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Neuromodulatory regulation of synaptic transmission in the ARC AgRP→PVN circuit revealed by optogenetics

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MAIN POINTS

- Optogenetic and electrophysiological recordings revealed functional synaptic connectivity in the ARC AgRP→PVN pathway.
- Activation of leptin and kappa-opioid receptors significantly reduced synaptic transmission in this circuit.
- Dopamine and MTII did not significantly affect synaptic strength; presynaptic release probability remained unchanged.

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ABSTRACT

Aim: To investigate how dopamine, leptin, kappa opioid receptor signaling, and melanocortin receptors modulate synaptic transmission in the ARC AgRP→PVN pathway.

Materials and Methods: We combined optogenetic stimulation with whole-cell electrophysiological recordings to directly assess synaptic strength and connectivity. ARC AgRP neurons were selectively activated via AAV-FLEX-ChR2-mediated expression of channelrhodopsin, and postsynaptic responses were recorded from PVN neurons. The effects of dopamine, leptin, kappa opioid, and MTII on synaptic transmission were evaluated, allowing precise analysis of modulatory influences on this hypothalamic feeding circuit.

Results: Leptin and a kappa opioid receptor agonist significantly reduced the synaptic strength of the ARC AgRP→PVN pathway, as reflected by a decrease in the peak amplitude of optogenetically evoked synaptic responses in PVN neurons. In contrast, neither dopamine nor MTII produced significant changes in synaptic strength or neurotransmitter release at this connection ($p>0.05$).

Conclusion: These findings demonstrate that leptin and kappa-opioid receptor activation suppress synaptic transmission in the ARC AgRP→PVN circuit, whereas dopamine and melanocortin receptor activation by MTII have minimal effects on this pathway. Collectively, these results provide new insights into the neuromodulatory mechanisms regulating hypothalamic feeding circuits and highlight potential targets for interventions aimed at controlling appetite and energy balance.

Keywords: AgRP neurons, Synaptic transmission, Dopamine, Leptin, Opioid receptor, Electrophysiology

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INTRODUCTION

Agouti-related peptide (AgRP) neurons located in the arcuate nucleus (ARC) of the hypothalamus play a central role in the regulation of feeding behavior and whole-body energy homeostasis. These neurons are strongly activated during energy deficit and promote food intake and weight gain through their widespread projections to multiple hypothalamic and extra-hypothalamic regions [1,2]. Among these projection targets, the paraventricular nucleus (PVN) of the hypothalamus is considered one of the most critical nodes in the neural circuitry controlling appetite, neuroendocrine signaling, and autonomic regulation [3]. Functional studies have demonstrated that the ARC AgRP→PVN pathway represents a key circuit that rapidly drives feeding behavior when AgRP neurons are activated [1,4].

AgRP neurons exert their effects through the release of several neurotransmitters and neuropeptides, including γ-aminobutyric acid (GABA), neuropeptide Y (NPY), and AgRP itself. NPY is a potent orexigenic peptide that stimulates feeding through activation of Y receptors in downstream hypothalamic targets such as the PVN [2]. In addition, AgRP functions as an endogenous antagonist of melanocortin receptors, particularly melanocortin-4 receptors (MC4R), which are abundantly expressed in PVN neurons and are well known to regulate appetite and energy expenditure [5,6]. Pharmacological activation of melanocortin signaling using agonists such as melanotan-II (MTII) has been shown to suppress food intake and modulate hypotha-

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lamic neuronal activity, highlighting the importance of the melanocortin system in feeding regulation [7].

Beyond classical neuropeptide signaling, feeding circuits are also modulated by several neuromodulatory systems. Dopamine signaling has been implicated in motivational and reward-related aspects of feeding behavior and may influence hypothalamic circuits involved in energy balance [8,9]. Leptin, an adipocyte-derived hormone, provides a key hormonal signal of energy status and acts directly on hypothalamic neurons, including AgRP neurons, to suppress feeding and regulate energy expenditure [10,11]. In addition to these signals, opioid systems have emerged as important modulators of feeding behavior. In particular, activation of kappa opioid receptors (KOR) has been shown to influence appetite, stress responses, and reward processing, suggesting that KOR signaling may interact with hypothalamic circuits that regulate energy homeostasis [12,13].

Recent advances in optogenetics and electrophysiological techniques have enabled precise investigation of functional connectivity within hypothalamic circuits. Several studies have used these approaches to examine how neuromodulators influence synaptic transmission between AgRP neurons and their downstream targets [1,14]. Despite extensive evidence that dopamine, leptin, melanocortin signaling, and opioid systems influence feeding behavior, the direct effects of these neuromodulators on synaptic transmission within the ARC AgRP→PVN pathway remain poorly understood.

Therefore, in the present study we investigated how dopamine, leptin, a kappa opioid receptor agonist, and the melanocortin receptor agonist MTII modulate synaptic transmission between ARC AgRP neurons and PVN neurons. Using a combination of optogenetic stimulation and whole-cell electrophysiological recordings, we aimed to directly characterize the modulatory effects of these signaling pathways on the ARC AgRP→PVN synaptic connection.

MATERIALS AND METHODS

Mice

A total of twenty AgRP-Cre male mice (4–6 weeks old; stock number 012899; Jackson Laboratories, ME, USA) were included in the experiments. Animals were maintained under controlled conditions (21 ± 1 °C) with ad libitum access to standard chow and water. The AgRP-Cre line expressing Cre recombinase [15] was maintained through homozygous × homozygous backcrossing. Mouse breeding was performed at the Experimental Research Center of the Yeditepe University Faculty of Medicine (YUDETAM) in Istanbul, Türkiye. The Yeditepe University Animal Experiments Ethics Committee approved all experimental protocols (Decision No: 2023/11-06, Date: 09.11.2023).

Stereotaxic surgical procedures

Intracranial injections were carried out as previously described [16]. Briefly, mice aged P50–P60 were anesthetized with isoflurane and secured in a stereotaxic frame (David Kopf Inst, CA, USA). After a small scalp incision was made, the skull was exposed and drilled to form an injection site. Bilateral injections of 250–500 nL pAAV-FLEX-ChR2 virus were performed in the ARC using a pulled glass pipette (50 μm tip; Drummond PA, USA) [15] at a rate of 60 nL/min. Stereotaxic coordinates relative to bregma were: anterior–posterior (AP) −1.30 mm, dorsal–ventral (DV) −5.75 mm, and lateral ±0.35 mm. Injections were carried out using a micromanipulator (Narishige, NY, USA), taking approximately 30 minutes per site. After pipette withdrawal, the incision was sutured. Mice were allowed 1-2 weeks for recovery and for sufficient ChR2 virus expression before subsequent experiments.

Combined electrophysiology and optogenetic manipulation

Brain slice preparation was conducted as previously described [17]. Briefly, mice were euthanized and their brains were swiftly transferred into an N-methyl-D-glucamine (NMDG)–HEPES–based cutting solution consisting of artificial cerebrospinal fluid (aCSF; in mM: 92 NMDG, 2.5 KCl, 1.25 NaH_2PO_4, 30 $NaHCO_3$, 20 HEPES, 25 glucose, 2 thiourea, 5 Na-ascorbate, 3 Na-pyruvate, 0.5 $CaCl_2{\cdot}2H_2O$, and 10 $MgSO_4{\cdot}7H_2O$). Brain tissue was maintained in ice-cold carbogenated solution (5% CO_2/95% O_2), and 275 μm coronal slices containing the hypothalamus were prepared using a vibratome. Slices were subsequently transferred into HEPES-based incubation aCSF (in mM: 92 NaCl, 30 $NaHCO_3$, 25 glucose, 2.5 KCl, 1.25 NaH_2PO_4, 3 Na-pyruvate, 20 HEPES, 2 $MgSO_4{\cdot}7H_2O$, 2 $CaCl_2{\cdot}2H_2O$, 2 thiourea, 5 Na-ascorbate), which was continuously bubbled with 95% O_2/5% CO_2, and the slices were incubated for at least 1-2 h. Following recovery, slices were transferred to a recording chamber and perfused with standard recording aCSF (in mM: 124 NaCl, 12.5 glucose, 2.5 KCl, 1.25 NaH_2PO_4, 5 HEPES, 24 $NaHCO_3$, 2 $MgSO_4{\cdot}7H_2O$, and 2 $CaCl_2{\cdot}2H_2O$). Whole-cell recordings were performed on PVN neurons using electrodes with tip resistances of 5–6 MΩ. Blue light (470 nm) delivered by a CoolLED system was used to identify synaptic connections. PVN neurons were randomly sampled in AgRP-Cre mice, and upon confirmation of $ARC^{AgRP→PVN}$ synaptic connectivity, a 6–12 min baseline was recorded before applying pharmacological agents (Leptin, 100 nM; dopamine, 50 μM; ACEA, 200 nM; AM241, 200 nM) to the bath solution. The internal recording solution (in mM) consisted of 125 CsCl, 10 HEPES, 5 NaCl, 4 Mg-ATP, 0.6 EGTA, 0.3 Na_2GTP, and 10 QX-314, adjusted to pH 7.30 and 290-300 mOsm. Signals were recorded and analyzed using a MultiClamp 700B amplifier coupled with pCLAMP 11.3 software (Molecular Devices, San Jose, CA) [18].

Imaging

Deeply anesthetized mice were transcardially perfused with 4% paraformaldehyde (PFA) in 0.1 M phosphate buffer

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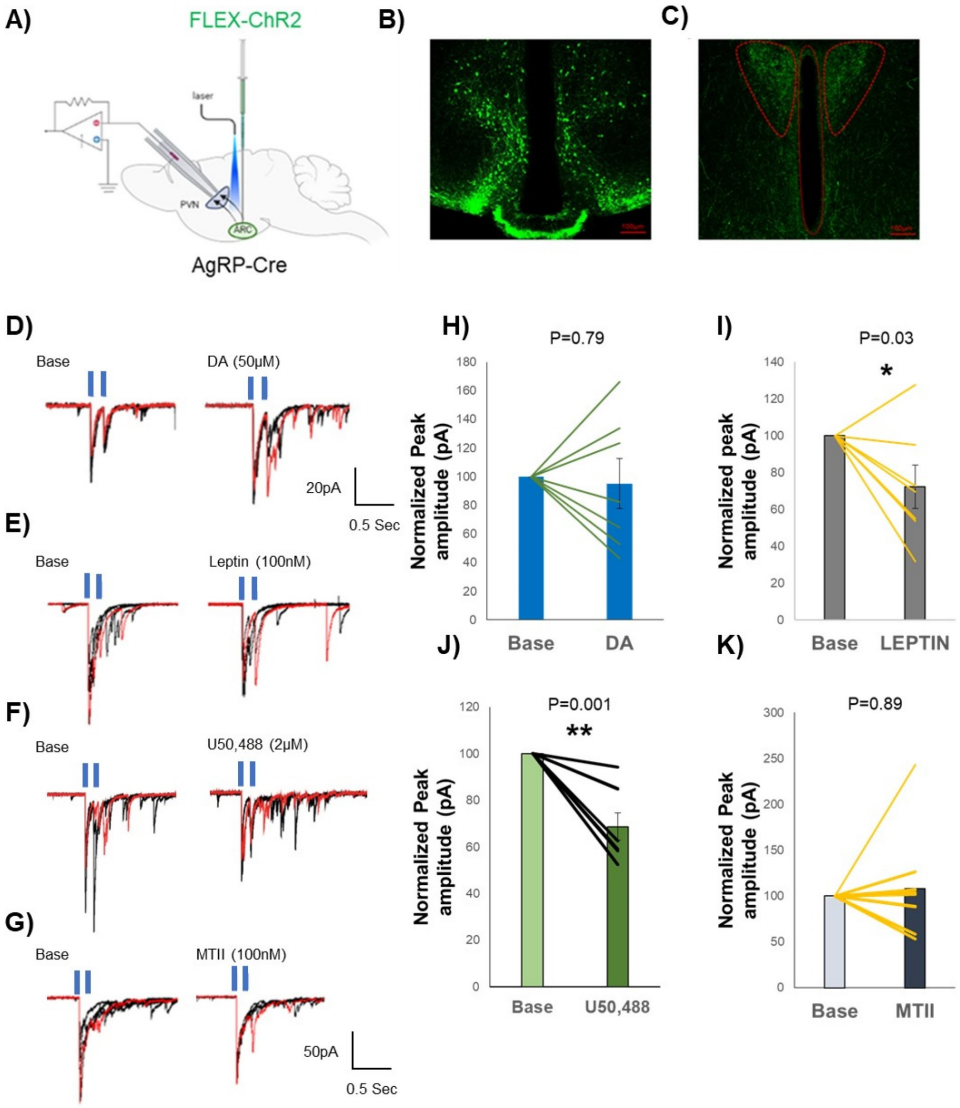

Figure 1. Pharmacological modulation of ARC AgRP→PVN synaptic transmission. (A) ChR2 expression in ARC AgRP axons and photostimulation of their terminals in PVN-containing brain slices from AgRP-Cre mice. Inset: representative image showing whole-cell recording from a PVN neuron with the recording pipette indicated. (B) ChR2 expression in ARC AgRP neurons of AgRP-Cre mice (scale bar: 100 μm). (C) Synaptic projections of arcuate AgRP neurons to the PVN. (D--G) Representative electrophysiological recording traces obtained under baseline conditions and after application of pharmacological agents: dopamine, leptin, the kappa opioid receptor agonist U50,488, and the MC4R agonist MTII (H--K). Effects of pharmacological agents on ARC AgRP→PVN synaptic responses: (H) dopamine, (I) leptin, (J) U50,488, and (K) MTII. Each line represents individual neurons (Dopamine n=8; Leptin n=7; U50,488 n= 8; MTII n=8 neurons; 5 mice were used in each groups. (Data are mean ± standard deviation. Statistical analysis: Student's paired t-test; *p<0.05, **p<0.01)

(pH 7.35) and subsequently decapitated. Brains were extracted, post-fixed in the same solution for 4 h, and then cryoprotected overnight in 30% sucrose. Coronal sections (60 μm) were prepared using a vibratome and permeabilized in 0.1% Triton-X in PBS for 1 h at 4 °C. After rinsing, sections were mounted onto microscope slides and coverslipped with Fluoromount (Sigma, F4680, MO, USA). Confocal images were acquired using a Carl Zeiss microscope (Thornwood, NY, USA) [19].

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software, USA). The normality of paired differences was assessed using the Shapiro–Wilk test before applying parametric tests. Since the assumption of normality was satisfied, comparisons between baseline and pharmacological conditions were performed using Student's paired t-test. Data are presented as mean ± standard deviation (SD). Exact p-values are reported throughout the manuscript, and $p<0.05$ is considered statistically significant. Post hoc power analyses were conducted using G*Power based on the observed effect sizes (Cohen's dz) for paired comparisons (two-tailed, $\alpha = 0.05$). Power analysis, effect size calculations, and normality test results are provided in the Supplementary Materials.

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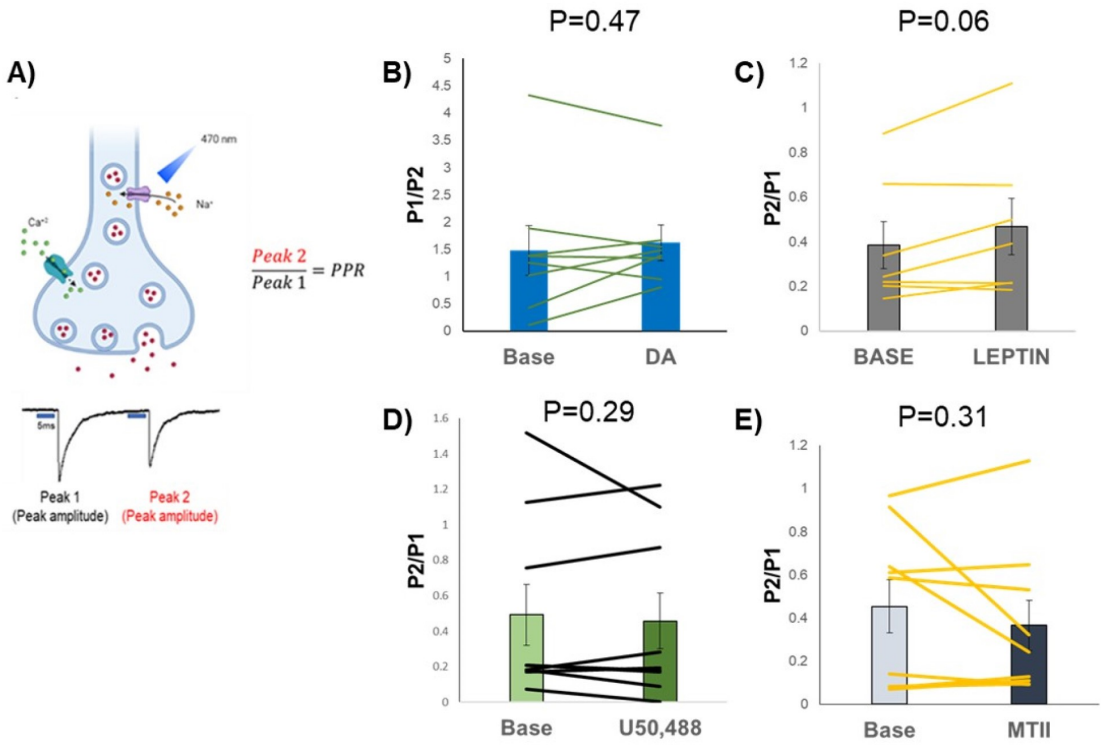

Figure 2. Effects of pharmacological agents on presynaptic release probability in the ARC AgRP→PVN pathway. (A) Schematic illustration of paired-pulse ratio (PPR; P2/P1) used to estimate neurotransmitter release probability. (B–E) Effects of pharmacological agents on PPR: (B) dopamine, (C) leptin, (D) the kappa opioid receptor agonist U50,488, and (E) the MC4R agonist MTII. Each line represents individual neurons (Dopamine n=8; Leptin n=7; U50,488 n= 8; MTII n=8 neurons; 5 mice were used in each groups. (Data are mean ± standard deviation).

RESULTS

Effects of pharmacological agents on peak amplitude in ARC$^{AgRP\rightarrow PVN}$ synaptic connectivity

To examine the pharmacological modulation of the ARC AgRP→PVN pathway, we employed channelrhodopsin-assisted circuit mapping (CRACM) to selectively isolate AgRP axon–mediated synaptic responses in PVN neurons. An AAV-FLEX-ChR2 vector was stereotaxically delivered into the arcuate nucleus of AgRP-Cre mice, and whole-cell patch-clamp recordings were subsequently performed on PVN neurons in acute hypothalamic slices. Laser stimulation (10 Hz, 2 pulses) targeting AgRP terminals evoked postsynaptic currents (Figure 1A–C). After establishing a 5-min baseline recording, pharmacological agents were bath-applied and responses were monitored for an additional 15 min (Figure 1D–G). Application of dopamine (50 μM) did not significantly modify the peak amplitude of light-evoked responses in the ARC AgRP→PVN pathway (Figure 1H). In contrast, leptin (100 nM) produced a significant reduction in response amplitude relative to baseline recordings (Figure 1I). To evaluate the potential contribution of opioid signaling, the kappa opioid receptor agonist U50,488 (2 μM) was applied to the bath solution. Activation of kappa opioid receptors significantly reduced the amplitude of optogenetically evoked currents (Figure 1J), consistent with a weakening of synaptic transmission in the ARC AgRP→PVN circuit. By comparison, application of the MC4R agonist MTII (100 nM) did not produce a detectable change in evoked responses relative to baseline conditions (Figure 1K). Post hoc power analyses (two-tailed, $\alpha = 0.05$) revealed low power for dopamine (dz = 0.19, power = 0.075) and MTII (dz = 0.08, power = 0.055), intermediate power for leptin (dz = 0.96, power = 0.57), and high power for U50,488 (dz = 1.8, power = 0.99).

Effects of pharmacological agents on the probability of GABA release

To determine whether the observed pharmacological effects on ARC AgRP→PVN synaptic transmission involve changes in presynaptic neurotransmitter release, we analyzed the paired-pulse ratio (PPR) as an indicator of release probability. Whole-cell recordings were performed in the presence of glutamate receptor antagonists (AP5 and CNQX) to isolate inhibitory postsynaptic currents (IPSCs) (Figure 2A). Paired-pulse photostimulation (470 nm; 2 × 5 ms pulses at 10 Hz) was applied to ChR2-expressing AgRP axon terminals in the PVN. Under these conditions, the P2/P1 ratio was used to assess potential changes in presynaptic release probability. Application of dopamine, leptin, the kappa opioid receptor agonist U50,488, and the MC4R agonist MTII did not significantly alter the paired-pulse ratio compared with baseline recordings (Figure 2B–E), indicating that these pharmacological manipulations do not significantly affect the probability of GABA release from AgRP presynaptic terminals in the ARC AgRP→PVN pathway.

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DISCUSSION

In this study, we investigated the effects of several neuromodulatory signals, including dopamine, leptin, the kappa opioid receptor agonist U50,488, and the melanocortin receptor agonist MTII, on synaptic transmission in the ARC AgRP→PVN pathway. This circuit represents a critical component of hypothalamic networks regulating appetite, body weight, and energy homeostasis [20-22].

Our results demonstrate that leptin and the activation of kappa-opioid receptors significantly suppress the peak amplitude of ARC AgRP→PVN synaptic transmission. In contrast, neither dopamine nor the melanocortin receptor agonist MTII significantly altered synaptic peak amplitude. These findings indicate that specific neuromodulatory systems can differentially regulate synaptic strength within this key hypothalamic feeding circuit.

Leptin is a well-established anorexigenic hormone that engages multiple hypothalamic nuclei to reduce food intake and enhance energy expenditure [11]. Previous studies have shown that leptin can directly inhibit AgRP neuron activity and reduce their orexigenic output [23]. Our data extend these findings by demonstrating that leptin also suppresses the synaptic efficacy of AgRP neuron projections to the PVN, suggesting a dual mechanism by which leptin can inhibit feeding: both by reducing AgRP neuron firing and by weakening their downstream synaptic influence on PVN neurons. This is consistent with reports that leptin signaling in the ARC is essential for the long-term regulation of energy balance and that leptin resistance in this region contributes to obesity [19,23]. Importantly, these findings provide direct electrophysiological evidence that leptin can weaken synaptic transmission from AgRP neurons to PVN neurons, revealing a circuit-level mechanism through which leptin may regulate feeding behavior.

Activation of the kappa opioid receptor (KOR) significantly reduced the peak amplitude of optogenetically evoked synaptic responses in the ARC AgRP→PVN pathway. This finding indicates that KOR activation suppresses synaptic transmission between AgRP and PVN neurons. Opioid signaling has been implicated in the regulation of feeding behavior, reward processing, and stress-related responses, and KOR activation has been shown to influence neuronal activity in brain regions involved in energy balance and motivational states [24-26]. Our results extend these observations by demonstrating that activation of KOR signaling can directly modulate synaptic strength within the ARC AgRP→PVN circuit, suggesting that kappa opioid pathways may participate in the regulation of hypothalamic feeding networks.

In contrast, activation of melanocortin receptors with the agonist MTII did not significantly affect synaptic transmission in the ARC AgRP→PVN pathway. Melanocortin signaling, particularly through MC4R-expressing PVN neurons, is widely recognized as a major regulator of appetite and energy expenditure [27]. The lack of acute synaptic modulation observed in our recordings suggests that MTII may influence feeding behavior primarily through mechanisms other than direct modulation of AgRP→PVN synaptic strength. For example, melanocortin signaling may act by altering the intrinsic excitability of PVN neurons or through network-level modulation involving additional hypothalamic circuits [28].

Interestingly, dopamine did not significantly affect ARC AgRP→PVN synaptic transmission in our experiments. Dopamine is a key neuromodulator of reward and motivation, and its role in feeding behavior is well established [29,30]. However, its direct effects on AgRP neuron synaptic output have not been clearly defined. Our results suggest that, at least acutely and in the context of the ARC AgRP→PVN pathway, dopamine does not modulate synaptic strength, although it may influence feeding behavior through other circuits or via longer-term mechanisms.

Furthermore, analysis of paired-pulse ratio (PPR) revealed that none of the tested agents significantly altered the probability of GABA release from AgRP presynaptic terminals onto PVN neurons [31]. This finding indicates that the observed changes in synaptic peak amplitude are unlikely to arise from alterations in presynaptic release probability. Instead, these effects may reflect postsynaptic mechanisms or changes in synaptic efficacy within the ARC AgRP→PVN circuit. Previous studies have shown that AgRP neurons release both GABA and NPY to inhibit PVN neurons and promote feeding behavior [1], suggesting that multiple signaling mechanisms contribute to the regulation of this pathway.

Limitations

The experiments were performed in acute brain slices, which may not fully reflect in vivo circuit dynamics. In addition, the pharmacological manipulations represent acute effects and may not capture long-term regulatory mechanisms. Further studies are required to clarify the precise cellular mechanisms underlying the observed synaptic modulation.

CONCLUSION

Overall, our findings highlight the complex neuromodulatory regulation of the ARC AgRP→PVN circuit and identify leptin and kappa opioid receptor signaling as important modulators of synaptic transmission within this pathway. These results provide new insights into the synaptic mechanisms underlying the hypothalamic control of feeding behavior and may inform the development of therapeutic strategies targeting hypothalamic circuits implicated in obesity and metabolic disorders.

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Ethics Committee Approval: All experimental protocols were reviewed and approved by the Yeditepe University Experi-

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

Author Contributions: YY: Performed electrophysiological recordings, imaging, and surgeries; BY and YY: Conceived experiments, analyzed data, and wrote the manuscript.

Financial Disclosure: No financial support was obtained for this study.

Data availability: Data will be made available on request.

Artificial Intelligence Disclosure: ChatGPT (OpenAI, GPT-5.5) was used solely for language editing and to improve readability in the Abstract and Discussion sections during manuscript preparation. The AI tool was not involved in the study design, data analysis, interpretation of results, or the generation of scientific conclusions. All content was carefully reviewed, validated, and approved by the authors, who retain full responsibility for the manuscript.

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The effect of ibrutinib therapy on sarcopenia in patients with hematologic malignancies

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MAIN POINTS

- Ibrutinib therapy was not associated with a significant deterioration in skeletal muscle mass in patients with hematologic malignancies.
- Muscle density decreased during follow-up despite relatively stable muscle mass, suggesting a potential deterioration in muscle quality.
- These findings highlight the importance of considering sarcopenia-related parameters during treatment; however, larger prospective studies are required to clarify their clinical implications.

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ABSTRACT

Aim: Sarcopenia, characterized by progressive loss of skeletal muscle mass and function, is associated with poor prognosis in patients with hematologic malignancies. Given the potential musculoskeletal effects of Bruton tyrosine kinase inhibitors, this study aimed to investigate sarcopenia-related parameters in patients with hematologic malignancies receiving ibrutinib therapy.

Materials and Methods: This retrospective study included 55 patients diagnosed with hematologic malignancies. Using computed tomography (CT) images obtained before and after ibrutinib therapy, we calculated total abdominal muscle area (TAMA), skeletal muscle index (SMI), and muscle density in Hounsfield Units (HU). Changes in these imaging-based parameters, sarcopenia prevalence, and their associations with mortality were statistically analyzed.

Results: The mean age of the patients was 67.38 ± 8.66 years, and 72.7% were male. No significant difference in the prevalence of sarcopenia was observed between patients who received ibrutinib and those who did not ($p>0.05$). While SMI and TAMA values did not change significantly after treatment ($p>0.05$), muscle density (HU) decreased significantly ($p=0.001$). In the ROC analysis, baseline and follow-up SMI values in females, as well as follow-up SMI values in males, showed good discriminatory ability for predicting mortality (AUC>0.88).

Conclusion: In this retrospective cohort, ibrutinib therapy was not associated with significant changes in skeletal muscle mass; however, a decline in muscle density was observed, suggesting potential alterations in muscle quality. No restorative effect on pre-existing sarcopenia was demonstrated in this limited cohort. These findings should be considered exploratory; larger prospective studies that incorporate functional assessments are needed to clarify the clinical implications of sarcopenia in patients receiving ibrutinib.

Keywords: Sarcopenia, Skeletal muscle index, Computed tomography

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INTRODUCTION

Sarcopenia is a muscle disease characterized by progressive and generalized loss of skeletal muscle mass, strength, and function. Although traditionally considered a natural consequence of aging, it is now understood that sarcopenia can also emerge earlier in life, particularly in association with chronic illnesses such as hematologic malignancies. In its 2018 update, the European Working Group on Sarcopenia in Older People (EWGSOP2) emphasized low muscle strength as the principal determinant of sarcopenia, while identifying low muscle mass and reduced physical performance as confirmatory criteria for diagnosis and indicators of disease severity [1].

In cancer patients, sarcopenia has been associated with increased chemotherapy toxicity, higher risk of mortality, more

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frequent postoperative complications, and longer hospital stays. Sarcopenia is linked to poor prognosis across nearly all types of cancer, including hematologic malignancies [2]. In recent years, the prognostic relevance of sarcopenia in hematologic malignancies has received growing attention. Its high prevalence in this patient population is thought to be related to systemic inflammation, metabolic disturbances, and treatment-associated toxicities. A meta-analysis published in 2023 reported that the average prevalence of pre-treatment sarcopenia in patients with hematologic malignancies was 47%, rising to 51% in patients aged 60 years and older [3]. Furthermore, sarcopenia was independently associated with poorer overall and progression-free survival. Treatment response was also impacted, with notably lower complete response rates in male patients and those with a body mass index ≥25.

These observations suggest that sarcopenia represents a clinically relevant condition interacting with disease biology and treatment response, rather than being solely an age-related phenomenon. However, most available data are derived from heterogeneous patient populations and retrospective analyses, highlighting the need for further disease- and treatment-specific investigations.

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, has been approved for the treatment of various hematologic malignancies, most notably chronic lymphocytic leukemia (CLL). Clinical studies have reported musculoskeletal adverse effects such as arthralgia and myalgia in approximately 30–40% of patients receiving ibrutinib therapy [4]. These side effects can impair quality of life and hinder treatment adherence. Although these adverse events are generally low grade, their potential impact on physical activity and muscle function may be particularly relevant in older patients and those with pre-existing vulnerability to sarcopenia.

Despite the widespread use of ibrutinib, its effects on skeletal muscle mass and muscle quality remain poorly characterized.

In this study, we aimed to evaluate the effect of ibrutinib therapy on sarcopenia-related parameters by comparing, using computed tomography (CT), changes in total abdominal muscle area (TAMA), muscle density expressed in Hounsfield Units (HU), and skeletal muscle index (SMI) before and after treatment in patients with hematologic malignancies. Given the retrospective design, this analysis was intended to be exploratory and hypothesis-generating.

MATERIALS AND METHODS

Study design and patient selection

This retrospective study included patients diagnosed with chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) between 2020 and 2024 who had undergone at least two abdominal computed tomography (CT) scans. The study population consisted of 53 patients with CLL and 2 patients with MCL. Patients were required to undergo an abdominal CT scan at the time of diagnosis and a follow-up CT scan at least six months after treatment initiation or during a drug-free follow-up period. Skeletal muscle mass measurements were performed on CT images acquired at diagnosis and at least six months after treatment initiation, or during drug-free follow-up.

Patients without baseline or follow-up CT imaging and those whose image quality did not allow reliable muscle segmentation were excluded from the study. No additional exclusion criteria were applied. Due to the retrospective study design, informed consent was waived. The study was approved by the Samsun University Non-Invasive Clinical Research Ethics Committee (Decision No: 2025/10/17, Date: 14.05.2025).

Data collection

Sociodemographic and clinical data were retrieved from the hospital information system. Recorded variables included sex, diagnosis, age at diagnosis, height, laboratory values at diagnosis (e.g., white blood cell count, lactate dehydrogenase), presence of endocrine disorders, history of chemotherapy, and survival status. Treatment-related data included whether patients received ibrutinib, other chemotherapy regimens, or both. Chemotherapy exposure was recorded irrespective of disease stage at diagnosis because some patients initially diagnosed at early stages subsequently experienced disease progression requiring systemic treatment; this approach reflects real-world treatment practices and patients' prior treatment histories.

Imaging and muscle mass assessment

Sarcopenia assessment was performed using axial CT slices obtained at the level of the third lumbar vertebra (L3). A radiologist with 10 years of experience conducted the measurements using the Horos software. After the images were transferred to the Horos program, total abdominal muscle area (TAMA) was measured using a semi-automated segmentation method. The Hounsfield Unit (HU) threshold range was set between −29 and +130. The psoas major, erector spinae, quadratus lumborum, and abdominal wall muscles were included in the analysis.

The skeletal muscle index (SMI) was calculated as TAMA divided by the square of the patient's height in meters:

$SMI = TAMA(cm^2)/ height^2(m^2)$

Sarcopenia classification

Sarcopenia was classified using gender-specific SMI cut-off values determined by receiver operating characteristic (ROC) curve analysis of this study's dataset. Based on this analysis, optimal cut-off values were defined as $\leq 33.24\ cm^2/m^2$ for females and $\leq 38.25\ cm^2/m^2$ for males.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social

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Table 1. Distribution of sociodemographic and clinical variables.

Variable	N	%
Age		
Mean±SD	67.38±8.66	
Median (min-max)	68.0 (50-87)	
Age at diagnosis (years)		
Mean±SD	62.72±9.44	
Median (min-max)	64.0 (41-85)	
≤65	21	38.2
>65	34	61.8
Height (m)		
Mean±SD	1.68±0.08	
Median (min-max)	1.71 (1.50-1.81)	
Sex		
Female	15	27.3
Male	40	72.7
Diagnosis		
CLL	53	96.4
MCL	2	3.6
Disease stage at diagnosis		
0	2	3.6
1	15	27.3
2	21	38.2
3	6	10.9
4	11	20.0
Chemotherapy		
Not received	12	21.8
Received	43	78.2
Ibrutinib		
Not received	42	76.4
Received	13	23.6
Endocrine disease		
Absent	34	61.8
Present	21	38.2
WBC at diagnosis		
Mean±SD	60541.56±68821.22	
Median (min-max)	29740.0 (600.0-334000.0)	
LDH at diagnosis (U/L)		
Mean±SD	261.96±144.25	
Median (min-max)	225.0 (139.0-1129.0)	
Mortality		
Alive	44	80.0
Deceased	11	20.0

Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as numbers and percentages for categorical variables and as mean ± standard deviation and median (minimum–maximum) for continuous variables. The assumption of normality was assessed using the Kolmogorov–Smirnov test, and a p-value <0.05 was considered statistically significant.

For non-normally distributed data, the Mann–Whitney U test was used for comparisons between two independent groups, and the Wilcoxon signed-rank test was applied for repeated measures. Pearson's chi-square test and Fisher's exact test were used to compare categorical variables. Relationships between continuous variables were evaluated using Spearman correlation analysis. A p-value <0.05 was considered statistically significant.

This study was a retrospective, observational analysis. Given the limited number of patients receiving ibrutinib therapy, a priori sample size calculation and power analysis were not planned. Accordingly, all statistical analyses were considered exploratory and hypothesis-generating rather than hypothesis-testing.

RESULTS

A total of 55 patients were included in the study. As presented in Table 1, the mean age was 67.38 ± 8.66 years, with a median of 68.0 (range: 50–87) years. The mean age at diagnosis was 62.72 ± 9.44 years, and 61.8% of the patients were aged ≥65 years. Of the participants, 72.7% were male and 27.3% were female. The mean height was 1.68 ± 0.08 m, with a median of 1.71 (range: 1.50–1.81) m.

The majority of patients were diagnosed with chronic lymphocytic leukemia (CLL, 96.4%), while 3.6% had mantle cell lymphoma (MCL). At diagnosis, the most frequent stage was stage 2 (38.2%), followed by stages 1 (27.3%), 4 (20.0%), 3 (10.9%), and 0 (3.6%). Chemotherapy was administered to 78.2% of patients, whereas 21.8% did not receive chemotherapy. 23.6% of the cohort received Ibrutinib therapy, while 76.4% did not.

Endocrine comorbidities potentially associated with sarcopenia were present in 38.2% of patients. The mean white blood cell (WBC) count at diagnosis was 60,541.56 ± 68,821.22/μL, with a median of 29,740.0 (range: 600.0–334,000.0). The mean lactate dehydrogenase (LDH) level was 261.96 ± 144.25 U/L, with a median of 225.0 (range: 139.0–1129.0) U/L. During follow-up, the overall mortality rate was 20.0%, while 80.0% of patients remained alive.

Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of sarcopenia-related parameters for predicting mortality, as shown in Table 2. In female patients, both baseline skeletal muscle index (SMI1; AUC = 0.909, 95% CI: 0.752–1.000, p=0.019) and follow-up SMI (SMI2; AUC = 0.886, 95% CI: 0.710–1.000, p = 0.026) demonstrated strong discriminative ability. The optimal cut-off value for SMI1 in women was ≤33.24 cm^2/m^2, yielding a sensitivity of 75.0% and specificity of 72.7%.

In male patients, follow-up SMI2 showed a high discriminative performance (AUC = 0.903, 95% CI: 0.808–0.997), with 85.7% sensitivity and 84.8% specificity (p=0.001). Similarly, baseline and follow-up total abdominal muscle areas (TAMA1 and TAMA2) demonstrated significant predictive value for mortality in female patients (TAMA1: AUC = 0.932, p = 0.013; TAMA2: AUC = 0.826, p = 0.010). In male patients, TAMA2 also showed significant discriminative ability (AUC = 0.883, 95% CI: 0.765–1.000), with 71.4% sensitivity and 72.7% specificity (p = 0.002). In contrast, baseline and follow-up muscle density values (HU1 and HU2) did not

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

Variables	AUC	%95 CI	Cut-off	Sensitivity (%)	Specificity (%)	p
SMI1-Female	0.909	0.752-1.000	≤33.24	75.0	72.7	**0.019**
SMI1-Male	0.545	0.320-0.771	≤41.05	57.1	57.6	0.545
SMI2-Female	0.886	0.710-1.000	≤32.45	75.0	72.7	**0.026**
SMI2-Male	0.903	0.808-0.997	≤38.25	85.7	84.8	**0.001**
TAMA1-Female	0.932	0.787-1.000	≤80.38	75.0	72.7	**0.013**
TAMA1-Male	0.645	0.460-0.830	≤123.77	57.1	57.6	0.233
TAMA2-Female	0.826	0.699-1.000	≤82.74	75.0	72.7	**0.026**
TAMA2-Male	0.883	0.765-1.000	≤116.01	71.4	72.7	**0.002**
HU1	0.535	0.336-0.734	≥45.83	54.5	54.5	0.535
HU2	0.651	0.453-0.848	≤38.11	63.6	63.6	0.125

AUC: Area under the curve; 95% CI: Confidence interval; 1: measurements at diagnosis; 2: follow-up measurements.

Table 3. Development of sarcopenia.

	SMI-1		
Variables	Non-Sarcopenic N (%)	Sarcopenic N (%)	p
SMI-2			
Non-Sarcopenic	23 (85.2)	15 (53.6)	0.019
Sarcopenic	4 (14.8)	13 (46.4)	
	TAMA-1		
	Non-Sarcopenic N (%)	Sarcopenic N (%)	p
TAMA-2			
Non-Sarcopenic	23 (85.2)	13 (46.4)	0.049
Sarcopenic	4 (14.8)	15 (53.6)	
	HU-1		
	Non-Sarcopenic N (%)	Sarcopenic N (%)	p
HU-2			
Non-Sarcopenic	45 (90)	2 (40)	0.453
Sarcopenic	5 (10)	3 (60)	

McNemar test, p<0.05 considered statistically significant. 1: measurements at diagnosis; 2: follow-up measurements.

demonstrate a statistically significant predictive value for mortality (AUC = 0.535 and 0.651, respectively; p>0.05).

As presented in Table 3, significant associations were observed between baseline and follow-up measurements of SMI (SMI1 vs. SMI2, p=0.019) and of TAMA (TAMA1 vs. TAMA2, p=0.049). Among patients who were non-sarcopenic at baseline, 85.2% remained non-sarcopenic at follow-up, whereas 53.6% of those who were sarcopenic at baseline remained sarcopenic. No significant association was observed between baseline and follow-up HU values and sarcopenia status (p=0.453).

As shown in Table 4, no statistically significant changes were observed in SMI or TAMA values during follow-up in either female or male patients (all p > 0.05). In contrast, muscle density values demonstrated a significant decrease over time (p=0.001), with median HU declining from 45.3 (range: 10.9–65.6) at baseline to 39.6 (range: 10.3–60.0) at follow-up.

As presented in Table 5, no statistically significant differences were observed in sarcopenia prevalence—assessed by SMI, TAMA, or HU parameters—between patients who received ibrutinib therapy and those who did not (all p>0.05). In contrast, chemotherapy exposure was significantly associated with the prevalence of sarcopenia when sarcopenia was assessed using baseline SMI and HU values. Based on SMI1, sarcopenia was present in 58.3% of chemotherapy-naïve patients and in 86.0% of patients who received chemotherapy (p=0.049). According to HU1, sarcopenia was observed in 25.0% of chemotherapy-naïve patients and 4.7% of those who received chemotherapy (p=0.030).

As shown in Table 6, when patients were stratified by baseline sarcopenia status (SMI1), only the WBC count at diagnosis differed significantly between sarcopenic and non-sarcopenic groups (medians: 42,860.0 vs. 16,845.0; p=0.012). No significant differences were observed regarding age, age at diagnosis, LDH levels, endocrine comorbidities, disease stage, or mortality (all p>0.05). When sarcopenia status was defined using follow-up SMI2 values, a significant association with mortality was observed (p<0.001); mortality occurred in 52.9% of sarcopenic patients compared with 5.3% of non-sarcopenic patients.

DISCUSSION

Sarcopenia has been shown to negatively impact survival and increase chemotherapy-related toxicity, particularly in elderly patients with hematologic malignancies such as diffuse large B-cell lymphoma (DLBCL). However, in other hematologic cancers, including leukemia and multiple myeloma, the association between sarcopenia and survival remains inconsistent. This heterogeneity suggests that the clinical impact of sarcopenia may vary according to the specific subtype of hematologic malignancy. The ability to assess sarcopenia using routine imaging modalities, such as computed tomography (CT), without incurring additional cost or radiation exposure, makes screening highly feasible in hematology clinics. When complemented by assessments of muscle strength and physical performance, such screening may facilitate more individualized treatment strategies and potentially reduce treatment-related toxicity. Nevertheless, the lack of prospective interventional studies targeting sarcopenia in

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Table 4. Pre- and Post-treatment changes in SMI, TAMA, and HU values.

Variables	SMI-1 Median (min-max)	SMI-2 Median (min-max)	p
SMI-Female (n=15)	36.3 (18.0-46.8)	35.1 (13.0-49.4)	0.394
SMI-Male (n=40)	43.2 (32.1-54.1)	40.6 (22.2-53.0)	0.528
	TAMA-1 Median (min-max)	TAMA-2 Median (min-max)	p
TAMA-Female (n=15)	87.7 (47.2-114.2)	87.1 (32.9-118.8)	0.394
TAMA-Male (n=40)	127.6 (99.4-169.3)	121.2 (62.7-157.2)	0.519
	HU-1 Median (min-max)	HU-2 Median (min-max)	p
HU (n=55)	45.3 (10.9-65.6)	39.6 (10.3-60.0)	0.001

1: measurements at diagnosis; 2: follow-up measurements. Wilcoxon test, p<0.05 considered statistically significant.

Table 5. Sarcopenia status by treatment group.

	Ibrutinib			Other Standard Regimens		
Variables	Not Received N (%)	Received N (%)	p	Not Received N (%)	Received N (%)	p
SMI-1						
Non-Sarcopenic	9 (21.4)	2 (15.4)	0.486[b]	5 (41.7)	6 (14)	0.049[b]
Sarcopenic	33 (78.6)	11 (84.6)		7 (58.3)	37 (86)	
SMI-2						
Non-Sarcopenic	30 (71.4)	8 (61.5)	0.511[b]	9 (75)	29 (67.4)	0.753[b]
Sarcopenic	12 (28.6)	5 (38.5)		3 (25)	14 (32.6)	
TAMA-1						
Non-Sarcopenic	23 (54.8)	4 (30.8)	0.130[a]	6 (50)	21 (48.8)	0.941[b]
Sarcopenic	19 (45.2)	9 (69.2)		6 (50)	22 (51.2)	
TAMA-2						
Non-Sarcopenic	29 (69)	7 (53.8)	0.336[b]	9 (75)	27 (62.8)	0.511[b]
Sarcopenic	13 (31)	6 (46.2)		3 (25)	16 (37.2)	
HU-1						
Non-Sarcopenic	37 (88.1)	13 (100)	0.324[b]	9 (75)	41 (95.3)	0.030[b]
Sarcopenic	5 (11.9)	0 (0)		3 (25)	2 (4.7)	
HU-2						
Non-Sarcopenic	35 (83.3)	12 (92.3)	0.664[b]	10 (83.3)	37 (86)	0.563[b]
Sarcopenic	7 (16.7)	1 (7.7)		2 (16.7)	6 (14)	

[a]: Pearson Chi-Square test, [b]: Fisher's Exact test, p<0.05 considered statistically significant. 1: measurements at diagnosis; 2: follow-up measurements.

hematologic populations continues to limit the translation of these findings into routine clinical practice [5].

In patients with DLBCL receiving R-CHOP therapy, sarcopenia has been shown to significantly impair treatment tolerance and adversely affect both overall survival and progression-free survival [6]. The markedly increased rates of early mortality and treatment discontinuation among sarcopenic individuals suggest that sarcopenia may function as an active prognostic marker rather than a passive clinical finding. Similar associations between sarcopenia and treatment-related toxicity have been consistently reported in studies involving patients with solid tumors [7,8].

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, is widely used to treat chronic lymphocytic leukemia and mantle cell lymphoma. Musculoskeletal adverse effects associated with ibrutinib therapy are of particular relevance in the context of sarcopenia research. In a large analysis involving 1,178 patients, low-grade adverse events such as arthralgia, myalgia, and musculoskeletal pain were reported in a substantial proportion of patients receiving ibrutinib [9]. These symptoms typically occurred within the first year of treatment and resolved spontaneously in most cases and rarely necessitated treatment discontinuation or dose modification. While these findings suggest that ibrutinib-related musculoskeletal adverse effects are generally mild and manageable, whether ibrutinib exerts any direct effects on skeletal muscle tissue remains unclear.

In the present study, no significant changes in muscle mass parameters were observed in patients with hematologic malignancies treated with ibrutinib during follow-up. This finding may be related to the targeted mechanism of action of ibrutinib and its relatively favorable toxicity profile [10]. While

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Table 6. Comparison of clinical parameters between sarcopenic and non-sarcopenic patients.

	SMI-1			SMI-2		
Variables	Non-Sarcopenic N=11	Sarcopenic N=44	p	Non-Sarcopenic N=38	Sarcopenic N=17	p
Age	64.0 (51.0-74.0)	69.0 (50.0-87.0)	0.226[c]	66.5 (50.0-82.0)	70.0 (51.0-87.0)	0.325[c]
Age at diagnosis	63.0 (41.0-71.0)	64.0 (46.0-85.0)	0.424[c]	62.0 (46.0-77.0)	65.0 (41.0-85.0)	0.554[c]
WBC	16845.0 (6490.0-113000.0)	42860.0 (600.0-334000.0)	0.012[c]	26100.0 (600.0-334000.0)	37450.0 (3800.0-248000.0)	0.478[c]
LDH	219.5 (139.0-337.0)	232.0 (139.0-1129.0)	0.964[c]	214.0 (139.0-380.0)	271.0 (161.0-1129.0)	0.131[c]
Endocrine disease						
Absent	6 (54.5)	28 (63.6)	0.731[b]	21 (55.3)	13 (76.5)	0.135[a]
Present	5 (45.5)	16 (36.4)		17 (44.7)	4 (23.5)	
Stage at Diagnosis						
0	2 (18.2)	0 (0)		1 (2.6)	1 (5.9)	
1	4 (36.4)	11 (25)		11 (28.9)	4 (23.5)	
2	3 (27.3)	18 (40.9)	0.097[b]	13 (34.2)	8 (47.1)	0.416[b]
3	1 (9.1)	5 (11.4)		6 (15.8)	0 (0)	
4	1 (9.1)	10 (22.7)		7 (18.4)	4 (23.5)	
Mortality						
Absent	10 (90.9)	34 (77.3)	0.430[b]	36 (94.7)	8 (47.1)	<0.001[b]
Present	1 (9.1)	10 (22.7)		2 (5.3)	9 (52.9)	

[a]: Pearson Chi Square test, [b]: Fisher's Exact test,c: Mann Whitney U test. p<0.05 considered statistically significant. 1: measurements at diagnosis; 2: follow-up measurements. WBC: White Blood Cell Count, LDH: Lactate Dehydrogenase.

ibrutinib does not appear to exert a direct catabolic effect on skeletal muscle, the current data do not suggest a restorative effect on pre-existing sarcopenia. These findings underscore that the pathophysiology of sarcopenia cannot be attributed solely to pharmacologic toxicity but is instead shaped by multifactorial processes, including aging, physical inactivity, chronic inflammation, anorexia, and metabolic alterations [11].

Notably, despite the absence of significant changes in muscle mass, muscle density — expressed in Hounsfield Units — decreased significantly during follow-up. Muscle radiodensity is increasingly recognized as a surrogate marker of muscle quality and is closely associated with intramuscular fat infiltration (myosteatosis) [12,13]. Previous studies have demonstrated that reduced muscle density may reflect inflammatory and metabolic alterations within skeletal muscle and may occur independently of changes in muscle mass. Importantly, declines in muscle quality have been linked to impaired physical function, increased frailty, and adverse clinical outcomes, even in patients with preserved muscle mass [14]. In this context, our findings suggest that deterioration in muscle quality may occur in patients with hematologic malignancies who receive long-term therapy, despite relative stability in muscle quantity, and that this deterioration may have clinically relevant implications, particularly for older patients and those with comorbidities.

The lack of significant improvement in muscle mass among sarcopenic patients despite ibrutinib therapy suggests that pharmacological treatment alone may be insufficient to preserve muscle health in this population. Accordingly, management strategies focusing exclusively on oncologic treatment may not adequately address sarcopenia. Early identification of sarcopenic patients, combined with nutritional support, structured exercise programs, and, when appropriate, anabolic interventions, may improve overall clinical management and patient outcomes [15].

Few studies have evaluated the effects of ibrutinib on skeletal muscle parameters; to our knowledge, this study is among the first to investigate the association between ibrutinib therapy and sarcopenia-related parameters in patients with hematologic malignancies. An important limitation of this study is that sarcopenia assessment was based solely on CT-derived muscle parameters. Due to the retrospective design, direct assessments of muscle strength and physical performance, which are prioritized in the EWGSOP2 criteria, could not be performed. Although the retrospective design and relatively small sample size may limit the generalizability of our findings, the objective assessment of muscle area and muscle density using CT represents an important methodological strength and provides a valuable foundation for future large-scale prospective studies.

CONCLUSION

This study suggests that ibrutinib therapy is not associated with a significant deterioration in muscle mass in patients with hematologic malignancies. However, no improvement in pre-existing sarcopenia was observed during follow-up, indicating that sarcopenia may persist despite effective oncologic treatment. In addition, the observed decline in muscle

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density highlights the potential for deterioration in muscle quality even in the absence of measurable muscle mass loss. Together, these findings underscore the importance of considering sarcopenia-related parameters as part of a comprehensive clinical assessment. Although routine implementation in clinical practice cannot be recommended based on the present data alone, early identification of patients at risk and the use of supportive strategies, such as nutritional and physical interventions, may contribute to improved treatment tolerance and patient-centered outcomes. Further prospective studies are warranted to clarify the clinical implications of sarcopenia and changes in muscle quality during targeted therapies.

Ethics Committee Approval: The study was approved by the Samsun University Non-Invasive Clinical Research Ethics Committee (Decision No: 2025/10/17, Date: 14.05.2025).

Informed Consent: Because this study was conducted retrospectively using anonymized medical records, informed consent was not required.

Peer-review: Externally peer-reviewed.

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

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The impact of premenstrual syndrome, premenstrual dysphoric disorder, and coping with premenstrual symptoms on work-life

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MAIN POINTS

- Women with negative income have higher prevalence of PMS.
- Women who take time off from work due to PMS can better adjust their energy levels.
- The worse the working conditions, the more severe the premenstrual symptoms.
- Healthcare providers should screen all women for PMS.
- Health policy should provide group education on PMS and PMDD for hospitals and workplaces.

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ABSTRACT

Aim: This study investigated the impact of premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), and coping strategies for premenstrual symptoms on work life.

Materials and Methods: This study had a cross-sectional design. The sample consisted of 466 women with premenstrual symptoms. Data were collected online using the Premenstrual Symptoms Screening Tool and the Premenstrual Coping Measure.

Results: The prevalences of PMS and PMDD were 19.5% and 31.1%, respectively. Participants coped moderately well with premenstrual symptoms. Participants with higher incomes had significantly lower rates of PMS and PMDD than other participants. Employed women who did not take time off from work to cope with premenstrual symptoms, and who wanted the legal right to do so, were more likely to have severe premenstrual symptoms, PMS, and PMDD. Women experiencing PMDD who were unable to cope with premenstrual symptoms because they were unable to "communicate" and "adjust energy" experienced negative impacts on their work efficiency, productivity, and relationships with coworkers. A negative correlation was observed between working time per day and the "adjusting energy" subscale scores.

Conclusion: Women should be screened for premenstrual symptoms that affect work life. Policymakers should develop legislation to address premenstrual symptoms.

Keywords: Coping, Premenstrual syndrome, Premenstrual dysphoric disorder, Work life, Women's health

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INTRODUCTION

Most non-pregnant women of reproductive age menstruate every month [1]. However, most women experience emotional and physical symptoms during the luteal phase of the menstrual cycle (days 14-28) that negatively affect their quality of life. These symptoms include food cravings, bloating, weight gain, breast tenderness, gastrointestinal symptoms, skin problems, headache, fatigue, insomnia, changes in sexual desire, irritability, angry outbursts, crying spells, anxiety, and poor concentration [2]. A woman has premenstrual syndrome (PMS) if she has symptoms that 1- happen five days before her period, 2- occur for at least three menstrual cycles in a row, 3- end within four days after her period starts, and 4- keep her from enjoying or doing some of her normal activities [3]. In addition to these criteria, 5- if she has at least one of five or more cognitive-affective symptoms associated with distress, and 6- if premenstrual symptoms negatively affect social or work life, this is defined as premenstrual dysphoric disorder (PMDD) by the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) [4].

Nine out of ten women of reproductive age experience premenstrual symptoms. The prevalence of PMS is 20-40%, while that of PMDD is 2-8% [5]. One in ten women in France has PMS (12%), while almost all women in Iran have it (98%) [6]. The prevalence of PMS in Turkey is 52.2% [7].

We, as healthcare professionals, need to educate women about coping strategies for PMS because they experience premenstrual symptoms for a significant part of their lives. We first need to raise their awareness of PMS to help them cope with it. Healthcare professionals teach women how to engage in

PMS-specific self-screening and self-care practices (lifestyle changes, such as regular exercise, adequate and quality sleep, dietary modification, coping with stress, etc.) and refer them to non-pharmacological (cognitive behavioral therapy, complementary and alternative therapies) and pharmacological treatments [3, 8-10]. However, most women do not seek assistance in coping with PMS because they believe premenstrual symptoms are typical.

Most women in their late twenties to their mid-forties actively participate in working life. However, that is when PMS is most common [9-11]. It is known that women who work under high pressure and competition are more likely to experience PMS [12,13]. Women with PMS are more likely to experience reduced productivity, poor performance, and increased absenteeism. Reduced productivity during the premenstrual period is the most apparent labor loss [12,14].

It is essential to investigate the impact of PMS on work-life for two main reasons. First, the prevalence of PMS among women is relatively high. Second, more and more women are actively participating in the labor force [15]. Although there is a large body of research on the relationship between PMS and quality of life, researchers have not investigated the impact of coping with PMS on work life. Therefore, this study investigated the impact of PMS, PMDD, and coping with premenstrual symptoms on work-life.

Research questions

Q1. How do PMS and PMDD affect women's work lives?

Q2. How does coping with premenstrual symptoms affect women's work life?

Variables of research

Dependent variables: Severity of premenstrual symptoms (PMS/PMDD) and coping with premenstrual symptoms.

Independent variables: Demographic characteristics (e.g., age, education level, economic status, income) and work-related characteristics (e.g., employed (working with income), working sector, taking time off work due to PMS, and the impact of PMS on work efficiency or productivity and relationships with coworkers).

MATERIALS AND METHODS

The study was approved by the Karamanoglu Mehmetbey University Non-Interventional Clinical Research Ethics Committee (Decision No: 02-2022/12, Date: 30.03.2022). The study was conducted in accordance with the ethical principles set forth in the World Medical Association's Declaration of Helsinki. Participation was voluntary. Written informed consent was obtained from those who agreed to participate.

Research design and sampling

This cross-sectional study was conducted in Turkey from April 1 to July 30, 2022. The study used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [16]. The sample size was calculated using the formula "the sample size from an unknown population" [$n = t^2.p.q / d^2$] [17], based on the prevalence of PMS [52%] reported by Erbil and Yücesoy [7]. The results indicate that a sample of 352 would be large enough to detect significant differences. The final sample consisted of 466 women. Participants were recruited using the snowball sampling method. However, data collection continued beyond this number to compensate for potentially incomplete responses and enhance the statistical power of subgroup analyses. Consequently, the final sample consisted of 466 women.

Criteria for inclusion and exclusion

The eligibility criteria were as follows: 1. Being between 18 and 49 years of age (in the reproductive period), 2. Having premenstrual symptoms (marking at least one of the first 14 items of the Premenstrual Symptoms Screening Tool), 3. Having regular menstrual periods every 21 to 35 days [1], 4. Having no pregnancy or lactation in the past 12 months, 5. Not being on hormonal contraceptives, 6 Not undergoing medical treatment for chronic disease, 7. Not having mental health problems (anxiety disorder, depression, severe psychosocial problems, etc.), and 8. Volunteering.

In the society where the research was conducted, a worker is defined as "a real person who works on the basis of an employment contract," and a civil servant is defined as "a person who is assigned to perform primary and permanent public services carried out by the state and other public legal entities in accordance with the principles of general administration" [18,19].

Procedure

Participants meeting the inclusion criteria were selected through snowball sampling because of its convenience, targeted reach, and purposive nature. We reached women across Turkey via social media platforms (WhatsApp, Twitter, Instagram, Facebook, Pinterest, and Snapchat). Data were collected online using "Google Forms" from women who met all the inclusion criteria for the study. The inclusion and exclusion criteria were explained in the voluntary consent form, which was included at the beginning of the data collection forms. Women who did not meet the criteria were instructed not to complete the forms. Women who did not meet the criteria were warned not to complete the forms. Snowball sampling was employed due to the absence of a comprehensive sampling frame for women experiencing varying levels of premenstrual symptoms across Turkey and the sensitive and personal nature of the study topic. This approach facilitated access to eligible participants who might otherwise be difficult to reach through probability-based sampling methods, particularly in an online data collection context.

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Data collection tool

The researchers prepared the Inclusion Criteria Questionnaire. The form contained questions regarding the study's inclusion and exclusion criteria and was used to identify women eligible for participation. Participants who answered yes to all of the study's inclusion criteria and no to all of the exclusion criteria were instructed to complete the remaining data collection forms. Those who gave different answers were instructed not to continue participating in the study.

The Individual Information Form (IIF) was prepared by the researchers [12,20-23]. It consisted of 14 items covering women's sociodemographic and work-life characteristics.

The Premenstrual Symptoms Screening Tool (PSST) was developed by Steiner, Macdougall, and Brown to identify premenstrual symptoms, PMS, and PMDD [24]. The tool consists of 22 items : 14 four-point Likert-type items on premenstrual symptoms; 5 four-point Likert-type items on (1) work efficiency or productivity, (2) relationships with coworkers, (3) relationships with family, (4) social life activities, and (5) home responsibilities; and 3 items that can be answered "Yes" or "No," which are not included in the calculation used for the diagnosis of PMS and PMDD, which determines the severity of premenstrual symptoms and the extent to which they affect life. It was adapted to Turkish by Özdel et al. The Turkish version has a Cronbach's alpha of 0.92 [25], which was 0.91 in the present study.

The Premenstrual Coping Measure (PMCM) was developed by Read et al. [26] and adapted into Turkish by Abay and Kaplan [27]. The measure consists of 27 items rated on a five-point Likert-type scale (ranging from "doesn't apply to me" to "almost always applies to me"). The total score is not considered in the evaluation. Higher subscale scores indicate less severe premenstrual symptoms and coping behaviors. The instrument comprises five subscales assessing methods of coping with premenstrual symptoms: "avoiding harm," "awareness and acceptance of premenstrual change," "adjusting energy," "self-care," and "communicating. Subscales of the Turkish version have Cronbach's alpha values of 0.88, 0.89, 0.75, 0.83, and 0.86, respectively [27]. In the present study, the subscales "avoiding harm," "awareness and acceptance of premenstrual change," "adjusting energy," "self-care," and "communicating" had Cronbach's alpha values of 0.89, 0.87, 0.77, 0.85, and 0.89, respectively.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, IBM, version 22, Chicago, IL, USA) with a significance level of 0.05. Number (n), percentage (%), mean, and standard deviation (SD) were used for descriptive statistics. The Kolmogorov-Smirnov test was used to assess normality. The data were analyzed using independent-samples t-tests, one-way analyses of variance (ANOVAs), Chi-square tests, and Pearson's correlation coefficients. The Bonferroni-corrected dependent-groups t-test was used for post hoc comparisons.

RESULTS

Sociodemographic and work-life characteristics

The sample consisted of 466 Turkish women. Participants had a mean age of 30.23 ± 8.021 years (min = 18, max = 53). More than half of the participants had bachelor's degrees (60.1%). Less than half of the participants were married (43.6%). More than a quarter of the participants had children (32.8%). More than half of the participants were employed (58.4%). 22.1% of the participants worked in shifts (9.10 ± 5.587 hours). Most employed participants reported that they did not take time off from work to cope with premenstrual symptoms (81.6%) and that they wanted legal rights to take such time off (78.7%). Other sociodemographic and work-life characteristics are presented in Table 1.

PMS/PMDD and coping with premenstrual symptoms

Table 2 shows the prevalence, severity, and effects of premenstrual symptoms (PMS/PMDD). Nearly half of the participants (49.4%) had premenstrual symptoms. One in five participants (19.5%) had moderate to severe PMS, while three in ten (31.1%) had PMDD. 42.9% of participants had severe physical premenstrual symptoms. A quarter of participants reported that premenstrual symptoms severely affected their work efficiency or productivity (24.2%). Participants coped moderately with premenstrual symptoms. The PMCM subscale scores are included in Table 2.

Work-life characteristics and PMS/PMDD

Participants with higher income had significantly lower rates of premenstrual symptoms, PMS, and PMDD than participants with lower income ($p < .05$). Those who did not take time off work to cope with premenstrual symptoms were more likely to have severe premenstrual symptoms, including PMS and PMDD, than those who did. In addition, among employed women, those who requested legal leave to cope with premenstrual symptoms were more likely to have severe symptoms, PMS, and PMDD than those who did not request leave ($p < .05$). Moreover, as the severity of premenstrual symptoms' effects on work efficiency or productivity increased, the prevalence of PMDD increased ($p < .05$). The prevalence of PMDD was higher among those who experienced moderate effects of premenstrual symptoms on relationships with coworkers ($p < .05$) (Table 3).

Work-life characteristics and coping with premenstrual symptoms

Economic status affected participants' PMCM "communicating" subscale scores ($F = 4.773$, $p = .009$). The post hoc analysis showed that participants with lower incomes had significantly poorer communication scores on the PMCM than those with higher incomes. Employed participants had a

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Table 1. Distribution of women by sociodemographic and work life characteristics (n=466).

Characteristics	n	%
Age, mean (SD), years	30.23 (8.021)	
Education		
High school	48	10.3
Bachelor's degrees	280	60.1
Postgraduate education	138	29.6
Marital status		
Married	203	43.6
Single	263	56.4
Having children		
Yes	153	32.8
No	313	67.2
Family type		
Nuclear family	411	88.2
Extended family	36	7.7
Other	19	4.1
Economic status		
Lower income	121	26.0
Middle income	278	59.7
Higher income	67	14.4
Employed (working with income)		
Yes	272	58.4
No	194	41.6
Working sector[a]		
Government	187	68.8
Private	85	31.3
Type of work[a]		
Daytime work	197	72.4
Shift / on-duty work	60	22.1
Home-office	15	5.5
Working time, mean (SD), hours/day	9.10 (5.587)	
Take time off from work to cope with premenstrual symptoms[a]		
Yes	50	18.4
No	222	81.6
Want to have legal rights to take time off to cope with premenstrual symptoms[a]		
Yes	214	78.7
No / not necessary	58	21.3

SD: Standard deviation, n: number, %: percentage. [a] Since the evaluation was made on working women (n=272), the n value was not evaluated over 100%.

significantly higher PMCM "communicating" subscale score than their non-working with income counterparts (t = 2.093, p = .038) (Table 4).

A positive correlation was observed between working time per day and PMCM "awareness and acceptance of premenstrual change" subscale scores (r = 0.118, p = .050). Working time per day was negatively correlated with PMCM "adjusting energy" subscale scores (r = -0.115, p = .049) (Table 4).

Participants who took time off from work due to premenstrual symptoms had significantly higher PMCM "adjusting energy" subscale scores than those who did not (t = 4.262, p = .000). Participants who desired legal rights to take time off to cope with premenstrual symptoms had significantly higher PMCM "adjusting energy" (t = 4.001, p = .000) and "self-care" (t = 2.007, p = .046) subscale scores than those who did not (Table 4).

PMCM subscale scores for "awareness and acceptance of premenstrual change," "communicating," and "adjusting energy" differed significantly according to the extent to which work efficiency or productivity was affected by premenstrual symptoms (F = 7.692, p = .000; F = 4.253, p = .006; F = 24.193, p = .000, respectively). Post hoc analyses revealed that participants whose work efficiency or productivity was moderately or severely affected by premenstrual symptoms

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Table 2. Distribution of women by results of the PSST and the PMCM subscale scores (n=466).

PSST results	n	%
Premenstrual symptoms	230	49.4
Moderate/severe PMS	91	19.5
PMDD	145	31.1

Premenstrual symptoms	Not at all n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Anger/irritability	13 (2.8)	95 (20.4)	214 (45.9)	144 (30.9)
Anxiety/tension	17 (3.6)	119 (25.5)	209 (44.8)	121 (26.0)
Tearful/increased sensivity to rejection	54 (11.6)	80 (17.2)	176 (37.8)	156 (33.5)
Depressed mood/hopelessness	46 (9.9)	92 (19.7)	184 (39.5)	144 (30.9)
Decreased interest in work activities	58 (12.4)	116 (24.9)	201 (43.1)	91 (19.5)
Decreased interest in home activities	58 (12.4)	116 (24.9)	201 (43.1)	91 (19.5)
Decreased interest in social activities	62 (13.3)	107 (23.0)	209 (44.8)	88 (18.9)
Difficulty concentrating	90 (19.3)	126 (27.0)	166 (35.6)	84 (18.0)
Fatigue/lack of energy	24 (5.2)	85 (18.2)	172 (36.9)	185 (39.7)
Overeating/food cravings	57 (12.2)	101 (21.7)	143 (30.7)	165 (35.4)
Insomnia	199 (42.7)	102 (21.9)	123 (26.4)	42 (9.0)
Hypersomnia (needing more sleep)	129 (27.7)	105 (22.5)	128 (27.5)	104 (22.3)
Feeling overwhelmed or out of control	88 (18.9)	110 (23.6)	140 (30.0)	128 (27.5)
Physical symptoms: breast tenderness, headaches, joint/muscle pain, bloating, weight gain	22 (4.7)	67 (14.4)	177 (38.0)	200 (42.9)
Effects of premenstrual symptoms	**Not at all n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Work efficiency or productivity	37 (7.9)	115 (24.7)	201 (43.1)	113 (24.2)
Relationships with coworkers	91 (19.5)	133 (28.5)	189 (40.6)	53 (11.4)
Relationships with family	52 (11.1)	137 (29.4)	189 (40.6)	88 (18.9)
Social life activities	40 (8.6)	145 (31.1)	176 (37.8)	105 (22.5)
Home responsibilities	48 (10.3)	126 (27.0)	183 (39.3)	109 (23.4)

PMCM subscales (Coping with premenstrual symptoms)	Mean ± SD (min-max)
Avoiding harm	21.36 ± 6.098 (7-35)
Awareness and acceptance of premenstrual change	35.61 ± 5.662 (11-45)
Adjusting energy	9.13 ± 2.979 (3-15)
Self-care	13.72 ± 3.660 (4-20)
Communicating	12.01 ± 4.106 (4-20)

PSST: Premenstrual Symptoms Screening Tool, PMS: Premenstrual Syndrome, PMDD: Premenstrual Dysphoric Disorder, PMCM: Premenstrual Coping Measure, n: number, %: percentage, SD: Standard deviation.

had significantly lower scores on the PMCM "awareness and acceptance of premenstrual change" and "communicating" subscales and significantly higher scores on the "adjusting energy" subscale, compared with those reporting no or mild impact. PMCM "adjusting energy" (F = 19.789, p = .000) and "communicating" (F = 3.354, p = .019) subscale scores differed significantly depending on the extent to which relationships with coworkers were affected by premenstrual symptoms. When the level of impact of premenstrual symptoms on relationships with coworkers (not at all, mild, moderate, and severe) was considered, post hoc analyses indicated that the no-impact group differed significantly from all other groups, and that the mild- and moderate-impact groups each differed significantly from the no-impact and severe-impact groups in terms of PMCM "adjusting energy" and "communicating" subscale scores (Table 4).

DISCUSSION

This study focused on women with premenstrual symptoms and investigated how they experienced PMS or PMDD and coped with these symptoms in the workplace. Several studies show that women with premenstrual symptoms are more likely to suffer from low productivity, poor work quality and performance, and high rates of absenteeism [21,28,29]. PMS causes impaired workplace functioning in at least 3-8% of women of reproductive age [30]. Women with PMS experience high rates of absenteeism and low productivity [14,31]. PMS also causes some women to experience high sensitivity to external stress and emotions [26]. Moreover, work-related stress exacerbates premenstrual symptoms [21,32]. Our results showed that nine in ten women with premenstrual symptoms — and almost all women with PMS and PMDD — experienced reduced work efficiency or productivity. The Results also showed that harsh working conditions affected their experience of PMS or PMDD. In other words, work-related stress exacerbates premenstrual symptoms and vice versa. Therefore, we should teach women strategies to cope with premenstrual symptoms to break the vicious cycle. Thus, employers can also avoid the average economic loss (USD 4,333 per person per year) caused by PMS [28].

Our results showed that students and healthcare profession-

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Table 3. Distribution of women's work life characteristics by premenstrual symptoms, PMS, PMDD experience (n=466).

Characteristics	Premenstrual symptoms n (%)	Moderate/severe PMS n (%)	PMDD n (%)	Analysis
Education				
High school	33 (14.3)	6 (6.6)	9 (6.2)	X^2 = 8.441
Bachelor's degrees	129 (56.1)	58 (63.7)	93 (64.1)	p = .077
Postgraduate education	68 (29.6)	27 (29.7)	43 (29.7)	
Economic status				
Lower income	44 (9.1)	28 (30.8)	49 (33.8)	X^2 = 11.920
Middle income	147 (63.9)	52 (57.1)	79 (54.5)	p = .018*
Higher income	39 (17.0)	11 (12.1)	17 (11.7)	
Employed (working with income)				
Yes	143 (62.2)	48 (52.7)	81 (55.9)	X^2 = 2.929
No	87 (37.8)	43 (47.3)	64 (44.1)	p = .231
Working sector[a]				
Government	95 (66.4)	35 (72.9)	57 (70.4)	X^2 = 0.844
Private	48 (33.6)	13 (27.1)	24 (29.6)	p = .656
Type of work[a]				
Daytime work	103 (72.0)	33 (68.8)	61 (75.3)	X^2 = 2.059
Shift / on-duty work	30 (21.0)	13 (27.1)	17 (21.0)	p = .725
Home-office	10 (7.0)	2 (4.2)	3 (3.7)	
Take time off from work to cope with premenstrual symptoms[a]				
Yes	16 (11.2)	6 (12.5)	28 (34.6)	X^2 = 20.183
No	127 (88.8)	42 (87.5)	53 (65.4)	p = .000*
Want to have legal rights to take time off to cope with premenstrual symptoms[a]				
Yes	100 (69.9)	40 (83.3)	74 (91.4)	X^2 = 14.906
No / not necessary	43 (30.1)	8 (16.7)	7 (8.6)	p = .001*
Effects of premenstrual symptoms on work efficiency or productivity				
Not at all	35 (15.2)	1 (1.1)	1 (0.7)	
Mild	99 (43.0)	15 (16.5)	1 (0.7)	X^2 = 248.996
Moderate	74 (32.2)	72 (79.1)	55 (37.9)	p = .000*
Severe	22 (9.6)	3 (3.3)	88 (60.7)	
Effects of premenstrual symptoms on relationships with coworkers				
Not at all	80 (34.8)	6 (6.6)	5 (3.4)	
Mild	84 (36.5)	30 (33.0)	19 (13.1)	X^2 = 162.871
Moderate	57 (24.8)	54 (59.3)	78 (53.8)	p = .000*
Severe	9 (3.9)	1 (1.1)	43 (29.7)	

PMS: Premenstrual Syndrome, PMDD: Premenstrual Dysphoric Disorder, n: number, %: percentage, X^2: Ci-spuare test. a n = 272 (Employed women), *p<0.05.

als had higher rates of premenstrual symptoms (PMS) and PMDD than other groups. Students exhibit a high prevalence of premenstrual symptoms due to various factors. First, they reside in dormitories, separate from their families. Second, they experience high stress due to their exams and have difficulty managing it. Healthcare professionals have a high rate of premenstrual symptoms, probably because they have been working day and night under stress since the onset of the pandemic [33]. For example, nurses with PMS experience more work-related stress, and PMS reduces the quality of their work life [34]. Our results pointed to a negative correlation between working time per day and "adjusting energy," suggesting that women who work longer hours have more difficulty adjusting their energy, which is necessary to cope with premenstrual symptoms. Participants who were workers had the lowest "self-care" subscale score. This may not be surprising because workers labor under conditions as harsh as those experienced by nurses in Turkey.

The severity of premenstrual symptoms was associated with several work outcomes, such as work efficiency or productivity, relationships with colleagues, taking time off from work, and asserting legal rights to take time off to cope with pre-

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Table 4. The relationship between women's work life characteristics and the PMCM subscale scores (n=466).

Work life characteristics		PMCM subscales				
		Avoiding harm Mean ± SD	Awareness and acceptance of premenstrual change Mean ± SD	Adjusting energy Mean ± SD	Self-care Mean ± SD	Communicating Mean ± SD
Economic status	Lower income	21.18 ± 6.075	34.76 ± 5.381	9.45 ± 2.820	13.84 ± 3.580	11.12 ± 3.918
	Middle income	21.51 ± 6.049	35.73 ± 5.761	9.04 ± 3.009	13.77 ± 3.510	12.19 ± 4.098
	Higher income	21.09 ± 6.414	36.61 ± 5.616	8.93 ± 3.130	13.31 ± 4.380	12.90 ± 4.240
Analysis		F = 0.198, p = .821	F = 2.494, p = .084	F = 0.994, p = .371	F = 0.503, p = .605	F = 4.773, p = .009*
Working sector	Government agency	21.81 ± 6.128	35.71 ± 5.723	9.17 ± 3.164	13.69 ± 3.713	12.62 ± 3.957
	Private sector	21.11 ± 6.069	35.91 ± 5.713	9.01 ± 2.876	13.07 ± 3.634	11.79 ± 4.290
Analysis		t = 0.888, p = .379	t = -0.267, p = .789	t = 0 .397, p = .692	t = 1.294, p = .198	t = 1.518, p = .131
Type of work	Daytime work	21.61 ± 6.397	35.82 ± 5.881	9.07 ± 3.179	13.31 ± 3.774	12.28 ± 4.195
	Shift / on-duty work	21.30 ± 5.524	35.80 ± 5.364	9.15 ± 2.686	14.07 ± 3.546	12.63 ± 3.849
	Home-office	22.53 ± 4.373	35.00 ± 5.000	9.60 ± 3.247	13.67 ± 3.109	12.33 ± 3.478
Analysis		F = 0.246, p = .782	F = 0.143, p = .867	F = 0.210, p = .811	F = 0.983, p = .376	F = 0.173, p = .841
Employed (working with income)	Yes	21.59 ± 6.107	35.77 ± 5.710	9.12 ± 3.072	13.50 ± 3.693	12.36 ± 4.074
	No	21.04 ± 6.087	35.38 ± 5.601	9.15 ± 2.850	14.04 ± 3.600	11.53 ± 4.111
Analysis		t = 0.961, p = .337	t = 0.729, p = .466	t = -0.134, p = .894	t = -1.57, p = .115	t = 2.168, p = .031*
Working time, mean (SD), hours/day Analysis		r = 0.020, p = .740	r = 0.118, p = .050*	r = -0.115, p = .049*	r = -0.079, p = .192	r = 0.034, p = .572
Take time off from work to cope with premenstrual symptoms	Yes	21.42 ± 6.091	35.12 ± 5.546	10.74 ± 2.891	13.84 ± 3.814	11.98 ± 4.740
	No	21.63 ± 6.124	35.91 ± 5.749	8.75 ± 2.999	13.42 ± 3.670	12.45 ± 3.916
Analysis		t = -0.220, p = .826	t = -0.888, p = .375	t = 4.262, p = .000*	t = 0.728, p = .467	t = -0.730, p = .466
Want to have legal rights to take time off to cope with premenstrual symptoms	Yes	21.72 ± 6.026	35.66 ± 5.652	9.50 ± 2.910	13.73 ± 3.587	12.36 ± 4.135
	No	21.12 ± 6.429	36.17 ± 5.953	7.72 ± 3.276	12.64 ± 3.977	12.34 ± 3.878
Analysis		t = 0.662, p = .509	t = -0.607, p = .544	t = 4.001, p = .000*	t = 2.007, p = .046*	t = 0.033, p = .974
Effects of premenstrual symptoms in work efficiency or productivity	Not at all	19.59 ± 7.998	37.46 ± 5.362	6.81 ± 3.324	13.14 ± 4.104	13.62 ± 4.172
	Mild	21.63 ± 5.654	37.35 ± 4.854	8.14 ± 2.721	13.83 ± 3.747	12.70 ± 3.885
	Moderate	21.81 ± 5.742	34.84 ± 5.968	9.31 ± 2.654	13.59 ± 3.658	11.61 ± 4.040
	Severe	20.88 ± 6.382	34.60 ± 5.472	10.59 ± 2.859	14.04 ± 3.429	11.51 ± 4.245
Analysis		F = 1.715, p = .163	F = 7.692, p = .000*	F = 24.193, p = .000*	F = 0.730, p = .535	F = 4.253, p = .006*
Effects of premenstrual symptoms in relationships with coworkers	Not at all	20.91 ± 7.017	37.00 ± 5.461	7.27 ± 3.030	13.54 ± 3.953	12.92 ± 4.078
	Mild	21.70 ± 5.018	35.57 ± 5.220	9.09 ± 2.633	13.57 ± 3.534	12.23 ± 3.933
	Moderate	21.69 ± 6.074	35.13 ± 6.024	9.67 ± 2.756	13.76 ± 3.670	11.75 ± 4.100
	Severe	20.11 ± 6.885	35.00 ± 5.488	10.51 ± 3.061	14.26 ± 3.454	10.85 ± 4.330
Analysis		F = 1.229, p = .299	F = 2.508, p = .580	F = 19.789, p = .000*	F = 0.545, p = .652	F = 3.354, p = .019*

PMCM: The Premenstrual Coping Measure, SD: Standard deviation, F: One way analysis of variance (ANOVA), t: Independent samples t-tests, r: Pearson's correlation coefficients, *p<0.05.

menstrual symptoms. Participants with premenstrual symptoms experienced mildly reduced work efficiency or productivity. Participants with PMS exhibited moderately low work efficiency (productivity). Participants with PMDD experienced severely reduced work efficiency or productivity. Participants with premenstrual symptoms had mildly poor relationships with their coworkers, whereas those with PMS and PMDD had moderately poor ones. Borenstein et al. also

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reported that women with PMS and PMDD suffered from poor productivity and impaired personal relationships [14]. Hardy and Hardie determined that women with premenstrual symptoms experienced difficulty concentrating, self-doubt, fatigue, social isolation, and outbursts of anger [21]. Since these symptoms cause absenteeism, women feel guilty and engage in over compensatory behaviors such as working longer hours and taking work home after the symptoms have disappeared. Women occupy a more disadvantaged position in working life. Women are considered 'unstable and uncontrollable' during menstruation, pregnancy, motherhood, and menopause [20].

Our results showed that although eight out of ten working participants wanted to be legally entitled to take time off to cope with premenstrual symptoms, only two out of ten took time off because of premenstrual symptoms. Research also shows that very few women take time off from work to cope with premenstrual symptoms, because they view the challenges these symptoms cause as personal issues and feel ashamed of them. They also fear that their managers (primarily men) might decline their demands or stigmatize them [12].

Our results showed that participants who took time off from work due to premenstrual symptoms reported higher energy levels than those who did not. However, our results showed that more than half of participants with PMDD did not take any time off from work. Hardy and Hardie reported that this cycle experienced every month by women who cannot cope with PMS causes them to leave the workforce and give up their careers voluntarily or involuntarily [21]. Therefore, employers, managers, policymakers, and health professionals must be cognizant of PMS. More importantly, women should be aware of premenstrual symptoms and believe they are manageable [26]. Wyatt et al. found that more than a quarter of women with PMS and PMDD considered premenstrual symptoms normal, as they believed them to be an inevitable part of being a woman [35]. Our results may support this situation and indicate that women who were unaware of premenstrual changes or who had difficulty accepting them experienced poorer work efficiency or productivity and more impaired relationships with coworkers.

Limitations

Women's experience of PMS/PMDD was assessed by self-report using the PSST; a limitation of the study is that a clinical evaluation could not be performed. Moreover, the results are limited to Turkish women. The online nature of data collection and the use of snowball sampling may also have limited the generalizability of the results.

CONCLUSION

As a result, PMS and PMDD are major health problems that cause difficulties in occupational functioning. Harsh working conditions and stress exacerbate premenstrual symptoms, making it harder for women to cope. Therefore, it is recommended that managers and employers learn more about women's experiences of PMS and PMDD and provide support and resources to women in need. Turkish policymakers should enact legislation granting women legal leave to cope with premenstrual symptoms. Healthcare professionals should screen all women who present to a health center for premenstrual symptoms. Healthcare organizations and workplaces should offer group training programs on coping with PMS and PMDD. Future research should be conducted prospectively using qualitative methods and involving women, employers, and managers. The physical and psychological conditions of working environments for women with PMS/PMDD should be investigated.

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Ethics Committee Approval: The study was approved by the Karamanoglu Mehmetbey University Non-Interventional Clinical Research Ethics Committee (Decision No: 02-2022/12, Date: 30.03.2022).

Informed Consent: Written informed consent was obtained from those who agreed to participate.

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Associations between screen exposure, pain, postural alignment, physical activity, and quality of life in young adults: A cross-sectional study

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MAIN POINTS

- Increased screen exposure is significantly associated with higher levels of pain and neck disability in young adults.
- High screen use is linked to postural deterioration, reduced spinal flexibility, and lower physical activity levels.
- Excessive screen time adversely affects both the physical and mental components of quality of life, underscoring the need for preventive strategies.

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ABSTRACT

Aim: To examine the associations between screen exposure and pain, postural alignment, spinal flexibility, physical activity level, and quality of life in young adults.

Materials and Methods: Of the 283 young adults included in the study, 213 (75.3%) were female and 70 (24.7%) were male. Screen exposure was evaluated using the Screen Time Exposure Form, while addiction levels were assessed using the Smartphone Addiction Scale–Short Form and the Young Internet Addiction Test–Short Form. Pain and disability levels were measured using the Numeric Pain Rating Scale (NPRS) and the Neck Disability Index (NDI). Postural assessment was performed using cranio-cervical angle (CCA) measurement and a scoliometer, while spinal flexibility was determined using the forward reach test and the lateral bending test. Physical activity levels were assessed using the Short Form of the International Physical Activity Questionnaire (IPAQ), and quality of life was evaluated using the Short Form-36 Quality of Life Survey (SF-36).

Results: Of the participants, 4.2% had very low, 37.1% low, 42.1% high, and 16.6% very high screen exposure. Strong, statistically significant positive correlations were found between screen exposure and both the NDI and NPRS ($p<0.05$). In contrast, strong negative correlations were observed between screen exposure and IPAQ scores, and between screen exposure and the physical and mental health subscales of the SF-36 ($p<0.05$). Additionally, screen exposure showed strong negative correlations with CCA and with the results of the trunk rotation, forward reach, and lateral bending tests ($p<0.05$).

Conclusion: Increased screen exposure in young adults was significantly associated with higher pain and neck disability, postural deterioration, reduced spinal flexibility, lower physical activity levels, and decreased quality of life. These findings highlight the importance of preventive strategies aimed at limiting excessive screen use.

Keywords: Screen exposure, Posture, Physical activity, Quality of life

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INTRODUCTION

With the rapid advancement of digital technologies, the duration of smartphone, tablet, and computer use has markedly increased, particularly among young adults [1]. This trend is further amplified by the growing digitalization of both academic and social environments. The World Health Organization and multiple international studies report that daily screen time among young individuals has doubled in recent years, with potentially substantial consequences for behavioral, physical, and psychosocial health [2]. In this context, young adults are considered a high-risk population owing to prolonged sedentary behavior and intensive screen exposure [3].

Recent national studies indicate that smartphone use has become highly prevalent among adults in Turkey, with a substantial proportion reporting prolonged daily usage, as evidenced by research showing that 85.6% of young adults have used a smartphone for at least three years and 77.3% use it for more than four hours per day [4]. Spending long periods of time in front of screens, especially smartphones and the

internet, has become a current health issue affecting all segments of society, leading to many negative physical and mental effects [5]. Increased screen time in young adults is identified as a significant risk factor for the development of musculoskeletal disorders [6]. Spending long periods in front of a screen contributes to the development of poor posture, inadequate ergonomics, neck pain, and other related symptoms [7]. Increased screen time, especially in the cervical region, leads to tension in the muscles, triggering pain and causing individuals to adopt different head positions, thus predisposing them to postural disorders [8]. In a study, an increase in daily screen time was reported to be associated with a significant increase in the risk of neck, shoulder, and back pain [9]. Spinal flexibility is a fundamental determinant of spinal health, as it ensures appropriate load distribution and preserves normal biomechanical function of the vertebral segments. However, prolonged screen exposure and sedentary behaviors have been proposed to reduce spinal flexibility, lead to impaired postural control, and increase susceptibility to musculoskeletal pain and functional limitations [10, 11].

Increased screen exposure is closely associated with reduced physical activity levels in young adults. Prolonged screen use, a significant indicator of sedentary behavior, reduces daily energy expenditure and limits the time dedicated to physical activity. This situation not only negatively affects musculoskeletal health but can also lead to adverse outcomes for cardiovascular endurance, muscle strength, and overall functionality [12]. Low levels of physical activity affect not only physical performance but also various dimensions of quality of life. Studies point out that increased screen time among young adults may be associated with lower quality of life, reduced physical functioning, and higher levels of psychosocial problems [13].

Despite the growing body of evidence demonstrating the independent effects of screen exposure on musculoskeletal symptoms, physical activity, and quality of life, most existing studies have focused on a limited number of outcome variables and have evaluated these relationships separately [14,15]. There is a lack of comprehensive research simultaneously examining pain, postural alignment, spinal flexibility, physical activity level, and quality of life within the same population. Moreover, few studies have integrated objective postural and flexibility measurements with subjective health-related quality of life and addiction-related parameters [16].

Understanding the multidimensional impact of screen exposure is crucial for identifying early risk factors and developing preventive strategies aimed at reducing long-term musculoskeletal and psychosocial problems in young adults [17]. A holistic evaluation that includes biomechanical, behavioral, and psychosocial components may provide stronger evidence for clinical interventions and public health policies targeting excessive screen use [18].

Therefore, using reliable and validated measurement tools, this study was designed to investigate the relationships between screen exposure and pain intensity, neck disability, postural alignment, spinal flexibility, physical activity level, and quality of life in young adults. In this context, it has been hypothesized that higher screen exposure and smartphone/internet addiction among young adults may be associated with (i) increased pain intensity and neck disability; (ii) poorer postural alignment and reduced spinal flexibility; (iii) lower physical activity levels; and (iv) lower quality of life.

MATERIALS AND METHODS

Study design and ethical approval

This research was designed as an observational, cross-sectional study. This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional observational studies. Before starting the study, ethical approval was obtained from the Karamanoğlu Mehmetbey University Health Sciences Scientific Research and Publication Ethics Committee (Decision No: 04-2024/55, Date: 18.12.2024). The ethical principles outlined in the Declaration of Helsinki were adhered to throughout the research process. All participants were informed in detail about the study, and voluntary written and verbal consent was obtained before their inclusion in the research.

Participants

A total of 283 young adults aged 18–35 who volunteered to participate in the study and had no history of chronic diseases (orthopedic, neurological, cardiac, rheumatological, etc.) were included. Individuals who were not volunteers, who had chronic illnesses, who had a history of regular medication use, or who had undergone spinal surgery or any surgical procedure affecting the musculoskeletal system in the past year were excluded from the study. A non-probability convenience sampling approach was employed, and participants were selected from among young adults who met the inclusion criteria and provided informed consent during the data collection period. Our study was carried out using the snowball sampling method [19]. Initially, researchers reached out to individuals residing in Karaman province who met the inclusion criteria and were identified among their friends, relatives, and work colleagues, inviting them to participate in the study. The sociodemographic information, records and assessments of individuals who volunteered to participate in the study and met the inclusion criteria were performed at the Karamanoğlu Mehmetbey University Faculty of Health Sciences Department of Physical Therapy and Rehabilitation laboratory. To assess screen exposure, the Screen Time Exposure Form, the Smartphone Addiction Scale-Short Form (SAS-SF), and the Young Internet Addiction Test-Short Form (YIAT-SF) were used. Pain and disability status were assessed using the Numeric Pain Rating Scale (NPRS) and the Neck Disability Index (NDI). The cranio-cervical angle (CCA) measurement and a scoliometer were used to assess

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postural alignment. Spinal flexibility was assessed using the forward reach and lateral bending tests. Physical activity levels and quality of life were assessed using the Short Form of the International Physical Activity Questionnaire (IPAQ) and the Short Form-36 Quality of Life Survey (SF-36), respectively.

Sample size

In this study, the sample size was predetermined based on a correlation analysis of the relationship between levels of telephone and internet dependency and the CCA. Previous studies [5] conducted in similar age groups have generally reported low correlations (small effect sizes) between screen or smartphone use and postural parameters; therefore, the expected correlation coefficient in this study was set at r = 0.18, representing a small effect. Under this assumption, and with a two-tailed significance level of $\alpha = 0.05$ and a statistical power of 80% ($1-\beta = 0.80$), the required sample size for the correlation analysis was calculated using G*Power 3.1 software. The calculations indicated that at least 240 participants were needed to detect a statistically significant relationship. To account for potential missing data, exclusions, and non-response, an estimated dropout rate of 15% was assumed, resulting in a total of 283 individuals included in the study.

Data collection tools

The primary outcome measure of the study was the screen-exposure score, while the secondary outcome measures were smartphone- and internet-addiction scores, pain intensity, neck disability, postural alignment, spinal flexibility, physical activity level, and quality of life.

Screen time exposure form

To determine screen exposure, the time participants spent in front of various digital devices in their daily lives was recorded from their self-reports. The activities examined within the scope of the evaluation were defined as (i) working on a computer or tablet, (ii) playing games on a computer or tablet, (iii) Internet use, (iv) watching video or television content on a computer or tablet, and (v) using a smartphone. For each activity, individuals were asked to select one of six time ranges, ranging from "I don't use it at all" to "more than 8 hours a day."Scores corresponding to time intervals range from 0 and 5. The total score participants received from all activities was calculated to reflect their overall level of screen exposure, and these total scores were classified into four levels: "very low," "low," "high," and "very high" [20].

Smartphone Addiction Scale-Short Form (SAS-SF)

To determine participants' tendencies toward smartphone addiction, the Turkish version of the SAS-SF, developed by Kwon et al. [21], was used. This ten-item scale includes a scoring system ranging from 1 to 6 for each item. The total score obtainable from the scale ranges from 10 to 60, and an increase in the score indicates a higher risk of smartphone addiction. SAS-SF has been adapted into Turkish by Şata et al. [22], and the Turkish version has been found to be valid and reliable. The Turkish version of the SAS-SF has been reported to have high construct and content validity. Additionally, Cronbach's α was calculated to assess the scale's reliability and found to be 0.90 [22].

Young Internet Addiction Test-Short Form (YIAT-SF)

To determine participants' levels of internet addiction, the Turkish version of the YIAT-SF developed by Pawlikowski et al. [23], was utilized. This scale, consisting of 12 items, is a five-point Likert-type scale in which each item is scored from 1 and 5. The total score obtainable from the scale ranges from 12 to 60, with an increasing score indicating a rise in the individual's tendency toward internet addiction [23,24]. The Turkish version of the YIAT-SF, adapted by Kutlu et al. [24], has been found to be a valid scale with high reliability (Cronbach's alpha = 0.91, intraclass correlation coefficient-ICC=0.93).

Numeric Pain Rating Scale (NPRS)

The presence and intensity of pain were assessed using the NPRS. On this scale, individuals rate their pain levels from 0 (no pain) to 10 (the most severe pain possible). The NPRS has been reported to be a reliable scale for assessing pain intensity (ICC=0.76 for test-retest reliability) [25].

Neck Disability Index (NDI)

The level of disability related to the neck region in participants was assessed using the Turkish version of the NDI developed by Vernon and Mior [26]. The scale includes a total of 10 sub-dimensions: pain intensity, personal care, lifting, reading, headache, concentration, work, driving, sleep, and leisure activities. Each item is scored between 0 and 5 points, and high score obtained from the test indicates a high level of disability [26,27]. The NDI, adapted into Turkish by Aslan et al. [27], has been noted to be a valid and reliable (ICC= 0.98) scale.

Postural alignment assessment

Individuals' neck posture was assessed using CCA measurements. CCA is the angle between a horizontal reference line passing over the spinous process of the C7 vertebra and a line extending to the tragus of the ear. This parameter is considered a reliable indicator of head and neck posture, providing important information about the spatial position of the lower cervical segments. In the present study, CCA measurements were performed using a standard goniometer while participants stood in a relaxed, upright posture with their arms at their sides. All measurements were conducted by the same trained examiner to ensure measurement consistency. To minimize potential measurement error, each measurement was repeated twice and the mean value was recorded for analysis [28].

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To assess deviations in the horizontal plane and asymmetry of trunk rotation associated with postural disorders, trunk rotation was measured with a scoliometer, a specialized inclinometer. Measurements were performed with participants standing upright, with their feet together and parallel. Participants were then asked to assume Adam's forward-bend test position with their arms loosely joined and to bend forward until the trunk reached the horizontal plane. In this position, the angle of trunk rotation was recorded using the scoliometer [29].

Forward Reach Test

The sit-and-reach test was administered using a reach box to assess spinal flexibility. In standing flexibility tests, variables such as pelvic tilt, spinal rotation, and posterior pelvic displacement can affect the measurement. Therefore, this study was conducted in a seated testing position. Participants were asked to position themselves in a long-sitting position with their knees straight, their feet 15 cm apart, and their feet touching the support surface of the coffee table. Individuals were instructed to push the moving indicator on the coffee table as far forward as possible without bending their knees or straightening their elbows. The maximum distance reached by the guide was recorded as 30 centimeters [30].

Side Bending Test

In the side-bending test administered to assess spinal lateral flexibility, the participant was positioned with their back against the wall to minimize compensatory movements. The feet were placed 20 cm apart and parallel to each other; the individual was positioned approximately 10 cm from the wall. Before starting the measurement, the position of the distal end of the third finger on the thigh was marked. Then, the participant was asked to bend their torso laterally and slide their hand down their thigh. The final point reached was re-marked, and the distance from it to the starting point was measured with a tape measure and recorded. During the application period, care was taken to ensure that the body did not engage in flexion, hyperextension, or rotational movements [31].

International Physical Activity Questionnaire-Short Form

The Turkish version of the IPAQ-Short Form developed by Craig et al. [32] was used to determine individuals' levels of physical activity. The Short Form of the IPAQ consists of 7 items that assess sitting time, walking, and physical activities of varying intensities. Physical activity level is assessed based on the total metabolic equivalent (MET-min/week), which is calculated from the weekly frequency and duration of each activity. The total weekly duration for each activity is multiplied by the MET coefficient defined for that activity to obtain the individual's total MET score. An increase in total MET points indicates a higher level of physical activity. The physical activity level classified as high (>3.000 MET-min/week), moderate (600-3.000 MET-min/week), and low (<600 MET-min/week) [32,33]. The Turkish version of the scale, adapted by Sağlam et al. [33], has been shown to be valid and reliable (ICC= 0.78).

Short Form-36 Quality of Life Survey

To determine individuals' health-related quality of life levels, the Turkish adaptation of the SF-36 developed by Ware and Sherbourne [34] was used. The SF-36 is a 36-item scale that assesses quality of life across multiple dimensions and comprises eight subdomains. In practice, the physical component score and the mental component score are calculated by averaging the scores obtained from four subscales related to physical and mental health, respectively. Both components are scored on a scale of 0-100, with higher scores indicating a better quality of life [34,35]. The Turkish adaptation of the SF-36, carried out by Koçyiğit et al. [35], has been shown to be valid and reliable (Cronbach's α values between 0.73 and 0.76).

Statistical analysis

In this study, all statistical analyses were performed using SPSS (Version 24.0, IBM Corp., Armonk, NY, USA) . The means and standard deviations of individuals' demographic characteristics and clinical assessments are reported. Whether the data were normally distributed was examined using visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test). All the data were normally distributed. Descriptive statistics for numerical variables were expressed as mean±standard deviation, whereas categorical variables were summarized using frequencies and percentages. The relationships between the parameters were evaluated using Pearson correlation analysis. A correlation coefficient greater than 0.60 was considered a strong relationship, between 0.30 and 0.60 was considered a moderate relationship, and less than 0.30 was considered a weak relationship [36]. The level of statistical significance was set at $p<0.05$.

RESULTS

A total of 283 young adults were included in the study; 213 (75.3%) were female and 70 (24.7%) were male. When screen exposure levels were examined, it was determined that 12 (4.2%) of the participants were in the very low exposure category, 105 (37.1%) were in the low category, 119 (42.1%) were in the high category, and 47 (16.6%) were in the very high category. Detailed data on the demographic and clinical characteristics of the participants are provided in Table 1.

The relationships between individuals' Screen Time Exposure Form scores, SAS-SF scores, and YIAT-SF scores and the NDI and NPRS are given in Table 2. Statistically significant strong positive relationships were found between screen exposure and NDI ($r=0.79$) and between screen exposure and NPRS ($r=0.74$) ($p<0.05$). In addition, strong, statistically significant positive correlations were found between SAS-SF and YIAT-SF scores and NDI and NPRS ($r>0.60$, $p<0.05$).

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Table 1. Findings regarding the demographic and clinical characteristics of the participants.

		Mean ± Standard Deviation	
Age (years)		27.48±2.91	
Body Mass Index (kg/m^2)		25.74±3.04	
NPRS (cm)		4.82±1.17	
Neck Disability Index (score)		19.12±3.72	
Screen Time Exposure Form (score)		11.73±2.14	
SAS-SF (score)		31.19± 5.58	
YIAT-SF (score)		28.54±4.37	
SF-36 physical health (score)		65.28±10.05	
SF-36 mental health (score)		59.45±9.16	
IPAQ (MET value)		1686.30±241.12	
CCA (°)		43.24± 4.18	
Forward Reach Test (cm)		17.21±3.25	
Side Bending Test (cm)		15.64±2.87	
Trunk Rotation (°)		3.69±0.85	
		n	%
Gender	Female	213	75.3
	Male	70	24.7
Screen Exposure Category	Very low	12	4.2
	Low	105	37.1
	High	119	42.1
	Very high	47	16.6
Physical Activity Level	Low	73	25.8
	Moderate	152	53.7
	High	58	20.5

NPRS: Numeric Pain Rating Scale, SAS-SF: Smartphone Addiction Scale - Short Form, YIAT-SF: Young Internet Addiction Test – Short Form, SF-36: Short Form-36 Quality of Life Survey, IPAQ: Short Form of the International Physical Activity Questionnaire, CCA: Cranio-cervical angle.

Table 2. Relationships between scores of Screen Time Exposure Form, SAS-SF, YIAT-SF NDI, and NPRS.

		Screen Time Exposure Form	SAS-SF	YIAT-SF
NDI	r	0.79	0.69	0.67
	p	**p<0.001**	**0.005**	**0.002**
NPRS	r	0.74	0.65	0.63
	p	**p<0.001**	**0.011**	**0.016**

NPRS: Numeric Pain Rating Scale, NDI: Neck Disability Index, SAS-SF: Smartphone Addiction Scale - Short Form, YIAT-SF: Young Internet Addiction Test – Short Form, r: Pearson correlation coefficient, p<0.05.

The relationships between the Screen Time Exposure Form, SAS-SF, and YIAT-SF scores and the IPAQ and SF-36 physical and mental health scores are presented in Table 3. Strong, statistically significant negative relationships were observed between screen exposure and IPAQ scores and SF-36 physical and mental health scores, with magnitudes from -0.75 to -0.78 (p<0.05). In addition, strong, statistically significant negative relationships were found between SAS-SF and YIAT-SF scores and the IPAQ and SF-36 physical and mental health scores (r<-0.60, p<0.05).

Strong, statistically significant negative relationships were detected between screen exposure and CCA, forward reach test, and side-bending test scores, with magnitudes ranging from -0.77 to -0.86 (p<0.05). In addition, a statistically significant moderate relationship was found between screen exposure and trunk rotation (r=0.40). Strong negative correlations were found between SAS-SF and YIAT-SF scores and CCA, forward reach test, and side-bending test scores (r=-0.60-0.69), whereas moderate positive correlations were found between these scores and trunk rotation (r=0.34-0.36) (p<0.05) (Table 4).

Table 3. Relationships between scores of Screen Time Exposure Form, SAS-SF, YIAT-SF, IPAQ, and SF-36 scores.

		Screen Time Exposure Form	SAS-SF	YIAT-SF
IPAQ	r	-0.75	-0.69	-0.67
	p	**p<0.001**	**0.013**	**0.006**
SF-36 physical health	r	-0.78	-0.66	-0.72
	p	**p<0.001**	**0.010**	**0.002**
SF-36 mental health	r	-0.76	-0.65	-0.74
	p	**0.004**	**0.011**	**0.002**

SAS-SF: Smartphone Addiction Scale - Short Form, YIAT-SF: Young Internet Addiction Test – Short Form, IPAQ: Short Form of the International Physical Activity Questionnaire, SF-36: Short Form-36 Quality of Life Survey, r: Pearson correlation coefficient, p<0.05.

Table 4. Relationships between Screen Time Exposure, SAS-SF, and YIAT-SF scores with CCA, trunk rotation, forward reach test, and side bending test scores.

		Screen Time Exposure Form	SAS-SF	YIAT-SF
CCA	r	-0.86	-0.69	-0.67
	p	**p<0.001**	**0.002**	**0.005**
Forward Reach Test	r	-0.80	-0.65	-0.63
	p	**p<0.001**	**0.015**	**0.020**
Side Bending Test	r	-0.77	-0.60	-0.64
	p	**p<0.001**	**0.024**	**0.014**
Trunk Rotation	r	0.40	0.36	0.34
	p	**0.019**	**0.026**	**0.022**

SAS-SF: Smartphone Addiction Scale-Short Form, YIAT-SF: Young Internet Addiction Test – Short Form, CCA: Craniocervical angle, r: Pearson correlation coefficient, p<0.05.

DISCUSSION

This comprehensive study evaluated the effects of screen time on pain levels, neck disability, postural parameters, spinal flexibility, physical activity levels, and quality of life in young adults using a multifaceted approach. The findings revealed that increased screen time had significant negative effects on both biomechanical and psychosocial indicators. Among the most notable findings were increased neck pain, higher cervical disability scores, deterioration in quality-of-life components, decreased physical activity levels, and deterioration in postural alignment.

One of the most striking findings of our study was the strong positive correlation between screen exposure and both NPRS and NDI scores. This result demonstrates that screen use in

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young adults is directly related to musculoskeletal symptoms. The literature indicates that prolonged computer and smartphone use places mechanical stress on the cervical spine, leading to pain and functional limitations [10].

Our findings also revealed significant positive correlations between smartphone- and internet-addiction scores and both pain severity and neck disability. This supports the notion that not only screen time but also addiction levels have a decisive impact on musculoskeletal health. The concept of "problematic phone use," in particular, has been discussed in occupational therapy and physiotherapy in recent years, and the relationship between screen addiction and postural disorders is increasingly being investigated [37].

Our study revealed significant negative correlations among screen exposure, physical activity levels, and quality-of-life components. These findings suggest that increased screen exposure may contribute to reduced physical activity and poorer health-related quality of life in young adults. Similar results were reported by Saltan et al. [38], who demonstrated that lower physical activity levels were associated with decreased functional capacity and increased symptom burden. Together, these findings highlight the potential role of sedentary behaviors in the development of musculoskeletal symptoms and reduced quality of life among young adults. The World Health Organization recommends that adults engage in at least 150 minutes of moderate-intensity physical activity per week; however, screen addiction complicates implementation of this recommendation [39]. Furthermore, the literature reports that sedentary behavior predisposes to the development of obesity, cardiometabolic disorders, and psychosocial problems in the long term [40]. The literature consistently indicates that increased sedentary behavior and lower physical activity levels are associated with higher pain intensity, greater functional disability, and reduced quality of life in young adults [38]. However, most studies are cross-sectional and rely on self-reported measures, which limits causal interpretation and introduces potential reporting bias [15-18,38]. These recurring limitations emphasize the need for longitudinal designs and objective assessment methods in future research.

When postural alignment and spinal flexibility parameters were evaluated, significant negative correlations were observed between screen exposure and the CCA, the forward-reach test, and the side-bending test. This finding suggests that long-term screen use disrupts the cervical lordosis angle, limits trunk range of motion, and predisposes individuals to postural deformities. In particular, the forward-tilted head position, known as "text neck," has been associated with chronic tension in the cervical muscles and increased mechanical loading on the spinal joints [11].

The present study demonstrated moderate positive correlations between trunk rotation and scores for screen exposure, smartphone addiction, and internet addiction. This finding suggests that prolonged screen use may lead to compensatory postural adaptations. Although limited data exist on this topic, our study makes a unique contribution by examining the relationship between trunk rotation and digital addiction. Although the findings of the present study are in agreement with those reported by Şentürk et al. [4], important methodological distinctions underscore the added value of the present study. Whereas Şentürk et al. [4] predominantly examined self-reported musculoskeletal complaints in relation to smartphone addiction, the present study implemented a comprehensive and multidimensional evaluation framework incorporating both subjective indices (pain intensity, neck disability, quality of life, and addiction scales) and objective biomechanical parameters (cranio-cervical angle, trunk rotation, and standardized spinal flexibility tests). Furthermore, by assessing screen exposure, smartphone and internet addiction, physical activity levels, postural alignment, and spinal flexibility within a single analytical model, this study provides a more integrative and mechanistic perspective on the biomechanical and functional consequences of prolonged screen-based behaviors in young adults.

One of the strengths of our study is its multidimensional assessment of screen exposure. We combined addiction and quality-of-life scales, and biomechanical tests (postural measurements and flexibility tests). This holistic approach reveals not only the psychosocial effects of screen exposure but also its physiological consequences.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, the cross-sectional design precludes causal inference; therefore, the observed relationships between screen exposure, spinal flexibility, postural alignment, pain, physical activity, and quality of life should be interpreted as correlational rather than causal. It remains unclear whether prolonged screen exposure leads to musculoskeletal impairments or whether individuals with existing pain and postural problems are more likely to engage in excessive screen use. Second, participants were recruited from a single geographic region using convenience and snowball sampling methods. These non-probability sampling approaches may introduce selection bias and reduce sample representativeness, thereby limiting the generalizability of the findings to broader populations with different sociodemographic characteristics. In addition, although validated instruments were used, the reliance on self-reported questionnaires may have introduced recall bias and social desirability bias. The long-term clinical implications of reduced spinal flexibility and postural deterioration associated with prolonged screen exposure warrant further investigation, as these factors may contribute to the development of chronic musculoskeletal disorders and functional limitations over time. Future research should, therefore, focus on longitudinal and intervention-based studies involving more diverse populations and employing probability-based sampling

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methods to better clarify causal pathways and to evaluate the effectiveness of preventive and rehabilitative strategies, such as ergonomic education, posture-correction programs, and structured physical-activity interventions, aimed at mitigating the adverse biomechanical and psychosocial effects of excessive screen use.

CONCLUSION

In conclusion, increased screen exposure among young adults is strongly associated with greater pain and neck disability, lower quality of life, reduced physical activity levels, and a higher prevalence of postural disorders. These findings highlight the importance of improving ergonomic settings, limiting screen time, encouraging regular exercise habits, and increasing digital health awareness among university students. Future longitudinal studies will demonstrate more clearly the long-term effects of screen use and provide opportunities to evaluate the effectiveness of early interventions.

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Informed Consent: Voluntary written and verbal informed consent was obtained from all participants before they were included in the study.

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A retrospective evaluation of the effects of dimethyl fumarate on hematological parameters in patients with multiple sclerosis

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MAIN POINTS

- Dimethyl fumarate significantly modulates peripheral blood cell profiles in relapsing–remitting multiple sclerosis.
- Treatment-related lymphocyte suppression substantially influences composite systemic inflammation indices.
- Elevated inflammatory indices during dimethyl fumarate therapy do not necessarily indicate increased disease activity.
- Standard inflammatory markers remain largely unchanged despite hematological shifts.
- Interpretation of immune–inflammation indices in treated patients requires integration with clinical and radiological findings.

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ABSTRACT

Aim: Multiple Sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system. Typically seen in young adults, MS progressively leads to neurological impairments and significantly affects the quality of life. The lack of a definitive cure necessitates long-term monitoring and disease-modifying treatments. Dimethyl fumarate (DMF), a disease-modifying agent used in MS treatment, is notable for its antioxidant and anti-inflammatory effects.

Materials and Methods: In the present study, hematological, biochemical, and systemic inflammation parameters in MS patients were retrospectively analyzed before and after DMF treatment. The study aimed to investigate the effects of DMF on peripheral blood parameters and immune indices in MS patients.

Results: DMF treatment resulted in statistically significant decreases in leukocyte, neutrophil, lymphocyte, and platelet counts. Although a significant reduction was detected in creatinine levels, no significant changes were observed in BUN, ALT, AST, sedimentation rate, CRP, eosinophils, basophils, hemoglobin, and monocytes. After DMF treatment, statistically significant increases were observed in PIV, PLR, NLR, MLR, and SIRI. However, these increases likely reflect a mathematical artifact driven by DMF-induced lymphopenia (i.e., reduced lymphocytes in the denominator), rather than true systemic inflammatory activation. Therefore, these indices should be interpreted in the context of absolute cell counts and clinical and radiological findings.

Conclusion: The present study demonstrates that DMF treatment significantly affects peripheral hematological parameters and inflammatory indices. These parameters may serve as practical, low-cost biomarkers for monitoring treatment response in MS patients.

Keywords: Dimethyl fumarate, Hematology, Immune indices, Multiple sclerosis
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INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disease of the central nervous system (CNS), predominantly affecting young adults and causing substantial long-term disability [1,2]. Among its clinical phenotypes, relapsing–remitting MS (RRMS) is the most prevalent, characterized by episodes of neurological dysfunction followed by partial or complete remission. Pathogenesis involves the activation of autoreactive T and B lymphocytes in the periphery, disruption of the blood–brain barrier, and infiltration of inflammatory cells into the CNS, leading to demyelination, axonal loss, and progressive neurodegeneration [3-5]. Globally, the prevalence of MS is rising, thereby contributing to an increasing burden on health systems and society [6].

The etiology of MS is multifactorial. Genetic susceptibility, particularly HLA-DRB1*15:01, significantly increases disease risk [7-9]. Among environmental triggers, Epstein–

Barr virus (EBV) infection is the strongest, with prospective studies demonstrating a marked rise in MS risk following EBV seroconversion [10]. Vitamin D deficiency, adolescent obesity, smoking, and low sunlight exposure further modulate disease susceptibility [4,11]. Immunopathologically, Th1/Th17-polarized T cells, B-cell-mediated antigen presentation, and intrathecal IgG production establish the inflammatory milieu observed in MS lesions [12,13]. The revised McDonald criteria integrate dissemination in space and time, supported by cerebrospinal fluid oligoclonal bands, to provide a standardized diagnostic framework [14,15].

Disease-modifying therapies (DMTs) represent the cornerstone of treatment, aiming to reduce relapse frequency, delay progression, and mitigate long-term disability. Among them, dimethyl fumarate (DMF) has emerged as a widely used oral DMT with both immunomodulatory and antioxidant properties [16,17]. DMF exerts its effects by activating the nuclear factor erythroid 2 2-related factor 2(Nrf2)antioxidant pathway while simultaneously inhibiting nuclear factor kappa B (NF-κB)–mediated proinflammatory signaling [18-20]. Pivotal phase III trials demonstrated that DMF significantly reduced annualized relapse rates and the number of new T2 lesions [21,22]. However, treatment requires hematological monitoring due to the risk of lymphopenia, which is frequently observed during therapy [23,24].

Increasing evidence indicates that MS is not solely a CNS-restricted disease; it also involves measurable systemic immune alterations. Hematological indices derived from complete blood counts (CBCs), such as the Systemic Immune-Inflammation Index (SII) and Systemic Inflammation Response Index (SIRI), have been investigated as surrogate markers of systemic immune activation. These indices integrate neutrophil, lymphocyte, monocyte, and platelet dynamics into composite measures that reflect the inflammatory burden. Initially validated in oncology and cardiovascular disease, SII and SIRI have shown potential prognostic value in autoimmune and neuroinflammatory disorders, including MS [25-27]. A related metric, the Pan-Immune-Inflammation Value (PIV), expands this approach by combining neutrophils, monocytes, and platelets relative to lymphocytes, though its role in MS remains to be established [28-30]. Therefore, this study aimed to comprehensively evaluate the effects of dimethyl fumarate therapy on peripheral hematological parameters and systemic immune–inflammatory indices in patients with relapsing–remitting multiple sclerosis.

MATERIALS AND METHODS

Study design

The study protocol was approved by the Uludağ University Clinical Research Ethics Committee (Approval no: 2024-6/15, Date: 13.05.2024), and all procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki. The aim was to evaluate hematological changes in patients with multiple sclerosis (MS) receiving dimethyl fumarate (DMF) therapy by comparing pre- and post-treatment values after at least 6 months of continuous therapy. No direct patient contact or clinical intervention was performed. All data were obtained from the hospital information system, MIA (Medical Information Archive). In this respect, the study provides real-world evidence of the hematological effects of a commonly used disease-modifying therapy.

Patient selection and inclusion criteria

A total of 100 patients diagnosed with MS according to the McDonald criteria and who were initiated on DMF therapy at Bursa Uludağ University Health Application and Research Center between 2020 and 2024 were included. Eligible participants were ≥18 years of age, had been continuously treated with dimethyl fumarate (DMF) for at least 6 months, and had complete hematological data available both before treatment and at follow-up; post-treatment laboratory values corresponded to the last available follow-up visit after initiation of DMF therapy. Patients who switched to another immunomodulatory treatment during follow-up were excluded (Table 1). The mean age of the study cohort was 36.5 years, and the mean duration of DMF treatment was 2.94 years. Of the participants, 52% were male, and 48% were female. Detailed inclusion and exclusion criteria, along with the baseline demographic and clinical characteristics of the study population, are presented in Table 2.

Data collection

The dataset was obtained retrospectively from the MIA electronic medical records system. Collected variables included demographic characteristics, date of MS diagnosis, initiation date and duration of DMF therapy, comorbidities, concomitant medications, and results of hematological tests before treatment initiation and at least six months thereafter. All data were anonymized, and no personal identifiers were recorded at any stage.

Evaluated parameters

Pre- and post-treatment complete blood count results were compared. The following hematological and biochemical parameters were analyzed: hemoglobin (Hb), red blood cells (RBC), white blood cells (WBC), neutrophils, lymphocytes, monocytes, platelets, hematocrit (Hct), mean corpuscular volume (MCV), and mean platelet volume (MPV). In addition, derived systemic inflammation indices were calculated, including the Systemic Immune-Inflammation Index (SII), Pan-Immune-Inflammation Value (PIV), Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Systemic Inflammation Response Index (SIRI).

Index formulas were defined as follows: NLR = neutrophils/lymphocytes; PLR = platelets/lymphocytes; MLR =

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monocytes/lymphocytes; SII = (platelets × neutrophils)/lymphocytes; SIRI = (neutrophils × monocytes)/lymphocytes; PIV = (neutrophils × monocytes × platelets)/lymphocytes.

Data quality and control

To ensure data quality, electronic patient records were reviewed independently by two researchers. Extracted data were double-checked, and any missing, inconsistent, or suspicious entries were re-evaluated. Outliers were identified and excluded from the statistical analysis. This rigorous control process enhanced the methodological reliability of the study and strengthened the validity of the findings.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Normality of the data distribution was assessed using the Shapiro–Wilk test. For continuous variables with normal distributions, paired-sample t-tests were used; non-normally distributed data were analyzed using the Wilcoxon signed-rank test. Descriptive statistics were expressed as mean ± standard deviation (SD), median (minimum–maximum), and percentage (%). Values exceeding ±3 standard deviations from the mean were considered potential outliers and excluded from the analysis (A total of 5 observations were excluded based on these criteria). A p-value of <0.05 was considered statistically significant.

RESULTS

Biochemical parameters

No significant difference was observed in blood urea nitrogen (BUN) levels following DMF treatment (baseline: 25.73 ± 9.09 mg/dL; post-treatment: 25.40 ± 8.58 mg/dL; p = 0.788), suggesting no adverse effect on renal function. However, serum creatinine levels decreased slightly but significantly (baseline: 0.715 mg/dL; post-treatment: 0.670 mg/dL; p = 0.008), suggesting a possible indirect effect of DMF on renal excretion. Liver enzymes did not show significant changes. Both AST (p = 0.163) and ALT (p = 0.780) remained stable, indicating no hepatotoxic effect in this patient cohort (Table 3).

Complete blood count and leukocyte subpopulations

A statistically significant decrease was observed in total leukocyte counts after DMF treatment (baseline: 7703 ± 3103/μL; post-treatment: 6400 ± 2465/μL; p = 0.0012). This decline was primarily attributable to a pronounced reduction in lymphocyte counts (baseline: 2145 ± 890.5/μL; post-treatment: 1613 ± 786.1/μL; p<0.0001), consistent with the well-recognized lymphopenic effect of DMF. Neutrophil counts also decreased significantly (baseline: median 5060; post-treatment: 4030; p<0.0001), suggesting that DMF exerts suppressive effects not only on lymphocytes but also on other leukocyte subsets. In contrast, eosinophils (p = 0.060), monocytes (p = 0.541), and basophils (p = 0.372) did not differ significantly. Platelet counts demonstrated a mild but statistically significant reduction (baseline: 267.6 ± 79.2 $\times 10^3$/μL; post-treatment: 251.2 ± 8.1 $\times 10^3$/μL; p = 0.022), though values remained within normal limits. Hemoglobin levels were unaffected (p = 0.297) (Table 4).

Inflammatory markers

No significant differences in erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels were observed after DMF treatment (ESR: p = 0.205; CRP: p = 0.066). However, CRP exhibited a slight upward trend, which might indicate persistent low-grade inflammation and warrant further monitoring (Table 3).

Systemic inflammation indices

Composite systemic inflammation indices showed notable changes following DMF therapy: the Pan-Immune-Inflammation Value (PIV) increased significantly from a median of 288,689 to 340,077 (p = 0.043) and the platelet-to-lymphocyte ratio (PLR) rose from 127.7 to 170.3 (p<0.0001). Despite an absolute decrease in neutrophil counts, the neutrophil-to-lymphocyte ratio (NLR) increased (p = 0.035) owing to a more pronounced reduction in lymphocytes; the monocyte-to-lymphocyte ratio (MLR) also increased (p<0.0001). The systemic inflammation response index (SIRI) exhibited a statistically significant increase (p = 0.001), whereas the systemic immune-inflammation index (SII) did not change significantly (p = 0.415) (Table 5).

Clinical and radiological findings: EDSS Score and MRI lesions

The Expanded Disability Status Scale (EDSS) scores improved significantly after DMF treatment (baseline: 2.8 ± 0.9; post-treatment: 2.3 ± 0.7; p = 0.014), reflecting a slowing of disease progression. This clinical improvement was paralleled by a significant reduction in annual relapse rate (baseline: median 1 [0–5]; post-treatment: median 0 [0–1]; p<0.0001). MRI findings demonstrated a significant reduction in T2 lesion counts, decreasing from 7.4 ± 2.2 at baseline to 5.6 ± 1.9 after treatment (p = 0.009) (Table 6). These findings confirm that DMF reduces both clinical and radiological disease activity (Table 5). Correlation analyses did not reveal any significant association between systemic inflammatory indices and clinical disease activity parameters, including EDSS scores and MRI findings.

DISCUSSION

This study investigated the effects of dimethyl fumarate (DMF) therapy on peripheral blood parameters and systemic inflammation indices in patients with relapsing–remitting multiple sclerosis (RRMS). It evaluated their relationship

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Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years	History of heart failure
Definite MS diagnosis according to McDonald criteria	Coronary artery disease
DMF therapy ≥ 6 months	Renal failure (GFR <60 ml/min)
Complete hematological data available (pre- and post-treatment)	Abnormal liver function tests (ALT/AST >3× ULN)
No switch to another immunomodulatory treatment during follow-up	Known autoimmune disease
Absence of chronic or acute systemic diseases	Rheumatologic diseases
	Malignancy
	Hematological disorders (e.g., leukopenia)
	Active infection
	Pregnancy or breastfeeding
	Missing or inaccessible data

GFR: glomerular filtration rate.

Table 2. Baseline demographic and clinical characteristics of the study population.

Variable	Value
Number of patients	100
Age (years)	36.5 ± 10.4
Female	48 (48%)
Male	52 (52%)
Disease duration (years)	4.9 ± 3.6
Baseline EDSS score	2.8 ± 0.9
Duration of DMF treatment (years)	2.94 ± 1.9

with clinical and radiological findings. The results demonstrated that DMF significantly suppresses not only lymphocytes but also total leukocytes and neutrophils. Furthermore, the observed increases in systemic inflammation indices likely represent mathematical artifacts driven by DMF-induced lymphopenia and related hematological alterations, rather than reflecting true systemic inflammatory activation or increased disease activity. In this context, our study contributes novel insights to the existing literature and proposes a new interpretative framework for the clinical evaluation of inflammation indices.

The approximately 25% reduction in lymphocyte counts clearly reflects the immunosuppressive effect of DMF. This finding aligns with pivotal studies, such as those by Gold et al. [21] and Wright et al. [31], which reported that DMF can reduce lymphocyte counts by up to 30% after one year of treatment. The literature reports that this effect may cause severe lymphopenia (<500 cells/μL) in approximately 5% of patients, thereby increasing the risk of infection. Gold et al. [32] further highlighted that DMF selectively suppresses $CD8^+$ T cells, underscoring the need for careful monitoring of immune balance and infection risk. The lymphocyte reduction observed in our study reflects this biological mechanism at the peripheral blood level.

In addition to a decrease in lymphocytes, our findings revealed a statistically significant decrease in total leukocyte and neutrophil counts. Although neutropenia under DMF therapy has been less frequently reported, studies by Longbrake et al. [33] and Goldman et al. [34] have raised awareness of this potential risk. In our cohort, neutrophil levels remained within the physiological range, but showed a statistically significant decline, suggesting that DMF may exert broader immunomodulatory effects beyond lymphocytes. This observation is clinically relevant to treatment safety and monitoring strategies. Notably, neutrophil decline may have clinical relevance independent of lymphopenia, as reduced innate immune reserve can predispose susceptible patients to bacterial and fungal infections. Accordingly, comprehensive CBC follow-up should include monitoring absolute neutrophil count trajectories as well as lymphocyte counts, particularly in patients with recurrent infections or other risk factors.

The mild reduction in platelet count was statistically significant but not clinically meaningful. This is consistent with phase III trial data reported by Fox et al. [35], which indicated that DMF does not significantly alter platelet counts. Thus, our results reaffirm DMF's favorable safety profile regarding thrombocytopenia. Moreover, given that rare cases of thrombocytopenia are typically associated with other predisposing factors, the changes observed here are unlikely to represent a clinically significant risk.

With respect to systemic inflammation indices, we observed a statistically significant after treatment increase composite parameters (PIV, PLR, NLR, MLR, and SIRI), whereas levels of SII and CRP remained unchanged. Since many of these indices are calculated using lymphocyte count as the denominator, the treatment-induced reduction in lymphocyte count mathematically increases them. For example, despite the observed decrease in neutrophils, NLR increased because the decline in lymphocytes was more pronounced. Therefore, the observed increases in these indices are more likely a reflection of treatment-related hematological changes rather than evidence of heightened systemic inflammation. This interpretation diverges from previous studies, such as those by Gökçe et al. [36] and Fathy et al. [37], which associated such indices with disease activity; however, they did not clearly account for treatment regimens. By focusing exclusively on DMF-treated patients, our study provides stronger causal evidence support-

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Table 3. Biochemical parameters and inflammatory markers.

Parameter	Baseline	Post-treatment	p-value
BUN (mg/dL) (mean ± SD)	25.73 ± 9.09	25.40 ± 8.58	0.788
Creatinine (mg/dL) (median [max--min])	0.715 (1.59--0.43)	0.670 (1.04--0.47)	0.008*
AST (U/L) (median [max--min])	17 (60--8)	18 (50--8)	0.163
ALT (U/L) (median [max--min])	16 (128--6)	17.5 (108--6)	0.780
ESR (mm/h) (mean ± SD)	7.11 ± 5.47	8.11 ± 7.02	0.205
CRP (mg/L)	1.99 (8.40--0.04)	2.10 (57.8--0.20)	0.066

* p<0.05.

Table 4. Complete blood count and leukocyte subsets.

Parameter	Baseline	Post-treatment	p-value
Leukocyte count (/μL) (mean ± SD)	7703 ± 3103	6400 ± 2465	0.0012*
Lymphocytes (/μL) (mean ± SD)	2145 ± 890.5	1613 ± 786.1	<0.0001*
Neutrophils (/μL) (median [max--min])	5060 (17600--1890)	4030 (12460--1600)	0.0001*
Eosinophils (/μL)	110 (623--0)	128 (770--1)	0.060
Monocytes (/μL)	540 (1205--71)	529 (1190--68)	0.541
Basophils (/μL) (mean ± SD)	55.0 ± 47.0	59.6 ± 39.9	0.372
Hemoglobin (g/dL)	13.8 (24.5--9.0)	13.4 (16.2--9.8)	0.297
Platelets (10^3/μL) (mean ± SD)	267.6 ± 79.2	251.2 ± 81.1	0.022*

* p<0.05.

Table 5. Systemic inflammation indices.

Parameter	Baseline	Post-treatment	p-value
SII	682 (4387--137)	671 (5908--154)	0.415
PIV	288,689 (1,740,026--35,861)	340,077 (6,823,630--62,867)	0.043*
PLR	127.7 (483.3--25.9)	170.3 (719.2--46.9)	<0.0001*
NLR	2.38 (18.0--0.18)	2.86 (20.5--0.59)	0.035*
MLR	0.244 (0.714--0.039)	0.356 (1.821--0.057)	<0.0001*
SIRI	1112 (7598--127.6)	1397 (15,130--284.5)	0.001*

* p<0.05.

Table 6. Clinical and radiological findings.

Parameter	Baseline	Post-treatment	p-value
Annual relapse rate	1 (5--0)	0 (1--0)	<0.0001*
EDSS score (mean ± SD)	2.8 ± 0.9	2.3 ± 0.7	0.014
T2 lesion count on MRI (mean ± SD)	7.4 ± 2.2	5.6 ± 1.9	0.009

* p<0.05.

ing interpretation of these changes.

The absence of significant changes in monocyte counts supports the notion that increases in PIV and SIRI primarily result from lymphocyte decline. Similarly, the lack of significant changes in CRP further supports the conclusion that the observed shifts in indices do not reflect a genuine inflammatory response. Radiological outcomes demonstrated that gadolinium-enhancing active lesions were present in 52% of patients at baseline versus 24% post-treatment, alongside a significant reduction in mean T2 lesion number (7.4 ± 2.2 to 5.6 ± 1.9) and an improvement in mean EDSS (2.8 ± 0.9 to 2.3 ± 0.7). These findings confirm the clinical and radiological efficacy of DMF while supporting the interpretation that increases in systemic indices reflect hematological variation rather than disease progression. Although Zivadinov et al. [38] suggested correlations between MRI lesion burden and inflammatory biomarkers, such analyses did not account for treatment effects, limiting their interpretation.

Thus, our study provides both substantive and methodological contributions to the field. The existing literature has proposed systemic inflammation indices as prognostic markers in MS; however, limited data exist on how these indices behave under specific treatments. Our results show that increases in such indices under DMF therapy do not indicate worsening disease. Accordingly, the treatment regimen must be carefully considered when interpreting these markers, and hematological changes must be recognized as potential confounders. Moreover, our findings emphasize that indices such as NLR and PLR should not be interpreted in isolation but must be integrated with clinical and radiological outcomes.

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From a clinical perspective, one of the most important implications of the present study is that indices of systemic inflammation in DMF-treated patients might reflect treatment effects rather than true inflammatory activity. Clinicians should therefore exercise caution in interpreting these parameters. Furthermore, our data suggest that lymphocytes, neutrophils, and platelets should also be monitored in patients on DMF therapy to ensure patient safety and optimize therapeutic follow-up. These findings provide a methodological basis for future studies exploring the integration of hematological biomarkers into clinical decision-making.

Limitations

This study has several limitations. Due to its retrospective design, detailed data on prior disease-modifying therapies and corticosteroid exposure were not available, which may represent a potential source of confounding. In addition, lymphopenia severity grading could not be assessed due to dataset constraints. These limitations should be taken into account when interpreting the results.

CONCLUSION

Dimethyl fumarate therapy in RRMS is associated with significant alterations in peripheral hematological parameters, leading to apparent increases in several systemic inflammation indices. These changes appear to reflect a treatment-related reduction in lymphocyte counts rather than true inflammatory disease activity. Therefore, hematological inflammation indices should be interpreted cautiously in DMF-treated patients, particularly when clinical and radiological outcomes indicate disease stability.

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Ethics Committee Approval: This retrospective study was approved by the Clinical Research Ethics Committee of Bursa Uludağ University Faculty of Medicine (Approval no: 2024-6/15, Date: 13.05.2024).

Informed Consent: Due to the retrospective design of the study and the use of anonymized patient data, the requirement for informed consent was waived by the ethics committee.

Peer-review: Externally peer-reviewed.

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Epidemiological profile of viral meningitis agents based on molecular diagnosis, Muğla, Türkiye (2019--2024)

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MAIN POINTS

- This is the first study investigating viral meningitis agents and their current distribution in Muğla Province.
- Rapid and accurate identification of viral pathogens is essential for appropriate management, reducing unnecessary antibiotic use and shortening hospital stays.
- Viral detection rates were lower than those reported nationally and internationally, possibly because some samples were collected mainly to exclude acute viral meningitis.
- Although enteroviruses are the leading cause of viral meningitis worldwide, HSV-1 and VZV were the most frequently detected pathogens in our study.

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ABSTRACT

Aim: Meningitis is an inflammation of the meninges, and viruses are among the most common causative agents. Due to the lack of regional data, this study aimed to evaluate the etiology and frequency of viral meningitis in Muğla, with a particular focus on the most common pathogens in pediatric and adult patients.

Materials and Methods: The study included 867 individuals whose CSF samples were tested by PCR between August 2019 and September 2024. Pathogens causing viral meningitis, including Enterovirus, Parechovirus, HSV-1, HSV-2, VZV, and Mumps, were assessed using the Fast Track Diagnostic multiplex real-time PCR viral panel kit.

Results: The mean age of the 867 participants was 46.96 ± 24.93 years, with 45.8% being female, 14.6% pediatric cases, and 1.0% of foreign nationality. Viral pathogens were detected in 35 cases (4.0%). Among these, 5.5% were male, a proportion that was statistically higher than that of females (p=0.015). Additionally, 6.3% were children, and 11.1% were foreign nationals. The most frequently identified pathogens were HSV-1 (2.1%) and VZV (1.0%). The least detected pathogens were Mumps and Parechovirus, with one case each. In pediatric cases, the most common pathogen was VZV (2.4%), whereas in adults, it was HSV-1 (2.2%). Among foreign nationals, only HSV-1 was identified (1 case). Viral pathogens were detected at the highest rate in 2023 (5.2%). The highest prevalence across age groups was observed in individuals aged 35--64 years (37.1%).

Conclusion: This study represents the first report of the molecular diagnosis of viral meningitis in Muğla. Our findings reflect the incidence of viral meningitis in the region. The use of molecular methods to identify viral pathogens plays a critical role in patient management. Detecting the causative agent in viral meningitis reduces inappropriate antibiotic use, length of hospital stay, and associated costs.

Keywords: Viral meningitis, HSV-1, HSV-2, VZV, Mumps, Enterovirus, Parechovirus

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INTRODUCTION

Central nervous system (CNS) viral infections, including meningitis, encephalitis, and myelitis, are commonly encountered in clinical practice worldwide. Among these, viral meningitis constitutes the majority of total viral CNS infections, making it one of the most prevalent CNS infections [1]. Meningitis is defined as inflammation of the meninges associated with an abnormal number of cells in the CSF. Aseptic meningitis, characterized by the absence of bacterial growth in cultures, is the most frequent form and is commonly caused by viruses. Because vaccination has reduced the prevalence of bacterial meningitis, viral causes of meningitis have become more prominent, and viral meningitis is now the most common form in many countries.

Viral meningitis typically presents with acute onset of fever, headache, photophobia, neck stiffness, and often nausea and vomiting; however, young children may not exhibit signs of meningeal irritation [2]. While viral meningitis is generally self-limiting in most children and requires only supportive treatment, advances in diagnostic capabilities, including the widespread use of polymerase chain reaction (PCR), have reduced hospital stays and antibiotic use. Nevertheless, aseptic meningitis continues to pose a significant healthcare burden [3].

Among viral meningitis agents, enteroviruses account for up to 80% of cases with an identified etiologic agent. Another pathogen of significance is parechovirus, particularly type 3, which represents a major cause of CNS infections in neonates. Both are RNA viruses belonging to the *Picornaviridae* family [4]. Herpes Simplex Virus 1 (HSV-1) and Herpes Simplex Virus 2 (HSV-2) can also cause viral meningitis. HSV-1 is more commonly associated with sporadic encephalitis, while HSV-2 can cause benign recurrent viral meningitis, often occurring in the absence of genital lesions or a history of genital herpes infection [4]. HSV reaches the CNS through cranial nerves. Varicella-Zoster Virus (VZV) is more likely to cause viral meningitis during reactivation than during primary infection, and varicella meningitis can occur without cutaneous lesions [2].

Before the introduction of the measles, mumps, and rubella (MMR) vaccine, mumps was a leading cause of viral meningitis and was more frequently observed in male patients [5]. Other viral causes include adenovirus, lymphocytic choriomeningitis virus (LCMV), influenza, parainfluenza, and Mumps [2]. Arboviruses capable of causing viral meningitis include West Nile virus (WNV), Zika virus, chikungunya virus, dengue virus, LaCrosse virus, Saint Louis encephalitis virus, Powassan virus, and Eastern equine encephalitis virus. Viral meningitis is most commonly observed in young children, and its incidence decreases with age. In temperate climates, viral meningitis occurs predominantly in the summer and autumn months, whereas in tropical and subtropical regions, it is seen year-round [6].

The current standard of care for viral infections includes antiviral therapy. However, these drugs are often ineffective in depleting viral reservoirs, either due to their lack of specificity or failure to cross specialized CNS barrier structures [7]. Therefore, the rapid and accurate identification of causative agents, along with targeted therapy, is critically important for managing these viral diseases. This study aims to evaluate the etiology and frequency of viral meningitis and to identify its most common causative agents in pediatric and adult patients in Muğla, Turkey. Muğla is a major tourist destination that experiences significant seasonal population mobility. In addition, its Mediterranean climate and coastal geography may influence viral transmission patterns. These regional characteristics may have implications for the epidemiology of viral central nervous system infections.

MATERIALS AND METHODS

A total of 867 cerebrospinal fluid (CSF) samples, sent between August 2019 and September 2024 to the Medical Microbiology Laboratory of Muğla Training and Research Hospital for nucleic acid testing to diagnose viral central nervous system infections, were retrospectively evaluated. This study was approved by the Ethics Committee of Muğla Sıtkı Koçman University Faculty of Medicine and the Muğla Training and Research Hospital (Decision no: 163, Date: 09.12.2024). Cerebrospinal fluid (CSF) samples that were analyzed by multiplex real-time PCR in the molecular microbiology laboratory and were obtained from patients with a preliminary diagnosis of viral meningitis were included in the study. Samples that did not meet this criterion, as well as those not analyzed by multiplex real-time PCR between August 2019 and September 2024, were excluded from the study.

Nucleic acids of viral pathogens, including HSV-1, HSV-2, Mumps virus, VZV, Enteroviruses (EV), and Parechovirus (HPeV), were routinely screened weekly in all cerebrospinal fluid (CSF) samples using the Fast-Track Diagnostics (FTD) multiplex real-time PCR panel (Fast Track Diagnostics Ltd., Luxembourg), which is CE-IVD approved for in vitro diagnostic use in Europe. Microbial nucleic acids were extracted from CSF samples using the EZ1 automated system with the EZ1 and 2 Virus Mini Kit v2.0 (Qiagen, Germany). The amplification step of the assay was performed on the Rotor-Gene Q analyzer (Qiagen, Germany). The cases of viral meningitis were assessed by age groups: ≤1, 1-5, 6-17, 18-34, 35-64, and ≥65 years.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous variables was assessed using visual (histograms) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods. To compare continuous variables between groups, either the Student's t-test or the Mann-Whitney U test was used, depending on the distribution of the data. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Results with a p-value less than 0.05 were considered statistically significant. Power analysis was performed using the G*Power 3.1.9.4, which indicated that a sample size of at least 128 was required. Our study used a non-probability sampling method; all consecutive cerebrospinal fluid samples collected between August 2019 and September 2024 that met the inclusion criteria were included. The 95% confidence intervals (95% CI) for the incidence rates were calculated using the binomial distribution.

RESULTS

A total of 867 CSF samples from individuals who underwent testing for viral meningitis agents by multiplex real-time PCR were included in this study. The mean age of the 867 participants was 46.96 ± 24.93, with 45.8% being female, 14.6% children, and 1.0% foreign nationals.

A viral agent was detected in 35 (4.0%) of the 867 individuals tested with the viral meningitis panel. Of the 35 patients with a viral agent, 26 (5.5%) were males, a proportion that was significantly higher than that in females (p = 0.015). The mean age was 40.9 ± 24.8 years in males and 43.0 ± 26.5 years in females, with no statistically significant difference between the groups (p=0.83). Of the 35 patients, 8 (6.3%) were children

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Table 1. Demographic and laboratory data of the study population.

		HSV-1		HSV-2		VZV	
	Total n	Positive n (%)	OR (95% CI)	Positive n (%)	OR (95% CI)	Positive n (%)	OR (95% CI)
Number	867	18 (2.1)		2 (0.2)		9 (1.0)	
Age (mean)	46.96±24.93	44.28±26.16		63.5±16.26		39±29.80	
Sex							
Female	397	6 (1.5)	1.67 (1.43- 1.91)	1 (0.3)	1.50 (-4.85- 7.85)	2 (0.5)	1.78 (1.44- 2.12)
Male	470	12 (2.6)		1 (0.2)		7 (1.5)	
Age Group							
Child	127	2 (1.6)	1.89 (1.73- 2.05)	0 (0.0)		3 (2.4)	1.67 (1.28- 2.05)
Adult	740	16 (2.2)		2 (0.3)		6 (0.8)	
Nationality							
Turkish	858	17 (2.0)	4.61 (4.10- 5 .13)	2 (0.2)	5.50 (-0.85- 11 .85)	9 (1.0)	4.22 (2.85- 5 .60)
Foreigner	9	1 (11.1)		0 (0.0)		0 (0.0)	
Years							
2019	41	2 (4.9)	4.11 (3.19- 5 .03)	0 (0.0)	3.50 (-15.56- 22 .56)	0 (0.0)	5.00 (4.33- 5 .67)
2020	89	3 (3.4)		1 (1.1)		0 (0.0)	
2021	159	1 (0.6)		0 (0.0)		1 (0.6)	
2022	177	3 (1.7)		0 (0.0)		0 (0.0)	
2023	211	3 (1.4)		1 (0.5)		6 (2.8)	
2024	190	6 (3.2)		0 (0.0)		2 (1.1)	
	Mumps Positive n (%)	Enterovirus Positive n (%)	OR (95% CI)	Parechovirus Positive n (%)	Total Positive n (%)	OR (95% CI)	p
Number	1 (0.1)	4 (0.5)		1 (0.1)	35 (4.0)		
Age (mean)	1±0.0	43.5±30.12		0±0.0	42.65±27.25		
Sex							
Female	0 (0.0)	0 (0.0)		0 (0.0)	9 (2.3)	1.74 (1.59- 1.90)	0.015
Male	1 (0.2)	4 (0.9)		1 (0.2)	26 (5.5)		
Age Group							
Child	1 (0.8)	1 (0.8)	1.75 (0.95- 2.55)	1 (0.8)	8 (6.3)	1.77 (1.63- 1.92)	0.161
Adult	0 (0.0)	3 (0.4)		0 (0.0)	27 (3.6)		
Nationality							
Turkish	1 (0.1)	4 (0.5)		1 (0.1)	34 (4.0)	4.37 (3.86- 4.88)	0.278
Foreigner	0 (0.0)	0 (0.0)		0 (0.0)	1 (11.1)		
Years							
2019	0 (0.0)	0 (0.0)	3.25 (0.86- 5 .64)	0 (0.0)	2 (4.9)	4.31 (3.75- 4.88)	0.164
2020	0 (0.0)	2 (2.2)		0 (0.0)	6 (6.7)		
2021	0 (0.0)	0 (0.0)		0 (0.0)	2 (1.3)		
2022	0 (0.0)	1 (0.6)		0 (0.0)	4 (2.3)		
2023	0 (0.0)	1 (0.5)		0 (0.0)	11 (5.2)		
2024	1 (0.5)	0 (0.0)		1 (0.5)	10 (5.3)		

Laboratory data : CSF Glucose (40-70 mg/dl); median (Rance) 65.62 (23-117.2), CSF Protein (15-45 mg/dl); median (Rance) 44.90 (2-264.9), CRP (0-5 mg/dl); median (Rance) 46.97 (0.26-373.34).

and 1 (11.1%) was a foreign national; no statistically significant differences were observed between children and adults (p = 0.161) or between Turkish citizens and foreign nationals (p = 0.278). The most frequently detected viral agents were HSV-1 (18 cases, 2.1%) and VZV (9 cases, 1.0%). The least frequently detected viral agents were mumps and parechovirus, each detected in one case. In children, the most common viral agent was VZV, detected in 3 (2.4%) cases; HSV-2 was not detected. In adults, HSV-1 was the most frequent, detected in 16 (2.2%) cases, whereas Mumps and Parechovirus were not detected. Among foreign nationals, only one case of HSV-1 was identified. When the viral agents were evaluated by year, the highest rates were observed in 2023 (5.2%, 11 cases) and 2024 (5.3%, 10 cases), while the lowest rate was observed in 2021 (1.3%, 2 cases). No statistically significant difference in the detection of viral meningitis agents between years was found (p = 0.164) (Table 1).

The distribution of viral meningitis cases by age group was as follows: 2 cases (5.7%) in the ≤1 year group, 3 cases (8.6%) in the 1-5 years group, 4 cases (11.4%) in the 6-17 years group,

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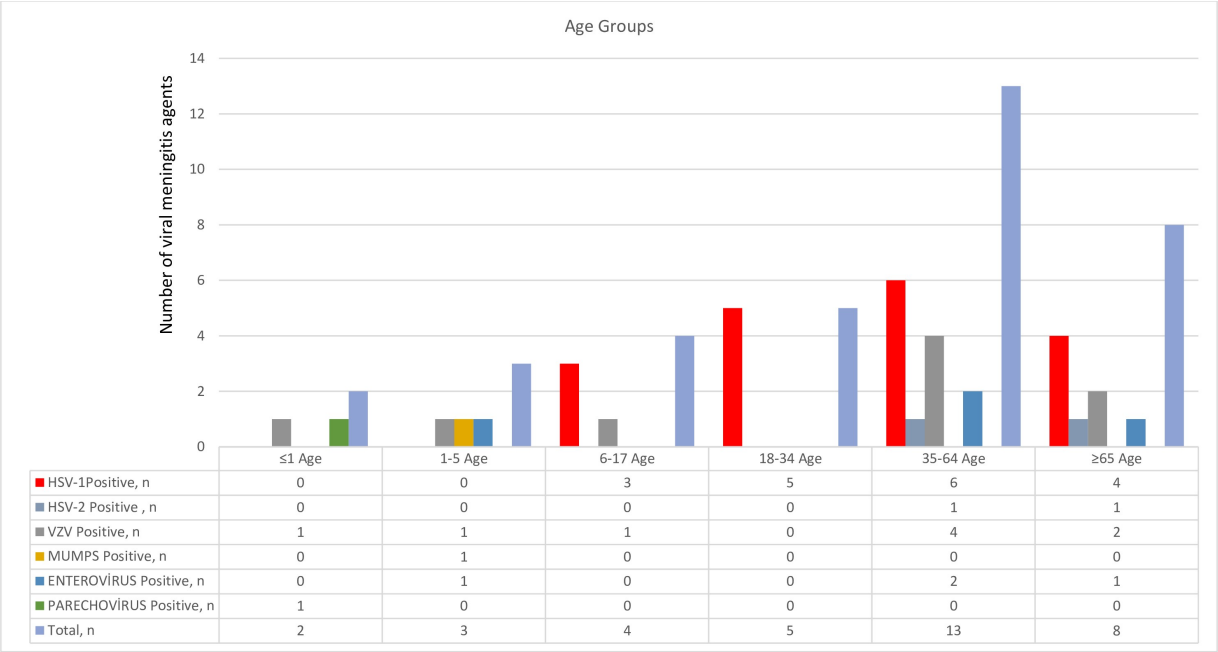

	≤1 Age	1-5 Age	6-17 Age	18-34 Age	35-64 Age	≥65 Age
HSV-1Positive, n	0	0	3	5	6	4
HSV-2 Positive , n	0	0	0	0	1	1
VZV Positive, n	1	1	1	0	4	2
MUMPS Positive, n	0	1	0	0	0	0
ENTEROVİRUS Positive, n	0	1	0	0	2	1
PARECHOVİRUS Positive, n	1	0	0	0	0	0
Total, n	2	3	4	5	13	8

Figure 1. Distribution of Hsv-1, Hsv-2, Vzv, Mumps, Enterovırus and Parechovırus by age group.

5 cases (14.3%) in the 18-34 years group, 13 cases (37.1%) in the 35-64 years group, and 8 cases (22.9%) in the ≥65 years group. The positivity rates for HSV-1, HSV-2, VZV, Mumps, Enterovirus, and Parechovirus in each age group are shown in Figure 1.

DISCUSSION

Viral meningitis is one of the most severe clinical conditions affecting individuals of all ages. In adults, viral meningitis is often self-limiting and may go undetected in many cases. However, in children and infants, serious complications such as high fever and mental retardation are common, and some cases may lead to death [8]. Viral meningitis can be associated with demographic factors, underlying conditions, causal agents, and treatment sensitivity, making regional information critical for its accurate and timely management. In this study, we aim to determine the frequency of viral meningitis cases and the current status of its causative agents in Muğla. In recent years, viruses have increasingly been recognized as significant causes of meningitis. Although the disease can initially be diagnosed based on clinical symptoms and routine biochemical tests, accurate identification of the pathogen is crucial. Therefore, molecular techniques are currently the gold standard for identifying the etiology of viral meningitis, as they not only allow for rapid and precise identification of the causative agent but also help reduce unnecessary antibiotic use and hospital stay duration [9].

The diagnosis of central nervous system viral infections has undergone a revolutionary change with the use of molecular diagnostic techniques to detect viral nucleic acids in cerebrospinal fluid (CSF); however, the etiology of up to 70% of CNS infections remains unknown [10]. Looking at studies on viral pathogen detection rates, a study conducted in Qatar between 2015 and 2019 found that 10.9% (732) of 6705 CSF samples tested positive for viral agents, with women accounting for 39.1% (286/732) of these cases [8]. In a 2023 study in Egypt, 19.0% (330) of 1735 CSF samples tested positive for viral agents, with 33.6% being women [11]. In a study conducted in Germany, similar to our study, 4.0% (125) of 3085 patients had viral nucleic acid detected [12]. In Turkey, studies have reported varying results; for instance, a study by Çiçek et al. [13] found that 32.4% (36) of CSF samples were positive, with 33.3% (12) being women. In contrast, a study by Soylar et al. [14] reported a viral detection rate of 2.0% (7) in 289 patients, with 5 being women. In this study, 4.0% (35 of 867) of individuals tested for viral meningitis via CSF PCR were found to have a viral agent. Of these, 5.5% (26) were male, a proportion that was significantly higher than that among females ($p = 0.015$). Although comparable to some reports, The low viral detection rate (4.0%) observed in our study was lower than that reported in many other studies. Several factors may account for this finding. First, the limited coverage of PCR panels used for cerebrospinal fluid (CSF) analysis may have contributed to this result because they may not include certain rare or newly identified neurotropic viruses, resulting in underdiagnosis. Second, the timing of sample collection is a critical factor. In viral meningitis, the viral load in CSF is generally higher during the early stages of the disease. Delayed patient presentation or late collection of CSF samples may reduce the detectability of viral nucleic acids, resulting in false-negative findings. Furthermore, the characteristics of the study population may be influential. Among patients undergoing CSF analysis with a clinical suspicion of viral meningitis, a proportion may actually have bacterial, fungal, or non-

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infectious etiologies (such as autoimmune encephalitis). In addition, CSF sampling and test requests that were made without sufficient clinical indication may have contributed to the relatively low detection rate observed in our study.

Several factors could explain the higher rate of viral meningitis in men compared to women, including biological differences between male and female immune systems; women generally have a stronger immune response, which could make them more resistant to some infections. This phenomenon can be explained by hormonal factors: estrogen has a positive effect on the immune system, while testosterone can suppress immune function. Moreover, men, particularly in younger age groups, may be more engaged in high-risk activities such as group sports, travel, or military service, increasing their exposure to viral infections. Social and environmental factors also play a role; men may be exposed to conditions that promote viral transmission, especially in high-risk areas or occupations.

The viral pathogen detection rates found in our study are lower than those reported in other studies in Turkey and abroad. This could be due to some of the samples we analyzed having been submitted to rule out acute viral meningitis in patients without prominent clinical symptoms. In Germany, a study by Kleines et al. [12] found that 36% of viral meningitis cases were caused by enterovirus (EV), 15% by herpes simplex virus (HSV), and 12% by varicella zoster virus (VZV). The highest incidence of EV infections was found in individuals aged 25-35, while HSV infections peaked in those aged 30-60, and VZV infections were most common in individuals younger than 30 and older than 70 [15]. Another German study reported that 1.3% (34/2624) of patients had VZV nucleic acid detected, 1.24% (37/2994) had HSV nucleic acid, and 0.4% (10/2364) had EV nucleic acid detected [12]. In a Danish study, EV was found in 39% (419) of 1066 cases, HSV-2 in 16% (171), and VZV in 15% (162) [16]. In the UK, McGill et al. [17] reported that enteroviruses were the most common cause of viral meningitis, accounting for 55% (127/231) of all cases. Abdelrahim et al. [10] identified enterovirus as the most common virus, accounting for 25% (60) of cases, followed by HHV-6 (7.9%, 19) and VZV (3.8%, 9). Enterovirus was most prevalent in the pediatric age group, particularly among children under 4 years old. HSV-2 was identified in two female patients aged 34-64 years. In Qatar, Mathew et al. [8] reported that EV was the most frequently detected virus, accounting for 68.7% (503/732) of cases. EV was the dominant infection across all age groups, and it was most common in children (85.1%, 428/503), followed by adolescents (8.94%, 45/503) and adults (5.77%, 29/503). In Turkey, studies by Çiçek et al. [13] found that enterovirus was the most common viral agent, detected in 69.4% (25) of cases, while Zeytinoğlu et al. [18] found Epstein-Barr virus (EBV) (4.35%) and enterovirus (3.37%) to be the most common. Akkaya et al. [19] reported enterovirus as the most common agent, detected in 6.5% (13) of cases, with the highest incidence in the 0-5 age group. Enteroviruses are the leading cause of viral meningitis worldwide. However, in our study, they were detected as the third most frequent viral agents, with one case in the 6-17 age group and two cases in the 35-64 age group. The most frequently detected viral agents in our study were HSV-1 (2.1%, 18 cases) and VZV (1.0%, 9 cases), which differ from the findings of European and local studies. Several factors could explain why HSV-1 is more frequently observed as a causative agent of viral meningitis than enteroviruses. Some cases diagnosed as meningitis may have had associated encephalitis. Additionally, HSV-1 may more frequently cause viral meningitis in immunocompromised individuals. Immunosuppressive treatment increases the likelihood that HSV-1 will affect the central nervous system and cause meningitis. In our study, the retrospective data we analyzed consisted of samples tested for viral meningitis by PCR. These samples are not always sent to clinics when meningitis is suspected, and clinicians may request screening for non-meningitis cases using the viral meningitis panel. For this reason, and unlike in other studies, enterovirus may have been the third most commonly detected virus in our results. Furthermore, our viral meningitis PCR diagnostic panel does not identify all enterovirus types, which may be an important consideration. Muğla is a major tourist destination in Turkey. It experiences an influx of domestic and international tourists throughout much of the year. This type of activity can increase the risk of contact with individuals who are HSV-1 carriers. Additionally, factors such as access to healthcare, language and cultural barriers, and delayed symptom reporting or referral may contribute.

The least frequently detected viral agents in our study were mumps and parechovirus, with only one case each. Mumps, which was once the most common cause of viral meningitis, was detected in only one case in our study, likely because the measles, mumps, and rubella (MMR) vaccine was introduced in Turkey in 2006.

In children, the most frequently observed viral agent was VZV (3 cases, 2.4%), whereas in adults HSV-1 was most common (16 cases, 2.2%). VZV is a highly contagious virus that is commonly observed in childhood. The virus can establish latency in neurons, which allows it to reactivate and affect the central nervous system later in life. In immunocompromised children, VZV may present more aggressively, potentially causing meningitis. Vaccination programs and other environmental factors can alter the prevalence of certain viral infections over time. Immunity to, or reduced exposure to classic viral meningitis agents, such as enteroviruses, may make other viruses, such as VZV, more apparent. The distribution of viral meningitis cases by age showed that 5.7% (2) were $\leq$1 years, 8.6% (3) were 1-5 years, 11.4% (4) were 6-17 years, 14.3% (5) were 18-34 years, 37.1% (13) were 35-64 years, and 22.9% (8) were $\geq$65 years. The highest incidence of EV, HSV-1, HSV-2, and VZV infections was observed in the 35-64 age group, while parechovirus infections were most common in the $\leq$1 year group, and mumps was most frequent in the 1-5 year

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group. In our study, viral pathogens were detected in 6.3% (8) of pediatric cases, although this rate is relatively low because of insufficient differentiation among patients. Clinically, some inflammatory and infectious diseases may mimic infectious meningitis because infectious meningitis has a broad definition, leading to a lower detection rate.

In a 2023 study in Egypt, the highest viral meningitis detection rate was observed in 2018, at 43.6% (144) [11]. A study conducted in Qatar found that the highest viral meningitis detection rate occurred in 2017, at 42.5% (311). In our study, the detection rate for viral agents was highest in 2024 (5.3%, 10 cases), followed closely by 2023 (5.2%, 11 cases). No statistically significant difference was found between the years ($p = 0.164$). Although no significant difference was observed between years, the increase in viral meningitis cases could be attributed to the relaxation of pandemic-related precautions (social distancing, mask use, hygiene measures) after 2022, as well as changes in healthcare-seeking behaviors. This may have contributed to a rise in viral infections, including viral causes of meningitis such as enteroviruses, HSV, and VZV. The resumption of normal activities following the pandemic likely increased the circulation of these viruses and, consequently, contributed to the rise in meningitis cases.

Limitations

We included only patients who underwent lumbar puncture and cerebrospinal fluid (CSF) PCR. This inclusion criterion may have missed cases with milder infections, potentially underestimating the true incidence of viral central nervous system (CNS) infections. Furthermore, only prespecified pathogens were tested, meaning that negative cases may be infected with organisms not included in our diagnostic algorithms. The lack of detailed clinical data, including clinical presentations, patients' comorbidities, and survival outcomes, as well as the limited scope of the PCR panel—covering only a restricted number of viral pathogens and potentially failing to detect rare or newly identified neurotropic viruses—constitutes additional limitations of the study.

CONCLUSION

This study is the first to report the molecular diagnosis of viral meningitis in Muğla. Our findings largely reflect the incidence of viral meningitis. Among the 867 patients who underwent CSF PCR for suspected viral meningitis, a viral pathogen was identified in 4.0% (35) of cases. This rate was 3.6% (27) in adults and 6.3% (8) in children, with no statistically significant difference between the two groups. The most commonly identified pathogens were HSV-1, VZV, and EV, which is consistent with global literature; however, the most frequently identified pathogen was HSV-1 rather than EV, which we believe may be due to encephalitis accompanying some cases presenting with suspected meningitis. The use of molecular methods to identify viral pathogens plays a crucial role in patient management. Early and accurate identification of viral pathogens improves the likelihood of effectively managing viral meningitis by enabling timely administration of antiviral agents. Moreover, diagnosing a specific virus in cases of viral meningitis can reduce inappropriate antibiotic use, the duration of hospital stays, and hospital admission costs. Further studies are needed to determine the frequency of pathogens in Turkey and to obtain sufficient epidemiological data.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Muğla Sıtkı Koçman University Faculty of Medicine, Department of Medical Sciences (Decision no: 163, Date: 09.12.2024).

Informed Consent: Since our article is retrospective, patient consent is not required.

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Reasons for refusal of newborn heel-prick screening and associated factors

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MAIN POINTS

- There is a connection between heel-prick blood test refusal and vaccine refusal. Heel-prick blood test refusal appears to arise from a "general distrust of health interventions."
- The most important reasons for refusal of heel-prick blood screening are lack of information and misinformation. Misinformation and digital disinformation appear to influence parents' decisions.
- The underlying reason for vaccine refusal is a trust issue. It is seen that parents' perception of trust is more decisive than access to information.
- 63.2% of families did not have heel-prick tests done on their previous children either. The refusal behavior has become a permanent attitude and behavior pattern among parents.

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ABSTRACT

Aim: This study was conducted to examine the reasons for refusal among families who declined newborn heel-prickheel-prick screening, determine the relationship between heel-prickheel-prick screening and childhood vaccination, identify factors influencing this refusal.

Materials and Methods: The cross-sectional study was conducted from January to February 2026. The study included 171 parents who refused heel-prick screening in Şanlıurfa province during 2024-2025. Data were collected using a 14-item structured information form. The analysis used descriptive statistics, univariate analyses, chi-square tests (Pearson chi-square, continuity correction, Fisher chi-square), and a logistic regression model.

Results: Of the babies who did not have a heel prick blood test, 54.4% had not received their childhood vaccinations. 84.0% of parents stated that vaccines were not safe, and 70.2% expressed concern about the vaccine content. 63.2% of families who refused heel-prick screening did not have heel-prickthe screening performed on their other children. The most common reason for refusing the heel-prick test was suspicion about its purpose. According to the logistic regression model, the decision to vaccinate the current child was positively associated with the vaccination status of other children (odds ratio = 51.2). The vaccination variable was associated with an 8.6-fold increase in heel screening among other children (p<0.001).

Conclusion: Families do not consider newborn heel-prick screening and childhood vaccination safe. This demonstrates parents' distrust of preventive health services and highlights the importance of effective communication skills among healthcare personnel.

Keywords: Newborn screening, Vaccine refusal, Attitude, Preventive health services

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INTRODUCTION

Screening programs are implemented to facilitate the early diagnosis of certain congenital diseases that are predominantly autosomal recessive and can be fatal if left untreated. Newborn heel-prick screening tests are at the forefront of these programs [1]. Although the scope of testing varies, newborn heel-prickheel-prick screening is performed to detect congenital diseases in Europe, North America, and Australia. The test is mandatory for all infants, particularly in the United Kingdom, France, Italy, and Germany. Phenylketonuria is the most commonly screened disease worldwide under these programs [2]. Turkey is known as one of the countries that implement mandatory newborn heel-prick screening. In Turkey, newborn heel-prick screening is used to screen for phenylketonuria, hypothyroidism, cystic fibrosis, biotinidase deficiency, and adrenal hyperplasia [1]. Unlike Turkey, many countries, including those in Europe and the US, include Glutaric Acidemia type 1, Maple Syrup Urine Disease, and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency in their screening programs. In our country, where consanguineous marriage is prevalent at a rate of 25%, it is reported that many diseases will be detected and, if necessary, addi-

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tional diseases will be added to the screening list [2]. Indeed, Spinal Muscular Atrophy (SMA), a disease frequently heard of in recent years, has been added to the newborn heel-prick screening program starting in 2022 [3]. Heel blood screening, a critical component of health policy in many countries, cannot be performed on all newborns despite all improvements in health services due to economic, administrative, personnel training, and social barriers [4]. Recently, there have been concerns that some families in Turkey and around the world are hesitant about heel-prick screening, with participation rates falling below 99% [5]. Misinformation circulating on social media and unscientific opinions from non-experts are causing confusion among parents and preventing them from having their children screened [1,6,7]. On the other hand, the belief that the procedure is painful for the baby, views that place greater importance on alternative medicine, and prejudices against childhood vaccinations are leading families to refuse heel-prick screening [5]. Furthermore, false positives in the tests and the lack of sufficient information and psychological support for parents regarding the possibility of disease detection increase anxiety about the test [8]. There is limited information in the literature regarding parents' current perceptions of heel-prickheel-prick screening. Research on the reasons for refusing heel-prick screening and combating concerns about the spread of opposition is crucial [5]. In this regard, the study aims to determine the reasons why families in Şanlıurfa province refuse newborn heel-prick screening in 2024 and 2025, the relationship between heel-prick refusal and childhood vaccination, and the factors influencing that refusal.

MATERIALS AND METHODS

Research design

The cross-sectional study was conducted in the province of Şanlıurfa from January to February 2026. Permission to conduct the study was obtained from the Harran University Clinical Research Ethics Committee (Approval number: 25.20.05, Date: 15.12.2025). The research was conducted with the consent of the families. The study was conducted in accordance with the Declaration of Helsinki and data protection principles.

Research population and sample

The study population comprised the parents of 500 infants in Şanlıurfa province who did not undergo heel-prickheel-prick screening in 2024–2025. The sample size was calculated as 113, assuming 80% power, 95% confidence interval, and a level of finding heel-prick screening to be ineffective of 8% [9]. The aim was to contact the parents of 113 infants selected by simple random sampling from the list of 500 newborns. Parents from families who refused screening were assigned random numbers, and odd-numbered parents were included in the study sequentially. The study included 171 parents who were randomly selected and volunteered to participate.

Variables of the study

The dependent variables are heel-prickheel-prick screening and childhood vaccination status. The independent variables are age, gender, marital status, educational status, socioeconomic status, employment status, social security status, number of children, family type, childhood vaccination status of the current child, childhood vaccination status of other children, and heel-prickheel-prick test status.

Research criteria

Inclusion criteria

- Residing in Şanlıurfa province
- Having refused heel blood screening in 2024-2025 and agreeing to participate in the study,
- Possessing the cognitive ability to understand and answer questions,
- Being 18 years of age or older is an inclusion criterion.

Exclusion criteria

- Incomplete questionnaires, invalid responses (answers that do not align with the question and do not provide sufficient information for evaluation),
- Difficulty understanding the questions (despite being asked repeatedly, providing incorrect interpretations, incomplete answers, or inconsistent statements),
- Refusal to participate at any stage of the study.

Data collection tools

Data were collected using a structured information form created by researchers. The information form included the following: age, gender, marital status, educational status, socioeconomic status, occupation, social security, number of children, family type, childhood vaccination status, reasons for not vaccinating, heel-prickheel-prick test status, and reasons for refusing the heel-prickheel-prick test.

Data collection method

Data were collected by researchers through face-to-face interviews with each parent, lasting an average of 15 minutes. Interpreters were provided for parents who did not speak Turkish.

Statistical analysis

Data were evaluated using the IBM SPSS Statistics 25.0 software package. $P<0.05$ was considered statistically significant. Descriptive statistics (count, percentage, minimum, maximum, mean, standard deviation) and univariate analyses (chi-square tests: Pearson chi-square, continuity correction, Fisher's exact test) were used in the study. Logistic regression analysis was applied to variables found to be significant in univariate analysis. A logistic regression model was

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Table 1. Distribution of sociodemographic characteristics according to vaccination status.

Variables	N (%)	Vaccination status of the current child		X^2	P
		Yes N (%)	No N (%)		
Age					
30 years old and under	92 (53.8)	46 (50.0)	46 (50.0)	0.571	0.450
31 years old and over	79 (46.2)	34 (43.0)	45 (57.0)		
Parent gender					
Male	39 (22.8)	18 (46.2)	21 (53.8)	0.000	1.000
Female	132 (77.2)	62 (47.0)	70 (53.0)		
Number of children					
2 and under	99 (57.9)	47 (47.5)	52 (52.5)	0.003	0.954
3 and over	72 (42.1)	33 (45.8)	39 (54.2)		
Family type					
Nuclear	144 (84.2)	67 (46.5)	77 (53.5)	0.000	1.000
Extended	27 (15.8)	13 (48.1)	14 (51.9)		
Income status					
Income lower than expenses	53 (31.0)	28 (52.8)	25 (47.2)	2.957	0.228
Income equal to expenses	101 (59.1)	45 (44.6)	56 (55.4)		
Income higher than expenses	17 (9.9)	5 (29.4)	12 (70.6)		
Education status					
Literate and below	17 (10.0)	9 (52.9)	8 (47.1)	3.817	0.431
Elementary school graduate	23 (13.5)	10 (43.5)	13 (56.5)		
Middle school graduate	27 (15.8)	16 (59.3)	11 (40.7)		
High school graduate	46 (26.9)	21 (45.7)	25 (54.3)		
University graduate and above	58 (33.8)	22 (37.9)	36 (62.1)		
Employment status					
Employed	70 (40.9)	25(35.7)	45 (64.3)	4.031	**0.045**
Unemployed	101 (59.1)	53(52.5)	48 (47.5)		
Social security					
Yes	140 (81.9)	67 (47.9)	73 (52.1)	0.159	0.690
No	31 (18.1)	13 (41.9)	18 (58.1)		
Vaccination status of other children*					
Yes	91(73.4)	56 (61.5)	35 (38.5)	31.064	**<0.001**
No	33(26.6)	1 (3.0)	32 (97.0)		

*47 parents with one child did not answer the question.

Table 2. Distribution of reasons for vaccine refusal.

	Yes N (%)	No N (%)
I don't think vaccines are safe / I have concerns about side effects	79 (84.0)	15 (16.0)
I have concerns about the contents of the vaccine	66 (70.2)	28 (29.8)
I was influenced by negative things I read or heard about vaccines in the media	41 (43.6)	53 (56,4)
I didn't think getting vaccinated was necessary	37 (39.4)	57 (60.6)
I don't think vaccines protect against disease (are effective)	36 (38.3)	58 (61.7)
I had a bad experience with previous vaccinations / developed an adverse reaction	16 (17.0)	78 (83.0)
Someone else told me the vaccine is not safe.	16 (17.0)	78 (83.0)
Someone else told me their child had a bad reaction after vaccination.	15 (16.0)	79 (84.0)
Due to my other beliefs / preferences related to traditional medicine.	9 (9.6)	85 (90.4)
I did not get vaccinated for religious or faith-related reasons.	8 (8.5)	86 (91.5)
Due to previous bad experiences with healthcare personnel or healthcare institutions.	4 (4.3)	90 (95.7)
I am afraid of getting injections.	3 (3.2)	91 (96.8)

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Table 3. Distribution of reasons for refusing heel blood screening.

	Yes N (%)	No N (%)
I have doubts about the real purpose of the test (collection of my genetic information, creation of a database, etc.).	93 (54.4)	78 (45.6)
I was concerned that my baby would suffer because the blood would be taken from the heel.	71 (41.5)	100 (58.5)
Negative posts I saw on social media made me anxious about this.	55 (32.2)	116 (67.8)
My concerns about vaccines prevented me from having the heel prick test done.	48 (28.1)	123 (71.9)
I thought it would negatively affect breastfeeding or my baby's natural development.	25 (14.6)	146 (85.4)
I was concerned that the intervention on the heel would affect my child's sexual health.	14 (8.2)	157 (91.8)
I thought that if one of the screened diseases was detected, I would face financial or emotional hardship.	14 (8.2)	157 (91.8)
I find heel prick screening unnecessary.	35 (20.5)	136 (79.5)
The healthcare personnel said it would cause pain.	13 (7.6)	158 (92.4)
I was not sufficiently informed about heel prick screening.	7 (4.1)	164 (95.9)
I did not like the behavior of the healthcare personnel.	7 (4.1)	164 (95.9)
I did not have it done because my baby was unwell.	4 (2.3)	167 (97.7)
The obstetrician advised me not to have it done.	3 (1.8)	168 (98.2)
I could not go for the vaccination because my financial situation was poor.	2 (1.5)	169 (98.5)

Table 4. Distribution of heel prick screening status among children according to variables.

Variables	The situation of having heel prick blood tests done on other children		X^2	P
	Yes N (%)	No N (%)		
Age				
30 years old and under	47 (82.5)	10 (17.5)	1.330	0.249
31 years old and over	61 (91.0)	6 (9.0)		
Parent gender				
Male	26 (83.9)	5 (16.1)	*	0.544
Female	82 (88.2)	11 (11.8)		
Number of children				
2 and under	43 (82.7)	9 (17.3)	0.945	0.331
3 and over	65 (90.3)	7 (9.7)		
Family type				
Nuclear	90 (88.2)	12 (11.8)	*	0.482
Extended	18 (81.8)	4 (18.2)		
Income status				
Income lower than expenses	36 (92.3)	3 (7.7)		
Income equal to expenses	60 (84.5)	11 (15.5)	1.390	0.499
Income higher than expenses	12 (85.7)	2 (14.3)		
Education status				
Literate and below	13 (92.9)	1 (7.1)		
Elementary school graduate	18 (90.0)	2 (10.0)		
Middle school graduate	16 (84.2)	3 (15.8)	1.942	0.746
High school graduate	29 (90.6)	3 (9.4)		
University graduate and above	32 (82.1)	7 (17.9)		
Employment status				
Employed	40 (83.3)	8 (16.7)	0.516	0.472
Unemployed	68 (89.5)	8 (10.5)		
Social security				
Yes	87 (87.0)	13 (13.0)	*	0.626
No	21 (87.5)	3 (12.5)		
Vaccination status of other children*				
Yes	86 (94.5)	5 (5.5)	*	**<0.001**
No	22 (66.7)	11 (33.3)		

**Fisher's Chi-Square.

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Table 5. Distribution of variables affecting the status of heel prick screening and vaccination according to Logistic Regression analysis.

Have heel prick tests done for other children					
	B	Standard Error	P	O.R	95% Confidence Interval
Vaccinate other children (yes)	2.1	0.5	**<0.001**	8.6	2.7-27.3
Get the current child vaccinated					
	B	Standard Error	P	O.R	95% Confidence Interval
Vaccinate other children (yes)	3.9	1.0	**<0.001**	51.2	6.6-391.6

established using employment status and other children's vaccination status as predictors of the current child's vaccination status, and using other children's vaccination status as a predictor of whether other children have undergone heel-prick blood testing. The backward stepwise (conditional) method was used in logistic regression analysis.

RESULTS

57.9% of the participants reside in the three central districts. 53.8% of parents are aged 30 years or younger, and their ages range from 20 to 44 years. 42.1% of families have 3 or more children, with the number of children ranging from 1 to 8. 77.2% of participants are female, and 33.8% have a university degree or higher. 15.8% of families are extended, and 31.0% have incomes lower than their expenses. Of the participants, 13.5% are workers, 20.5% are civil servants, 5.8% are tradespeople, and 60.2% are not employed. 54.4% of infants who did not undergo heel-prick testing did not receive childhood vaccinations. Vaccination rates were higher among parents who were not employed (p=0.045) and lower among families who did not vaccinate their other children (p<0.001). The effects of age, parental gender, number of children, family type, income status, educational status, and social security variables on vaccination status could not be determined (p>0.05; Table 1).

Among parents who did not vaccinate one or more of their children, 84.0% stated that vaccines are not safe, and 70.2% expressed concern about the contents of vaccines (Table 2).

63.2% of participants did not have heel-prickheel-prick screening performed for their other children. The reasons for refusal were examined: the three most common were doubts about the purpose of the test (54.4%), concern that the baby would suffer during the screening (41.5%), and concern about negative posts on social media (32.2%) (Table 3).

In the study, 63.2% of families who did not have heel blood taken from their babies had not had heel blood screening for their previous children. The level of heel-prick-prick screening among children vaccinated by their families was higher than among those whose families did not vaccinate (p<0.001). The effect of other variables on heel-prick testing status could not be determined (Table 4).

A logistic regression model was fitted using variables that affect the decision to vaccinate the current child. The variable 'vaccinating other children' had a 51.2-fold positive effect. Vaccination was found to have an 8.6-fold positive effect on the decision to have heel-prick screening performed on other children (p<0.001) (Table 5).

DISCUSSION

This study examines the attitudes of families in Şanlıurfa province preventive health services, heel-prickspecifically newborn heel-prick and vaccination services.

The study found that a significant proportion (54.4%) of infants who did not undergo heel-prick testing also did not receive childhood vaccinations. This indicates that families' decisions to undergo heel-prickheel-prick screening are influenced by their refusal of vaccinations. Indeed, the study found that childhood vaccination status positively influenced families' decision to undergo heel-prickheel-prick screening by a factor of 8.6. The findings reveal a strong, statistically significant association between heel-prickrefusal of heel-prick screening and refusal of vaccination. This situation is thought to be related to parents' overall trust in the healthcare system. The study results are consistent with other studies in the literature showing that families with negative attitudes toward screening programs also take a distant approach to vaccination practices [5,7,10].

Parents' first contact with the healthcare system begins with newborn screening programs, and reports indicate that trust formed at this stage is critical in childhood vaccine refusals. Families' behaviors towards healthcare practices and their decisions regarding newborns are shaped by their experiences [9]. Indeed, in this study, the vaccination status of other children positively influenced the decision to vaccinate the current child by 51.2 times [7]. The study results support the notion that screening programs are seen as the foundation for trust in childhood vaccinations [7].

This study found that the vast majority of parents believe that vaccines are unsafe and therefore refuse vaccination because of serious concerns about vaccine content. This result is consistent with the findings of national and international studies highlighting vaccine safety perceptions and content concerns as factors in vaccine refusal [5,6,11]. The study found that negative social media posts about childhood vaccines affect families. It is reported that scientifically unfounded information spread on digital platforms increases parents' perception

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of risk and fuels vaccine hesitancy [1,5]. Furthermore, families' decisions to vaccinate are influenced by other parents' negative experiences and by their relatives' negative statements about vaccines. It has been determined that, even at a low level, preferences for traditional medicine, families' religious beliefs, and previous difficulties with healthcare institutions or personnel influence the decision to vaccinate children. It is thought that families are easily influenced by negative behaviors and misinformation they are exposed to through the media due to their lack of knowledge about vaccination practices and their purpose [5]. In a study conducted by Topuz and colleagues, it was emphasized that some mothers had a positive attitude towards newborn screening tests but lacked sufficient information about the purpose, scope, and results of the tests [6]. A lack of information in the literature is cited as one of the key determinants of screening refusal, leading families to perceive screening tests as a "mandatory procedure" and to develop distrust and anxiety about the test [12].

In this study, the majority (63.2%) of families who refused heel-prickheel-prick screening had also not had their previous children screened. When evaluating heel-prickreasons for refusal of heel-prick screening, the most frequently reported reason was suspicion about the actual purpose of the test. Parents' concerns that genetic information would be misused, that a database would be created, or that data would be stored for commercial purposes are frequently highlighted in the literature [5,8]. In the study by Van der Pal and colleagues, it was reported that parents' decisions to refuse screening tests were mostly based on ethical and privacy concerns rather than the technical content of the test [5]. This situation indicates that in addition to the medical benefits of the test, data security and privacy issues must be addressed in detail during the information process.

Concern that the baby would experience pain was the second most common reason for heel-prickrefusal of heel-prick blood sampling in our study. Some studies in the literature have also reported that parents perceive heel-prick blood sampling as invasive and traumatic, and that this perception influences their refusal of the test [6]. In contrast, reports of negative attitudes or of insufficient information provided by healthcare personnel were less frequent. This finding suggests that parental decisions are mostly shaped by pre-existing perceptions and information from external sources.

Notably, the study found no significant effect of sociodemographic variables on vaccination and heel-prickheel-prick screening rates. Although some studies in the literature have associated low educational level and low socioeconomic status with vaccine refusal [4], recent studies show that vaccine and screening refusal can be widespread in different socioeconomic groups in society [5,7]. This situation highlights that the problem is not specific to certain risk groups and that interventions targeting the general population are needed.

In the literature, the reasons for newborn screening refusal include fears of false positive results, ethical concerns about genetic testing, religious or cultural beliefs, distrust of government intervention, and general skepticism about the healthcare system [5,13-15]. The relatively low rate of religious or traditional reasons reported in our study suggests that the current trend of vaccine refusal is driven more by misinformation, a lack of clear and adequate information, and trust issues than by beliefs or culture.

The role of healthcare professionals is particularly emphasized in the literature. It has been reported that mothers mostly obtain information about screening tests from healthcare personnel, but that the likelihood of refusal increases when the content and method of information provision are inadequate [16]. A large proportion of families in our study reported that they were not sufficiently informed about screening test results and their long-term benefits, which is consistent with these findings.

Limitations

This study has some limitations. The research results apply only to families who refused heel blood screening and thus cannot be generalized to the entire parent population. The calculation of the minimum number of participants needed to be representative of the population may have yielded an insufficient sample size. Furthermore, self-reported data may have introduced recall bias. However, the use of face-to-face interviews and exceeding the target sample size are strengths of the study.

CONCLUSION

This study demonstrates that heel-pricknewborn heel-prick screening and childhood vaccine refusal are shaped by a common foundation of issues related to trust and knowledge. It is crucial for healthcare workers, especially during pregnancy and the early postpartum period, to establish evidence-based, transparent, and empathetic communication with parents and to provide systematic counseling on the purpose, benefits, and safety of screening and vaccination programs. This approach is considered an effective strategy for restoring trust in preventive healthcare services and reducing refusal rates. In this regard, expanding in-service training programs that strengthen healthcare professionals' communication skills can effectively address vaccine hesitancy and refusal to undergo screening.

Ethics Committee Approval: Permission to conduct the study was obtained from the Harran University Clinical Research Ethics Committee (Approval number: 25.20.05, Date: 15.12.2025).

Informed Consent: Written informed consent was obtained from all parents for the study.

Peer-review: Externally peer-reviewed.

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Do accompanying glenohumeral joint pathologies affect the clinical outcomes of arthroscopic rotator cuff repair surgery?

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MAIN POINTS

- Orthopedic surgeons commonly encounter rotator cuff tears.
- Accompanying glenohumeral joint pathologies significantly affect the clinical outcomes of arthroscopic rotator cuff repair.
- Patients with biceps tendinopathy have worse shoulder flexion, internal rotation, and ASES scores both before and after rotator cuff repair.

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ABSTRACT

Aim: To compare the clinical outcomes of arthroscopic rotator cuff repairs in patients with or without concomitant glenohumeral joint lesions.

Materials and Methods: Patients with a confirmed diagnosis of rotator cuff tear who underwent arthroscopic repair were included in this retrospective comparative study. Patients were grouped according to the presence of accompanying glenohumeral joint pathology identified during arthroscopic surgery. Demographic, clinical, and operative data were recorded for all patients. Physical examination findings and clinical scores were recorded for all patients at initial admission and at the 6-month postoperative follow-up examination.

Results: Group I included 61 patients (with accompanying glenohumeral pathologies) and Group II included 32 patients (with no glenohumeral pathology). The mean shoulder flexion of patients in Group II was significantly higher than that in Group I at both preoperative and postoperative 6 months of follow-up examinations (p=.015 and .001, respectively). The mean internal rotation of the shoulder in Group II was also significantly higher than that in Group I preoperatively and at 6 months postoperatively follow-up examinations (p=.029 and .038, respectively). The mean ASES score of patients in Group II was significantly higher preoperatively and at 6 months postoperatively than that in Group I (p=.002 and .020, respectively).

Conclusion: Among patients who underwent rotator cuff repair, those with accompanying glenohumeral joint pathologies had significantly lower shoulder flexion, internal rotation, and ASES scores than those without such pathologies.

Keywords: Shoulder arthroscopy, Rotator cuff tear, Clinical outcomes, Biceps tendinopathy, Glenohumeral arthritis, SLAP lesion

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INTRODUCTION

Rotator cuff tears are commonly encountered by orthopedic surgeons due to increased activity among older adults and increased life expectancy. Currently, open, mini-open, and arthroscopic surgical methods are used for the surgical treatment of rotator cuff tears [1-3]. Just as rotator cuff tears may be observed on their own, they may also be detected with other glenohumeral joint pathologies such as biceps tendinosis, glenohumeral arthrosis, superior labral anterior posterior (SLAP) tears, and anterior labrum tears [4-8]. Gartsman reported that 68% of 200 patients with full-layer rotator cuff tears had glenohumeral joint pathology and mentioned that 12.5% of these were major abnormalities such as glenohumeral osteoarthritis, labral tears, and biceps tendon tears [6,9].

Determining whether the presence of this pathology influences the clinical results of patients undergoing arthroscopic rotator cuff repair is of considerable importance [6]. Existing literature contains only a small number of studies examining how glenohumeral joint pathologies—identified intraoperatively during arthroscopic procedures—impact the clinical outcomes of patients undergoing arthroscopic rotator cuff repair [8-10]. We hypothesized that patients with concomitant glenohumeral joint pathologies would have worse clinical outcomes than those without such pathologies. Accordingly, this study sought to compare the clinical outcomes of patients un-

dergoing arthroscopic rotator cuff repair, distinguishing between those with concomitant glenohumeral joint abnormalities and those without such lesions.

MATERIALS AND METHODS

Study population

This retrospective case-control study received approval from the Erzincan University Clinical Research Ethics Committee (Decision no: 18/02, Date: 09.01.2018) and was carried out in compliance with the principles of the Declaration of Helsinki. Patients who had a rotator cuff tear verified by clinical and radiologic assessment and underwent arthroscopic repair between January 2014 and December 2017 were included.

Patients with incomplete medical records, a history of fracture or surgery on the affected side, or those lost to follow-up were excluded. A total of 93 patients who underwent arthroscopic rotator cuff repair surgery were evaluated in this study. All patients were informed about surgery and they signed consent form before surgery. Patients were grouped according to the presence of accompanying glenohumeral joint pathology identified during arthroscopic surgery. Additional glenohumeral joint pathologies were observed in 61 of 93 patients (Group I). Patients with no accompanying glenohumeral joint pathologies comprised Group II.

Surgical technique

The surgeries were performed with patients positioned either in the beach-chair or lateral decubitus position and anesthetized with general anesthesia or a regional nerve block. Double-row repair was performed for supraspinatus tears, and single-row repair was performed for subscapularis tears. The shoulder was immobilized for 6 weeks using an anti-rotation shoulder sling. A standardized rehabilitation program was performed for all patients, consisting of pendulum exercises and passive movements for the first 6 weeks, followed by muscle strengthening beginning 6 weeks postoperatively.

Data collection

At the time of initial presentation, data were collected on each patient's age, sex, body mass index, dominant and affected sides, smoking habits, duration of symptoms (months), and the underlying cause of the tear.

Subacromial interval distance (mm), acromion–glenoid angle, and supraspinatus–glenoid angle were measured by a single observer on magnetic resonance imaging (MRI) scans electronic records of our hospital. Patients' physical examination findings such as shoulder range of motion (ROM) measurement, presence of instability, and impingement were recorded for all patients at first admission and at postoperative 6 months of follow-up examination. Disability of arm and shoulder (Quick DASH) score, visual analog scale (VAS) score, and American Shoulder and Elbow Surgeons Shoulder (ASES) score were evaluated for each patient at first admission and at postoperative 6 months of follow-up. Clinical and functional outcomes were evaluated at the 6-month postoperative follow-up, which was defined as the primary endpoint of the study. Although the mean overall follow-up duration was 12.2 months (range: 6–40 months), standardized clinical assessments were consistently available at 6 months for all patients; therefore, this time point was used for comparative analysis.

Statistical analysis

Statistical analyses were conducted using SPSS version 20.0 (SPSS Inc., IBM, NY, USA). Continuous variables were reported as means with standard deviations, whereas categorical variables were presented as counts and percentages. The Kolmogorov–Smirnov test was used to assess the normality of the data distribution. Mean differences were examined using the Student's t-test, and categorical comparisons were performed with Pearson's chi-square test. A p-value below 0.05 was accepted as the threshold for statistical significance. However, when the assumptions of the chi-square test were not met (i.e., when more than 20% of expected cell counts were less than 5), Fisher's exact test was used. Additionally, post hoc power calculations were carried out using the G*Power 3.0 software (Germany).

RESULTS

Group I consisted of 61 patients (38 females, 23 males) with a mean age of 59.8 years who had accompanying glenohumeral joint pathologies. The group without accompanying glenohumeral joint pathologies (Group II) consisted of 32 patients

Table 1. The demographic data of the patients.

	Group I (n=61)	Group II (n=32)	P values
Gender			.823
Female	38 (62.3%)	21 (65.6%)	
Male	23 (37.7%)	11 (34.4%)	
Age (years)	59.8 ± 9.2	54.1 ± 10.4	**.009**
Body mass index(kg/m^2)	24.5 ± 1.9	24.1 ± 1.9	.367
Dominant hand			
Right	51 (83.6%)	30 (93.75%)	
Left	10 16.4%)	2 (6.25%)	
Affected side			.224
Right	41 (67.2%)	26 (81.25%)	
Left	20 (32.8%)	6 (18.75%)	
Smoking			.743
Yes	8 (13.1%)	3 (9.4%)	
No	53 (86.9%)	29 (90.6%)	
Duration of symptoms (months)	10.3 ± 4.1	8.8 ± 3.7	.091
Etiology			.192
Traumatic	25 (41%)	18 (56.25%)	
Degenerative	36 (59%)	14 (43.75%)	

n: number. Bold p value indicate statistically significance.

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Table 2. Preoperative Magnetic Resonance Imaging (MRI) findings of the patients.

	Group I (n=61)	Group II (n=32)	P values
Subacromial interval distance (mm)			
Coronal	6.1 ± 0.7	6 ± 0.8	.327
Sagittal	6.2 ± 0.7	6 ± 0.8	.324
Acromion-Glenoid angle (degree)	85 ± 1	84.9 ± 1	.781
Supraspinatus-Glenoid angle (degree)	84.8 ± 0.6	84.6 ± 0.9	.288
Tendon Tear			.513
Supraspinatus	44 (72.1%)	25 (78.1%)	
Subscapularis	0	1 (3.1%)	
Supraspinatus+Subscapularis	17 (27.9%)	6 (18.8%)	
Tear Type			.623
Partial	44 (72.1%)	25 (78.1%)	
Full-Thickness	17 (27.9%)	7 (21.9%)	
Tear Side			.865
Bursal	8 (13.1%)	5 (15.6%)	
Articular	48 (78.7%)	23 (71.9%)	
Intratendinosus	5 (8.2%)	4 (12.5%)	

n: number.

Table 3. Surgical procedure data of the groups.

	Group I (n=61)	Group II (n=32)	P values
Anesthesia Type			.932
General Anesthesia	50 (82%)	26 (81.25%)	
Regional Anesthesia	11 (18%)	6 (18.75%)	
Patient Position			.549
Beach Chair	3 (4.9%)	0	
Lateral Decubitis	58 (95.1%)	32 (100%)	
Repaired Tendon			.717
Supraspinatus	43 (70.5%)	25 (78.1%)	
Subscapularis	2 (3.3%)	1 (3.1%)	
Supraspinatus+Subscapularis	16 (26.2%)	6 (18.8%)	
Biceps Tenotomy			**< .001**
+	43 (70.5%)	0	
-	18 (29.5%)	32 (100%)	
Acromioplasty			.889
+	43 (70.5%)	23	
-	18 (29.5%)	9	
SLAP Repair			.09
+	6 (9.8%)	0	
-	55 (90.2%)	32 (100%)	
Labrum Repair			.161
+	5 (8.2%)	0	
-	56 (91.8%)	32 (100%)	
Glenohumeral Arthrosis			**.007**
+	12 (19.7%)	0	
-	49 (80.3%)	32 (100%)	

n: number. Bold p value indicate statistically significance.

(21 females, 11 males) with a mean age of 54.1 years. The demographic data of the groups are presented in Table 1.

The mean age of patients in Group I was significantly higher than that in Group II (p=.009) (Table 1). There were no statistically significant differences between the two groups regarding preoperative MRI measurements or imaging findings (Table 2). Of the 93 patients, 68 (73%) underwent supraspinatus repair, 3 (3%) underwent subscapularis repair, and 22 (24%) underwent both supraspinatus and subscapularis repair. Arthroscopic acromioplasty was performed on 66 patients (71%) for extrinsic compression identified during surgery. We observed biceps tendinopathy in 50 patients, glenohumeral osteoarthritis in 12 patients, SLAP tears, and anterior labral tears. Biceps tenodesis or tenotomy was performed in cases in which the long head of the biceps tendon demonstrated degenerative tendinopathy. SLAP tear repair was performed in 6 patients (6%), whereas anterior labrum repair was performed in 5 patients (5%) (Table 3).

The mean shoulder flexion of patients in Group II was significantly higher than that of Group I at both the preoperative and the 6-month postoperative follow-up examinations (p=.015 and .001, respectively). The mean internal rotation of shoulder in Group II was also significantly higher than that in Group I at preoperative and postoperative 6 months of follow-up examinations (p= .029 and .038, respectively) (Table 4). VAS, ASES, and QuickDASH functional scores were evaluated both before surgery and at the 6-month postoperative follow-up. The mean ASES scores differed significantly between the two groups when evaluated preoperatively and at the 6-month postoperative follow-up. The mean ASES score of patients in Group II was significantly higher than in Group I both preoperatively and at the 6-month postoperative follow-up (p=.002 and .020, respectively) (Table 5).

DISCUSSION

The most important outcome of this study was the observation that concomitant glenohumeral joint pathologies significantly affected the clinical outcomes of patients undergoing arthroscopic rotator cuff repair. As previously reported in the

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Table 4. Preoperative and postoperative 6-months shoulder range of motion (ROM) of the groups.

	Group I (n=61)	Group II (n=32)	P values
Preoperative ROM (degrees)			
Flexion	141.4 ± 9.6	147.5 ± 13.4	**.015**
Internal rotation	42.9 ± 8.6	47.8 ± 12.3	**.029**
External rotation	53.9 ± 11.1	58.4 ± 15.6	.112
Abduction	80.1 ± 12.3	85 ± 17.4	.124
Postoperative 6-months ROM (degrees)			
Flexion	152.7 ± 7.3	158.7 ± 8.7	**.001**
Internal rotation	58.5 ± 6.7	61.5 ± 6.2	**.038**
External rotation	68 ± 10.1	68.7 ± 11.8	.761
Abduction	112.7 ± 14	117.8 ± 15.8	.120

n: number. Bold p value indicate statistically significance.

Table 5. Preoperative and postoperative 6-months follow-up clinical scores of the patients.

	Group I (n=61)	Group II (n=32)	P values
Visual Analog Scale			
Preoperative	7.2 ± 0.5	7 ± 0.5	.318
Postoperative	1.4 ± 0.4	1.2 ± 0.4	.096
Quick DASH score			
Preoperative	58.7 ± 6	58.1 ± 4.1	.632
Postoperative	21.4 ± 2.3	20.9 ± 3.2	.392
ASES score			
Preoperative	21 ± 1.6	22.4 ± 2.4	**.002**
Postoperative	37.9 ± 2.5	39.2 ± 2.6	**.020**

n: number, DASH: Disabilities of Arm, Shoulder and Hand, ASES: American Shoulder and Elbow Surgeons bold p values indicate statistically significance.

literature, accompanying glenohumeral joint pathologies that were not identified at preoperative radiological assessment but identified during arthroscopic rotator cuff repair may have a negative impact on the clinical outcomes in the postoperative period [11-14]. Miller and Savoie [10] documented that 74% of patients presenting with full-thickness rotator cuff tears had associated glenohumeral joint pathologies. Other studies in the literature have reported similar rates of accompanying glenohumeral joint pathologies accompanying rotator cuff tears [6, 15-19]. Forsythe et al. [5] compared 28 patients with isolated rotator cuff tear and 34 patients with accompanying SLAP lesion. Their outcomes revealed that shoulder range of motion did not differ significantly between the groups [5].

According to their results, the ASES score in the preoperative period was found to be

statistically significantly low in patients with an accompanying SLAP lesion; whereas, no

statistically significant difference was identified in the ASES score in the postoperative period [5]. Authors reported that patients with an accompanying SLAP lesion to rotator cuff tear had no statistically significant differences in the preoperative Constant score; however, in the postoperative period, the Constant score for these patients was found to be statistically significantly high [5].

A study by Franceschi et al. [20] compared 31 patients with additional SLAP lesion repair and 32 patients with additional biceps long-head tenotomy. The authors reported that patients with biceps tenotomy had better UCLA score and shoulder ROM [20]. In literature, SLAP lesion was frequently associated with rotator cuff tears and mentioned that this lesion is commonly missed [21,22]. Abbot et al. [4] compared patients with an additional SLAP lesion or biceps long-head tenotomy who underwent rotator cuff repair. Authors reported that the UCLA score of biceps tenotomy was found to be significantly higher due to increased functional activity and reduced pain relief than the UCLA score of patients with SLAP repair [4]. In addition, the authors found that patients with biceps long-head tenotomy had better shoulder internal rotation and external rotation [4].

Our study group, which presented with accompanying glenohumeral joint pathologies, mostly consisted of patients with biceps tendinopathy, and our results demonstrated that these patients had worse preoperative and postoperative outcomes in shoulder flexion, internal rotation, and ASES score. The observed differences in internal rotation and flexion may be explained by the high prevalence of biceps tendinopathy in the concomitant pathology group. The long head of the biceps plays a role in shoulder stabilization and kinematics, and its pathology may contribute to altered glenohumeral mechanics. Additionally, associated intra-articular pathologies may lead to pain-related limitation of motion and capsular stiffness, which could explain deficits in internal rotation. Although limitation of internal rotation is not typically expected in SLAP lesions, altered labral function and associated pain may indirectly affect shoulder biomechanics and lead to functional restrictions.

The main limitation of this study was its retrospective design. The results of this study reflect early postoperative out-

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comes, as the primary evaluation time point was 6 months. Longer-term functional outcomes may differ and should be evaluated in future studies. Another important consideration is the presence of glenohumeral osteoarthritis in a subset of patients. Unlike in other concomitant pathologies such as SLAP lesions or biceps tendinopathy, no additional surgical intervention was performed specifically for osteoarthritis. This may have influenced both pain and functional outcomes, particularly the range of motion. Therefore, the inclusion of these patients may be a confounding factor.

Nonetheless, all patients were managed at a single center and followed prospectively using a standardized treatment protocol, which helped reduce variability. Moreover, the retrospective design of this study prevents potential patient selection bias. Second, our study included patients with partial- or full-thickness tears, which may have affected the clinical outcomes. Although previous studies have evaluated the outcomes of rotator cuff repair in the presence of concomitant pathologies, heterogeneity in study designs and patient populations limits direct comparison. This study compares the clinical outcomes of arthroscopic rotator cuff repair in patients presenting with concomitant glenohumeral joint pathologies and those without such lesions.

In addition, a post hoc power analysis was conducted for the variables that reached statistical significance, and the minimum and maximum statistical power for comparisons of means ($\alpha = 0.05$) were 0.67 and 0.96, respectively.

CONCLUSION

Based on the results of this study, among patients who have undergone rotator cuff repair, those with accompanying glenohumeral joint pathologies had significantly lower shoulder flexion, shoulder internal rotation, and ASES score than those without accompanying pathologies. These findings suggest that concomitant intra-articular pathologies, particularly biceps-related disorders, should be carefully evaluated and considered during surgical planning and patient counseling. Orthopedic surgeons should be aware of this condition and inform their patients about the effects of additional shoulder pathologies on the clinical outcome.

Ethics Committee Approval: This retrospective case-control study received approval from the Erzincan University Clinical Research Ethics Committee (Decision no: 18/02, Date: 09.01.2018).

Informed Consent: It was not deemed necessary due to the retrospective nature of the study.

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Association of congenital anomalies with NICU course and early outcomes in neonates with esophageal atresia

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MAIN POINTS

- In this tertiary NICU cohort of neonates with esophageal atresia, overall in-hospital mortality was 27.3%, indicating that EA remains associated with substantial mortality despite modern neonatal care.
- Infants with esophageal atresia and associated congenital anomalies required longer mechanical ventilation and experienced delayed nutritional recovery, characterized by a prolonged time to reach full enteral feeding and an extended duration of postoperative TPN.
- The presence of additional anomalies was associated with increased surgical complications (OR 4.71) and increased mortality (33.3% vs 20%).

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ABSTRACT

Aim: Esophageal atresia (EA) is a serious congenital malformation that requires early surgical intervention during the neonatal period and is frequently associated with additional structural anomalies. This study aimed to evaluate the impact of accompanying major congenital anomalies on the neonatal intensive care unit (NICU) course and early clinical outcomes in neonates with EA.

Materials and Methods: In this retrospective cohort study, neonates who were diagnosed with EA and managed in a tertiary-level NICU between January 2010 and December 2025 were reviewed. Patients were categorized into two groups based on the presence of major structural anomalies: those with EA without associated anomalies and those with EA with associated anomalies. Demographic and perinatal characteristics, surgical variables, and NICU-related parameters were analyzed. The primary outcome measures were the durations of mechanical ventilation and total parenteral nutrition (TPN), and the time to achieve full enteral feeding. Secondary outcomes included surgical complication rates and mortality.

Results: A total of 33 patients were included in the analysis. At least one major congenital anomaly was identified in 54.5% of the cases. Compared with infants with EA without associated anomalies, infants with EA and associated anomalies had significantly longer durations of mechanical ventilation (p = 0.049), postoperative total parenteral nutrition (p = 0.007), and time to achieve full enteral feeding (p = 0.009). Although the risk of short-term surgical complications was greater in patients with associated anomalies (OR: 4,71; 95% CI: 0.94–23.68), this finding did not reach statistical significance (p = 0.052). The mortality rates did not differ significantly between the groups (p = 0.392).

Conclusion: The presence of major concomitant congenital anomalies in neonates with EA is associated with increased postoperative morbidity and a prolonged NICU course. These findings underscore the importance of incorporating comorbidity burden into prognostic assessment and clinical management strategies in this high-risk population.

Keywords: Esophageal atresia, Congenital abnormalities, Newborn, Mechanical ventilation, Parenteral nutrition

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INTRODUCTION

Esophageal atresia represents a relatively rare congenital malformation of the upper gastrointestinal tract, with an estimated incidence of 1 per 2,500–4,000 live births. Infants with esophageal atresia generally require early surgical intervention, and the neonatal course is often complicated by substantial morbidity, primarily related to respiratory instability, difficulties in establishing enteral feeding, and infection-related complications [1,2]. Over the past three decades, advances in neonatal intensive care practices, improvements in ventilatory technologies, and the standardization of perioperative management have led to a significant increase in survival rates. In developed countries, mortality has decreased to very low levels among term infants without major associated congenital anomalies, with survival approaching nearly 100% [3]. However, mortality rates range between 30% and 80% in

the presence of prematurity, low birth weight, major anomalies, or resource-limited settings [4,5]. Despite these improvements in survival, the burden of postoperative morbidity and prolonged intensive care hospitalization remains clinically significant [2,6].

A substantial proportion of infants with EA have associated anomalies involving the cardiovascular, gastrointestinal, renal, central nervous system, and musculoskeletal systems. Cardiac anomalies, in particular, are among the principal determinants of mortality and contribute to increased hemodynamic vulnerability during the perioperative period [7-9]. These anomalies should not be regarded solely as anatomical associations; rather, they represent clinical modifiers that diminish physiological reserve, reduce tolerance to surgical stress, and prolong the recovery process.

Although numerous studies have focused on mortality and survival, and several have demonstrated the impact of associated anomalies on overall outcomes in esophageal atresia, data specifically addressing the neonatal intensive care unit course remain relatively limited. In particular, relatively few studies have directly compared infants with isolated esophageal atresia and those with associated major congenital anomalies using objective indicators of postoperative morbidity. The available data are heterogeneous, and further evidence is needed regarding clinically relevant parameters such as the duration of mechanical ventilation, progression to enteral feeding, total parenteral nutrition (TPN) requirements, and length of intensive care stay. Therefore, a more detailed evaluation of the impact of associated anomalies on these clinical outcomes may contribute to prognostic assessment and help optimize perioperative management strategies.

In this study, neonates with esophageal atresia treated at our center were categorized as having EA without associated anomalies or EA with associated anomalies. We hypothesized that compared with infants without associated anomalies, infants with associated major congenital anomalies would experience a more complicated NICU course and increased postoperative morbidity. Accordingly, demographic and clinical characteristics and intensive care parameters were analyzed, and the effects of associated anomalies on morbidity and mortality were evaluated using objective, quantitative outcome measures.

MATERIALS AND METHODS

Study design and setting

This retrospective cohort study was conducted in the neonatal intensive care unit of a tertiary referral center. All consecutive neonates diagnosed with esophageal atresia (EA) who were followed in the NICU from January 2010 to December 2025 were screened. Patients who met the predefined eligibility criteria were included in the analysis.

The study protocol was approved by the Clinical Research Ethics Committee of Inonu University Faculty of Medicine (Approval No: 2026/9522, Date: 24.02.2026). Given the study's retrospective design, the ethics committee waived the requirement for informed consent. The investigation was performed in accordance with the principles of the Declaration of Helsinki. All the data were anonymized prior to analysis, and patient confidentiality was strictly maintained.

Sample size

Owing to the retrospective nature of the study, a sample size calculation was not applicable. Therefore, the study population consisted of all consecutive infants diagnosed with esophageal atresia who met the inclusion criteria during the study period.

Participants

Inclusion criteria

- Clinically and radiologically confirmed diagnosis of esophageal atresia,
- Initial preoperative admission to the study center during the specified study period,
- Availability of complete clinical records.

Exclusion criteria

- Patients transferred from another center during the postoperative period,
- Patients who died before surgical intervention,
- Cases with missing data regarding critical study variables.

Grouping and definitions

The study population was categorized according to the presence or absence of associated major congenital anomalies.

1. EA without associated major congenital anomalies: Patients without any clinically significant additional major structural anomalies.

2. EA with associated major congenital anomalies: Patients with at least one major structural congenital anomaly.

Major structural anomalies were defined as congenital defects involving the cardiovascular system, renal system, gastrointestinal system, central nervous system, or musculoskeletal system that required clinical follow-up, medical treatment, or surgical intervention. Minor anomalies and clinically insignificant anatomical variations were not considered in this classification.

Data collection and outcome measures

Demographic, perinatal, and clinical data were retrospectively extracted from patient medical files and the institutional electronic medical records system.

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Demographic, perinatal, and clinical information was retrospectively obtained from patient charts and the institutional electronic medical database. The collected baseline variables included gestational age at birth, birth weight, sex, mode of delivery (cesarean or vaginal birth), and small for gestational age (SGA) status. SGA was defined as a birth weight below the 10th percentile for gestational age.

Clinical characteristics included prenatal diagnosis, intubation in the delivery room, respiratory distress, tracheoesophageal fistula (TEF), and associated congenital anomalies. Associated anomalies were subclassified into gastrointestinal, cardiovascular, central nervous system, renal, or limb anomalies.

NICU-related variables included: duration of mechanical ventilation (days), requirement for mechanical ventilation lasting longer than seven days, duration of total parenteral nutrition (TPN) (days), day of initiation of enteral feeding, day of achievement of full enteral feeding, and total length of hospital stay (days). The presence of sepsis, early postoperative mortality within the first seven days, and overall in-hospital mortality were evaluated. Episodes were categorized as culture-confirmed or clinical sepsis. Culture-confirmed sepsis was diagnosed when blood culture positivity was accompanied by clinical findings compatible with systemic infection. Clinical sepsis was defined as the presence of clinical and laboratory features suggestive of sepsis that required intravenous antibiotic therapy for at least 5 days despite the absence of microbiological growth in blood cultures.

With respect to surgical and postoperative parameters, the day of the operation, additional surgical procedures (gastrostomy, cervical esophagostomy, or colostomy),and surgical complications were recorded. Surgical complications were defined as radiologically or clinically confirmed anastomotic leakage, anastomotic stricture, or perforation occurring during the postoperative period.

The primary outcome measures were duration of mechanical ventilation, duration of total parenteral nutrition, and time to full enteral feeding. Secondary outcomes included surgical complication rates and mortality.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 26 (IBM, USA). The distributional characteristics of the continuous variables were examined with the Shapiro–Wilk test. Variables demonstrating a normal distribution are reported as the mean ± standard deviation, whereas variables not meeting normality assumptions are presented as medians with ranges (minimum–maximum).

For group comparisons, the independent-samples t-test was used for normally distributed continuous variables, and the Mann–Whitney U test was used for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) for surgical complications and mortality were calculated using 2×2 contingency tables. A two-tailed p value of <0.05 was considered to indicate statistical significance.

RESULTS

During the study period, 36 neonates diagnosed with esophageal atresia (EA) were admitted to our unit. Three patients who died during the preoperative period were excluded, leaving 33 patients in the final analysis. Thirteen infants (39.4%) had been referred from outside the province.

Among the study population, 51.5% were female. The median gestational age was 37 weeks (range: 28–40), and 48.5% of the infants were born before 37 weeks of gestation. The mean birth weight was 2280 ± 536 grams, and 48.5% were classified as SGA. Cesarean delivery was performed in 84.8% of the cases, and a prenatal diagnosis was established in 39.4% of the cases. Intubation in the delivery room was required for 36.4% of patients, while respiratory distress during follow-up was documented in 60.6%. A tracheoesophageal fistula was present in 84.8% of the infants. Early postoperative mortality within the first 7 days was 12.1%, and overall in-hospital mortality was 27.3%. The median length of hospital stay was 35 days (range: 15–110). Reported surgical complications included anastomotic stricture (20%), anastomotic leakage (16.7%), and esophageal perforation (3.3%) (Table 1).

The study population was categorized into two groups: infants with esophageal atresia without associated major congenital anomalies (n = 15) and those with associated major congenital anomalies (n = 18). Baseline comparisons revealed no statistically significant differences between the groups in demographic characteristics, gestational age, birth weight, prenatal diagnosis, the presence of a tracheoesophageal fistula, or early mortality (Table 2).

Late-onset sepsis was identified in 22 of 33 infants (66.7%). Among these, 11 infants (33.3%) were classified as having clinical sepsis, and 11 (33.3%) had culture-proven sepsis. The frequency and distribution of sepsis subgroups were comparable between the study groups, with no statistically significant differences detected (p = 0.333).

Analysis of NICU-related parameters showed that the duration of mechanical ventilation was significantly longer in the group with associated anomalies (p = 0.049). The time to initiation of postoperative enteral feeding was comparable between the groups (p = 0.852). However, the time to achieve full enteral feeding (p = 0.009) and the duration of postoperative total parenteral nutrition were significantly prolonged in patients with associated anomalies (p = 0.007).

A subgroup analysis comparing inborn and outborn infants revealed no statistically significant differences in mortality, the presence of associated anomalies, the duration of mechanical ventilation, postoperative TPN duration, or the time to achieve full enteral feeding. The cesarean delivery rate was

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Table 1. Demographic, clinical and intensive care characteristics of patients with esophageal atresia.

Variables	(n=33)
Demographic and Perinatal Characteristics	
Female sex, n (%)	17 (51.5)
Gestational age, weeks*	37 (28–40)
<37 weeks, n (%)	16 (48.5)
≥37 weeks, n (%)	17 (51.5)
Birth weight, g**	2280 ± 536
SGA, n (%)	16 (48.5)
Cesarean delivery, n (%)	28 (84.8)
Prenatal diagnosis, n (%)	13 (39.4)
Clinical Characteristics	
Delivery room intubation, n (%)	12 (36.4)
Respiratory distress, n (%)	20 (60.6)
Presence of tracheoesophageal fistula, n (%)	28 (84.8)
Late-onset sepsis, n (%)	22 (66.6)
Culture-proven sepsis n (%)	11 (33.3)
Clinical sepsis n (%)	11 (33.3)
Day of operation*	2 (1–15)
Need for intubation >7 days, n (%)	11 (36.7)
Duration of mechanical ventilation, days*	5 (2–30)
Postoperative enteral feeding initiation day*	6 (2–17)
Time to full enteral feeding, days*	14 (10–30)
Postoperative TPN duration, days**	11.1 ± 5.2
Length of hospital stay, days*	35 (15–110)
Associated Anomalies, n (%)	
Gastrointestinal anomaly	8 (24.2)
Cardiovascular anomaly	7 (21.2)
Central nervous system anomaly	3 (9.1)
Renal anomaly	3 (9.1)
Limb anomaly	3 (9.1)
Gross Classification, n (%)	
Type A	5 (15.6)
Type C	27 (84.4)
Surgical Outcomes, n (%)	
Gastrostomy	8 (24.2)
Cervical esophagostomy	5 (15.2)
Colostomy	4 (12.1)
Surgical complications, n (%)	
Anastomotic stricture	6 (20.0)
Anastomotic leakage	5 (16.7)
Perforation	1 (3.3)
Mortality, n (%)	
Early postoperative 7-day mortality	4 (12.1)
Total mortality	9 (27.3)

Gross classification data were available for 32 patients. Surgical complication data were available for 30 patients (14 patients without associated anomalies and 16 patients with associated anomalies). *Values are presented as the median(minimum–maximum).**Values are presented as the mean ± standard deviation.

significantly higher among inborn infants (p = 0.003), which likely reflects the impact of prenatal diagnosis and planned perinatal management at our tertiary referral center. Although outborn infants underwent surgery at a relatively later postnatal age, this difference did not reach statistical significance (p = 0.057).

Although the short-term risk of surgical complications appeared to be greater among patients with associated anomalies (OR: 4,71; 95% CI: 0.94–23.68), this association did not reach statistical significance (p = 0.052).

Overall mortality was higher in the EA with associated anomalies group than in the EA without associated anomalies group (33.3% vs. 20%); however, the difference was not statistically significant (p = 0.392; OR: 2.18; 95% CI: 0.44–10.8).

The association between Spitz risk classification and mortality was also evaluated. An overall increase in mortality rates was

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Table 2. Comparison of clinical characteristics between patients with and without associated anomalies

Variables	EA without Associated Anomalies (n=15)	EA with Associated Anomalies (n=18)	p
Demographic and Perinatal Characteristics			
Female sex, n (%)	8 (53.3)	9 (50.0)	0.849
Gestational age, weeks*	37 (30--40)	37 (28--39)	0.898
<37 weeks, n (%)	7 (46.7)	9 (50.0)	0.849
≥37 weeks, n (%)	8 (53.3)	9 (50.0)	0.849
Birth weight, g**	2150 ± 546	2250 ± 614	0.626
SGA, n (%)	10 (66.7)	6 (33.3)	0.056
Cesarean delivery, n (%)	13 (86.7)	15 (83.3)	0.790
Prenatal diagnosis, n (%)	5 (33.3)	8 (44.4)	0.515
Clinical Characteristics			
Delivery room intubation, n (%)	4 (26.7)	8 (44.4)	0.290
Respiratory distress, n (%)	8 (53.3)	12 (66.7)	0.435
Presence of TEF, n (%)	13 (86.7)	15 (83.3)	1.000
Late-onset sepsis			
Culture-proven sepsis n (%)	3 (20.0)	8 (44.4)	0.333
Clinical sepsis n (%)	6 (40.0)	5 (27.8)	
Day of operation*	2 (1--4)	2 (1--15)	0.610
Need for intubation >7 days, n (%)	4 (28.6)	7 (43.8)	0.389
Duration of mechanical ventilation, days*	4.5 (2--13)	6 (3--30)	**0.049**
Postoperative enteral feeding day*	6 (2--10)	6 (3--17)	0.852
Time to full enteral feeding, days*	13 (10--20)	22 (10--30)	**0.009**
Postoperative TPN duration, days**	8.5 ± 3.0	13 ± 5.7	**0.007**
Length of hospital stay, days*	27 (15--110)	60 (22--90)	0.193
Gross Classification			
Type A	2 (13.3)	3 (17.6)	1.000
Type C	13 (86.7)	14 (82.4)	
Surgical Outcomes, n (%)			
Gastrostomy, n (%)	2 (13.3)	6 (33.4)	0.182
Cervical esophagostomy, n (%)	1 (6.7)	4 (22.2)	0.215
Colostomy, n (%)	0 (0.0)	4 (22.8)	0.051
Surgical complication, n (%)	3 (21.4)	9 (56.3)	0.052
Mortality, n (%)			
Early postoperative 7-day mortality, n (%)	2 (13.3)	2 (11.1)	0.846
Total mortality, n (%)	3 (20.0)	6 (33.3)	0.392

Surgical complication data were available for 30 patients (14 patients without associated anomalies and 16 patients with associated anomalies). *Values are presented as the median (minimum–maximum). **Values are presented as the mean ± standard deviation. SGA: Small for gestational age; TPN: Total parenteral nutrition; TEF: Tracheoesophageal fistula.

observed across higher-risk categories: 18.7% (3/16) in Spitz Type 1, 33.3% (3/9) in Spitz Type 2, 25% (1/4) in Spitz Type 3, and 50% (2/4) in Spitz Type 4. Overall, mortality tended to increase across higher Spitz risk categories.

Gross classification could be determined in 32 of 33 infants. Among these, 5 infants (15.6%) had gross type A lesions, and 27 infants (84.4%) had gross type C lesions. The gross type distribution did not differ significantly between infants with EA without associated anomalies and those with associated anomalies (p = 1.000).

DISCUSSION

Esophageal atresia (EA) is a complex congenital disorder frequently accompanied by multisystem anomalies, which are important determinants of clinical outcomes. In our cohort, associated congenital anomalies were identified in 54.5% of patients, which is consistent with previously reported rates ranging from 40% to 60% [8-10]. These findings support the clinical relevance of the comorbidity burden in shaping the neonatal intensive care course of infants with EA.

Associated anomalies may directly affect the NICU course by reducing the physiological reserve during the perioperative period. In our study, at least one major congenital anomaly was identified in 54.5% of the patients (n = 18), with gastrointestinal and cardiovascular pathologies being the most common. VACTERL association was identified in two patients, and no chromosomal abnormalities were detected in these patients. These findings are consistent with previously reported data and further support the clinical relevance of the comorbidity burden in infants with esophageal atresia [11,12].

Postoperative mechanical ventilation requirements and duration are important determinants of the clinical course. In our

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cohort, 36.4% of patients required invasive ventilatory support for longer than 7 days. When infants with esophageal atresia without associated anomalies were compared with those with associated anomalies, the duration of mechanical ventilation was significantly longer in the latter group (p = 0.049). These findings suggest that concomitant anomalies may impair cardiopulmonary stabilization during the postoperative period and increase the need for respiratory support. Consistent with our findings, Piro et al. [12] reported prolonged durations of invasive mechanical ventilation (IMV) in infants with associated congenital anomalies, with the duration of IMV extending to 9 days in the subgroup of infants with more than one associated anomaly. In addition, prolonged mechanical ventilation has been associated with postoperative morbidities such as pneumonia and atelectasis [13,14].

In our cohort, the median duration to achieve full enteral feeding was 14 days (range, 10–30 days), whereas the mean duration of total parenteral nutrition (TPN) was 11.1 ± 5.2 days. Compared with those without associated anomalies, infants with esophageal atresia and associated major congenital anomalies had a significantly delayed progression to full enteral feeding (p = 0.009) and a significantly longer requirement for TPN support (p = 0.007). These findings suggest that comorbid anomalies may delay gastrointestinal adaptation and impair feeding tolerance during the postoperative period. Consistent with our findings, Piro et al. [12] reported that the duration of TPN extended to 13 days in infants with esophageal atresia and associated anomalies, with significant differences compared with that in isolated cases. Similarly, Lees et al. [15] demonstrated that structural cardiac anomalies were associated with delayed feeding progression and prolonged parenteral nutritional support.

Consistent with previous reports, esophageal atresia type C has been described as the most common anatomical subtype [6,10], and the frequency of tracheoesophageal fistulas has been reported to be comparable between isolated cases and those with associated anomalies [1]. Similarly, in our cohort, type C was the predominant anatomical subtype, and no significant association was observed between the presence of major associated anomalies and either the gross anatomical subtype distribution or the presence of a tracheoesophageal fistula. These findings suggest that the clinical differences observed between the groups may be more closely related to the burden of comorbidities than to the anatomical subtype itself.

The Spitz classification remains among the most widely used prognostic tools in infants with esophageal atresia [9]. In our cohort, mortality progressively increased with higher Spitz categories, reaching 50% in the Type 4 group. Although statistical significance could not be demonstrated because of the limited sample size, this trend supports the prognostic relevance of the Spitz classification. Further studies with larger cohorts are needed to clarify its potential role in predicting morbidity and postoperative clinical outcomes.

Previous studies have consistently identified associated congenital anomalies, particularly cardiac defects, as major determinants of mortality in infants with esophageal atresia [1,7,16]. In our cohort, early postoperative mortality was comparable between the groups. Although overall mortality was numerically higher in infants with associated anomalies than in those without, this difference was not statistically significant. Nevertheless, the observed trend suggests that comorbidity burden may contribute to adverse clinical outcomes and that further validation in larger cohorts is needed.

In our cohort, infants with associated anomalies had higher rates of early postoperative complications. However, these observations did not reach statistical significance and should be interpreted with caution, given the limited sample size and a wide confidence interval. Similarly, the absence of a significant difference in mortality should not be interpreted as evidence of no clinical association, as the study may have been underpowered to detect clinically meaningful differences. Therefore, larger multicenter studies are warranted to further clarify the impact of associated anomalies on postoperative morbidity and survival in infants with esophageal atresia.

A key strength of the present study lies in its comparative cohort design, allowing direct assessment of the clinical course and postoperative outcomes in infants with esophageal atresia according to the presence or absence of associated major congenital anomalies. The analysis extended beyond mortality to include morbidity-related clinical parameters, such as the duration of mechanical ventilation and nutritional adaptation, thereby providing a more comprehensive assessment of the postoperative clinical course. Furthermore, the inclusion of a relatively homogeneous patient cohort managed at a single center under comparable surgical techniques and standardized intensive care protocols may have reduced practice-related variability and supported the consistency of the findings.

Limitations

The main limitations of our study include its retrospective, single-center design and its relatively small sample size. In particular, the limited number of patients within high-risk categories may have reduced the statistical power of mortality analyses and should therefore be considered when interpreting statistically nonsignificant findings in subgroup comparisons. Excluding neonates who died within the first 24 hours may have introduced selection bias by omitting the most critically ill patients. However, their inclusion could also have confounded the interpretation of postoperative outcomes, including duration of mechanical ventilation, duration of TPN, and enteral feeding parameters. Referral status may represent a potential confounding factor, as differences in prenatal diagnosis, transfer timing, and preoperative management may influence the clinical course in infants with

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esophageal atresia and limit the generalizability of our findings.

CONCLUSION

Overall, our findings indicate that associated anomalies play a central role in shaping the clinical trajectory of esophageal atresia. The significantly prolonged duration of mechanical ventilation and the delayed nutritional adaptation observed in infants with additional anomalies highlight the comorbidity burden as an important determinant of postoperative morbidity. However, no statistically significant difference in mortality was observed between the groups. These findings underscore the importance of careful clinical assessment of comorbidity burden in infants with esophageal atresia as part of postoperative management.

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Inonu University Faculty of Medicine (Approval No: 2026/9522, Date: 24.02.2026).

Informed Consent: Owing to the retrospective nature of the study, informed consent was waived.

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