***
G-ratio	0.41±0.06	0.44±0.06	0.43±0.07	0.38±0.05	0.55±0.13	F=4.263	**0.008***
Myelin thickness	2005.00±319.72	1520.71±158.19	1349.86±174.43	1543.14±87.04	1162.80±324.86	χ^2=19.698	**0.001***
Myelin count	24.00±2.58	20.43±4.16	7.86±1.46	17.00±4.58	7.00±1.41	χ^2=26.572	**<0.001***
CASPASE-3	0.14±0.38	0.43±0.53	4.57±2.76	4.43±2.37	5.00±5.21	χ^2=23.888	**<0.001***
S100	4.00±0.00	3.57±0.53	3.71±0.49	3.14±0.90	2.83±0.98	χ^2=9.092	0.059

F: One-way analysis of variance; χ^2: Kruskal–Wallis test statistic; SD: Standard deviation; *: P<0.05 statistical significant value.

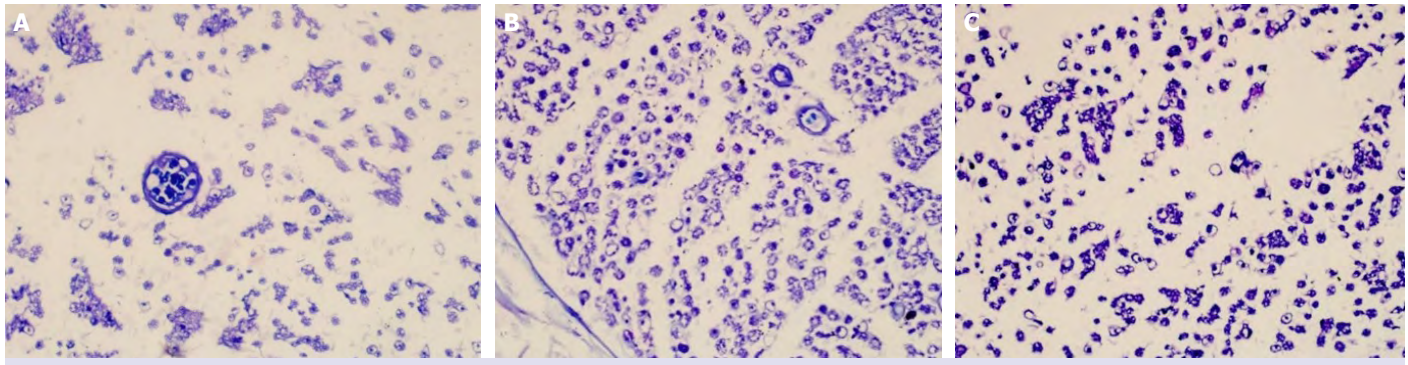

FIGURE 1. **(A)** In the trauma group, loss and damage to the myelin sheath and decrease in myelin number (Toluidine blue ×200). **(B)** Partial loss, degeneration, and thinning of the myelin sheath in the isotonic group (Toluidine blue ×200). **(C)** Decrease in the number of myelinated axons, thinning and damage in the sheath thickness in the diclofenac group (Toluidine blue ×200).

increase in the G-ratio was observed within the group as the days progressed. In the pairwise comparison between the diclofenac groups and the control group, a statistically significant decrease in myelin thickness (p=0.010, p=0.001) and myelin count (p=0.003, p=0.001) was observed in both the early and late periods compared to the control group. A significant increase in axon diameter (p=0.004) was observed in the late period (Fig. 1C). Furthermore, a statistically significant increase in the G-ratio was observed as the days progressed. In the comparison of the control and early-stage groups (Table 3, 4), myelin thickness was decreased in the trauma, isotonic, and diclofenac groups, while myelin count was significantly decreased in the isotonic and diclofenac groups. Furthermore, myelin thickness and count were significantly decreased in the isotonic and diclofenac groups compared to the sham group. The G-ratio was significantly increased in the trauma group, especially in the isotonic and diclofenac groups. Nerve diameter was significantly increased in the diclofenac group (p=0.029), and axon diameter was also found to be increased (p=0.001).

In the comparison of the control and late-stage groups (Table 5, 6), axon diameter was significantly increased in the diclofenac group (p=0.015). Myelin thickness was significantly decreased in the isotonic (p=0.044) and diclofenac (p<0.001) groups, while myelin count was significantly decreased in the trauma (p=0.008), isotonic (p=0.006), and diclofenac (p<0.001) groups. This decrease was more pronounced in the diclofenac group. The G-ratio was found to be increased in the trauma

Table 4. Histomorphological results of the day 3 groups

Measured parameter	Control Mean±SD	Sham-2 Mean±SD	Isotonic-2 Mean±SD	Trauma-2 Mean±SD	Diclofenac-2 Mean±SD	Test statistic	
						χ^2; F	p
Axon diameter	2688.17±678.16	2417.43±528.86	2969.46±920.65	1992.28±249.64	3779.80±543.15	χ^2=17.150	**0.002***
Nerve diameter	6469.51±916.96	5173.53±763.04	5091.54±1064.14	4495.60±562.16	5968.80±545.69	χ^2=16.555	**0.002***
G-ratio	0.41±0.06	0.46±0.06	0.56±0.08	0.45±0.07	0.62±0.05	F=12.687	**<0.001***
Myelin thickness	2005.00±319.72	1377.67±213.36	1060.57±157.02	1251.14±300.36	1094.00±212.04	χ^2=19.779	**0.001***
Myelin count	24.00±2.58	18.00±4.52	6.00±1.83	8.86±2.19	5.86±1.86	χ^2=26.948	**<0.001***
CASPASE-3	0.14±0.38	0.50±0.55	5.57±3.36	4.71±1.70	4.29±3.04	χ^2=23.628	**<0.001***
S100	4.00±0.00	3.33±0.82	3.57±0.53	2.86±1.07	3.43±0.79	χ^2=7.866	0.097

F: One-way analysis of variance; χ^2: Kruskal–Wallis test statistic; SD: Standard deviation; *: P<0.05 statistical significant value.

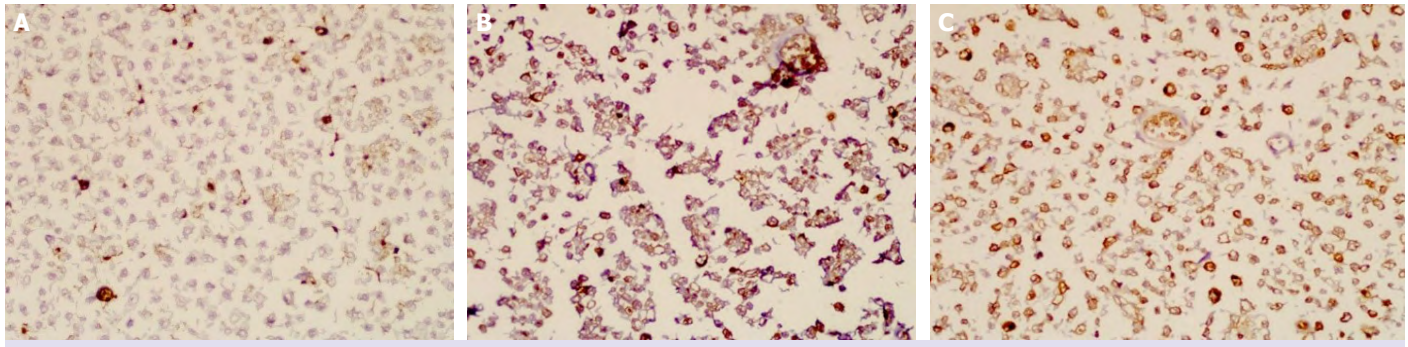

Figure 2. **(A)** The highest Caspase 3 activation in the diclofenac-treated group (Caspase 3 ×200). **(B)** S100 showed similar staining pattern among diclofenac-treated groups (S100 ×200). **(C)** S100 expression was similar between the isotonic group and the control group (S100 ×200).

group, and more pronounced in the isotonic (p=0.006) and diclofenac (p<0.001) groups.

Immunohistochemical Results

In the pairwise comparison of the sham and control groups, no statistically significant difference was observed in CASPASE-3 values. In the pairwise comparison between the trauma groups and the control group, a significant increase in CASPASE-3 values was observed in the trauma groups in both the early and late periods (p=0.026, p=0.003, p=0.005). In the pairwise comparison of the isotonic groups, a significant increase in CASPASE-3 was observed in the early period compared to the control group (p=0.009, p=0.002). In the pairwise comparison between the diclofenac groups and the control group, a significant increase in CASPASE-3 was observed in both the early and late periods (p=0.033, p=0.001) (Fig. 2A).

In the comparison of the control and early-stage groups (Table 3, 4), a significant increase in CASPASE-3 was observed in the trauma (p=0.005), isotonic (p=0.005), and diclofenac (p=0.026) groups compared to the control group. This increase was more pronounced in the diclofenac group, but also in the isotonic group. In the comparison of the control and late-stage groups (Table 5, 6), a significant increase in CASPASE-3 was observed in the trauma (p=0.001), isotonic (p=0.028), and diclofenac (p=0.001) groups compared to the sham and control groups. When S-100 values were evaluated, a significant decrease was observed only in the late-stage

Table 5. Histomorphological results of the day 7 groups

Measured parameter	Control Mean±SD	Sham-3 Mean±SD	Isotonic-3 Mean±SD	Trauma-3 Mean±SD	Diclofenac-3 Mean±SD	Test statistic	
						χ^2; F	p
Axon diameter	2688.17±678.16	2776.74±728.46	3590.11±853.71	2533.20±1034.21	3412.97±489.07	χ^2=7.148	0.128
Nerve diameter	6469.51±916.96	5661.97±511.68	5968.17±1147.51	5615.67±1338.76	5909.73±524.97	χ^2=3.357	0.500
G-ratio	0.41±0.06	0.48±0.11	0.58±0.04	0.43±0.09	0.57±0.05	F=7.383	**<0.001***
Myelin thickness	2005.00±319.72	1442.29±257.17	1188.71±185.76	1540.83±301.64	1248.00±143.39	χ^2=19.338	**0.001***
Myelin count	24.00±2.58	19.57±3.69	7.86±1.95	8.43±3.73	6.86±1.68	χ^2=25.610	**<0.001***
CASPASE-3	0.14±0.38	0.86±0.69	3.43±2.29	6.00±3.16	2.71±2.36	χ^2=19.662	**0.001***
S100	4.00±0.00	3.29±0.95	3.71±0.49	2.57±0.98	3.57±0.53	χ^2=12.126	**0.016***

F: One-way analysis of variance; χ^2: Kruskal–Wallis test statistic; SD: Standard deviation; *: P<0.05 statistical significant value.

Table 6. Histomorphological results of the day 14 groups

Measured parameter	Control Mean±SD	Sham-4 Mean±SD	Isotonic-4 Mean±SD	Trauma-4 Mean±SD	Diclofenac-4 Mean±SD	Test statistic	
						χ^2; F	p
Axon diameter	2688.17±678.16	3054.17±650.07	3341.68±569.29	2365.77±399.83	4368.34±744.07	χ^2=18.311	**0.001***
Nerve diameter	6469.51±916.96	5932.86±1110.68	6026.97±1120.51	5837.77±719.46	6430.00±738.69	χ^2=4.974	0.290
G-ratio	0.41±0.06	0.51±0.07	0.54±0.05	0.41±0.05	0.67±0.08	F=20.224	**<0.001***
Myelin thickness	2005.00±319.72	1438.86±317.26	1342.14±347.51	1735.67±286.19	1016.14±277.46	χ^2=20.558	**<0.001***
Myelin count	24.00±2.58	18.00±2.00	7.29±1.38	7.00±1.79	5.57±1.51	χ^2=27.059	**<0.001***
CASPASE-3	0.14±0.38	1.14±0.90	3.57±3.41	6.57±4.39	8.57±6.75	χ^2=23.148	**<0.001***
S100	4.00±0.00	3.43±0.79	3.71±0.49	3.14±0.90	3.29±0.76	χ^2=6.927	0.140

F: One-way analysis of variance; χ^2: Kruskal–Wallis test statistic; SD: Standard deviation; *: P<0.05 statistical significant value.

trauma group (p=0.026). However, there was no statistically significant difference between the early and late stages in the comparison of the sham, isotonic, and diclofenac groups (Fig. 2B, C).

Functional Results

The subjects were found to be neurologically sound before the procedure. Motor deficits developed in some subjects in the trauma, isotonic, and diclofenac groups. The severity of motor deficits was greater in the diclofenac groups. However, in our study, no statistically significant difference was found in the pairwise comparison of the groups in functional evaluation.

DISCUSSION

Nerve damage after intramuscular injections is common, and these injections are widely used in the treatment of diseases. Although the incidence of injection neuropathy has decreased in developed societies in the last decade, it

remains a serious health problem in both developed and developing countries. Ischemic, toxic, and mechanical causes play a role in the pathogenesis of post-injection neuropathy. While injection neuropathy is clinically variable, it generally manifests as pain, sensory deficits, and motor loss [16]. Diclofenac sodium has been reported as one of the most frequently used agents for intramuscular injections. Diclofenac sodium has been shown to be a neurotoxic agent in many studies [1, 14, 17].

Although many molecules associated with neuronal damage and repair have been identified, the mechanism is not fully understood. Oxidative stress is thought to be responsible for the damage that occurs after injury. Many antioxidants are found in cells and tissues to prevent oxidative damage by scavenging reactive oxygen species [18]. In this study, the biochemical approach evaluated TAS, TOS, and OSI. There are no studies on post-injection sciatic nerve damage. In our study, when the groups were compared with each other, it was found that TOS and OSI levels decreased gradually but were higher than the control group. In addition, it was determined that TAS levels between the groups were statistically insignificantly lower than the control group. It has been suggested that low TAS levels may be associated with fibrosis.

In our study, when the early groups were compared, a significant increase in TOS ($p=0.001$, $p=0.017$) and OSI ($p=0.002$, $p=0.009$) was observed in the trauma and diclofenac groups. When the late groups were compared, a significant increase in TOS and OSI levels was found only in the trauma group ($p=0.007$, $p=0.013$). It has been suggested that high serum TOS and OSI levels may be associated with fibrosis [19, 20].

Axon diameter, nerve diameter, G-ratio, myelin thickness, and myelin count, which we used as histological parameters in our study, are still important markers in evaluating regeneration after nerve injury [21]. Previous studies have associated degeneration with a low G-ratio value; it has been emphasized that a high G-ratio value indicates regeneration or demyelination in myelinated nerves [22].

When we compared the groups in our study, it was found that the myelin count and thickness decreased compared to the control group. The G-ratio was shown to gradually increase in the sham, isotonic, and diclofenac groups. In addition, it was observed that the axon diameter gradually increased in the isotonic and diclofenac groups. Nerve diameters were found to be lower compared to the control group. These results show that there was more damage in the diclofenac and isotonic groups as the days progressed. In the pairwise comparison of the early-stage groups in our study, the most significant decrease in myelin count and thickness was observed in the diclofenac and isotonic groups, indicating that degeneration was greater in these groups. In addition, the diclofenac group showed the greatest increase in G-ratio and axon diameter, suggesting that the damage was more severe than in the isotonic group. When comparing the late-stage groups, the G-ratio increased more in both the diclofenac and isotonic groups, and myelin thickness decreased more in the diclofenac group. Furthermore, myelin count decreased more in the diclofenac group. Our early and late-stage results demonstrate that degeneration and regeneration are more pronounced in the diclofenac group. Furthermore, it shows that the damage was more severe in the diclofenac group compared to the isotonic group.

Caspase-3 is known to play a significant role in dose-dependent apoptosis, and S-100 is a biomarker associated with axon diameter and myelination in Schwann cells and may reflect the regeneration phase [13, 23]. According to Bostan et al. [14], the S-100 percentage value is classified as mild (0–20, +), moderate (20–40, ++), severe (40–60, +++), and very severe (>60, ++++) positivity. When we compared the CASPASE-3 level groups in our study, the S-100 score was higher and lower compared to the control group. When we compared the early-stage groups, a significant increase in CASPASE-3 levels was found in the diclofenac, isotonic, and trauma groups. There was an insignificant decrease in S-100 levels. We hypothesized that high CASPASE-3 and low S-100 levels would be associated with a decrease in Schwann cell number. Furthermore, low S-100 levels are associated with drug toxicity. When comparing the late-stage groups, a significant increase in CASPASE-3 levels was observed in the trauma, isotonic, and diclofenac groups, respectively. This indicated that apoptosis was higher in the diclofenac group and more toxic than in the isotonic group. The diclofenac sodium used in our study was the lowest dose reported in the literature, and our histopathological findings were consistent with those of other researchers [13, 14]. No statistically significant difference was found in the functional evaluation of our study.

The Limitations of this Study

Electrophysiological methods were not included in the evaluation of sciatic nerve injury in this study.

Conclusion

Post-injection sciatic nerve damage can result in a clinical picture ranging from permanent and temporary pain to loss of strength. Therefore, it is considered a significant health problem with socioeconomic and medico-legal dimensions. This study demonstrates the potential harmful effects of intramuscular injections of diclofenac sodium, frequently prescribed by physicians, on peripheral nerves using histopathological and biochemical methods. Due to the potential complications associated with this drug, we recommend that alternative methods be preferred for intramuscular use of diclofenac sodium whenever possible, that healthcare professionals receive the necessary training on intramuscular administration, that procedures be performed more carefully, and that patients be informed about these complications.

Ethics Committee Approval: This study was approved by The Ethics Committee for Animal Experiments of Hatay Mustafa Kemal University Rectorate (2021/04-03 – 18/06/2021).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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

Financial Disclosure: The authors declared that this study received no financial support.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Authorship Contributions: Concept – YS; Design – MA; Supervision – AMA; Resource – TO, SD; Materials – AY; Data Collection and/or Processing – SO; Analysis and/or Interpretation – MEK; Literature Search – MEK; Writing – AMA; Critical Reviews – AM.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Kadioglu HH. Sciatic Nerve Injuries from Gluteal Intramuscular Injection According to Records of the High Health Council. Turk Neurosurg 2018;28:474-8. [CrossRef]
2. Maugeri G, D'Agata V, Trovato B, Roggio F, Castorina A, Vecchio M, et al. The role of exercise on peripheral nerve regeneration: from animal model to clinical application. Heliyon 2021;7:e08281. [CrossRef]
3. Park CW, Cho WC, Son BC. Iatrogenic Injury to the Sciatic Nerve due to Intramuscular Injection: A Case Report. Korean J Neurotrauma 2019;15:61-6. [CrossRef]
4. Esquenazi Y, Park SH, Kline DG, Kim DH. Surgical management and outcome of iatrogenic radial nerve injection injuries. Clin Neurol Neurosurg 2016;142:98-103. [CrossRef]
5. Jung Kim H, Hyun Park S. Sciatic nerve injection injury. J Int Med Res 2014;42:887-97. [CrossRef]
6. Toopchizadeh V, Barzegar M, Habibzadeh A. Sciatic nerve injection palsy in children, electrophysiologic pattern and outcome: a case series study. Iran J Child Neurol 2015;9:69-72.
7. Brull R, Hadzic A, Reina MA, Barrington MJ. pathophysiology and etiology of nerve injury following peripheral nerve blockade. Reg Anesth Pain Med 2015;40:479-90. [CrossRef]
8. Abushukur Y, Knackstedt R. The impact of supplements on recovery after peripheral nerve injury: a review of the literature. Cureus 2022;14:e25135. [CrossRef]
9. Dong R, Liu Y, Yang Y, Wang H, Xu Y, Zhang Z. MSC-derived exosomes-based therapy for peripheral nerve injury: a novel therapeutic strategy. Biomed Res Int 2019;2019:6458237. [CrossRef]
10. Hussain G, Wang J, Rasul A, Anwar H, Qasim M, Zafar S, et al. Current status of therapeutic approaches against peripheral nerve injuries: a detailed story from injury to recovery. Int J Biol Sci 2020;16:116-34. [CrossRef]
11. Açıkgöz M, Kaş HS, Hıncal AA. Diklofenak Sodyum. FABAD Farmasötik bilimler Dergisi 1994;19,37-47. [Article in Turkish]
12. Şentürk T. Non-steroid anti-inflamatuar ilaçlar. In: Tokgöz G, editor. Romatoloji Kitabı. Ankara: Ankara Üniversitesi Yayınları; 2011. p. 490-495.
13. Çömez MS, Borazan Y, Özgür T, İşler CT, Cellat M, Güvenç M, et al. Effects of dexamethasone on bupivacaine-induced peripheral nerve injection injury in the rat sciatic model. J Invest Surg 2021;34:1339-47. [CrossRef]
14. Bostan H, Cabalar M, Altinay S, Kalkan Y, Tumkaya L, Kanat A, Balik S, et al. Sciatic nerve injury following analgesic drug injection in rats: A histopathological examination. North Clin Istanb 2018;5:176-85. [CrossRef]
15. Gale K, Kerasidis H, Wrathall JR. Spinal cord contusion in the rat: behavioral analysis of functional neurologic impairment. Exp Neurol 1985;88:123-34. [CrossRef]
16. Topuz K, Kutlay M, Simşek H, Atabey C, Demircan M, Senol Güney M. Early surgical treatment protocol for sciatic nerve injury due to injection--a retrospective study. Br J Neurosurg 2011;25:509-15. [CrossRef]
17. Kabeloğlu V, Soysal A, Ataklı D, Şen A, Baştuğ Gül Z. Enjeksiyon nöropatisi olgularında siyatik sinir tutulumunun ve derecesinin değerlendirilmesi. diclemedj 2022;49:125-30. [Article in Turkish] [CrossRef]
18. Lanza C, Raimondo S, Vergani L, Catena N, Sénès F, Tos P, et al. Expression of antioxidant molecules after peripheral nerve injury and regeneration. J Neurosci Res 2012;90:842-8. [CrossRef]
19. Demirkol A, Uludag M, Soran N, Aksoy N, Gun K, Incebıyık S, et al. Total oxidative stress and antioxidant status in patients with carpal tunnel syndrome. Redox Rep 2012;17:234-8. [CrossRef]
20. Kasznicki J, Kosmalski M, Sliwinska A, Mrowicka M, Stanczyk M, Majsterek I, Drzewoski J. Evaluation of oxidative stress markers in pathogenesis of diabetic neuropathy. Mol Biol Rep 2012;39:8669-78. [CrossRef]
21. Rayner MLD, Brown HL, Wilcox M, Phillips JB, Quick TJ. Quantifying regeneration in patients following peripheral nerve injury. J Plast Reconstr Aesthet Surg 2020;73:201-8. [CrossRef]
22. Ugrenović S, Jovanović I, Vasović L, Kundalić B, Čukuranović R, Stefanović V. Morphometric analysis of the diameter and g-ratio of the myelinated nerve fibers of the human sciatic nerve during the aging process. Anat Sci Int 2016;91:238-45. [CrossRef]
23. Bombeiro AL, Lima BHM, Bonfanti AP, Oliveira ALR. Improved mouse sciatic nerve regeneration following lymphocyte cell therapy: Molecular Immunology 2020;121:81-91. [CrossRef]

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Original Article ENDOCRINOLOGY & METABOLISM

Biochemical and clinical outcomes of once-daily teriparatide in refractory chronic hypoparathyroidism: A single-center experience

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ABSTRACT

OBJECTIVE: Chronic hypoparathyroidism causes disrupted calcium-phosphate balance due to parathyroid hormone (PTH) deficiency. In refractory disease, recombinant PTH (1–34) (teriparatide) can support conventional therapy. This study assessed short-term biochemical and clinical outcomes under real-word of once-daily teriparatide in refractory hypoparathyroidism.

METHODS: Ten patients with chronic hypoparathyroidism who received subcutaneous teriparatide (20 μg/day) between January 2021 and September 2025 were retrospectively analyzed. The median duration of teriparatide therapy was 9 months (interquartile range: 4–22), with a maximum of 27 months. Clinical records, biochemical parameters, and calcium/vitamin D supplementation requirements were systematically reviewed.

RESULTS: Albumin-corrected calcium increased significantly at 3 months (median 7.79 vs. 6.5 mg/dL, p=0.038) but not at 6 months (p>0.05). Phosphorus decreased at 3 months (p=0.012) with a non-significant trend thereafter (p=0.06). No correlation was observed between calcium change and treatment duration (ρ=-0.8, p=0.2). All patients reported symptomatic relief and reduced intravenous calcium requirements, though complete independence was not achieved.

CONCLUSION: Once-daily teriparatide provided transient biochemical improvement and clinical relief in refractory hypoparathyroidism but was insufficient to maintain sustained normocalcemia, suggesting possible pharmacological limitations of once-daily intermittent PTH replacement that warrant further investigation in larger prospective studies. Individualized treatment duration, alternative dosing regimens, and longer-term controlled studies are warranted to optimize therapeutic outcomes.

Keywords: Hypocalcemia; hypoparathyroidism; parathyroid hormone; teriparatide.

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Chronic hypoparathyroidism is a rare but challenging endocrine disorder caused by insufficient or absent secretion of parathyroid hormone (PTH), resulting in disrupted calcium–phosphate homeostasis, chronic hypocalcemia, and hyperphosphatemia [1]. In adults, the most common acquired etiology is post-surgical hypoparathyroidism, which typically occurs as an iatrogenic complication following anterior neck surgery involving the thyroid or parathyroid glands [2]. Other causes include autoimmune destruction, genetic defects in parathyroid development or calcium-sensing receptor signaling, and previous neck irradiation [1, 2].

Although the condition is uncommon, its chronicity often imposes a substantial treatment burden, frequent hospitalizations, and impaired quality of life [3, 4]. Current standard therapy relies on oral calcium supplements and active Vitamin D analogs, aiming to maintain serum calcium within the low-normal range [5]. However, this

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approach does not replace the deficient hormone itself and fails to restore physiological calcium–phosphate regulation [1, 6]. Long-term conventional treatment may lead to hypercalciuria, nephrocalcinosis, renal impairment, and fluctuating serum calcium levels, while some patients continue to experience symptomatic hypocalcemia despite optimized medical therapy [1, 5]. These cases are considered refractory hypoparathyroidism, representing an important therapeutic challenge [7, 8].

In recent years, recombinant human PTH (rhPTH) analogs have emerged as potential replacement therapies for such patients [6]. Among them, rhPTH (1–34), or teriparatide, represents the biologically active N-terminal fragment of the native hormone [9]. Initially approved for osteoporosis, teriparatide has demonstrated efficacy in improving calcium control, reducing the need for calcium and calcitriol supplementation, and alleviating hypocalcemic symptoms in patients with chronic hypoparathyroidism refractory to conventional therapy [9, 10]. Beyond its calciotropic effects, intermittent PTH (1–34) administration preferentially stimulates bone formation, whereas continuous exposure has broader renal and phosphaturic actions, potentially influencing calcium–phosphate balance [11]. Subcutaneous administration once or twice daily has been the most widely used regimen, whereas continuous infusion through insulin pump systems has also been investigated to achieve smoother biochemical stability in selected patients [12].

While rhPTH (1–84) represents the first and currently the only approved hormone replacement therapy for chronic hypoparathyroidism, its limited availability in many countries, including our region, has led clinicians to rely on off-label teriparatide (PTH 1–34) use [13–15]. Nevertheless, real-world evidence regarding its efficacy, optimal dosing frequency, and safety profile remains scarce, particularly in non-trial settings [15].

Herein, we present our institutional experience with subcutaneous teriparatide administered at a fixed dose of 20 μg once daily in ten patients with refractory chronic hypoparathyroidism, evaluating short-term biochemical and clinical outcomes under real-world clinical settings.

Highlight key points

- Once-daily teriparatide therapy resulted in an early improvement in calcium–phosphate balance in patients with refractory chronic hypoparathyroidism in real-world clinical practice.
- The biochemical improvement observed at the 3rd month was not sustained at later follow-up, suggesting limited long-term efficacy of intermittent once-daily PTH replacement.
- Although sustained normocalcemia was not achieved, patients consistently experienced symptomatic improvement and a reduced need for intravenous calcium supplementation.
- No significant association was found between treatment duration and calcium response, indicating that therapeutic efficacy may be influenced by factors other than exposure time alone.
- These findings support the need for individualized treatment strategies and alternative dosing regimens to improve long-term metabolic control in refractory hypoparathyroidism.

MATERIALS AND METHODS

Study Design and Population

This retrospective case series was conducted at the Department of Endocrinology and Metabolism, Basaksehir Cam and Sakura City Hospital, a tertiary referral center. Ten patients diagnosed with chronic hypoparathyroidism and treated with teriparatide between January 2021 and September 2025 were included in the analysis. All patients had persistent hypocalcemia despite optimized conventional therapy with oral calcium and active Vitamin D analogs. Refractory hypoparathyroidism was defined as persistent symptomatic hypocalcemia requiring recurrent intravenous calcium supplementation despite maximally tolerated doses of oral calcium and active Vitamin D. Written informed consent was obtained from all participants before inclusion.

Treatment Protocol

All patients received subcutaneous teriparatide administered at a fixed dose of 20 μg once daily. The treatment was initiated after inadequate biochemical and symptomatic control under standard therapy. Once-daily dosing was preferred due to local clinical practice patterns and reimbursement constraints. As teriparatide is reimbursed exclusively for osteoporosis in our region, its use in hypoparathyroidism requires a formal off-label application; accordingly, dose escalation was not pursued during the study period in patients who demonstrated partial clinical and biochemical benefit, though it remains a viable option through renewed regulatory application in cases of insufficient long-term response. Oral calcium and calcitriol doses were titrated as clinically indicated to maintain serum calcium within the target range. Patients were followed up at baseline, 3 months, and 6 months after teriparatide initiation.

Data Collection and Variables

Clinical and biochemical data were retrieved from electronic medical records, including demographic characteristics, disease etiology, duration of hypoparathyroidism, and treatment history. Laboratory variables included serum albumin-corrected calcium, phosphorus, magnesium, creatinine, PTH, alkaline phosphatase (ALP), and 25-hydroxyvitamin D concentrations, along with 24-h urinary calcium excretion. The primary outcome was the change in serum calcium concentration from baseline to 3 and 6 months, while secondary outcomes included changes in serum phosphorus, urinary calcium excretion, and the requirement for intravenous calcium supplementation. Adverse events, particularly symptoms of hypo- or hypercalcemia, were recorded at each visit to assess treatment efficacy and tolerability.

Statistical Analysis

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median values with interquartile ranges (IQR; between the 25th [Q1] and 75th [Q3] percentiles), given the small sample size and non-normal data distribution. Accordingly, non-parametric statistical tests were applied. Paired comparisons of biochemical parameters between baseline, 3-month, and 6-month time points were conducted using the Wilcoxon signed-rank test. The relationship between changes in serum calcium levels (ΔCa) and the total duration of teriparatide therapy was assessed using Spearman's rank correlation coefficient (ρ). Due to the exploratory nature of the study, no adjustment for multiple comparisons was applied. All statistical tests were two-tailed, and a $p<0.05$ was considered statistically significant.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Basaksehir Cam and Sakura City Hospital and conducted in accordance with the principles of the Declaration of Helsinki. The ethics committee approval number was E96317027-514.10-277446986, dated May 30, 2025.

RESULTS

Patient Characteristics

A total of ten patients with chronic hypoparathyroidism were included, eight of whom were female and two male. The median age was 39.5 years (IQR: 35–41.5). Eight patients had post-surgical hypoparathyroidism, and two had the idiopathic form. Among the post-surgical group, three had previously received radioactive iodine ablation. The median duration from the initial surgery to teriparatide initiation was 43.5 months (IQR: 18.75–172).

All patients had previously received conventional therapy consisting of oral elemental calcium titrated up to 5 g/day and calcitriol up to 4 μg/day, in addition to 800 IU/day cholecalciferol and 720 mg/day oral magnesium salt. The median daily doses before teriparatide initiation were 5000 mg (IQR: 4800–5200) for oral calcium and 4 μg (IQR: 3.5–4.5) for calcitriol. Despite gradual optimization of these doses, all patients remained symptomatic and required regular intravenous calcium gluconate infusions to maintain biochemical or clinical stability. Quantitative data on intravenous calcium replacement were inconsistently available and thus excluded from analysis.

Evaluation for malabsorption syndromes was performed in nine patients; all had negative celiac serology. Upper gastrointestinal endoscopy was performed in four patients, and duodenal biopsies revealed gluten-sensitive enteropathy in one case.

Treatment Course and Biochemical Response

All patients received subcutaneous teriparatide at a fixed dose of 20 μg once daily. The median duration of therapy was 9 months (IQR: 4–22), with the longest follow-up period of 27 months in one patient. The reduced number of patients available for 6-month analysis (n=4) reflects the fact that four patients had not yet reached this timepoint at the time of data collection, rather than dropout or loss to follow-up; all ten patients remained on treatment throughout the observation period. The baseline, 3rd-, and 6th-month biochemical parameters – including serum albumin-corrected calcium, phosphorus, magnesium, ALP, 25-hydroxyvitamin D, and 24-h urinary calcium – are summarized in Table 1.

At baseline, the median albumin-corrected calcium was 6.5 mg/dL (IQR: 6.12–6.67). Median calcium increased to 7.79 mg/dL (IQR: 6.74–8.25) at month 3, showing a statistically significant increase compared with baseline ($Z=-2.07$, $p=0.038$). At month 6, the value was 6.96 mg/dL (IQR: 6.24–7.14), and the difference was not statistically significant compared with either baseline ($Z=-0.73$, $p=0.465$) or month 3 ($Z=-1.07$, $p=0.285$) (Fig. 1A). The association between the change in serum calcium concentrations (ΔCa; defined as the difference

TABLE 1. Biochemical parameters at baseline and during teriparatide therapy

Parameter	Baseline	3rd month	6th month
Albumin-corrected calcium (mg/dL)	6.5 (6.12–6.67)	7.79 (6.74–8.25) (n=9)	6.96 (6.24–7.14) (n=4)
Phosphorus (mg/dL)	5.5 (4.97–5.84)	4.95 (3.89–5.25) (n=9)	4.41 (4.3–5.08) (n=4)
Magnesium (mg/dL)	1.82 (1.6–1.91)	1.78 (1.62–1.93) (n=8)	1.59 (1.58–1.67) (n=4)
ALP (U/L)	72 (66.75–78.75)	87.5 (61.5–105.5) (n=8)	103 (80–151) (n=4)
25-hydroxyvitamin D (ng/mL)	21 (17.75–25.5)	16 (14.5–25.2) (n=6)	21 (20–31) (n=3)
24-h urinary calcium (mg/day)	55 (7–322) (n=5)	78, 75 (n=2)*	342, 34 (n=2)*

Data are presented as median (interquartile range) unless otherwise specified. For parameters available in fewer than four patients, median (range) is shown. *For parameters with data available in only two patients, individual values are presented instead of summary statistics. ALP: Alkaline phosphatase.

between 6th-month and baseline albumin-corrected calcium) and the total duration of teriparatide therapy was assessed. No statistically significant correlation was observed between ΔCa and the duration of treatment (ρ=-0.8, p=0.2), based on four paired observations, indicating that calcium response was not dependent on treatment duration within the observed follow-up period.

Median serum phosphorus levels decreased from 5.5 mg/dL (IQR: 4.97–5.84) at baseline to 4.95. mg/dL (IQR: 3.89–5.25) at month 3, demonstrating a statistically significant reduction (Z=-2.52, p=0.012). At month 6, the median phosphorus was 4.41 mg/dL (IQR: 4.3–5.08), showing a non-significant trend toward reduction compared with baseline (Z=-1.83, p=0.068), and no significant difference between months 3 and 6 (Z=-1.07, p=0.285) (Fig. 1B).

Other biochemical parameters are summarized in Table 1. Baseline median magnesium was 1.82 mg/dL (IQR: 1.6–1.91), 25-hydroxyvitamin D was 21 ng/mL (IQR: 17.75–25.5), PTH was 4.09 pg/mL (IQR: 3.1–10.2), and ALP was 72 U/L (IQR: 66.7–78.7). At month 3, median ALP was 87.5 U/L (IQR: 61.5–105.5). Baseline 24-h urinary calcium data were available in five patients, with a median of 55 mg/day (IQR: 7–322). Corresponding values at month 3 were 75 mg/day and 78 mg/day (two patients), and at month 6 were 342 mg/day and 34 mg/day (two patients). Urinary calcium data were insufficient for robust statistical analysis and were therefore interpreted descriptively.

Clinically, all patients reported a reduction in muscle cramps, paresthesias, or other hypocalcemic symptoms by the 3rd month of therapy. Due to the retrospective design, symptom improvement was based on patient reports rather than standardized clinical scales. At this point,

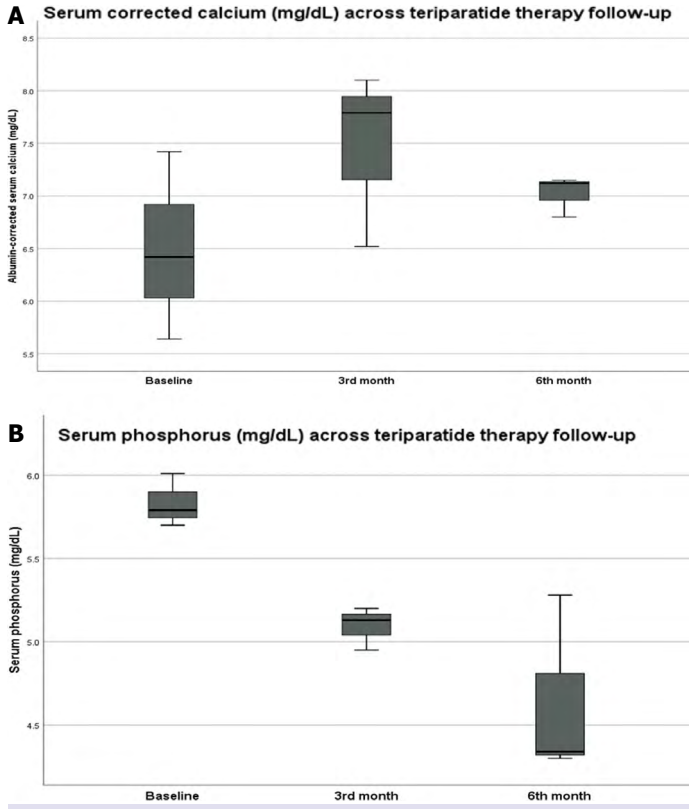

FIGURE 1. Changes in serum albumin-corrected calcium **(A)** and phosphorus **(A)** concentrations during teriparatide therapy in patients with refractory chronic hypoparathyroidism. **(A)** Serum albumin-corrected calcium concentrations (mg/dL) at baseline, 3rd, and 6th months of teriparatide therapy. **(B)** Serum phosphorus concentrations (mg/dL) at baseline, 3rd, and 6th months of teriparatide therapy. Boxplots represent median values (horizontal line), interquartile ranges (boxes), and ranges (whiskers).

requirements decreased in all cases, with median daily doses of 2000 mg (IQR: 1750–2250) for calcium and

1.5 µg (IQR: 1.25–1.75) for calcitriol. At the 6-month follow-up, mild recurrence of hypocalcemic symptoms was observed in all patients, accompanied by an increase in oral calcium and calcitriol doses compared to month 3, though still lower than pre-teriparatide levels. Median daily doses were 3500 mg (IQR: 3250–3750) for calcium and 2.5 µg (IQR: 2.25–2.75) for calcitriol.

Four patients no longer required intravenous calcium supplementation. Among the six patients who continued to require intravenous calcium, a marked reduction in infusion frequency was documented in all cases: One patient reduced from weekly to monthly infusions; one patient required only a single infusion throughout the entire follow-up period, compared with infusions every 3 weeks before treatment; two patients reduced from monthly infusions to two infusions over 6 months; and two patients reduced from monthly infusions to a single infusion over the 6-month follow-up period. No teriparatide-related adverse events were observed during follow-up. Patients remain under ongoing clinical and biochemical monitoring for long-term outcomes.

DISCUSSION

In this real-world cohort of ten patients with refractory chronic hypoparathyroidism, once-daily teriparatide (PTH [1–34], 20 µg/day) achieved temporary biochemical stabilization and marked symptomatic relief but was insufficient to ensure sustained normocalcemia. These findings illustrate both the clinical value and the inherent pharmacological constraints of intermittent PTH replacement in restoring long-term calcium homeostasis.

rhPTH (1–84) was approved by the U.S. Food and Drug Administration in 2015 for the treatment of refractory hypoparathyroidism, following the pivotal Phase III, randomized, double-blind, placebo-controlled replace trial [13]. In that study, once-daily subcutaneous administration of 50–100 µg of rhPTH (1–84) enabled 53% of patients to reduce their calcium and Vitamin D requirements by more than 50%, while 43% achieved independence from active Vitamin D with less than and 500 mg of daily elemental calcium supplementation [13]. Moreover, treatment was associated with significant reductions in serum phosphorus and urinary calcium levels, as well as improvements in quality of life compared with conventional therapy [13, 16]. Despite the approval of rhPTH (1–84), its availability and accessibility remain limited worldwide, leading to continued off-label use of teriparatide (rhPTH [1–34]) as an alternative in clinical practice [17].

Several case reports and small series have evaluated the use of both rhPTH (1–34) and rhPTH (1–84) in managing refractory hypocalcemia, employing either intermittent subcutaneous injections or continuous subcutaneous infusion systems [5, 9, 18]. Andrysiak-Mamos et al. [18] reported that subcutaneous injections of rhPTH (1–34) resulted in rapid correction of hypocalcemia and resolution of symptoms within days to weeks in three patients with post-operative hypoparathyroidism unresponsive to conventional therapy. Similarly, Saraiva et al. [9] Described a patient with chronic post-operative hypoparathyroidism who achieved sustained normocalcemia without supplementation using continuous subcutaneous infusion of rhPTH (1–34) through an insulin pump. Supporting these findings, Fuss et al. [5] Demonstrated that while twice-daily injections of rhPTH (1–34) or rhPTH (1–84) provided transient biochemical improvement, only continuous subcutaneous infusion of rhPTH (1–34) ensured long-term stability. Collectively, these reports suggest that continuous delivery systems may achieve more stable PTH concentrations and improved calcium-phosphate balance compared with once-daily administration.

In our cohort, all patients received once-daily subcutaneous teriparatide at 20 µg/day. A statistically significant biochemical improvement was observed at 3 months, characterized by increased serum calcium and decreased phosphorus levels. This reduction in serum phosphorus, together with transient calcium stabilization, underscores the short-term clinical utility of teriparatide as an adjunctive therapy in refractory hypoparathyroidism. However, by month 6, the improvement in calcium concentrations was not sustained, and mild recurrence of hypocalcemic symptoms was observed in all patients, necessitating escalation of oral calcium and calcitriol supplementation. While intravenous calcium requirements decreased, complete independence was not achieved in most cases. No significant correlation was found between changes in serum calcium and the total duration of teriparatide therapy, indicating that the biochemical response was not dependent on treatment length within the observed follow-up period. It should be noted, however, that this correlation analysis was based on four paired observations, which limits the statistical power of the test and precludes definitive conclusions regarding the relationship between treatment duration and calcium response. These findings are consistent with earlier reports showing that intermittent teriparatide administration may offer transient biochemical stabilization, but not the

steady-state control observed with continuous infusion regimens [5, 9]. The observed pattern may be explained by teriparatide's short plasma half-life (approximately 1 h) and its rapid renal clearance, leading to fluctuations in serum calcium levels [19]. Beyond these pharmacokinetic considerations, additional mechanisms may have contributed to the attenuation of response at 6 months. Repetitive intermittent PTH receptor stimulation has been proposed to induce progressive receptor desensitization, potentially reducing calciotropic efficacy over time; however, this mechanism has not been formally demonstrated in the context of hypoparathyroidism treatment and remains speculative. Adaptive renal mechanisms, including compensatory changes in tubular calcium reabsorption with prolonged PTH exposure, may represent a further contributing factor. In addition, the escalation of oral calcium and calcitriol doses observed at 6 months in our cohort reflected a deliberate clinical decision in response to insufficient biochemical control, rather than patient non-compliance, underscoring the limitations of fixed-dose once-daily teriparatide as a standalone stabilizing agent in this population. Furthermore, intermittent PTH exposure predominantly stimulates osteoblastic bone formation, whereas continuous exposure also influences renal calcium reabsorption and phosphate excretion to a greater extent, potentially explaining the differential biochemical outcomes [20].

The reduction in serum phosphorus observed at 3 months aligns with the known phosphaturic action of PTH, mediated through downregulation of sodium-phosphate cotransporters in the renal proximal tubules [21]. However, the non-significant trend toward higher phosphorus levels at 6 months may reflect waning hormonal efficacy, suboptimal compliance, or adaptive renal mechanisms. Notably, serum ALP levels showed a modest rise, which may reflect increased bone turnover associated with PTH exposure. Similar increases in bone turnover markers have been documented in patients receiving both rhPTH (1–34) and rhPTH (1–84) [10, 22]. Because teriparatide dose escalation was not attempted in our cohort, it remains uncertain whether higher or more frequent dosing could have yielded more stable biochemical control.

No adverse events related to teriparatide were observed during follow-up. Concerns about a potential osteosarcoma risk with long-term PTH exposure stem from pre-clinical rat models, where prolonged high-dose administration induced osteosarcoma formation [23]. However, extensive post-marketing surveillance and longitudinal data from osteoporosis trials have not confirmed an increased osteosarcoma risk in humans [24]. Moreover, the long-term extension of rhPTH (1–84) therapy in hypoparathyroidism, reported by Mannstadt et al. [22], demonstrated sustained efficacy and biochemical stability over a 5-year period without skeletal safety concerns or osteosarcoma occurrence. In our cohort, the median duration of teriparatide treatment was 9 months, with one patient continuing therapy for 27 months, and no adverse skeletal or systemic effects were observed. Although these findings support the short- to mid-term safety of teriparatide in refractory hypoparathyroidism, longer observation is warranted to confirm its long-term tolerability and bone safety profile. Our findings reflect real-world clinical practice in a tertiary referral center and may therefore differ from tightly controlled clinical trial settings. An important area of uncertainty in our cohort concerns renal calcium handling. Conventional therapy for chronic hypoparathyroidism is associated with a well-established risk of hypercalciuria and nephrocalcinosis, which represents one of the principal long-term complications of this treatment approach [1, 8]. Although teriparatide has been suggested to exert a more favorable effect on urinary calcium excretion compared with standard therapy [10, 13], the limited and inconsistent availability of 24-h urinary calcium data in our cohort, present in only five patients at baseline and two at follow-up, precludes any meaningful assessment of nephrocalcinosis risk in this series. This gap should be explicitly acknowledged not merely as a methodological constraint but as a clinically relevant unresolved question. Prospective studies in this population must incorporate mandatory, protocol-driven urinary calcium monitoring to adequately characterize the renal safety profile of teriparatide in refractory hypoparathyroidism.

This study has several limitations. The retrospective design, small sample size, and variability in follow-up intervals may limit the generalizability and external validity of our findings. Notably, the limited number of patients with 6-month data (n=4) is attributable to variable treatment durations at the time of data collection rather than attrition, though this nonetheless restricts the interpretability of longer-term outcomes. Symptom improvement was based on patient self-reports rather than standardized clinical scales, which introduces potential subjectivity. Quantitative urinary calcium data were incomplete, precluding a comprehensive assessment of renal calcium handling and nephrocalcinosis risk. Although 24-h urinary calcium collection was re-

quested at each clinical visit, a substantial proportion of patients did not provide complete samples at follow-up timepoints, reflecting the challenges of timed urine collection in a chronically ill population managed in a real-world clinical setting rather than under a prospective protocol. Furthermore, bone turnover markers other than ALP and bone mineral density measurements were not systematically evaluated, limiting conclusions regarding skeletal effects. Real-world evidence on teriparatide use in refractory hypoparathyroidism remains scarce, particularly in regions where approved PTH replacement therapy is inaccessible; in this context, even small observational cohorts contribute meaningful clinical data to guide future prospective investigations. Despite these constraints, the present study contributes real-world data to the scarce literature on teriparatide use in refractory hypoparathyroidism, particularly within a Middle Eastern clinical context that remains underrepresented in existing studies. Prospective, multicenter trials with standardized biochemical, skeletal, and patient-reported outcome measures, including mandatory 24-h urinary calcium monitoring to adequately characterize renal calcium handling and nephrocalcinosis risk, are warranted to better define the long-term efficacy, safety, and optimal dosing strategies for teriparatide in this population. Furthermore, the absence of adjustment for multiple comparisons, while consistent with the exploratory design of this study, represents an additional analytical limitation; accordingly, the reported p-values should be interpreted as hypothesis-generating rather than confirmatory.

Conclusion

Once-daily teriparatide (20 μg) contributed to the short-term improvement of calcium-phosphate homeostasis and reduced intravenous calcium dependency in patients with refractory chronic hypoparathyroidism. However, its effects were not sustained beyond 3 months, suggesting that once-daily administration at a fixed dose may be insufficient for long-term biochemical control in some patients, though definitive conclusions regarding optimal dosing strategies cannot be drawn from this limited dataset. Individualized therapeutic strategies and alternative dosing regimens warrant evaluation in future prospective studies. Larger, prospective, controlled studies are warranted to confirm the long-term efficacy, safety, and optimal administration protocols for teriparatide in this challenging patient population.

Ethics Committee Approval: This study was approved by The Republic of Turkiye, Istanbul Governorship, Provincial Directorate of Health, Basaksehir Cam and Sakura City Hospital Ethics Committee (E-96317027-514.10-277446986 – 30.05.2025).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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Authorship Contributions: Concept – AP, EH; Design – AP, SB; Supervision – AH; Materials – AP, SB, RDUT; Data Collection and/or Processing – AP, SB, RDUT; Analysis and/or Interpretation – AP, SB, RDUT; Literature Search – AP, SB; Writing – AP; Critical Reviews – EH.

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REFERENCES

1. Bilezikian JP, Khan A, Potts JT Jr, Brandi ML, Clarke BL, Shoback D, etal. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res 2011;26:2317-37. [CrossRef]
2. Shoback DM, Bilezikian JP, Costa AG, Dempster D, Dralle H, Khan AA, et al. Presentation of hypoparathyroidism: etiologies and clinical features. J Clin Endocrinol Metab 2016;101:2300-12. [CrossRef]
3. Büttner M, Singer S, Taylor K. Quality of life in patients with hypoparathyroidism receiving standard treatment: an updated systematic review. Endocrine 2024;85:80-90. [CrossRef]
4. Kaul S, Gosmanova EO, Castriota F, Hitchens A, Candrilli S, Parikh R, et al. Recent trends in hypoparathyroidism-related inpatient and emergency department admissions and costs in the United States. J Endocr Soc 2023;7:bvad050. [CrossRef]
5. Fuss CT, Burger-Stritt S, Horn S, Koschker AC, Frey K, Meyer A, et al. Continuous rhPTH (1-34) treatment in chronic hypoparathyroidism. Endocrinol Diabetes Metab Case Rep 2020;2020:EDM20-0009. [CrossRef]
6. Maeda SS, Moreira CA, Borba VZC, Bandeira F, Farias MLF, Borges JLC, et al. Diagnosis and treatment of hypoparathyroidism: a position statement from the Brazilian Society of Endocrinology and Metabolism. Arch Endocrinol Metab 2018;62:106-24. [CrossRef]
7. Rubin MR, Cusano NE, Fan WW, Delgado Y, Zhang C, Costa AG, et al. Therapy of hypoparathyroidism with PTH(1-84): A prospective six year investigation of efficacy and safety. J Clin Endocrinol Metab 2016;101:2742-50. [CrossRef]
8. Khan AA, Bilezikian JP, Brandi ML, Clarke BL, Gittoes NJ, Pasieka JL, et al. Evaluation and management of hypoparathyroidism summary statement and guidelines from the second international workshop. J Bone Miner Res 2022;37:2568-85. [CrossRef]
9. Saraiva M, Chaves AC, Assunção G, Saraiva J, Carvalho R. Continuous teriparatide treatment in chronic hypoparathyroidism: a case report. Am J Case Rep 2021;22:e931739. [CrossRef]
10. Winer KK, Ko CW, Reynolds JC, Dowdy K, Keil M, Peterson D, et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. J Clin Endocrinol Metab 2003;88:4214-20. [CrossRef]

11. Jilka RL. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. Bone 2007;40:1434-46. [CrossRef]
12. Winer KK, Zhang B, Shrader JA, Peterson D, Smith M, Albert PS, et al. Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism. J Clin Endocrinol Metab 2012;97:391-9.
13. Mannstadt M, Clarke BL, Vokes T, Brandi ML, Ranganath L, Fraser WD, et al. Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. Lancet Diabetes Endocrinol 2013;1:275-83. [CrossRef]
14. Marcucci G, Masi L, Cianferotti L, Giusti F, Fossi C, Parri S, et al. Chronic hypoparathyroidism and treatment with teriparatide. Endocrine 2021;72:249-59. [CrossRef]
15. Puliani G, Hasenmajer V, Simonelli I, Sada V, Pofi R, Minnetti M, et al. Safety and efficacy of PTH 1-34 and 1-84 therapy in chronic hypoparathyroidism: a meta-analysis of prospective trials. J Bone Miner Res 2022;37:1233-50. [CrossRef]
16. Cusano NE, Rubin MR, McMahon DJ, Irani D, Tulley A, Sliney J Jr, et al. The effect of PTH(1-84) on quality of life in hypoparathyroidism. J Clin Endocrinol Metab 2013;98:2356-61. [CrossRef]
17. Orloff LA, Wiseman SM, Bernet VJ, Fahey TJ 3rd, Shaha AR, Shindo ML, et al. American Thyroid Association statement on postoperative hypoparathyroidism: diagnosis, prevention, and management in adults. Thyroid 2018;28:830-41. [CrossRef]
18. Andrysiak-Mamos E, Żochowska E, Kaźmierczyk-Puchalska A, Popow M, Kaczmarska-Turek D, Pachucki J, et al. Treatment of severe life threatening hypocalcemia with recombinant human teriparatide in patients with postoperative hypoparathyroidism - a case series. Endokrynol Pol 2016;67:403-12.
19. Satterwhite J, Heathman M, Miller PD, Marín F, Glass EV, Dobnig H. Pharmacokinetics of teriparatide (rhPTH[1-34]) and calcium pharmacodynamics in postmenopausal women with osteoporosis. Calcif Tissue Int 2010;87:485-92. [CrossRef]
20. Bilezikian JP, Brandi ML, Cusano NE, Mannstadt M, Rejnmark L, Rizzoli R, et al. Management of Hypoparathyroidism: Present and Future. J Clin Endocrinol Metab 2016;101:2313-24. [CrossRef]
21. Murray RD, Lederer ED, Khundmiri SJ. Role of PTH in the renal handling of phosphate. AIMS Med Sci 2015;2:162-81. [CrossRef]
22. Mannstadt M, Clarke BL, Bilezikian JP, Bone H, Denham D, Levine MA, et al. Safety and efficacy of 5 years of treatment with recombinant human parathyroid hormone in adults with hypoparathyroidism. J Clin Endocrinol Metab 2019;104:5136-47. [CrossRef]
23. Jolette J, Wilker CE, Smith SY, Doyle N, Hardisty JF, Metcalfe AJ, et al. Defining a noncarcinogenic dose of recombinant human parathyroid hormone 1-84 in a 2-year study in Fischer 344 rats. Toxicol Pathol 2006;34:929-40. [CrossRef]
24. Andrews EB, Gilsenan AW, Midkiff K, Sherrill B, Wu Y, Mann BH, et al. The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years. J Bone Miner Res 2012;27:2429-37. [CrossRef]

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Original Article FAMILY MEDICINE

Researching impaired heart rate recovery index in patients who have had COVID-19

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ABSTRACT

OBJECTIVE: Heart rate recovery index (HRRI) occurs as a result of vagal reactivation and sympathetic retraction and is an independent risk factor used to assess autonomic nervous system (ANS) function and to determine prognosis in cardiovascular disease and all-cause mortality. It has been shown in various studies that cardiac autonomic dysfunction due to COVID-19 can occur. The aim of our study is to evaluate the effect of COVID-19 on ANS functions in people who have had this disease with HRRI.

METHODS: In this prospective and observational study, patients proven to have had COVID by molecular methods (polymerase chain reaction positivity) and healthy controls were examined. Electrocardiogram, Transthoracic Echocardiography, Hemogram and Biochemistry tests, and exercise stress test were performed in both groups. HRRIs were calculated by subtracting heart rates at the 1st, 2nd, 3rd, 4th, and 5th min during the post-exercise relaxation phase from the peak heart rate during exercise. P<0.05 were considered significant.

RESULTS: Study group (n=30) (Female/Male; n=15/15; mean age=39.8±13.3 years; median body mass index=25.9 kg/m^2) and control group's (n=33) (Female)/Male; n=16/17; mean age=41.9±13.2 years; median body mass index=27.2 kg/m^2). 1st min and 2nd min relaxation heart rates in the COVID-19 (+) group were found to be significantly higher than in the control group (p=0.042, p=0.049, respectively). In the COVID-19 (+) group, the 1st min, 2nd min, and 3rd min HRRI were found to be significantly lower than in the control group (p<0.001, p=0.006, p=0.039, respectively).

CONCLUSION: According to the results of our study, HRRI is impaired as an indicator of autonomic dysfunction in people who have had COVID-19. This situation correlates with other studies that have results of ANS dysfunction due to COVID-19, and this may pose a risk factor for increased mortality and morbidity.

Keywords: Autonomic nervous system; COVID-19; Heart Rate Recovery Index; mortality; parasympathetic nervous system; sympathetic nervous system.

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Heart rate is an important marker of long-term survival [1]. High heart rates at rest are known to play an important role in mortality [2]. Heart rate is under the control of the autonomic nervous system (ANS). ANS is divided into the sympathetic and parasympathetic nervous systems. Both systems have an effect on heart rate and work [3].

Inflammation and proinflammatory cytokines have been shown to increase sympathetic and decrease parasympathetic effects [4, 5]. In addition, viral pathogens that can cause the release of proinflammatory cytokines can cause permanent neuronal damage with T cell-mediated immunity and thus cause ANS dysfunction [6]. Proinflammatory cytokines have been shown to play a role in the pathogene-

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sis of COVID-19. It is thought that this proinflammatory process may cause autonomic dysfunction by suppressing parasympathetic activity and increasing sympathetic activity [7–9]. Furthermore, T cell-mediated immunity induced by COVID-19 can cause permanent damage to nerve cells [10, 11], which may lead to autonomic dysfunction [12, 13].

The heart rate recovery index (HRRI) is a marker of the ANS and an independent risk factor for cardiac mortality. It is obtained by subtracting the heart rates during each minute of the relaxation phase from the maximum heart rate obtained during exertion in the cardiac stress test. Low values are significant for impaired HRRI [14].

Objectives

In our study, we investigate whether COVID-19 has any effect on ANS function. Accordingly, HRRI was used as the main variable to assess ANS function. Accordingly, in our study, we aimed to compare the patient group who had COVID-19 and the healthy control group on HRRI and to evaluate whether there is a difference.

Highlight key points

- Inflammation and proinflammatory cytokines have been shown to increase sympathetic and decrease parasympathetic effects.
- Proinflammatory cytokines have been shown to play a role in the pathogenesis of COVID-19.
- T cell-mediated immunity induced by COVID-19 can cause permanent damage to nerve cells, which may lead to autonomic dysfunction.
- The HRRI is a marker of the autonomic nervous system and an independent risk factor for cardiac mortality.
- In our study, 1st, 2nd and 3rd min HRRI was lower in COVID-19 patients compared to healthy individuals (respectively $p<0.000$, $p<0.006$, $p<0.039$). This may be associated with increased mortality and morbidity.

MATERIALS AND METHODS

Design of the Study

In this prospective and observational study, patients between the ages of 18–65 who have had COVID-19, who meet the COVID-19 case definition according to the present guidelines (COVID-19 Guidelines of the Ministry of Health, General Directorate of Public Health) and were detected by molecular methods and healthy individuals between the ages of 18–65 who have not had COVID-19, both who were consecutively admitted to the Cardiology Outpatient Clinic of Istanbul Training and Research Hospital for any reason between December 01, 2022 and February 01, 2023 were included and any individual outside the range of age and any patients with history of chronic diseases, such as cardiovascular diseases, impaired kidney functions, impaired thyroid functions, hematological disorders, rheumatological diseases, central or peripheral nervous system diseases, were excluded. Patients with COVID-19 and healthy control groups who met the inclusion and exclusion criteria were prospectively evaluated with transthoracic echocardiography, hemogram and biochemistry examinations, exercise stress test, and HRRI. After statistical power analysis for sample size; effect size (Cohen's d): 0.99, alpha error level: 0.05, power value (1-beta): 0.95, Allocation ratio: 1, total sample size was calculated as a minimum of 56 (28 COVID-19 patients and 28 healthy volunteers). In this study, the sample size was calculated with the G Power v3.1.9.2 program based on the effect size obtained from the literature (the study by Yuksel et al. [14] was taken as a reference for sample size calculation). Our study was carried out in compliance with the ethical standards of the Republic of Türkiye and the Declaration of Helsinki.

Test Methods and Evaluations

The volunteer individuals included in the study, including both case and control groups, were first questioned in terms of age, gender, height, weight, smoking, and their data were recorded. Standardized exercise stress test, transthoracic echocardiography, and various blood tests were requested from both groups. The exercise stress test was performed according to the modified Bruce protocol. The HRRI was obtained by subtracting the heart rates at the end of each minute of the relaxation phase from the maximum heart rate obtained during exercise, separately at each minute of the relaxation phase.

Statistical Analysis

To evaluate the data, we have obtained statistically, minimum, maximum, mean, median, standard deviation, frequency, and ratio values were used. The Kolmogorov–Smirnov test was used to measure the distribution of variables. To analyze quantitative independent data, the Student's t-test and Mann–Whitney U-test were used. To analyze qualitative independent data, the Chi-square test was used. In statistical evaluation, data with a $p<0.05$ were considered significant. The Statistical Package for the Social Sciences 28.0 program (Armonk, NY 10504-1785 US: IBM Corp.) was used for statistical analysis.

Table 1. Sociodemographic characteristics of the groups

	COVID-19 (+) n=30				Control n=33				p
	Mean±SD	%	Median	Min–Max	Mean±SD	%	Median	Min–Max	
Age, years	39.8±13.3		38.5	19–65	41.9±13.2		41	18–62	0.525[t]
Gender									0.904χ^2
Female		50.0				48.5			
Male		50.0				51.5			
Height (cm)	169.9±10.8		169.5	150–187	168.3±9.4		168	155–188	0.525[t]
Weight (kg)	74±12.7		77	49–95	76±16.4		75	48–103	0.588[t]
Body mass index	25.7±4.8		25.9	19.7–42.2	26.7±4.8		27	17–38.1	0.191[m]
Cigarette use									0.060χ^2
No		56.7				78.8			
Yes		43.3				21.2			

t: Independent Sample t-Test; m: Mann–Whitney U Test; χ^2: Chi-Square Test; SD: Standard deviation; Min: Minimum; Max: Maximum.

RESULTS

Our study included a group of 30 patients who had contracted COVID-19, consisting of 15 men and 15 women, and a healthy control group of 33 people, consisting of 16 women and 17 men. The sociodemographic characteristics of each group, such as gender, age, height, weight, body mass index, and smoking status, are listed in Table 1. The minimum-maximum, median, mean, and standard deviation evaluations of the laboratory parameters of each group are presented in Table 2.

Age and gender distribution of the patients, height, weight, and body mass index values of the patients, and the rate of smoking did not differ significantly ($p>0.05$) between the study groups. Resting systolic and diastolic blood pressure values, resting and maximum heart rates, hemogram and biochemistry values, and echocardiographic values did not differ significantly ($p>0.05$) between the COVID-19 (+) and Control group. Exercise stage's 1. min, 2. min, 3. min heart rate values and target heart rate values, exercise duration, exercise maximum heart rate, exercise maximum heart rate, maximum heart rate target percentage, maximum metabolic equivalents (Mets) values, end-exercise systolic pressure and end-exercise diastolic pressure values did not differ significantly ($p>0.05$) between COVID-19 (+) and Control group.

The 1st min, 2nd min relaxation heart rate was significantly ($p<0.05$) higher in the COVID-19 (+) group than in the control group. The 3rd min, 4th min, and 5th min relaxation heart rate did not differ significantly ($p>0.05$) between the COVID-19 (+) and Control groups (Table 3). We can see the comparison of relaxation heart rates between groups in Figure 1.

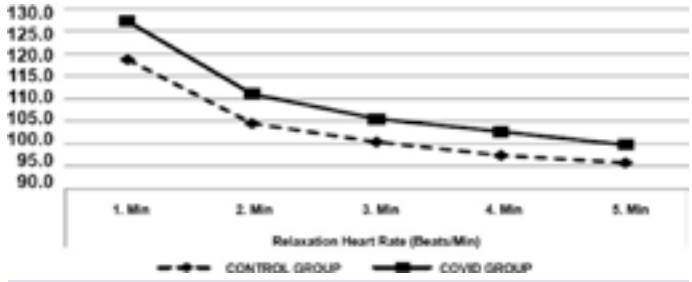

Figure 1. Comparison of relaxation heart rates of the groups.

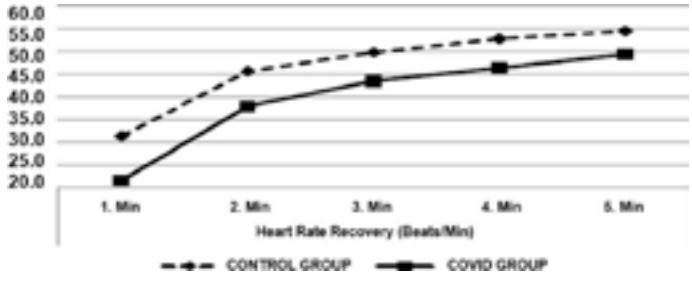

Figure 2. Comparison of heart rate recovery indexes of the groups, which are obtained by subtracting heart rates at each minute of the resting phase from the maximum heart rates.

Table 2. Laboratory parameters of the groups

	COVID-19 (+)			Control			p
	Mean±SD/n-%	Median	Min–Max	Mean±SD/n-%	Median	Min–Max	
Glucose (mg/dL)	92.7±10.3	91.5	75–118	96.7±12.6	93.5	71.0–140	0.176[t]
Creatinine (mg/dL)	0.8±0.2	0.8	0.4–1.2	0.8±0.2	0.8	0.4–1.1	0.231[t]
Urea (mg/dL)	26.2±7.7	25.9	13.9–43.7	26.4±6.8	24.9	14.7–39	0.938[t]
Sodium (mmol/L)	140±1.7	140	136–43	140.5±1.6	140.0	138.0–144	0.234[m]
Potassium (mmol/L)	4.6±0.4	4.6	3.9–5.3	4.5±0.4	4.5	3.6–5.4	0.656[t]
eGFR (CKD–EPI) . (mL/min/1.73 m^2)	103.2±21.6	104.8	48.5–138	104.7±16	107	67–135	0.753[t]
AST (u/L)	19.0±6.8	18	13–45	19.2±6.2	18	13–41	0.645[m]
ALT (u/L)	19.6±10.8	18	9–52	21.7±14.0	18	3–64	0.599[m]
LDH (u/L)	189.0±45.8	184.5	139–380	193.5±46.2	191	143–298	0.871[m]
Ferritin (mcg/L)	102.8±91.8	77.4	4.6–356.4	90.4±77.4	65	4.3–300	0.713[m]
TSH (mu/L)	2.1±2.5	1.5	0.5–14.7	2.3±3.2	1.6	0.6–18.1	0.617[m]
freeT4 (ng/L)	12.0±1.7	12.3	8.6–15	11.0±2.3	11.3	1.2–13.7	0.057[m]
freeT3 (ng/L)	3.5±0.7	3.5	2.4–6	3.1±0.6	3.1	1.7–4.3	0.105[m]
Uric Acid (mg/dL)	5.0±1.5	4.7	3.1–8	4.7±1.5	4.5	1.6–7.3	0.477[t]
Total cholesterol (mg/dL)	185.6±29.8	180.5	135–242	193.9±38.9	185	132–294	0.361[t]
HDLc (mg/dL)	54.1±12.0	51.5	27–91	53.3±13.5	53	24–89	0.813[t]
LDLc (mg/dL)	106.2±28.6	106	47–167	119.5±32.9	117.5	66–174	0.105[t]
Triglycerides (mg/dL)	131.6±133.9	96	41.0–765	101.0±45.7	84	41–206	0.716[m]
WBC ($\times 10^9$/L)	7.2±1.7	7.1	4.3–10.5	6.9±1.5	6.7	3.9–9.9	0.499[t]
Hemoglobin (g/dL)	13.6±1.9	13.8	8.6–17.2	14.2±1.8	14.7	8.2–16.5	0.262[t]
Platelet ($\times 10^9$/L)	277.9±58.3	270	182–427	289.5±52.6	287.5	158–385	0.420[t]

t: Independent Sample t-Test; m: Mann–Whitney U-Test; SD: Standard deviation; Min: Minimum; Max: Maximum; GFR: Estimated glomerular filtration rate; CKD-EPI: Chronic kidney disease epidemiology collaboration; AST: Aspartate transaminase; ALT: ALanine transaminase; LDH: Lactate dehydrogenase; TSH: Thyroid-stimulating hormone; HDLc: High-density lipoprotein cholesterol; LDLc: Low-density lipoprotein cholesterol; WBC: White blood cell.

The 1st min, 2nd min, and 3rd min HRRI was significantly lower in the COVID-19 (+) group than in the control group ($p<0.05$). Although the 4th min and 5th min HRRI were lower in the COVID-19 (+) group, there was no significant difference between the COVID-19 (+) and control groups ($p>0.05$) (Table 4). We can see the comparison of HRRIs between groups in Figure 2.

DISCUSSION

HRRI is an independent risk factor for mortality and morbidity that can be used to assess the effects of the ANS on the heart. Again, HRRI is also used to see the effects of many diseases with systemic effects on cardiac autonomy. For example, in a study conducted by Yuksel et al. [14] in 2014 with 33 patients with psoriasis and 26 healthy controls, both groups were evaluated on HRRI, and HRRI was found to be impaired in patients with psoriasis.

In normal physiology, increases or decreases in heart rate are controlled by the activation, withdrawal, and reactivation of the sympathetic and parasympathetic nervous systems. During mild-intensity exercise, parasympathetic withdrawal is effective at the onset of exertion, while during moderate- and high-intensity exercise, sympathetic nervous system stimulation becomes effective at the onset of exertion. During the recovery phase, parasympathetic nervous system stimulation is initially responsible for the rapid decrease in heart rate. Subsequently, sympathetic withdrawal comes into play. In a study conducted by Perini et al. [15] in 1989, it was observed that plasma catecholamine levels did not change significantly during and after low-intensity exer-

Table 3. Comparison of relaxation heart rates of the groups

Relaxation heart rate (beats/min)	COVID-19 (+)			Control			p
	Mean±SD/n-%	Median	Min–Max	Mean±SD/n-%	Median	Min–Max	
Min 1	127.2±14.1	125.0	93.0–157.0	118.7±15.7	119.0	93.0–160.0	**0.042**[m]
Min 2	111.0±13.6	110.5	80.0–138.0	104.5±13.2	104.0	80.0–136.0	**0.049**[m]
Min 3	105.5±11.9	104.0	80.0–132.0	100.4±12.8	99.0	78.0–135.0	0.096[m]
Min 4	102.7±12.0	102.0	80.0–126.0	97.4±12.5	96.0	74.0–135.0	0.088[m]
Min 5	99.7±12.4	99.0	72.0–123.0	95.8±12.6	96.0	67.0–136.0	0.170[m]

m: Mann–Whitney U Test; SD: Standard deviation; Min: Minimum; Max: Maximum.

Table 4. Comparison of HRRI of the groups

Heart rate recovery ındex (beats/min)	COVID-19 (+)			Control			p
	Mean±SD/n-%	Median	Min–Max	Mean±SD/n-%	Median	Min–Max	
Min 1	21.8±5.9	22.0	10.0–36.0	31.4±6.3	31.0	11.0–46.0	**0.000**[m]
Min 2	38.0±8.7	39.0	15.0–50.0	45.6±10.4	46.0	28.0–68.0	**0.006**[m]
Min 3	43.5±9.9	47.5	15.0–56.0	49.7±9.8	47.0	27.0–71.0	**0.039**[m]
Min 4	46.3±10.0	50.0	18.0–58.0	52.7±10.3	52.0	38.0–72.0	0.063[m]
Min 5	49.3±9.9	52.0	19.0–59.0	54.4±10.2	54.0	40.0–71.0	0.198[m]

HRRI: Heart rate recovery indices; m: Mann–Whitney U Test; SD: Standard deviation; Min: Minimum; Max: Maximum.

cise, while catecholamine levels increased during the advanced stages of moderate- and high-intensity exercise and began to decline after the 1st min of relaxation. In our study, the higher heart rates of the COVID group compared to the control group during the first 2 min of the post-exercise relaxation phase and the lower HRRI data of the COVID group during the first 3 min suggest that vagal reactivation is weaker in the COVID group.

There are some studies showing that increased vagal tone and thus increased activity of the parasympathetic nervous system decreases mortality [16], whereas increased sympathetic activity increases mortality [17]. It has been observed that heart rate recovery data, especially in the first 2 min of relaxation, are more important in determining the risk and prognosis of conditions, such as cardiovascular disease and coronary artery disease that may cause mortality [18]. The slow decline in the 1st min of relaxation may indicate decreased vagal activity and increased mortality [19]. The findings in our study showed decreased heart rate recovery in the first 3 min in the COVID group, which may be significant in terms of increased mortality risk. This condition may be caused by damage to the vagus nerve resulting from the interferon-mediated inflammatory response caused by COVID-19. In a study conducted by Woo et al. [20] in 2023, findings were obtained showing interferon-mediated inflammatory damage.

In COVID-19, which constitutes the basis of our study, it has been shown that the central and peripheral nervous system is damaged [21] and prolonged inflammatory syndromes may occur [22]. As a common result of all these effects, autonomic dysfunction may develop directly or indirectly [23]. As an example of studies evaluating the autonomic functions of individuals who have had COVID-19, in a study conducted by Erdal et al. [24] in 2022 with 112 COVID-19 patients and 106 healthy individuals, the autonomic evaluation of the participants was evaluated with the SCOPA-AUT scale, and dysautonomy was found to be higher in the COVID-19 group. Especially systemic inflammation may alter heart

rate variability (due to cytokines that can affect the sympathetic and parasympathetic system responses). In a study conducted by Cinar et al. [25] cytokines have been shown to play an important role in COVID-19 pathogenesis. In a study conducted by Cakir Guney et al. [26], it has been shown that inflammatory indices have been greatly altered in COVID-19.

Heart rate variability, another indicator of cardiac autonomic function, can be impaired; thus, mortality and morbidity may increase accordingly. According to a study conducted by Yin et al. [27] in 2023, heart rate variability decreased in people who had COVID-19. In our study, HRRI was impaired in patients who had COVID-19, and this was similar to the study by Yin et al. [27], as a finding of dysautonomy in patients who had COVID-19.

Conclusion

As a result of our study, HRRI was lower in COVID-19 patients compared to healthy individuals. This may be associated with increased mortality and morbidity. Our study is meaningful in evaluating the cardiac and autonomic effects of COVID-19 and is a reference for studies that will investigate the cardiovascular system and ANS disorders caused by COVID-19. Due to the scarcity of studies evaluating cardiac autonomic functions in COVID-19 with HRRI, more comprehensive new studies are needed.

Ethics Committee Approval: This study was approved by The Istanbul Training and Research Hospital Clinical Research Ethics Committee (334 – 27.10.2022).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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

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Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Authorship Contributions: Concept – MFG, AO; Design – MFG, AO; Supervision – MFG, AO, ZAS; Resource – MFG; Materials – MFG, AO; Data Collection and/or Processing – MFG, ENG; Analysis and/or Interpretation – MFG, AO; Literature Search – MFG; Writing – MFG; Critical Reviews – MFG, AO.

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REFERENCES

1. Seccareccia F, Pannozzo F, Dima F, Minoprio A, Menditto A, Lo Noce C, et al. Heart rate as a predictor of mortality: the MATISS project. Am J Public Health 2001;91:1258-63. [CrossRef]
2. Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. CMAJ 2016;188:E53-E63. [CrossRef]
3. Hall JE. Guyton and Hall Textbook of Medical Physiology. 14th ed. Philadelphia (PA): Elsevier; 2021. p. 132-40.
4. Bellocchi C, Carandina A, Montinaro B, Targetti E, Furlan L, Rodrigues GD, et al. The interplay between autonomic nervous system and inflammation across systemic autoimmune diseases. Int J Mol Sci 2022;23:2449. [CrossRef]
5. Porzionato A, Emmi A, Barbon S, Boscolo-Berto R, Stecco C, Stocco E, et al. Sympathetic activation: a potential link between comorbidities and COVID-19. FEBS J 2020;287:3681-88. [CrossRef]
6. Goodman BP, Khoury JA, Blair JE, Grill MF. COVID-19 Dysautonomia. Front Neurol 2021;12:624968. [CrossRef]
7. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med (Lond) 2021;21:e63-7. [CrossRef]
8. Konig MF, Powell M, Staedtke V, Bai RY, Thomas DL, Fischer N, et al. Preventing cytokine storm syndrome in COVID-19 using α-1 adrenergic receptor antagonists. J Clin Invest 2020;130:3345-7. [CrossRef]
9. Staedtke V, Bai RY, Kim K, Darvas M, Davila ML, Riggins GJ, et al. Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome. Nature 2018;564:273-7. [CrossRef]
10. Bayat AH, Azimi H, Hassani Moghaddam M, Ebrahimi V, Fathi M, Vakili K, et al. COVID-19 causes neuronal degeneration and reduces neurogenesis in human hippocampus. Apoptosis 2022;27:852-68. [CrossRef]
11. De Berardis D. How concerned should we be about neurotropism of SARS-Cov-2? A brief clinical consideration of the possible psychiatric implications. CNS Spectr 2022;27:258-9. [CrossRef]
12. Singh K, Kumar N, Kumar A, Kumar A, Shaju AR. Sympathetic storm or Cytokine storm: A diagnostic dilemma in patient of traumatic brain injury with COVID 19. Acta Neurol Taiwan 2021;30:78-80.
13. Al-Kuraishy HM, Al-Gareeb AI, Qusti S, Alshammari EM, Gyebi GA, Batiha GE. Covid-19-induced dysautonomia: a menace of sympathetic storm. ASN Neuro 2021;13:17590914211057635. [CrossRef]
14. Pancar Yuksel E, Yuksel S, Yenercag M, Soylu K, Aydin F, Senturk N, et al. Impaired heart rate recovery indices in psoriasis patients. Med Sci Monit 2014;20:350-4. [CrossRef]
15. Perini R, Orizio C, Comandè A, Castellano M, Beschi M, Veicsteinas A. Plasma norepinephrine and heart rate dynamics during recovery from submaximal exercise in man. Eur J Appl Physiol Occup Physiol 1989;58:879-83. [CrossRef]
16. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. Circulation 1992;85(1 Suppl):I77-91.
17. Tsuji H, Venditti FJ Jr, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation 1994;90:878-83. [CrossRef]
18. Morshedi-Meibodi A, Larson MG, Levy D, O'Donnell CJ, Vasan RS. Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events (The Framingham Heart Study). Am J Cardiol 2002;90(8):848-52. [CrossRef]

19. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341:1351-7. [CrossRef]
20. Woo MS, Shafiq M, Fitzek A, Dottermusch M, Altmeppen H, Mohammadi B, et al. Vagus nerve inflammation contributes to dysautonomia in COVID-19. Acta Neuropathol 2023;146:387-94. [CrossRef]
21. Galea M, Agius M, Vassallo N. Neurological manifestations and pathogenic mechanisms of COVID-19. Neurol Res 2022;44:571-82. [CrossRef]
22. Esposito S, Principi N. Multisystem inflammatory syndrome in children related to SARS-CoV-2. Paediatr Drugs 2021;23:119-29. [CrossRef]
23. Araújo CRDS, Fernandes J, Caetano DS, Barros AEVDR, de Souza JAF, Machado MDGR, et al. Endothelial function, arterial stiffness and heart rate variability of patients with cardiovascular diseases hospitalized due to COVID-19. Heart Lung 2023;58:210-6. [CrossRef]
24. Erdal Y, Atalar AC, Gunes T, Okluoglu T, Yavuz N, Emre U. Autonomic dysfunction in patients with COVID 19. Acta Neurol Belg 2022;122:885-91. [CrossRef]
25. Çınar T, Hayıroğlu Mİ, Çiçek V, Kılıç Ş, Asal S, Yavuz S, et al. Is prognostic nutritional index a predictive marker for estimating all-cause in-hospital mortality in COVID-19 patients with cardiovascular risk factors? Heart Lung 2021;50:307-12. [CrossRef]
26. Cakir Guney B, Hayiroglu M, Senocak D, Cicek V, Cinar T, Kaplan M. Evaluation of N/LP Ratio as a Predictor of Disease Progression and Mortality in COVID-19 Patients Admitted to the Intensive Care Unit. Medeni Med J 2021;36:241-8. [CrossRef]
27. Yin C, Li J, Wang Z, Zhi Y, Xu L. Decreased heart rate variability in COVID-19. Intensive Care Res 2023;3:87-91. [CrossRef]

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Original Article DERMATOLOGY

Seborrheic dermatitis in intensive care unit patients: A cross-sectional study of prevalence, severity, and associated clinical factors

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ABSTRACT

OBJECTIVE: Seborrheic dermatitis (SD) is a common inflammatory skin disorder; however, its characteristics in intensive care unit (ICU) patients are not well defined. This study aimed to assess the prevalence and severity of SD, as well as its potential associated factors, in ICU patients.

METHODS: This cross-sectional study included 102 adult patients admitted to the ICU. SD was assessed with a standardized clinical scoring system. Demographic characteristics, ICU length of stay, Glasgow Coma Scale scores, level of consciousness, sedation status, immunosuppression, immune dysfunction, comorbidities, and medication use were recorded. Patients with and without SD were compared, and a multivariable logistic regression analysis was performed to identify independent factors associated with SD.

RESULTS: SD was identified in 39 of 102 patients (38.2%). In multivariable analysis, level of consciousness was independently associated with SD (overall p=0.035). Compared with conscious patients, sedated patients had significantly higher odds of SD (odds ratio=5.05, 95% confidence interval 1.41–18.08; p=0.013). No significant associations were observed for age, sex, ICU length of stay, immunosuppression, or immune dysfunction.

CONCLUSION: SD was common among critically ill patients. Level of consciousness emerged as the only factor independently associated with SD, whereas systemic factors and medication use were not significantly associated. Further studies incorporating detailed assessments of skin care practices, local skin factors, and other potential contributing factors are needed to clarify the mechanisms underlying these associations.

Keywords: Critical illness; Glasgow Coma Scale; intensive care unit; prevalence; seborrheic dermatitis; skin care.

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Seborrheic dermatitis (SD) is a common, chronic, inflammatory skin disorder that typically presents with erythematous, scaly lesions in areas rich in sebaceous glands, such as the scalp, face, and upper trunk [1–3]. Worldwide, its prevalence has been estimated at approximately 3–5%, and recent epidemiological work suggests a prevalence of around 4.3% in the general population [4, 5]. SD is more frequently observed in specific populations, particularly in individuals with neurological disorders and immunosuppression [2, 3].

The mechanisms behind SD are complex. Sebaceous gland activity, the integrity of the skin barrier, the im-

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mune response, and microbial colonization all interact with Malassezia species, playing particularly important roles [2, 6, 7]. Although these lipophilic yeasts are part of the normal skin microbiota, they appear to be central to the inflammatory process that drives SD [6, 7].

Intensive care unit (ICU) patients represent a unique population in whom multiple factors may disrupt normal skin homeostasis. Critical illness itself, prolonged immobilization, impaired hygiene, broad-spectrum antibiotic use, immunosuppression, and invasive procedures may contribute to alterations in the skin barrier and microbiome [8]. It is reasonable to expect that such changes would predispose ICU patients to a wide range of dermatological problems.

However, dermatological disorders in ICU settings continue to be under-recognized and under-reported. Most of the existing literature focuses on conditions such as drug eruptions, pressure ulcers, infections, and contact dermatitis. SD, by contrast, is rarely studied as a separate entity and is usually grouped under nonspecific dermatitis categories [9–11].

As a result, there is a significant gap in the literature regarding the prevalence and clinical characteristics of SD in ICU patients. Filling this gap could help clinicians more reliably recognize dermatological conditions in critically ill patients and enhance overall patient care. With this in mind, we conducted the present study to determine the prevalence of SD in ICU patients and to evaluate the clinical and demographic factors associated with it.

Highlight key points

- SD was observed in 38.2% of ICU patients, a prevalence substantially higher than in the general population.
- Systemic factors, including comorbidities, immunosuppression, and medication use, were not significantly associated with SD.
- Level of consciousness was the only independent factor associated with SD, with sedated patients at higher risk.
- Findings suggest that SD occurrence in ICU patients cannot be fully explained by systemic disease burden alone, although the role of local and care-related factors remains uncertain.

MATERIALS AND METHODS

Study Design and Population

This cross-sectional, observational study was conducted in the ICU of a state hospital between March 10, 2026, and April 30, 2026. The study population consisted of adult patients hospitalized in the ICU during the study period. A total of 102 patients were included in the study.

Inclusion and Exclusion Criteria

Patients aged ≥18 years who had been hospitalized in the ICU for at least 48 h and were suitable for dermatological examination were included in the study.

Patients with a known active inflammatory dermatosis other than SD, those with severe burns or widespread skin barrier disruption, and those with clinical conditions preventing dermatological evaluation were excluded.

Sample Size

Since there was no prior data on the prevalence of SD among ICU patients, an expected prevalence of 50% was assumed to achieve the maximum sample size. With a 95% confidence level and a 10% margin of error, the minimum required sample size was calculated to be 96 patients.

Data Collection

Demographic and clinical information were collected from patients' electronic medical records. The recorded variables included age, sex, comorbid conditions, reason for ICU admission, length of ICU stay, Glasgow Coma Scale (GCS) scores, level of consciousness, sedation status, immunosuppression, immune dysfunction, and medication use.

Patients were grouped according to their GCS scores as mild (13–15), moderate (9–12), or severe (≤8). In addition to GCS, the level of consciousness was clinically categorized as conscious, confused, unconscious, or sedated. Since sedation reflects a pharmacological intervention rather than a true neurological state, it was also evaluated separately as a binary variable based on sedative agent administration during ICU follow-up.

Medication use was reviewed and classified into predefined categories, including systemic antibiotics, corticosteroids, sedatives, and vasopressors. These groups were selected based on their potential effects on immune response, skin microbiota, and patient immobility. Immunosuppression was also recorded as a clinical variable based on patients' treatment history and underlying conditions.

Assessment of SD

The diagnosis of SD was established clinically based on the presence of characteristic erythematous and

scaly lesions involving sebaceous gland-rich areas, including the scalp, face (forehead, eyebrows, and nasolabial folds), external ears, and presternal region. Clinical diagnosis was based on the typical morphology and distribution of lesions, and all examinations were performed by the same dermatologist to ensure consistency.

Disease severity was assessed using the SD Severity Score (SDSS), a semi-quantitative scoring system. The evaluation was performed across four predefined anatomical regions: The scalp, face (including eyebrows, nasolabial folds, and forehead), ears, and the sternal (presternal) area.

For each region, three clinical parameters were assessed: erythema, desquamation, and inflammation/infiltration. Each parameter was scored from 0 (absent) to 3 (severe). Regional scores were calculated by summing these parameters, and the total SDSS score was obtained by summing the scores from all regions. The maximum possible total score was 36. No weighting factors were applied to individual anatomical regions, and all components contributed equally to the total score.

Since no universally accepted or validated cutoff values have been established for SDSS, severity categories were defined for descriptive purposes based on clinical interpretation and the distribution of scores encountered in routine practice. Accordingly, total scores were categorized as mild (0–5), moderate (6–10), and severe (≥11). These categories were intended to facilitate clinical interpretation and should not be considered validated severity thresholds.

Definition of Immunosuppression

Immunosuppression was defined as the presence of systemic corticosteroid use or chemotherapy. Medication records were reviewed to identify relevant treatments.

Immune Dysfunction

In addition to immunosuppression, immune dysfunction was evaluated as a broader clinical condition. Immune dysfunction was defined as the presence of acute or chronic clinical conditions that may compromise immune responses, including sepsis, chronic kidney disease, chronic obstructive pulmonary disease, malignancy, and diabetes mellitus requiring insulin therapy. For analytical purposes, these conditions were evaluated separately from immunosuppression.

Assessment of Comorbidity Burden

Comorbid conditions were classified into major clinical groups, including cardiovascular, respiratory, endocrine/metabolic, neurological disorders, and malignancies. For each patient, the total number of coexisting conditions was calculated to reflect overall comorbidity burden.

For further analysis, patients were grouped according to comorbidity burden as low (0–1 conditions) or high (≥2 conditions).

Stratification by ICU Stay

Patients were categorized based on the duration of ICU stay using a cutoff of 6 days. This threshold corresponded to the median length of stay in our cohort and allowed differentiation between shorter and longer ICU stays for analysis.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences software (version 25.0; IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean±standard deviation or median with interquartile range, depending on data distribution, while categorical variables were presented as frequencies and percentages.

The relationships between categorical variables and SD status, as well as ICU length of stay (≤6 days vs. >6 days), were examined using the Chi-square test or Fisher's exact test, where appropriate. Logistic regression analysis was performed to identify variables potentially associated with SD. Given the limited number of events, the number of variables entered into the multivariable model was restricted to minimize the risk of overfitting. Multicollinearity among independent variables was assessed using the variance inflation factor diagnostics. Because GCS scores and level of consciousness represent closely related clinical constructs, the continuous GCS score was excluded from the final multivariable model, whereas level of consciousness was retained. Conscious patients served as the reference category for all categorical regression analyses. Statistical significance was defined as a $p<0.05$.

Ethical Considerations

Ethical approval for the study was obtained from the Institutional Ethics Committee of Marmara University (approval number: 09.2026.26-0064; approval date:

20.01.2026). Informed consent was obtained from all participants who were able to provide it, while consent for patients with impaired consciousness was obtained from their legally authorized representatives.

The study was carried out in accordance with the principles of the Declaration of Helsinki. No additional invasive procedures or therapeutic interventions were performed specifically for the purposes of this research. All data were anonymized before analysis and handled securely to ensure patient confidentiality.

The study was designed and reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

RESULTS

A total of 102 patients were analyzed. The baseline demographic and clinical characteristics of the cohort are summarized in Table 1. The median age was 76 years (interquartile range [IQR]: 64–84), and 52.9% of the patients were female. The median ICU length of stay was 5.5 days (IQR: 3–11), and the median GCS score was 10 (IQR: 7–15).

SD was identified in 39 of 102 patients (38.2%). Among affected patients, disease severity was predominantly mild (69.2%), followed by moderate (20.5%) and severe (10.3%).

Table 1. Baseline demographic and clinical characteristics of the study population (n=102)

Variables	Values
Age (years), median (IQR)	76 (64–84)
Sex, n=102 (%)	
Female	52.9
Male	47.1
ICU stay (days), median (IQR)	5.5 (3–11)
GCS score, median (IQR)	10 (7–15)
Sedation, (%)	42.2
Immunosuppression, (%)	16.7
Immune dysfunction, (%)	63.7
Systemic corticosteroid use, (%)	16.7
Antibiotic use, (%)	58.8
Sedative drug use, (%)	34.3
Vasopressor use, (%)	27.5
Systemic antifungal use, (%)	4.9

ICU: Intensive care unit; GCS: Glasgow Coma Scale; IQR: Interquartile range.

Univariate Analysis

The association between clinical variables and SD is shown in Table 2. A statistically significant relationship was observed between SD and level of consciousness (p=0.025). SD was more frequently observed in patients with impaired consciousness.

In contrast, no significant associations were found between SD and sex (p=0.312), age (p=0.499), ICU length of stay (p=0.542), immunosuppression (p=0.586), immune dysfunction (p=0.290), or GCS categories (p=0.098).

No statistically significant associations were observed between SD and the use of commonly administered ICU medications, including systemic corticosteroids, antibiotics, sedatives, vasopressors, and antifungal agents (all p>0.05).

Comorbidity burden was not associated with SD. The prevalence of SD was 28.2% in patients with low comorbidity burden and 39.1% in those with high comorbidity burden (p=0.812).

ICU admission diagnoses were categorized into clinically relevant groups, including respiratory, sepsis-related, neurological, gastrointestinal, and other causes. No statistically significant association was found between ICU admission reason and SD (p=0.36).

When patients were stratified according to ICU length of stay (≤6 days vs. >6 days), SD prevalence did not differ significantly between groups (p=0.542) (Table 3).

Multivariable Analysis

A multivariable logistic regression analysis was performed to identify independent predictors of SD (Table 4). To minimize the risk of multicollinearity and overfitting, a more parsimonious model was constructed in which GCS scores were excluded because of their close relationship with the level of consciousness. Conscious patients served as the reference category.

Among the variables included in the model, level of consciousness was the only factor independently associated with SD (overall p=0.035). Compared with conscious patients, sedated patients had significantly higher odds of SD (odds ratio [OR]=5.05, 95% confidence interval [CI]: 1.41–18.08; p=0.013). Although higher odds were

Table 2. Factors associated with seborrheic dermatitis in ICU patients

Variables	Category n=102	SD absent (%)	SD present (%)	p
Sex	Male	56.3	43.8	0.312
	Female	66.7	33.3	
Level of consciousness	Conscious	72.2	27.8	0.025
	Unconscious	33.3	66.7	
	Confused	35.3	64.7	
	Sedated	67.4	32.6	
Immunosuppression	Present	70.6	29.4	0.586
	Absent	60.0	40.0	
Immune dysfunction	Present	66.2	33.8	0.290
	Absent	54.1	45.9	
ICU stay	≤6 days	64.4	35.6	0.542
	>6 days	58.1	41.9	
GCS	Mild (13–15)	73.0	27.0	0.098
	Moderate (9–12)	46.2	53.8	
	Severe (≤8)	61.5	38.5	
Age	≤65	55.2	44.8	0.499
	≥66	64.4	35.6	

Data are presented as numbers (percentages) within each category. Associations between categorical variables and SD status were analyzed using the Chi-square test or Fisher's exact test, as appropriate. A $p<0.05$ was considered statistically significant. ICU: Intensive care unit; SD: Seborrheic dermatitis; GCS: Glasgow Coma Scale.

also observed among confused patients (OR=5.43, 95% CI: 0.73–40.30; p=0.098) and unconscious patients (OR=1.15, 95% CI: 0.40–3.29; p=0.784), these associations did not reach statistical significance.

No significant associations were identified for age, sex, ICU length of stay, immunosuppression, or immune dysfunction. The model demonstrated acceptable calibration according to the Hosmer–Lemeshow goodness-of-fit test (p=0.466), and the Nagelkerke R^2 value was 0.178.

DISCUSSION

In our cohort, SD was observed in 38.2% of ICU patients, which is considerably higher than the prevalence reported in the general population (approximately 3–5%) [4, 5]. This observation is consistent with previous reports indicating that dermatological conditions are relatively common among critically ill patients [9, 11]. Several ICU-related factors, including prolonged immobilization, changes in hygiene practices, and the surrounding care environment, may contribute to this increased frequency.

The pathogenesis of SD is considered multifactorial, involving interactions between sebaceous gland activity, Malassezia species, and host immune responses [2, 6]. Recent studies have increasingly emphasized the contribution of the skin microbiome to inflammatory skin disorders, suggesting that changes in the cutaneous microbial environment may play a role in the development of SD [12, 13]. Although Malassezia species are part of the normal skin flora, they are thought to contribute to disease development, particularly in conditions that disrupt the local skin environment and host–microbe balance [6].

In our cohort, most systemic and clinical variables – including age, sex, ICU length of stay, immunosuppression, immune dysfunction, medication use, comorbidity burden, and reasons for ICU admission – were not significantly associated with SD. This may indicate that overall systemic disease burden plays a more limited role in the development of SD in ICU patients. This pattern differs somewhat from the traditional view of SD, which has often emphasized the contribution of systemic and immunological factors [2, 3]. However, previous studies

Table 3. Comparison of patients according to ICU length of stay (≤6 days vs. >6 days)

Variables	Category n=102	≤6 days (n=59)	>6 days (n=43)	p
Age	≤65	69.0	31.0	0.185
	≥66	53.4	46.6	
Seborrheic dermatitis	Absent	60.3	39.7	0.542
	Present	53.8	46.2	
GCS	Mild (13–15)	86.5	13.5	<0.001
	Moderate (9–12)	30.8	69.2	
	Severe (≤8)	48.7	51.3	
Level of consciousness	Conscious	75.0	25.0	0.024
	Unconscious	16.7	83.3	
	Confused	52.9	47.1	
	Sedated	51.2	48.8	
Immunosuppression	Present	52.9	47.1	0.789
	Absent	58.8	41.2	
Immune dysfunction	Present	61.5	38.5	0.405
	Absent	51.4	48.6	
Corticosteroid use	Present	20.0	16.2	0.786
Antifungal use	Present	3.6	8.1	0.153

Data are presented as numbers (percentages) within each category. Associations between categorical variables and ICU length of stay (≤6 days vs. >6 days) status were analyzed using the Chi-square test or Fisher's exact test, as appropriate. A $p<0.05$ was considered statistically significant. ICU: Intensive care unit; SD: Seborrheic dermatitis; GCS: Glasgow Coma Scale.

conducted in ICU settings suggest that local environmental and care-related factors may contribute to dermatological manifestations in critically ill patients [9–11].

The most notable finding of this study was that the level of consciousness emerged as the only independent factor associated with SD. Sedated patients showed a significantly higher likelihood of developing SD. In contrast, GCS scores were not independently associated with SD after adjustment. This finding suggests that the association may not be solely explained by neurological severity itself. However, the mechanisms underlying this relationship remain unclear and warrant further investigation.

One possible explanation for this association may involve alterations in the local skin environment and skin barrier function associated with critical illness and prolonged immobilization. Previous studies have suggested that microbiome imbalance may contribute to inflammatory skin diseases [12, 13]. However, because skin microbiome characteristics and specific care-related variables were not directly evaluated in the present study, these mechanisms remain speculative and require further investigation.

Differences in routine patient care may also influence this relationship. In the ICU setting, patients with reduced consciousness often receive more standardized, protocol-based nursing care, including regular skin cleansing and repositioning. However, even with structured care, the overall microenvironment – shaped by prolonged immobilization, device-related occlusion, and impaired physiological skin regulation – may still increase susceptibility to skin barrier dysfunction and inflammatory skin conditions [10, 14]. In contrast, patients who are conscious or partially responsive may be exposed to more variability in daily care, along with additional mechanical factors such as friction or scratching, which can further compromise skin integrity.

This study was conducted in an ICU with established nursing practices, which likely contributed to a relatively consistent level of baseline care across patients. However, ICU care-related variables were not systematically measured or quantified. Therefore, these interpretations should be considered with caution, as they remain partly speculative.

Table 4. Independent predictors of seborrheic dermatitis in ICU patients: Multivariable logistic regression analysis

Variables	OR (95% CI)	p
Age	0.46 (0.17–1.24)	0.127
Sex (male)	1.62 (0.65–3.98)	0.294
ICU stay (>6 days)	1.96 (0.49–7.84)	0.341
Immunosuppression	0.71 (0.18–2.74)	0.628
Immune dysfunction	0.70 (0.26–1.82)	0.467
Level of consciousness (overall)	—	0.035
Unconscious	1.15 (0.40–3.29)	0.784
Confused	5.43 (0.73–40.30)	0.098
Sedated	5.05 (1.41–18.08)	0.013

Hosmer-Lemeshow goodness-of-fit test: p=0.466; Nagelkerke R^2=0.178, OR: Odds ratio; CI: Confidence interval; ICU: Intensive care unit.

Interestingly, ICU length of stay was not associated with SD, suggesting that the duration of hospitalization alone may not be sufficient to influence disease development. These findings raise the possibility that factors other than hospitalization duration may contribute to SD occurrence. However, because these variables were not directly assessed in the present study, their exact role remains uncertain and warrants further investigation.

Similarly, no association was found between SD and commonly used medications in the ICU, including corticosteroids, antibiotics, sedatives, vasopressors, and antifungal agents. Although these treatments can affect immune responses and the skin microbiome [12, 13], their impact on SD in critically ill patients appears to be limited based on our findings.

Overall, our findings suggest that SD occurrence in ICU patients cannot be fully explained by systemic disease burden alone. Other factors, including local skin conditions and aspects of routine patient care, may contribute to disease development. However, because these variables were not specifically assessed, their exact role remains uncertain.

Lesions were mainly distributed in sebaceous gland-rich areas, particularly the face and scalp, consistent with the typical clinical presentation of SD. From a practical perspective, these findings support increased awareness of SD during routine skin examinations in ICU patients. Particular attention to sebaceous gland-rich areas, including the scalp, face, external ears, and presternal region, may facilitate early recognition and timely management. However, because specific care-related variables were not systematically evaluated, the impact of particular nursing practices or other local factors remains uncertain and warrants further investigation.

This study has several limitations. It was conducted at a single center, which may limit the generalizability of the findings. In addition, detailed information on skin care practices, hygiene protocols, and nursing interventions was not systematically collected, which limits the ability to directly evaluate the proposed mechanisms. The cross-sectional design of the study also prevents conclusions about causality.

Moreover, the relatively modest explanatory power of the regression model (Nagelkerke R^2=0.178) suggests that additional unmeasured factors may contribute to the development of SD. Given the total event count of 39 cases of SD, the ability to detect smaller effect sizes may have been limited. In addition, because GCS scores and level of consciousness represent closely related clinical constructs, the simultaneous inclusion of these variables in the initial model may have affected model stability and contributed to wider confidence intervals. To reduce the risk of overfitting and multicollinearity, a more parsimonious model was subsequently constructed in which GCS scores were excluded. Nevertheless, the regression estimates should be interpreted with caution, and confirmation in larger cohorts is warranted.

In addition, SDSS has not been specifically validated in ICU populations, and the severity categories used in this study were intended for descriptive purposes only. Therefore, disease severity assessments should be interpreted with caution, and further studies are needed to establish standardized and validated scoring approaches for critically ill patients.

SD was assessed clinically by a single examiner. Although this approach helped maintain consistency and reduced inter-observer variability, it may have introduced a degree of observer bias.

Despite these limitations, this study offers new insight into a relatively underexplored condition in ICU patients. To our knowledge, the independent association between level of consciousness and SD has not been clearly described before. Further multicenter studies, including detailed evaluations of skin care practices and skin microbiome changes, are needed to better understand these relationships and to inform potential preventive approaches.

Conclusion

SD appears to be a common yet often underrecognized condition among ICU patients, with a prevalence notably higher than that observed in the general population. In this study, the level of consciousness was the only factor independently associated with SD, whereas systemic factors, comorbidities, and medication use were not significantly associated.

These findings suggest that the occurrence of SD in critically ill patients cannot be fully explained by systemic disease burden alone. Other factors, including local skin conditions and aspects of routine patient care, may contribute to disease development; however, these variables were not directly assessed, and their exact role remains uncertain.

Further multicenter studies incorporating detailed assessments of skin care practices and skin microbiome dynamics are needed to clarify the underlying mechanisms and to inform preventive strategies.

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of Marmara University (approval number: 09.2026.26-0064; approval date: 20.01.2026) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants or their legal representatives.

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REFERENCES

1. Borda LJ, Wikramanayake TC. Seborrheic dermatitis and dandruff: a comprehensive review. J Clin Investig Dermatol 2015;3:10.13188/2373-1044.1000019. [CrossRef]
2. Dessinioti C, Katsambas A. Seborrheic dermatitis: etiology, risk factors, and treatments: facts and controversies. Clin Dermatol 2013;31:343-51. [CrossRef]
3. Naldi L, Rebora A. Clinical practice. Seborrheic dermatitis. N Engl J Med 2009;360:387-96. [CrossRef]
4. Sanders MGH, Pardo LM, Franco OH, Ginger RS, Nijsten T. Prevalence and determinants of seborrhoeic dermatitis in a middle-aged and elderly population: the Rotterdam Study. Br J Dermatol 2018;178:148-53. [CrossRef]
5. Polaskey MT, Chang CH, Daftary K, Fakhraie S, Miller CH, Chovatiya R. The global prevalence of seborrheic dermatitis: a systematic review and meta-analysis. JAMA Dermatol 2024;160:846-55. [CrossRef]
6. Gaitanis G, Magiatis P, Hantschke M, Bassukas ID, Velegraki A. The Malassezia genus in skin and systemic diseases. Clin Microbiol Rev 2012;25:106-41. [CrossRef]
7. Vest BE, Krauland K. Malassezia furfur. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026. Available at: https://www.ncbi.nlm.nih.gov/books/NBK553091/ Accessed April 20, 2026.
8. Blaser MJ. Antibiotic use and its consequences for the normal microbiome. Science 2016;352:544-5. [CrossRef]
9. Al Bshabshe A, Mousa WF, Nor El-Dein N. An overview of clinical manifestations of dermatological disorders in ıntensive care units: what should ıntensivists be aware of? Diagnostics (Basel) 2023;13:1290. [CrossRef]
10. Kara A, Ortaç E, Hapa A, Öcal S, Topeli A. Dermatological problems in intensive care unit. Journal of Critical and Intensive Care 2015;6:1-3. [CrossRef]
11. Emre S, Emre C, Akoglu G, Demirseren DD, Metin A. Evaluation of dermatological consultations of patients treated in intensive care unit. Dermatology 2013;226:75-80. [CrossRef]
12. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol 2018;16:143-55. [CrossRef]
13. Flowers L, Grice EA. The skin microbiota: balancing risk and reward. Cell Host Microbe 2020;28:190-200. [CrossRef]
14. Gefen A, Alves P, Ciprandi G, Coyer F, Milne CT, Ousey K, et al. Device-related pressure ulcers: SECURE prevention. J Wound Care 2020;29:S1-S52. [CrossRef]

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Case Report Infectious Diseases

Simultaneous pneumocephalus and meningitis as a complication of ozone therapy

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ABSTRACT

Today, minimally invasive oxygen(O^2)-ozone(O_3) intramuscular lumbar paravertebral injections are used to relieve pain in conditions such as low back pain. Repeated paraspinal, peridural, or spinal O_3 injections, when performed under non-aseptic conditions or not performed with proper technique, may carry a risk of parameningeal inoculation of bacteria resulting in meningitis and pneumocephalus. Although this treatment is well tolerated in most cases, the patient may sometimes develop rare but very serious complications. Our study presents a case of pneumocephaly and meningitis due to the injection of an intramuscular O_2-O_3 mixture directed into the subarachnoid space after dural puncture for the treatment of low back pain. Air-density lesions were detected in the temporal and frontal horns of the left lateral ventricle on the patient's computed tomography scan of the brain. The cerebrospinal fluid appeared slightly cloudy, with a leukocyte count of 4000/mm^3, protein level of 483 mg/dL, glucose at 40 mg/dL, and chlorine at 113 mmol/L. Ensuring that ozone injection therapy is performed by qualified professionals and that strict aseptic precautions are taken before the procedure will prevent serious iatrogenic complications such as pneumocephalus and meningitis.

Keywords: Meningitis; ozone therapy; paravertebral injections; pneumocephalus.

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Chronic pain, particularly in conditions like non-specific low back pain, can evolve into a disease that requires specialized treatment and care [1]. Various non-pharmacological, non-invasive treatments for chronic musculoskeletal pain offer mild to moderate relief and may complement pharmacological or more invasive methods [2]. Lumbar paravertebral O_2-O_3 injections represent an easy-to-administer, minimally invasive, safe, cost-effective, and effective technique for alleviating both pain and disability [3]. O_3, also known as trioxygen, is an inorganic gas and a less stable allotrope of oxygen compared to diatomic oxygen (O_2) [4].

O_3 acts by influencing the breakdown of arachidonic acid into inflammatory prostaglandins, reducing inflammation-related pain [5]. Intramuscular lumbar paravertebral O_3 injections are considered a minimally invasive and safe option that effectively reduces pain, disability, and reliance on analgesic medications [6]. In a study where lumbar O_2-O_3 injections were combined with anti-inflammatory analgesics, Melchionda et al. [7] reported an 80% success rate for oxygen-O_3 therapy at a 6-month follow-up, compared to 50% for the group receiving only anti-inflammatory analgesics. Here, we present a case of pneumocephalus and meningitis following O_3 therapy for low back pain, likely due to a contaminated needle that inadvertently advanced from the epidural space into the subarachnoid space.

Ethical Approval

Approval for the study was obtained from the scientific research committee of Malatya Training and Research Hospital (date: March 26, 2026, no: 309081275).

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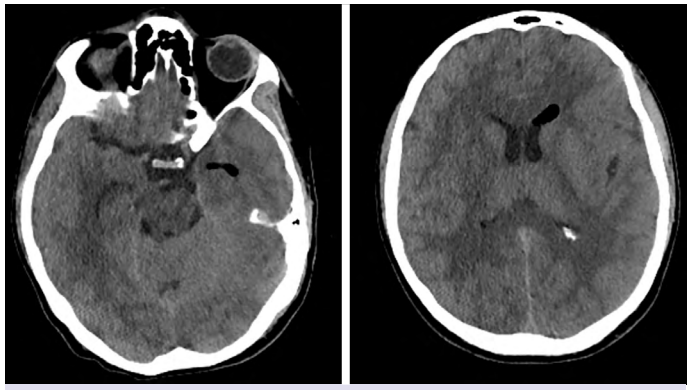

Figure 1. Pneumocephalus in the temporal and the frontal horn of the left lateral ventricle.

CASE REPORT

A 38-year-old male patient was admitted to the hospital with complaints of severe headache, somnolence, fever, chills, dizziness, and intense vomiting, which had persisted for approximately 1 day. His medical history includes a tonsillectomy performed 10 years ago and a diagnosis of ankylosing spondylitis for which he was offered treatment with the biological agent adalimumab 10 months prior, though he did not pursue it. The patient is known to experience widespread muscle pain, particularly in the lower back and neck areas.

Two days before his hospitalization, he underwent O_3 therapy in a private clinic to address back and lumbar pain. This therapy was administered to the right and left paravertebral regions of the back and lumbar area, as well as the front of the neck. One day following this procedure, which targeted the entire spine and neck area, he presented to the emergency department with symptoms of severe headache, fever, chills, dizziness, and vomiting.

Upon arrival at the emergency department, he displayed confusion, had positive neck stiffness, an arterial blood pressure of 160/70 mmHg, and a temperature of 37.8°C. Laboratory tests revealed a white blood cell count of $32.18\times10^3/\mu L$, a platelet count of $286\times10^3/\mu L$, hemoglobin of 15.9 g/dL, an erythrocyte sedimentation rate of 94 mm/h, C-reactive protein at 18.9 mg/L, and a plasma glucose level of 132 mg/dL. A computed tomography (CT) scan of the brain indicated "air densities observed in the temporal and frontal horn of the left lateral ventricle (pneumocephalus)" (Fig. 1).

The patient, with a history of recent intervention and clinical findings suggestive of bacterial meningitis upon systemic examination, was empirically started on intravenous meropenem (3×2 g), vancomycin (4×500 mg), and dexamethasone (4×8 mg) pending cerebrospinal fluid (CSF) culture results. Due to technical constraints at that time, a lumbar puncture (LP) was performed immediately after initiating antibiotic treatment. The CSF appeared slightly cloudy, with a leukocyte count of 4000/mm^3, protein level of 483 mg/dL, glucose at 40 mg/dL, and chlorine at 113 mmol/L. No organisms were observed in the CSF by acid-fast or Gram staining, and no growth was detected in CSF tuberculosis, blood, or CSF cultures.

It was considered that prior antibiotic treatment might have influenced the lack of growth in both sputum and blood cultures. The patient's somnolence improved within 24 h, and by the 10th day of treatment, his headaches and dizziness had significantly subsided. A follow-up CT scan of the brain on the 14th day of treatment revealed a normal appearance, indicating resolution of the pneumocephalus, and subsequent magnetic resonance imaging was also normal. After 2 weeks of treatment, the patient reported no further headaches or dizziness.

A repeated LP on the 14th day showed no cells in the CSF. CSF glucose was 45 mg/dL, chlorine was 121 mmol/L, protein was 72 mg/dL, and the control CSF culture remained negative. The patient showed clinical and laboratory recovery and was discharged. Upon follow-up in the outpatient clinic 1 week later, his examination was normal, and he reported no complaints.

DISCUSSION

We encountered a patient who developed rapidly progressing pneumocephalus and meningitis as side effects associated with O_3 therapy. In many countries across Europe, Asia, and South America, intramuscular O_2-O_3 therapy is used as a minimally invasive approach for treating lumbar disc herniation in patients who are unresponsive to conservative treatment or have contraindications to surgery [6]. An article reported that lumbar paravertebral O_2-O_3 injections are minimally invasive, safe, cost-effective, and effective in alleviating both pain and disability [3]. Apuzzo et al. [8] also supported the effectiveness of intramuscular O_3 injections for low back pain. The overall procedural complication rate for this treatment is estimated to be around 0.1% [9].

In the literature, side effects from O_2 to O_3 treatments are rare but include insomnia, itching, papules around the injection site, gastritis, dizziness, tachycardia, flushing, bilateral vitreoretinal hemorrhages, headache

due to pneumocephalus from accidental intrathecal puncture, paresthesia from spinal nerve injury following percutaneous intradiscal O_3 infiltration, hypoesthesia, vertebrobasilar stroke, subcutaneous hematoma at the puncture site, pyogenic spondylodiscitis due to epidural abscess, and fulminant septicemia [10].

Pneumocephalus, typically associated with tumors, trauma, brain surgery, radiation necrosis, or meningitis/encephalitis caused by gas-forming organisms, is defined as the presence of air or gas within the cranial cavity [11]. Cases of intrathecal access and pneumocephalus have been reported following epidural interventions, such as epidural steroid injections, catheter placement, and blood patches [12, 13]. Magalhaes et al. [14] published a report on pneumocephaly resulting from intrathecal puncture after O_2-O_3 therapy, and Toman et al. [15] described a case of pneumocephaly caused by O_2-O_3 entering the subarachnoid space following a dural puncture for lumbar pain treatment.

Meningitis, an inflammatory syndrome involving the meninges and commonly accompanied by headache and neck stiffness, is diagnosed through CSF examination [16]. Risk factors for nosocomial meningitis include invasive procedures such as craniotomy, use of internal ventricular catheters, external ventricular drains, external lumbar catheters, and LPs [17–19]. Many patients with low back pain receive outpatient treatments, including local paravertebral and epidural injections, which, though rarely associated with infections, can lead to significant complications. Gaul et al. [20] reported that 6.25% of all community-acquired central nervous system infections were iatrogenic, while another study highlighted the high morbidity and mortality associated with iatrogenic meningitis following LP into the subarachnoid space [21].

Conclusion

Contamination of the environment and syringe, along with unintended advancement of the technique beyond the target area and into the subarachnoid space, created an iatrogenic condition that allowed meningitis and pneumocephalus to develop. We believe that iatrogenic meningitis and pneumocephalus can be prevented by ensuring that O_3 therapy is performed by skilled professionals, avoiding entry into the subarachnoid space, and implementing strict aseptic precautions before the procedure. The side effects observed should not be attributed directly to O_3 itself but rather to the ozone application procedure and contamination of the syringe, as seen in our case.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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REFERENCES

1. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 2019;160:19–27. [CrossRef]
2. Flynn DM. Chronic Musculoskeletal Pain: Nonpharmacologic, Noninvasive Treatments. Am Fam Physician 2020;102:465–77.
3. Biazzo A, Corriero AS, Confalonieri N. Intramuscular oxygen-ozone therapy in the treatment of low back pain. Acta Biomed 2018;89:41–6.
4. Bocci VA. Scientific and medical aspects of ozone therapy. State of the art. Arch Med Res 2006;37:425–35. [CrossRef]
5. Rahimi-Movaghar V, Eslami V. The major efficient mechanisms of ozone therapy are obtained in intradiscal procedures. Pain Physician 2012;15:E1007–8. [CrossRef]
6. Paoloni M, Di Sante L, Cacchio A, Apuzzo D, Marotta S, Razzano M, Franzini M, Santilli V. Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection. Spine (Phila Pa 1976) 2009;34:1337–44. [CrossRef]
7. Melchionda D, Milillo P, Manente G, Stoppino L, Macarini L. Treatment of radiculopathies: a study of efficacy and tollerability of paravertebral oxygen-ozone injections compared with pharmacological anti-inflammatory treatment. J Biol Regul Homeost Agents 2012;26:467–74.
8. Apuzzo D, Giotti C, Pasqualetti P, Ferrazza P, Soldati P, Zucco GM. An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain. Funct Neurol. 2014 Jan-Mar;29:31–9. [CrossRef]
9. Steppan J, Meaders T, Muto M, Murphy KJ. A metaanalysis of the effectiveness and safety of ozone treatments for herniated lumbar discs. J Vasc Interv Radiol 2010;21:534–48. [CrossRef]
10. Vanni D, Galzio R, Kazakova A, Pantalone A, Sparvieri A, Salini V, Magliani V. Intraforaminal ozone therapy and particular side effects: preliminary results and early warning. Acta Neurochir (Wien) 2016;158:491–6. [CrossRef]
11. Barry C, Rahmani G, Bergin D. Pneumocephalus and meningitis as complications of mastoiditis. Case Rep Radiol 2019;2019:7876494. [CrossRef]
12. Verdun AV, Cohen SP, Williams BS, Hurley RW. Pneumocephalus after lumbar epidural steroid injection: a case report and review of the literature. A A Case Rep 2014;3:9–13. [CrossRef]
13. Shah AK, Bilko A, Takayesu JK. Epidural steroid injection complicated by intrathecal entry, pneumocephalus, and chemical meningitis. J Emerg Med 2016;51:265–8. [CrossRef]
14. Magalhaes FN, Dotta L, Sasse A, Teixera MJ, Fonoff ET. Ozone therapy as a treatment for low back pain secondary to herniated disc: a systematic review and meta-analysis of randomized controlled trials. Pain Physician 2012;15:E115–29. [CrossRef]

15. Toman H, Özdemir U, Kiraz HA, Lüleci N. Severe headache following ozone therapy: Pneumocephalus. Agri 2017;29:132–6. [CrossRef]
16. Richie MB, Josephson SA. A Practical Approach to Meningitis and Encephalitis. Semin Neurol 2015;35:611–20. [CrossRef]
17. Hussein K, Bitterman R, Shofty B, Paul M, Neuberger A. Management of post-neurosurgical meningitis: narrative review. Clin Microbiol Infect 2017;23:621–8. [CrossRef]
18. van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. N Engl J Med 2010;362:146–54. [CrossRef]
19. Baer ET. Post-dural puncture bacterial meningitis. Anesthesiology 2006;105:381–93. [CrossRef]
20. Gaul C, Neundörfer B, Winterholler M. Iatrogenic (para-) spinal abscesses and meningitis following injection therapy for low back pain. Pain 2005;116:407–10. [CrossRef]
21. Pandian JD, Sarada C, Radhakrishnan VV, Kishore A. Iatrogenic meningitis after lumbar puncture-a preventable health hazard. J Hosp Infect 2004;56:119–24. [CrossRef]

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Letter to the Editor

Clinical considerations for costoclavicular space evaluation after midshaft clavicle fracture

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To the Editor,

I read with great interest the article by Gulnahar and colleagues evaluating post-union area and volume changes in the costoclavicular region after non-operative treatment of unilateral midshaft clavicle fractures [1]. Using bilateral magnetic resonance imaging (MRI) and standardized axial levels, the authors report no statistically significant differences between the injured and contralateral sides despite a mean shortening of 14.3±8.2 mm, and they demonstrate generally favorable functional outcomes measured by the shortened Disabilities of the Arm, Shoulder, and Hand questionnaire (QuickDASH).

This work is valuable because it tests a widely discussed biomechanical premise – that clavicular shortening could reduce the costoclavicular space and potentially contribute to neurovascular symptoms – using a clearly defined imaging approach. In addition, the authors' pragmatic definition of the costoclavicular region (three axial levels and a cranio-caudal volume segment) provides a reproducible framework that can be refined and extended in future studies.

Several considerations may further strengthen subsequent research. First, the clinical relevance of costoclavicular narrowing is often position-dependent rather than static. Neurovascular compromise within the thoracic outlet may become apparent during provocative postures and activities (e.g., abduction, retraction, or load-bearing), even when resting imaging appears normal. Accordingly, supine post-union MRI may underestimate functionally meaningful variations across arm positions. Dynamic or posture-standardized imaging protocols, coupled with predefined reporting of thoracic outlet symptomatology, would likely enhance interpretability and clinical translation [2].

Second, measurement reproducibility deserves emphasis. Area and volume segmentation in the thoracic outlet is technically challenging; small differences in slice selection and boundary definition can obscure subtle changes, especially in modestly sized cohorts. Reporting inter- and intra-observer reliability (or repeat measurements) would strengthen confidence in negative findings. In addition, presenting effect sizes with confidence intervals and exploring threshold-based subgroups (for example, more substantial shortening) could help distinguish true equivalence from limited statistical power.

Third, symptom linkage is essential. While QuickDASH is appropriate for global upper-extremity function, it is not designed to capture intermittent paresthesia, venous congestion, fatigue, or activity-related symptom provocation typical of thoracic outlet complaints. A focused symptom inventory and standardized clinical assessment – aligned with contemporary reporting recommendations – could clarify the clinical meaning of imaging measurements [2].

Finally, incorporating a normative reference for the costoclavicular space could be informative. Recent computed tomography-based work has proposed standardized costoclavicular distance measurements at neurovascular crossing points and suggested percentile-based cutoffs that may indicate increased likelihood of thoracic outlet compromise [3]. Such normative anchors, combined with longitudinal imaging (acute phase, post-union, and later remodeling), may help identify a subset of patients in whom post-fracture clavicular morphology meaningfully alters the costoclavicular environment.

I congratulate the authors for introducing quantifiable MRI-based metrics of the costoclavicular region after clavicle fracture. Extending this framework to include dynamic assessment, measurement reliability, normative referencing, and symptom correlation may better define which patients – if any – develop clinically relevant thoracic outlet compromise related to clavicular shortening and malunion.

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REFERENCES

1. Gulnahar K, Okkan M, Buyukmurat N, Karadeniz E. Evaluation of area and volume changes in the costoclavicular region in patients treated nonoperatively after mid-shaft clavicle fracture. North Clin Istanb 2025;12:490–5. [CrossRef]
2. Illig KA, Donahue D, Duncan A, Freischlag J, Gelabert H, Johansen K, et al. Reporting standards of the Society for Vascular Surgery for thoracic outlet syndrome. J Vasc Surg 2016;64:e23–35. [CrossRef]
3. Duarte FH, Zerati AE, Gornati VC, Nomura C, Puech-Leão P. Normal Costoclavicular Distance as a Standard in the Radiological Evaluation of Thoracic Outlet Syndrome in the Costoclavicular Space. Ann Vasc Surg 2021;72:138–46. [CrossRef]

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Letter to the Editor

From description to clinical impact: Critical gaps in the evaluation of drug intoxication in the emergency department

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To the Editor,

The article by Oksuz et al. [1] on drug poisoning, a clinically significant problem that is becoming increasingly common in emergency departments, was read with great interest. While the study presents valuable descriptive regional data, several critical methodological limitations stand out, restricting the interpretability and clinical impact of the findings.

First, the lack of a standardized severity assessment is the most significant limitation of the study. Reporting hospitalization and intensive care unit (ICU) admission rates without scoring objective severity measures, such as Poisoning Severity Score or organ support requirements, prevents a meaningful interpretation of clinical necessity [2]. In particular, ICU admission is not appropriate as an indicator of toxicity severity, as it depends on institutional practices and resource availability. Without detailed outcome measures such as the need for mechanical ventilation, vasopressor support, or mortality, the study remains largely descriptive and is insufficient for risk stratification or clinical decision-making [3].

Second, the characterization of drug exposure is not detailed enough to support the authors' results. Relying on broad drug classes without reporting drug dosage, timing of administration, or concomitant patterns presents a significant confounding factor. Inclusion of intoxication cases involving unidentified substances further increases the risk of misclassification bias. Given that drug toxicity is primarily dose- and time-dependent, the absence of these parameters significantly limits causal interpretation [4].

Finally, although 77% of cases were reported to be associated with suicidal intent, the study did not include any psychiatric or psychosocial variables. This means that the opportunity to contextualize the findings within the broader framework of self-harm and mental health was missed. Given that psychiatric medications constitute a significant portion of the relevant agents, the lack of underlying psychiatric diagnoses, previous suicide attempts, or post-discharge psychiatric follow-up data greatly diminishes the clinical significance of the results and limits the development of prevention strategies [5].

In summary, while Oksuz et al.'s [1] article provides valuable descriptive information on drug poisoning, these limitations, when considered together, make the study more of a descriptive epidemiological snapshot than one offering highly impactful clinical implications. Future research should prioritize standardized severity scoring and objective outcome measures, detailed toxicological assessments encompassing drug dosage and timing, as well as multiple drug ingestions, and the integration of psychiatric risk profiling. It is believed that assessments using these parameters can improve outcomes and contribute to the development of preventive strategies.

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REFERENCES

1. Oksuz E, Demir B. Drug intoxications in the emergency department: Our 1-year experience. North Clin Istanb 2025;12:690–3. [CrossRef]
2. Persson HE, Sjöberg GK, Haines JA, Pronczuk de Garbino J. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol 1998;36:205–13. [CrossRef]
3. Bohnert ASB, Walton MA, Cunningham RM, Ilgen MA, Barry K, Chermack ST, et al. Overdose and adverse drug event experiences among adult patients in the emergency department. Addict Behav 2018;86:66–72. [CrossRef]
4. Thanacoody HK, Thomas SH. Antidepressant poisoning. Clin Med (Lond) 2003;3:114–8. [CrossRef]
5. Hawton K, Saunders KE, O'Connor RC. Self-harm and suicide in adolescents. Lancet 2012;379:2373–82. [CrossRef]

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