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VOLUME 6 ISSUE 1 YEAR 2026

CONTENTS

RESEARCH ARTICLES

1 **The Effect of a Structured Physiotherapy Program on Anxiety, Physical Activity Levels, and Kinesiophobia in Patients with Multiple Sclerosis**
A. G. Güneş, Ö. Keniş Coşkun, E. Karadağ Saygı

11 **Serum Procalcitonin for the Diagnosis of Spontaneous Bacterial Peritonitis in Patients With Decompensated Cirrhosis: A Prospective Study**
E. Şeyran, Ö. Topdağı, N. Okçu

17 **Early Vascular Remodeling and Hemorheological Alterations in Biopsy-Proven MASLD**
S. Sivridemir, M. Yaşan, G. Zararsız, S. Yıldız Taşkıran, S. Doğan, A. Doğan, et al.

21 **Evaluation of Complication Development and Laboratory Data Between Diabetic Individuals Regularly Check-Ups and Diabetic Individuals Not Regularly Attending Check-ups at the Endocrinology and Metabolism Diseases Polyclinic of Necmettin Erbakan University Meram Faculty of Medicine Hospital**
M. Çağlayan, M. Kulaksızoğlu, D. Çağlayan, A. Kaya

30 **Effects of Parathyroidectomy on Renal Anemia in End-Stage Renal Disease**
Ş. Yaşlıkaya, İ. Şahin

36 **Predictive Value of Development of Macroalbuminuria for Hypoglycemia in Patients with Type 2 Diabetes Mellitus**
A. Z. Bayhan, M. Evran

42 **Prognostic Value of the Neutrophil-to-Lymphocyte and Lymphocyte-to-Monocyte Ratios and Their Association with the International Prognostic Index in Patients with Diffuse Large B-Cell Lymphoma**
M. Demirtaş Gülmez, O. Bilgir

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Research Article

The Effect of a Structured Physiotherapy Program on Anxiety, Physical Activity Levels, and Kinesiophobia in Patients with Multiple Sclerosis

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Abstract

Objectives: Reduced physical activity and kinesiophobia may further impair quality of life and functional independence in individuals with MS. The aim of this study is to investigate the effects of a structured physiotherapy program on anxiety, depression, gait speed, kinesiophobia, and quality of life in individuals with MS.

Methods: This prospective clinical study included 25 ambulatory individuals. All participants completed a 10-week rehabilitation program consisting of 30 supervised sessions. Assessments performed before and after treatment included the Multiple Sclerosis Quality of Life Scale (MSQoL-54), Timed 25-Foot Walk Test (T25FW), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Tampa Scale for Kinesiophobia (TSK), International Physical Activity Questionnaire–Short Form (IPAQ-SF), and Expanded Disability Status Scale (EDSS).

Results: Significant improvements were observed in anxiety and depression scores following rehabilitation ($p<0.05$). The pain subscale of MSQoL-54 also improved significantly. No significant changes were observed in other subscale scores. However, no statistically significant changes were found in T25FW, TSK, or EDSS scores.

Conclusion: Structured rehabilitation programs may improve psychological symptoms and certain aspects of quality of life in individuals with MS. Additionally, no significant improvement was observed in walking speed, kinesiophobia, and disability levels. Further studies could be conducted to determine the effectiveness of longer-term, structured physiotherapy programs or studies incorporating different therapy methods.

Keywords: Kinesiophobia, multiple sclerosis, physiotherapy

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Multiple sclerosis (MS) is a chronic, inflammatory, and degenerative disease affecting the central nervous system. Typically emerging in young adulthood, this disease leads to impairments in motor, sensory, cognitive, and psychological functions, significantly affecting individuals' quality of life. During the clinical course of MS, psychological symptoms such as anxiety and depression are frequently observed alongside physical disability. These psychological conditions complicate disease management and negatively affect individuals' social, occupational, and personal lives.[1]

The prevalence of depression and anxiety in individuals with MS is higher than in the general population. Studies have shown that approximately 30–50% of MS patients

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experience depression, while 20–40% experience anxiety. These psychological disorders may arise not only from the direct effects of the disease but also from the stress and uncertainty associated with coping with a chronic illness.[2] Furthermore, depression and anxiety may lead to decreased quality of life, reduced treatment adherence, and increased social isolation in MS patients. In individuals with chronic diseases, disease-specific barriers related to disease type, stage of progression, and functional limitations exist in addition to barriers commonly observed in the general population.[3] Fear of movement in MS patients represents a barrier not only to regular physical activity but also to the maintenance of normal daily habits, thereby negatively affecting quality of life and biopsychosocial well-being.[4]

Quality of life (QoL) is a multidimensional concept encompassing an individual's physical health, psychological state, social relationships, and interaction with environmental factors. In patients with MS, quality of life is influenced not only by physical symptoms but also by psychological and social factors.[5] Depression and anxiety are among the primary psychological factors negatively affecting quality of life. Therefore, it is important that MS treatment addresses not only physical symptoms but also the psychological state of patients.[6]

Considering the high prevalence of psychological symptoms such as depression and anxiety in MS patients and their negative impact on QoL, it is of great importance that rehabilitation programs focus on these areas. The existing literature suggests that psychological interventions and physical activity can improve psychological well-being and enhance quality of life in patients with MS.[6,7] But the effect of a structured physiotherapy program on all areas of anxiety, depression, kinesiophobia, and physical activity has not been investigated in patients with MS.

The aim of this study is to investigate the effects of a structured physiotherapy program on anxiety, physical activity levels, kinesiophobia, depression, gait speed, and quality of life in individuals with MS.

Materials and Methods

Study Design

This study was conducted as a prospective, quantitative clinical study. The study was carried out in Marmara University Hospital Physical Medicine and Rehabilitation Clinic between July 2025 and January 2026. All patients were informed in detail about the treatment before participating in the study, and written informed consent was obtained. The study protocol was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (Approval No: 09.2025.25-05.12).

Participants

A total of 30 patients who had been diagnosed with multiple sclerosis for more than one year and met the inclusion criteria were initially included in the study. Due to the withdrawal of 5 patients during the treatment period, 25 patients were included in the final analysis. Two patients left the study because they experienced an attack, and three patients left because they discontinued treatment (Fig. 1).

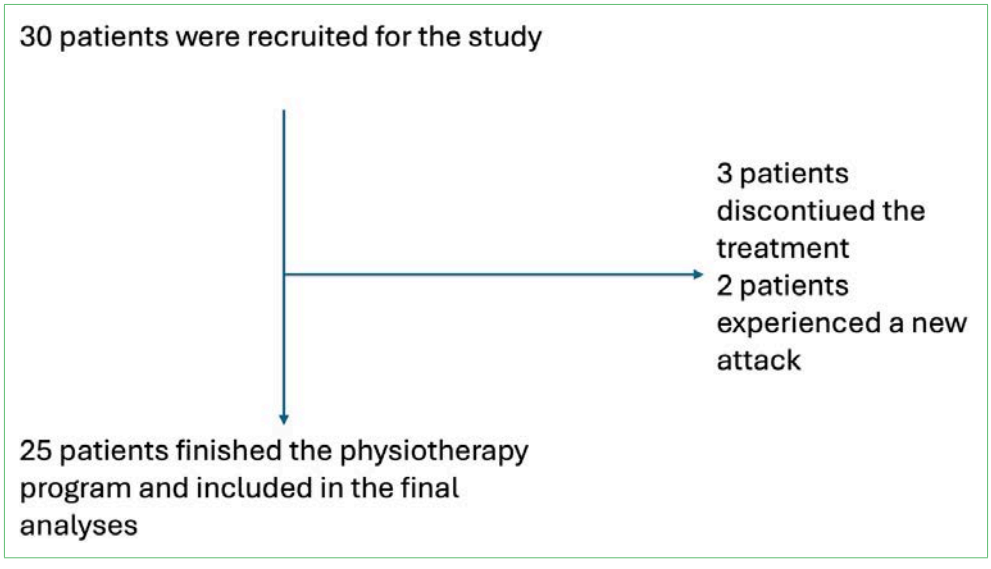


Figure 1. Flow diagram of patient recruitment and inclusion in the final analysis.

Inclusion Criteria

1. Age between 18–65 years
2. Being followed for at least one year with a diagnosis of multiple sclerosis
3. EDSS score below 7
4. Ability to ambulate

Exclusion Criteria

1. Non-ambulatory status
2. Presence of another neurological disease in addition to multiple sclerosis
3. Presence of severe physical, emotional, or cognitive impairment that could significantly interfere with the evaluation
4. History of surgery within the past year

Assessment Methods

Patients' demographic data and medical histories were recorded in the patient follow-up form.

After clinical evaluation, patients who were found eligible for the study underwent the predetermined rehabilitation program. Evaluation and questionnaire results were recorded both at baseline and after the completion of the 30-session rehabilitation program. To ensure standardization, all assessments were conducted by the same researcher.

The following assessment tools were used:

- Multiple Sclerosis Quality of Life Scale (MSQoL-54)
- Timed 25-Foot Walk Test (T25FW)
- Beck Anxiety Inventory (BAI)
- Beck Depression Inventory (BDI)
- Tampa Scale for Kinesiophobia (TSK)
- International Physical Activity Questionnaire–Short Form (IPAQ-SF)
- Expanded Disability Status Scale (EDSS)

Assessments

Multiple Sclerosis Quality of Life Scale

The Multiple Sclerosis Quality of Life Scale (MSQoL-54) questionnaire was used to assess quality of life. MSQoL-54 consists of two main composite scores (physical health and mental health), 12 subscales, and 2 independent items. Additionally, four MS-specific domains are included: cognitive function, health distress, sexual function, and overall quality of life. Scores range from 0 to 100, with higher scores indicating better quality of life.[8]

Timed 25-Foot Walk Test

This test measures lower extremity function. Patients are asked to walk a predetermined distance, and the time taken to complete the walk in both directions is recorded. The average of the two measurements is used.[9]

Beck Anxiety Inventory

The Beck Anxiety Inventory consists of 21 items, each scored on a 4-point Likert scale (0–3), ranging from "not at all" to "severely." Total scores range from 0 to 63, with higher scores indicating greater anxiety severity. Scores are categorized as follows: 8–15 mild anxiety, 16–25 moderate anxiety, and 26–63 severe anxiety.[10]

Beck Depression Inventory

The Beck Depression Inventory consists of 21 items, each scored between 0 and 3. Total scores range from 0 to 63. Scores are interpreted as follows: 0–9 minimal, 10–16 mild, 17–29 moderate, and 30–63 severe depressive symptoms. A score of 17 or above indicates the presence of depression.[11,12]

Tampa Scale for Kinesiophobia

The Tampa Scale for Kinesiophobia is a 17-item questionnaire used to assess fear of movement and re-injury after an initial event. It uses a 4-point Likert scale (1=strongly disagree, 4=strongly agree). After reverse scoring of items 4, 8, 12, and 16, the total score ranges from 17 to 68. A score of 37 or higher indicates a high level of kinesiophobia.[13]

International Physical Activity Questionnaire–Short Form (IPAQ-SF)

IPAQ-SF evaluates time spent sitting, walking, and engaging in moderate and vigorous physical activities during the past week. Energy expenditure is calculated as MET-minutes/week. Based on the total score, ≤600 MET-min/week indicates inactive, 600–3000 indicates moderately active, and ≥3000 indicates sufficiently active.[14]

Expanded Disability Status Scale (EDSS)

EDSS ranges from 0 (normal neurological examination) to 10 (death due to MS). It evaluates eight functional systems affected by MS, with scoring based on the level of impairment.[15,16]

Treatment Protocol

Rehabilitation Program

All patients participated in a rehabilitation program consisting of 30 sessions over 10 weeks, performed three times per week, each lasting 40 minutes (5 minutes warm-up, 30 minutes exercise, 5 minutes cool-down), under the supervision of a physiotherapist. All exercises were administered by the same physiotherapist. Patients were instructed not to receive additional MS-related treatment from other centers during the study period.

Breathing exercises were performed at the beginning of each session and between exercises to facilitate relaxation and transition.

1. Inhale through the nose for 4 seconds, hold for 4 seconds, and exhale through the nose for 8 seconds.

Flexibility exercises aimed to improve or maintain the range of motion in muscles and joints. Exercises were performed for the quadratus lumborum, hamstrings, and piriformis muscles.

2. Quadratus Lumborum Stretch: While lying in the supine position, the patient is rotated to the right and left sides with assistance from the physiotherapist.
3. Hamstring Stretch: While lying supine, the patient's leg is raised straight with assistance from the physiotherapist. Repeated for both extremities.
4. Piriformis Stretch: While lying supine with knees flexed, one leg is placed over the other. The patient supports the lower leg with their arms, and the knees are brought toward the abdomen with assistance. Repeated for both extremities.

Strengthening exercises were performed to improve muscle strength. In patients who could not actively complete the range of motion during strengthening exercises, the exercises were performed actively assisted with the help of a physiotherapist. In patients who could actively complete the range of motion, the exercises were performed using resistance bands of different colors according to their tolerance level.

5. Gluteus Maximus and Medius Strengthening: Performed in standing, moving the leg backward and laterally.
6. Iliopsoas Strengthening: While lying supine, one leg is stabilized while the other is pulled toward the abdomen.
7. Hamstring Strengthening: While lying prone, knee flexion and extension are performed.
8. Gastrocnemius Strengthening: While lying supine, ankle plantarflexion is performed.
9. Tibialis Anterior Strengthening: While lying supine, ankle dorsiflexion is performed.

Balance exercises were included due to postural instability and fall risk in MS patients. Exercises were selected and administered taking into account the participants' balance levels.

10. Tandem stance (eyes open and closed, 5–10 seconds)
11. Single-leg stance (eyes open and closed, 5–10 seconds)
12. Tandem stance (eyes open and closed, 5–10 seconds)

    All exercises were performed under physiotherapist supervision for safety.

The exercise program was designed based on common problems observed in individuals with MS. The number of repetitions was individualized, and additional rest was provided for participants experiencing fatigue. Participants were asked to rate their perceived exertion during sessions using the Modified Borg Scale (0=very, very light; 10 = very, very hard). A rest break was given when the patient's fatigue level reached 5.

Statistical Analysis

Based on a previous meta-analysis reporting a pooled standardized mean difference, with an average change rate of 0.16±0.3 in anxiety scores, it was calculated that 25 patients should be included in the study to achieve 80% power, with a margin of error of 0.05. Considering a 20% dropout rate, the goal was to invite a total of 30 patients to the study.[7]

Statistical analyses were performed using SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation (SD), whereas categorical variables were presented as frequency and percentage values.

The distribution of data was assessed using visual (histograms and probability plots) and analytical methods. Pre- and post-treatment comparisons were performed using paired-samples t-tests for normally distributed variables. Changes in physical activity levels between baseline and post-rehabilitation assessments were evaluated using the Wilcoxon signed-rank test, as IPAQ-SF categories (low, moderate, and high physical activity) represent paired ordinal data. Categorical variables were presented as frequencies and percentages.

A p value of <0.05 was considered statistically significant.

Results

Data from 25 patients were analyzed. The mean age of the patients was 47.36±10.58. Twenty-one of the patients (80.8%) were female. Detailed demographic data are given in Table 1.

When the patients' initial evaluations were compared with the final evaluations, the patients' MSQoL pain subscale improved significantly, from a mean score of 7.08±2.94 to 8.08±2.96 (p=0.04). There were no other significant changes in QoL. The results of QoL assessments are summarized in Table 2.

According to the IPAQ-SF classification, at baseline, 15 patients (60.0%) had low physical activity levels, 9 (36.0%) had

Table 1. Demographic properties of the patients.

	Mean ±SD		Min- Max
Age (year)	47.36 ± 10.58		22-66
Body-mass index (kg/m2)	25.5±4.59		18.70-33.30
Disease duration (years)	16.64±6.52		3-31
Gender	Female		Male
	21 (80.8%)		4 (19.2%)
Disease subtype (percent)	RRMS	PPMS	SPMS
	17 (65%)	6	2
Presence of walking aid (percent)	None	Cane	Walker
	18 (72%)	3 (12%)	4 (16%)
Medications used by the patients (percent)	Ocrelizumab, n=18 (72.0%) Fingolimod, n=2 (8.0%) Fampridine, n=1 (4.0%) Teriflunomide, n=1 (4.0%) Cladribine, n=1 (4.0%) Ozanimod, n=1 (4.0%) Tolebrutinib, n=1 (4.0%)		

SD: Standard deviation; RRMS: Relapsing remitting multiple sclerosis; PPMS: Primary progressive multiple sclerosis; SPMS: Secondary progressive multiple sclerosis.

moderate physical activity levels, and 1 (4.0%) had high physical activity levels. Following the rehabilitation program, the number of patients with low physical activity levels decreased to 10 (40.0%), while the number of patients with moderate and high physical activity levels increased to 12 (48.0%) and 3 (12.0%), respectively. Wilcoxon signed-rank analysis demonstrated a significant improvement in physical activity levels after rehabilitation compared with baseline (W=12.0, p=0.035).

Patients' anxiety and depression levels also showed significant improvement, documented by Beck Depression and Anxiety Scales. The mean Beck Depression Scale score

Table 2. Change in multiple sclerosis quality of life scale (MSQoL) scores

	Mean Before treatment (SD)	Mean After Treatment (SD)	p	%95 Confidence Interval
MSQoL physical function	8.33 (4.92)	9.49 (5.38)	0.10	-2.57 – 0.26
MSQoL rol limitations-physical	5.40 (5.34)	4.92 (5.47)	0.65	-1.69 – 2.65
MSQoL pain	**7.08 (2.95)**	**8.08 (2.96)**	**0.04**	**-1.98 – -0.01**
MSQoL energy	5.07 (3.06)	5.34 (2.95)	0.42	-0.96 – 0.42
MSQoL social function	7.96 (2.98)	7.32 (3.05)	0.24	-0.47 – 1.75
MSQoL health perceptions	8.67 (3.99)	9.25 (3.47)	0.33	-1.78 – 0.62
MSQoL health distress	5.57 (3.85)	5.90 (3.63)	0.47	-1.27 – 0.61
MSQoL sexual function	5.65 (2.53)	5.63 (2.36)	0.87	-0.32 – 0.38
MSQOL BFS	53.65 (21.39)	55.55 (21.94)	0.44	-6.91 – 3.12
MSQoL role limitations-emotional	11.20 (10.07)	9.92 (11.38)	0.597	-3.64 – 6.20
MSQoL Emotional well-being	17.59 (4.76)	17.08 (5.58)	0.567	-1.30 – 2.32
MSQoL health distress	7.08 (4.91)	7.50 (4.62)	0.474	-1.61 – 0.77
MSQoL cognitive function	9.57 (4.32)	9.45 (3.62)	0.841	-1.10 – 1.34
MSQoL Overall quality of life	10.55 (3.27)	11.00 (4.11)	0.531	-1.92 – 1.02
MSQoL BMLS	54.92 (20.70)	54.95 (22.93)	0.993	-8.55 – 8.47

Significant changes are marked in bold.

improved from 13.56±10.34 to 10.48±9.69 (p=0.02). The mean Beck Anxiety score changed from 17.32±9.68 to 14.92±12.21 (p=0.04). There were no significant changes in the 25FWT, Tampa Scale for Kinesiophobia, or EDSS levels of the patients. These findings are summarized in Table 3.

In subgroup analyses, only the change in scores between the PPMS and RRMS groups was analyzed, since there were only two patients with SPMS in the study. The changes in depression scores and MSQoL energy subscales were significantly better in patients in the PPMS group compared with the RRMS group, while there were no significant differences between other parameters. All changes are summarized in Table 4.

Discussion

This study demonstrates that a physiotherapy program may be helpful for patients with MS in terms of depression, anxiety, and physical activity levels, while it does not affect kinesiophobia and can only minimally improve quality of life.

The demographic profile of our participants was comparable to that reported in previous studies.[12] In particular, male individuals and less common MS phenotypes are generally underrepresented in the literature, and the findings of this study should therefore be interpreted within this context. The physical and psychological characteristics of the patients

Table 3. Changes in anxiety, depression, kinesiophobia, and 25 feet walk test (25FWT) and EDSS scores before and after treatment.

Variable	Mean Before Treatment (SD)	Mean After Treatment (SD)	p	%95 Confidence interval
Beck anxiety	**17.32 (9.69)**	**14.92 (12.22)**	**0.04**	**0.15 – 4.95**
Beck depression	**13.56 (10.35)**	**10.48 (9.69)**	**0.02**	**0.42 – 5.74**
Tampa kinesiophobia scale	37.12 (5.30)	39.36 (6.72)	0.12	-5.13 – 0.65
25FWT	79.31 (99.21)	69.93 (78.45)	0.10	-2.20 – 20.96
EDSS	3.96 (1.62)	4.02 (1.69)	0.37	-0.20 – 0.08

Significant changes are marked in bold.

Table 4. Comparison of changes in QoL, 25 m walk test, depression and anxiety levels between patients with primary progressive multiple sclerosis (PPMS) and relapsing remitting multiple sclerosis (RRMS)

Variable	PPMS (n=17) Mean (SD)	RRMS (n=6) Mean (SD)	p	%95 Confidence interval
delta Tampa kinesiophobia scale	3.35 (7.21)	1.83 (4.7)	0.638	-8.14 – 5.10
delta Beck anxiety scale	1.17 (7.57)	-3.59 (5.73)	0.122	-1.39 – 10.90
delta Beck Depression scale	**-6.83 (6.85)**	**-0.76 (2.86)**	**0.006**	**-10.19 – -1.95**
delta 25fwt	-9.98 (11.26)	-10.37 (33.51)	0.979	-29.01 – 29.78
Delta MsQoL pain	0.83 (2.28)	0.60 (2.11)	0.831	-1.91 – 2.35
Delta MsQoL Physical function	2.27 (2.13)	0.40 (3.73)	0.263	-1.51 – 5.24
delta MsQoL Role limitations - physical	-1.00 (5.90)	0.00 (5.30)	0.703	-6.38 – 4.38
Delta MsQoL Energy	**1.92 (1.77)**	**-0.17 (1.34)**	**0.006**	**0.66 – 3.52**
delta MsQoL Social function	0.33 (2.34)	-0.82 (2.90)	0.390	-1.58 – 3.90
delta MsQoL Health perceptions	2.13 (2.45)	-0.20 (2.71)	0.079	-0.29 – 4.94
delta MsQoL Sexual function	-0.33 (0.70)	0.24 (0.62)	0.076	-1.20 – 0.06
delta MsQoL combined physical score	6.42 (6.77)	-0.25 (13.54)	0.265	-5.45 – 18.79
delta MsQoL Role limitations - emotional	0.00 (15.18)	-0.94 (11.27)	0.874	-11.22 – 13.10
Delta MsQoL Emotional well-being	**2.71 (4.50)**	**-1.16 (3.67)**	**0.048**	**0.03 – 7.70**
delta MsQoL Health distress	-0.23 (1.14)	0.37 (3.34)	0.673	-3.54 – 2.33
Delta MsQoL Cognitive function	1.25 (2.95)	-0.35 (3.02)	0.274	-1.37 – 4.57
delta MsQoL Overall quality of life	0.95 (5.58)	0.56 (2.72)	0.822	-3.18 – 3.96
delta MsQoL combined mental score	4.67 (18.89)	0.06 (22.21)	0.655	-16.58 – 25.81

Significant differences are marked in bold.

included in our study were largely consistent with those reported in previous studies. Differences between studies may be explained by variations in disease subtype, medication use, and emotional status. Overall, the clinical profile of the MS patients included in our study reflects findings commonly reported in the general MS population.

Previous studies have consistently demonstrated that physical inactivity is one of the most important modifiable problems affecting individuals with MS and is closely associated with poorer quality of life, reduced functional independence, and increased psychological burden. Although different studies have used various instruments to evaluate physical activity, including self-reported questionnaires and objective activity monitoring, the overall conclusion has remained remarkably consistent: people with MS are generally less physically active than healthy individuals, even during the early stages of the disease. The baseline findings of our study are in agreement with these observations, as most participants demonstrated low physical activity levels before rehabilitation. Marck et al.[13] demonstrated that increased physical activity levels measured using the IPAQ were associated with significant improvements in quality of life. In contrast, Reguera-García et al.[14] reported that during the COVID-19 pandemic, 33.3% and 34.3% of MS patients demonstrated vigorous and moderate physical activity levels, respectively, according to the IPAQ-Short Form.[14] These findings are not consistent with the results of our study. The low physical activity levels observed in our participants may be related to fear of falling and fear of movement. Previous studies have suggested that this issue may be addressed through educational interventions aimed at improving coping strategies in patients with MS.

An interesting observation in the present study is that physical activity improved without parallel improvements in overall quality of life. Although this finding may initially appear contradictory, quality of life in MS is influenced by numerous physical, psychological, cognitive, and social determinants that cannot be fully modified within a relatively short rehabilitation program. Consequently, improvements in only one component, such as physical activity, may not immediately translate into higher overall quality-of-life scores. Longer follow-up periods may be necessary before behavioral changes become reflected in broader patient-reported outcome measures. Kubsik- Gidlewska et al.[16] demonstrated that exercise contributes not only to the physical abilities of MS patients but also to mood and attitudes toward exercise. Similarly, Grazioli et al.[17] reported that multicomponent exercise training improves quality of life, walking ability, and balance, while also reducing depression, fatigue, and disease severity in MS patients. Resistance and aerobic exercise have been identified as the most effective interventions for improving fatigue and quality of life, respectively. In this study, the results did not show a simultaneous increase in physical activity and quality of life with the application of a physiotherapy program. However, the long-term effects of such a program are still debatable due to the limited time frame of this study.[17]

There are reports suggesting that long-term and systematic physical activity may reduce relapse frequency and disease progression in some patients with MS. Despite the well-established beneficial effects of physical activity (PA) on functionality and quality of life in MS patients, several studies have demonstrated that PA levels in this population are generally lower than those observed in the healthy population.[18] Several exercise studies have demonstrated beneficial effects of rehabilitation on physical functioning, fatigue, mood, and health-related quality of life in MS. However, improvements across these domains are not necessarily expected to occur simultaneously. While some outcomes, such as psychological well-being or habitual physical activity, may respond within weeks, changes in walking performance, disability, or broader quality-of-life domains often require longer intervention periods or prolonged maintenance of an active lifestyle. Therefore, the absence of significant improvements in EDSS or T25FW in our study should not be interpreted as evidence that rehabilitation was ineffective. Rather, it may indicate that the duration of the intervention was sufficient to modify behavior and emotional status but insufficient to produce detectable neurological or functional changes.

In the 2012 study by Sandroff et al.[3], 77 individuals with MS and 77 matched healthy controls were included. Physical activity was assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ), the International Physical Activity Questionnaire (IPAQ), accelerometer activity counts, daily step counts, and time spent in moderate-to-vigorous physical activity (MVPA). There were statistically significant differences between the groups in accelerometer activity counts, step counts, time spent in moderate-to-vigorous physical activity, GLTEQ scores, and IPAQ scores. Significant differences in free-living physical activity were identified between the MS and control groups across all five measures. Although the authors suggested that the degree of physical inactivity in minimally disabled MS patients may be lower than previously reported in the literature, inactivity levels remain concerning when considering the well-documented prevalence of physical inactivity in the general population. Similarly, the individuals included in our study also demonstrated low physical activity levels on average.

However, the increase with the physiotherapy program is remarkable, and patients can be advised to adhere to such programs to increase physical activity and the additional benefits of this increase. An additional point worth considering is that increasing physical activity in individuals with MS may have benefits extending beyond simple improvements in exercise capacity. Participation in a structured rehabilitation program provides patients with regular supervision, individualized exercise progression, and continuous encouragement, all of which may enhance confidence in performing daily activities. This increased confidence may partially explain the improvement observed in physical activity levels despite the absence of measurable changes in disability or gait performance. It is possible that patients became more willing to engage in everyday activities because they perceived exercise as safe and manageable under professional guidance. Such behavioral adaptations may not be fully reflected by neurological disability scales but may nevertheless represent clinically meaningful outcomes. From a rehabilitation perspective, encouraging sustained participation in structured exercise programs may therefore contribute to maintaining an active lifestyle even before measurable functional gains become apparent.

In their 2023 study, Margoni et al.[19] suggested that MS diagnosis itself may represent a risk factor for the development of anxiety disorders, reporting that the prevalence of self-reported anxiety symptoms increased from 2.7% at disease onset to 6.2% at the time of diagnosis. In the cross-sectional study conducted by AlSaeed et al.[15] in Saudi Arabia, 323 MS patients were included. Anxiety and depression levels were evaluated using the Hospital Anxiety and Depression Scale (HADS). According to the results, 25.7% of patients demonstrated symptoms of anxiety, while 13.6% demonstrated symptoms of depression. The majority of patients had anxiety and depression scores within normal limits (57% and 70%, respectively). Although the mean depression score was within the normal range, the mean anxiety score corresponded to borderline anxiety symptoms. These findings suggest that MS patients may be more likely to experience anxiety than depression. The findings from this study are important in the sense that a structured physiotherapy program may aid in improving anxiety in patients with MS. In the meta-analysis conducted by Zhang et al.[20], the prevalence of anxiety in MS patients and the major risk factors contributing to anxiety development were evaluated. The authors estimated that approximately 36% of MS patients suffer from anxiety. Furthermore, age at assessment, female sex, living with family, psychiatric history, depression, adherence to MS medications, relapsing-remitting MS (RRMS), and baseline EDSS scores were identified as significant risk factors for anxiety in MS patients.

Considering the characteristics of the individuals included in our study, it may be stated that many participants belonged to these identified risk groups. In our study, anxiety and depression were evaluated using the Beck Anxiety Inventory and Beck Depression Inventory. Improvements in both anxiety and depression scores were observed following the rehabilitation program. These findings suggest that participation in a regular rehabilitation program may contribute to improvements in neuropsychiatric symptoms. The mechanisms underlying these psychological improvements are probably multifactorial. Besides the physiological effects of exercise on neuroplasticity and inflammatory pathways, regular rehabilitation may reduce emotional distress by improving self-efficacy, increasing social interaction, establishing daily routines, and providing continuous feedback from healthcare professionals. For many individuals with MS, participation in supervised rehabilitation also creates a sense of control over a disease that is otherwise characterized by unpredictability. Although these mechanisms were not specifically evaluated in the present study, they may explain why improvements in anxiety and depression were observed despite relatively stable disability scores. Future studies incorporating patient-reported measures of self-efficacy, exercise confidence, or perceived disease control may further clarify the pathways through which rehabilitation exerts its psychological benefits.

In the study conducted by Ruiz Sánchez et al.[21], which included 58 MS patients and 58 healthy controls, the TSK-11 questionnaire was used to evaluate fear of movement. According to the results, many MS patients were affected by kinesiophobia, and kinesiophobia levels were higher in MS patients compared with healthy controls. Further studies are needed to determine whether gait and balance impairments trigger fear of movement in MS patients and to evaluate the effectiveness of interventions aimed at reducing this fear. Similarly, in the study conducted by Wasiuk-Zowada et al.[18], 80 individuals with MS aged between 35 and 69 years were evaluated. The authors demonstrated that kinesiophobia is an important issue in MS patients and that low physical activity levels may represent one of its major determinants.

Mikuľáková et al.[22] reported in their cross-sectional study, which included 148 MS patients (105 women), that the mean kinesiophobia score was 39.27 points on the TSK scale. Higher levels of kinesiophobia were identified in 58.78% of participants, while lower levels were found in 41.22%. Additionally, 50% of participants reported moderate or severe anxiety. The authors identified three major independent predictors of kinesiophobia in patients with

MS: age, anxiety, and physical activity. Higher anxiety levels were associated with greater kinesiophobia, while lower physical activity levels measured using GLTEQ demonstrated the strongest association with kinesiophobia. Furthermore, older age was positively associated with fear of movement, whereas more physically active individuals reported lower levels of kinesiophobia. These findings are consistent with previous reports indicating that approximately 60% of MS patients demonstrate moderate-to-severe levels of kinesiophobia.

This study did demonstrate a significant increase in physical activity and an improvement in anxiety, but this change was not reflected in kinesiophobia. The reason might be the limited time frame and the possibility of not overcoming kinesiophobia despite an increase in physical activity. Fear of falling, movement avoidance, fatigue-related avoidance behavior, and uncertainty regarding relapse might still cause kinesiophobia. This study also did not demonstrate any significant difference in change in Tampa kinesiophobia scores between different patient groups, but considering the limited size of our sample, kinesiophobia or change within this parameter may still be dependent on the disease subtype. The exact factors that influence kinesiophobia in patients with MS still need to be studied. Another possible explanation is that kinesiophobia may not improve at the same rate as anxiety or depression because it reflects a learned behavioral response rather than an isolated emotional symptom. Fear of movement often develops gradually following repeated experiences of imbalance, falls, excessive fatigue, or symptom worsening, and these experiences may reinforce long-term avoidance behaviors. Consequently, patients may become more physically active during supervised rehabilitation sessions while continuing to avoid movement in unsupervised daily environments. Therefore, future rehabilitation protocols for MS may benefit from combining exercise therapy with educational interventions, cognitive-behavioral approaches, motivational interviewing, or graded exposure techniques specifically targeting maladaptive beliefs related to movement. Such multidimensional rehabilitation strategies may prove more effective in reducing kinesiophobia than exercise interventions alone.

An important strength of the present study is the simultaneous evaluation of physical, psychological, and behavioral outcomes following the same rehabilitation program. While previous studies have frequently focused on individual outcomes such as quality of life, fatigue, or walking performance, fewer studies have examined anxiety, depression, physical activity, kinesiophobia, disability, and quality of life together within a single rehabilitation protocol. This comprehensive approach provides a broader understanding of the multidimensional effects of physiotherapy in people with MS and highlights that different clinical domains may respond differently to the same intervention.

Our study has several limitations. First, the absence of a control group prevents us from clearly distinguishing whether the results are due to the effect of physiotherapy or the effect of the time factor. Second, the fact that the participants belonged to different MS subtypes, the relatively small sample size, and the wide age range limit the generalizability of the findings. Furthermore, the inclusion of patients with different disease durations may have introduced clinical heterogeneity that could have influenced the observed outcomes. Additionally, the relatively short duration of the rehabilitation program and the lack of long-term follow-up assessments may have limited our ability to detect changes in disability, walking performance, and kinesiophobia. Future studies should address these limitations by including larger and more homogeneous patient populations with longer follow-up periods.

Conclusion

This study, conducted to examine the effect of a structured physical therapy and rehabilitation program on physical activity level, anxiety, and kinesiophobia, found a significant decrease in participants' anxiety and depression levels. Partial improvement was observed in participants' quality of life. However, no significant improvement was found in participants' walking speed, kinesiophobia, and disability levels. In conclusion, the structured physiotherapy program used in our study reduced neuropsychiatric symptoms but did not provide significant improvement in disability level, walking speed, and kinesiophobia parameters. Nevertheless, considering the progressive nature of the disease, we believe that the lack of significant deterioration in disability level, walking speed, and kinesiophobia parameters can also be considered a positive outcome.

List of Abbreviations

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; EDSS, Expanded Disability Status Scale; EQ-5D-3L, EuroQOL Five-Dimensional Three-Level Questionnaire;; GLTEQ, Godin Leisure-Time Exercise Questionnaire; HADS, Hospital Anxiety and Depression Scale; IPAQ-SF, International Physical Activity Questionnaire–Short Form; MET, Metabolic Equivalent of Task; MS, Multiple Sclerosis; MSQoL-54, Multiple Sclerosis Quality of Life-54; MVPA, Moderate-to-Vigorous Physical Activity; PA, Physical Activity; PPMS, Primary Progressive Multiple Sclerosis; RRMS, Relapsing-Remitting Multiple Sclerosis; SD, Standard Deviation; SPMS, Secondary Progressive Multiple Sclerosis; T25FW, Timed 25-Foot Walk Test; TSK, Tampa Scale for Kinesiophobia

Disclosures

Ethics Committee Approval: Ethical approval was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (Approval No: 09.2025.25-05.12).

Informed Consent All patients were informed in detail about the treatment before participating in the study, and written informed consent was obtained.

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Research Article

Serum Procalcitonin for the Diagnosis of Spontaneous Bacterial Peritonitis in Patients With Decompensated Cirrhosis: A Prospective Study

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Abstract

Objectives: Spontaneous bacterial peritonitis (SBP) is a serious infectious complication in patients with decompensated cirrhosis. Although serum procalcitonin (PCT) has been evaluated as a potential indicator of bacterial infection, its clinical value in the diagnosis of SBP remains uncertain. This study investigated the diagnostic contribution of serum procalcitonin in cirrhotic patients with SBP.

Methods: This prospective, single-center study included 100 participants: 50 patients with SBP, 25 patients with sterile ascites, and 25 healthy controls. The diagnosis of SBP was established according to the ascitic fluid polymorphonuclear leukocyte (PMNL) count and/or positive ascitic fluid culture findings. Serum procalcitonin levels and ascitic inflammatory parameters were compared among the study groups.

Results: Serum procalcitonin levels were numerically higher in patients with SBP than in patients with sterile ascites and healthy controls; however, the differences were not statistically significant ($p>0.05$). In contrast, ascitic fluid leukocyte and PMNL counts were significantly elevated in the SBP group ($p<0.05$). No significant association was observed between serum procalcitonin concentrations and the Child–Turcotte–Pugh classification.

Conclusion: Serum procalcitonin alone showed limited diagnostic performance in distinguishing spontaneous bacterial peritonitis in patients with decompensated cirrhosis. Ascitic fluid inflammatory parameters, particularly the PMNL count, remained more informative for diagnostic evaluation.

Keywords: Ascites, biomarker, liver cirrhosis, procalcitonin, spontaneous bacterial peritonitis

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Cirrhosis represents the end stage of chronic liver injury and is marked by progressive hepatic fibrotic changes, distortion of the normal liver architecture, and portal hypertension, ultimately resulting in impaired hepatic function and systemic complications.[1,2] Bacterial infections occur more frequently in patients with decompensated cirrhosis because of cirrhosis-associated immune dysfunction, impaired intestinal barrier function, and enhanced bacterial translocation.[3,4] Among these infectious complications, spontaneous bacterial peritonitis (SBP) remains one of the most clinically significant conditions, particularly in individuals with ascites.[5]

Spontaneous bacterial peritonitis is defined as an infection of ascitic fluid without an evident, surgically treatable in-

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tra-abdominal source.[5,6] Despite improvements in antimicrobial therapy and supportive care, SBP continues to be associated with considerable morbidity and unfavorable clinical outcomes in advanced liver disease.[7] Diagnostic assessment mainly depends on paracentesis and evaluation of the ascitic polymorphonuclear leukocyte (PMNL) count, with a PMNL threshold of ≥250/mm^3 accepted as the standard diagnostic criterion.[5,8] Nevertheless, interest in alternative supportive biomarkers for the earlier identification of infection continues.

Procalcitonin (PCT), the precursor molecule of calcitonin, has been investigated as a biomarker of bacterial infection and systemic inflammatory activation.[9–11] Previous studies have suggested that serum PCT concentrations may increase in cirrhotic patients with SBP.[12,13] However, findings regarding its diagnostic performance remain inconsistent, especially in advanced cirrhosis, where chronic inflammation and immune dysregulation may influence serum biomarker levels independently of active infection.[14–17] Furthermore, the association between serum procalcitonin concentrations and the severity of hepatic dysfunction has not yet been clearly established.

Accordingly, this prospective study was designed to evaluate the diagnostic utility of serum procalcitonin in spontaneous bacterial peritonitis and to investigate its relationship with liver disease severity in patients with decompensated cirrhosis.

Methods

Study Population and Design

This prospective, observational, single-center study was carried out between January 2011 and December 2013 and included patients with decompensated cirrhosis and healthy control subjects.

A total of 100 participants were enrolled and divided into three study groups:

- Group 1 (n=50): patients diagnosed with spontaneous bacterial peritonitis (SBP)
- Group 2 (n=25): patients with sterile ascites
- Group 3 (n=25): healthy control subjects

The diagnosis of SBP was established based on the presence of an ascitic fluid polymorphonuclear leukocyte (PMNL) count of ≥250/mm^3 and/or positive ascitic fluid culture findings in the absence of a surgically treatable intra-abdominal infectious source.

Sterile ascites was defined as an ascitic PMNL count below 250/mm^3 together with negative ascitic fluid culture results.

Healthy individuals without known chronic systemic diseases were included in the control group.

Data Collection and Laboratory Evaluation

Peripheral venous blood and ascitic fluid specimens were obtained at hospital admission before the initiation of antimicrobial treatment.

Ascitic fluid evaluation included:

- Total leukocyte count
- Polymorphonuclear leukocyte count
- Microbiological culture analysis

Serum procalcitonin concentrations were measured in the institutional biochemistry laboratory using routinely applied laboratory procedures.

Demographic, clinical, and laboratory findings were obtained from archived patient records. The severity of liver disease was determined according to the Child–Turcotte–Pugh (CTP) classification.

Ethical Approval

Ethics committee approval was obtained from the Ethics Committee of Atatürk University before the initiation of the study (approval date: August 18, 2011; session no. 7; decision no. 12). Written informed consent was obtained from all study participants before enrollment. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as the mean±standard deviation, whereas categorical variables are expressed as numbers and percentages. Distribution normality was evaluated using appropriate statistical methods. Comparisons between groups were carried out using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables, where appropriate. A two-sided p-value of <0.05 was considered statistically significant.

Results

A total of 100 participants were included in the analysis, comprising 50 patients with spontaneous bacterial peritonitis (SBP), 25 patients with sterile ascites, and 25 healthy control subjects. Baseline demographic and clinical findings of the study population are summarized in Table 1. Viral hepatitis represented the most common etiology of cirrhosis in both patient groups, whereas alcohol-related

Table 1. Baseline clinical characteristics of the study population

Variable	SBP group (n=50)	Sterile ascites group (n=25)	Control group (n=25)
Clinical status	Decompensated cirrhosis with SBP	Decompensated cirrhosis with sterile ascites	Healthy controls
Ascitic fluid PMNL criterion	≥250/mm³ and/or positive culture	<250/mm³ and negative culture	NA
Predominant cirrhosis etiology	Viral hepatitis (~70–80%)	Viral hepatitis (~70–80%)	NA
Alcohol-related cirrhosis	Less frequent (~10–15%)	Less frequent (~10–15%)	NA
Cryptogenic cirrhosis	Less frequent (~10–15%)	Less frequent (~10–15%)	NA
Child–Turcotte–Pugh status	Predominance of Child B/C stages	Lower predominance of advanced Child–Turcotte–Pugh stages	NA

SBP: Spontaneous bacterial peritonitis; PMNL: Polymorphonuclear leukocyte; NA: Not applicable. Detailed subgroup distributions were unavailable in the archived thesis dataset; therefore, approximate proportional descriptions are provided for selected historical variables.

and cryptogenic cirrhosis were encountered less commonly. Advanced Child–Turcotte–Pugh stages were observed more frequently in the SBP group than in patients with sterile ascites.

Serum procalcitonin concentrations tended to be higher in patients with SBP than in the remaining study groups. Mean serum PCT values were 898.41±573.06 pg/mL (0.898±0.573 ng/mL) in the SBP group, 674.74±582.68 pg/mL (0.675±0.583 ng/mL) in patients with sterile ascites, and 436.99±210.71 pg/mL (0.437±0.211 ng/mL) in healthy controls. Nevertheless, the observed differences between the groups did not demonstrate statistical significance (p>0.05) (Table 2).

Ascitic fluid evaluation demonstrated markedly increased inflammatory cell counts in patients diagnosed with SBP. Mean ascitic leukocyte counts were significantly greater in the SBP group than in the sterile ascites group (1143.54±132.77/mm³ vs. 356.68±125.51/mm³, respectively; p<0.05). Likewise, ascitic fluid polymorphonuclear leukocyte (PMNL) counts were significantly elevated in patients with SBP relative to those with sterile ascites (601.72±97.09/mm³ vs. 125.68±61.13/mm³, respectively; p<0.05) (Table 3).

The association between serum procalcitonin concentrations and liver disease severity was further examined according to the Child–Turcotte–Pugh classification. Serum PCT levels were not significantly associated with Child–Turcotte–Pugh stages (p>0.05). Although serum procalcitonin concentrations demonstrated a gradual numerical increase from the Child A to the Child C groups, the observed trend did not achieve statistical significance. Mean serum PCT levels were 0.61±0.32 ng/mL in Child A patients, 0.74±0.41 ng/mL in Child B patients, and 0.88±0.56 ng/mL in Child C patients (Table 4).

Overall, serum procalcitonin concentrations demonstrated a numerical increase in patients with spontaneous bacte-

Table 2. Comparison of serum procalcitonin levels among the study groups

Parameter	SBP group (n=50)	Sterile Ascites group (n=25)	Control group (n=25)	p
Serum procalcitonin (pg/mL)	898.41±573.06	674.74±582.68	436.99±210.71	>0.05
Serum procalcitonin (ng/mL)	0.898±0.573	0.675±0.583	0.437±0.211	>0.05

SBP: Spontaneous bacterial peritonitis. Data are expressed as mean ± standard deviation. Original laboratory measurements were recorded in pg/mL; corresponding ng/mL values are additionally provided for consistency with contemporary literature.

Table 3. Comparison of ascitic fluid findings between SBP and sterile ascites groups

Parameter	SBP group (n=50)	Sterile ascites group (n=25)	p
Ascitic fluid total leukocyte count (/mm³)	1143.54±132.77	356.68±125.51	<0.05
Ascitic fluid PMNL count (/mm³)	601.72±97.09	125.68±61.13	<0.05
Positive ascitic fluid culture	Included in diagnostic criteria	Negative	—

SBP: Spontaneous bacterial peritonitis; PMNL: Polymorphonuclear leukocyte. Values are presented as mean ± standard deviation. Detailed culture positivity data were unavailable in the archived dataset.

Table 4. Serum procalcitonin levels according to Child–Turcotte–Pugh classification

Child–Turcotte–Pugh class	Serum procalcitonin (ng/mL)	p
Child A	0.61±0.32	
Child B	0.74±0.41	>0.05
Child C	0.88±0.56	

CTP: Child–Turcotte–Pugh. Values are presented as mean ± standard deviation.

rial peritonitis; however, serum PCT alone did not reliably differentiate SBP from sterile ascites or healthy controls within the present cohort. In contrast, conventional ascitic inflammatory markers, particularly leukocyte and PMNL counts, remained clearly different between the SBP and sterile ascites groups.

Discussion

Spontaneous bacterial peritonitis continues to represent a clinically significant infectious complication in patients with decompensated cirrhosis despite advances in supportive management and antimicrobial therapy.[5,7,17] Delayed recognition of infection may contribute to progressive hepatic dysfunction, renal impairment, and systemic complications, highlighting the importance of early diagnostic evaluation in this patient population.[18] Therefore, interest in supportive biomarkers that may facilitate earlier detection of SBP has continued to increase.

In the present study, serum procalcitonin concentrations tended to be higher in patients with spontaneous bacterial peritonitis than in patients with sterile ascites and healthy controls. Nevertheless, these differences did not achieve statistical significance. In contrast, conventional ascitic inflammatory markers, particularly leukocyte and polymorphonuclear leukocyte counts, clearly differentiated patients with SBP from those with sterile ascites. These findings suggest that serum procalcitonin alone may provide limited diagnostic benefit in patients with advanced cirrhosis.

Procalcitonin has been widely investigated as a biomarker reflecting bacterial infection and systemic inflammatory activation.[9–11] Viallon et al.[12] reported elevated serum and ascitic fluid procalcitonin concentrations in cirrhotic patients with spontaneous bacterial peritonitis and suggested a possible diagnostic role for PCT in this setting. Likewise, Connert et al.[13] demonstrated an association between increased serum procalcitonin levels and bacterial infections in decompensated cirrhosis. In contrast, Spahr et al.[14] observed that serum procalcitonin had limited usefulness in distinguishing SBP among cirrhotic patients. Overall, the findings of the current study appear to be more consistent with reports describing the limited diagnostic utility of serum PCT in advanced liver disease.

Several pathophysiological mechanisms may contribute to the restricted diagnostic performance of serum procalcitonin in advanced cirrhosis. Even in the absence of clinically apparent infection, patients with decompensated cirrhosis frequently exhibit chronic systemic inflammation, endotoxemia, bacterial translocation, and cirrhosis-associated immune dysregulation.[19] These persistent inflammatory alterations may result in elevated baseline biomarker concentrations and reduce the specificity of serum procalcitonin for differentiating infected from noninfected patients.[20] Consistent with this interpretation, serum PCT concentrations were also relatively increased in patients with sterile ascites in the present cohort.

Another important finding of the present study was the absence of a statistically significant association between serum procalcitonin levels and the Child–Turcotte–Pugh classification. Although serum PCT concentrations demonstrated a gradual numerical increase across the Child A, Child B, and Child C groups, this trend did not achieve statistical significance. Similar observations have been reported in previous studies evaluating inflammatory biomarkers in advanced cirrhosis.[14–16,21] These findings suggest that serum procalcitonin may not reliably reflect the severity of hepatic dysfunction.

In contrast, conventional ascitic inflammatory markers retained substantial diagnostic importance in the current study. Both total leukocyte and PMNL counts were significantly increased in patients with SBP compared with patients with sterile ascites. These findings further support the continuing clinical importance of diagnostic paracentesis and ascitic PMNL assessment in patients with suspected SBP.[5,8] Although serum inflammatory biomarkers may provide adjunctive clinical information, ascitic fluid analysis continues to represent the cornerstone of routine SBP diagnosis.[22]

Certain limitations should be considered when interpreting the findings of the present study. First, the study population was relatively limited, particularly for subgroup analyses. Second, the single-center design may limit the external generalizability of the results. Third, serum procalcitonin measurements were assessed only at baseline, and serial follow-up evaluations were unavailable. In addition, archived individual-level data were insufficient for receiver operating characteristic analysis and the determination of an optimal diagnostic cutoff value. Comparative inflammatory markers, including C-reactive protein, were not available for all study participants.

Nevertheless, several strengths of the present study should also be acknowledged. The prospective design, the inclusion of both sterile ascites and healthy control groups, and the standardized evaluation of ascitic inflammatory parameters increase the clinical relevance of the findings. Furthermore, the study reflects the real-world characteristics of patients with decompensated cirrhosis encountered in routine clinical practice.

Conclusion

In conclusion, serum procalcitonin demonstrated limited diagnostic utility as an isolated biomarker for spontaneous bacterial peritonitis in patients with advanced cirrhosis. Conventional ascitic fluid inflammatory parameters continue to represent the most reliable diagnostic approach in routine clinical practice.

In the current prospective study, patients with spontaneous bacterial peritonitis demonstrated numerically increased serum procalcitonin levels compared with patients without SBP. However, serum PCT alone did not reliably differentiate SBP from sterile ascites. Conventional ascitic inflammatory parameters, particularly polymorphonuclear leukocyte counts, remained more informative and clinically useful for diagnostic evaluation. Additional large-scale prospective studies may help further clarify the clinical utility of serum procalcitonin in cirrhotic patients with suspected SBP.

Disclosures

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee of Atatürk University before the initiation of the study (approval date: August 18, 2011; session no.: 7; decision no.: 12).

Informed Consent: Written informed consent was obtained from all study participants before enrollment

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Research Article

Early Vascular Remodeling and Hemorheological Alterations in Biopsy-Proven MASLD

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Abstract

Objectives: Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly associated with cardiovascular complications and early vascular injury. This study evaluated carotid intima–media thickness (CIMT) and its association with hemorheological parameters in patients with biopsy-proven MASLD.

Methods: This cross-sectional study included 25 patients with histologically confirmed metabolic dysfunction-associated steatohepatitis (MASH) and 28 age- and sex-matched healthy controls. CIMT was assessed using high-resolution ultrasonography. Whole blood viscosity and plasma viscosity were measured using a rotational viscometer at shear rates of 45 s^{-1} and 225 s^{-1}. Multivariable regression analyses were performed to determine independent predictors of CIMT.

Results: Patients with MASLD had significantly higher CIMT values than controls (0.92±0.16 mm vs. 0.76±0.13 mm, p=0.002). Whole blood viscosity at both shear rates was significantly increased in the MASLD group, whereas plasma viscosity did not differ significantly. In multivariable analyses, systolic blood pressure and waist circumference independently predicted CIMT, while hemorheological parameters were not independently associated with CIMT.

Conclusion: Biopsy-proven MASLD is associated with increased CIMT and altered hemorheological profiles, supporting the presence of early vascular remodeling and increased cardiovascular risk.

Keywords: Blood viscosity, cardiovascular risk, carotid intima-media thickness, MASLD, subclinical atherosclerosis

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most prevalent chronic liver disorder and is closely linked to obesity, insulin resistance, and metabolic syndrome.[1] In recent years, MASLD has been increasingly recognized as a multisystem disease extending beyond hepatic involvement.[2] Cardiovascular complications are considered the leading cause of mortality in affected individuals.[2,3]

Early vascular alterations may occur before clinically overt cardiovascular disease develops in MASLD. Carotid inti-

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ma–media thickness (CIMT) is widely used as a noninvasive marker reflecting subclinical arterial remodeling and atherosclerotic burden.[4–8] Increased CIMT values have previously been demonstrated in patients with metabolic liver disease; however, the underlying biological mechanisms remain incompletely understood.[2,9,10]

Abnormal blood rheology may contribute to vascular dysfunction in MASLD. Increased blood viscosity can impair endothelial function, alter shear stress, and reduce microvascular perfusion.[9–11] Nevertheless, evidence regarding the association between hemorheological disturbances and vascular structural changes in biopsy-confirmed MASLD remains scarce.[11]

The aim of the present study was to investigate carotid intima–media thickness and evaluate its relationship with hemorheological parameters in patients with histologically confirmed MASLD.

Methods

Study design and participants

Twenty-five individuals with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and 28 healthy control subjects were included in this cross-sectional study. Histopathological evaluation was performed according to the Brunt classification system.

Individuals with chronic inflammatory disorders, secondary liver disease, significant alcohol intake, active infection, malignancy, hematologic disease, or clinically evident cardiovascular disease were excluded from the study population.

Ethics committee approval was obtained from the Erciyes University Ethics Committee (Approval No. 373; Date: February 12, 2014). The study protocol complied with the ethical principles outlined in the Declaration of Helsinki.

Clinical and biochemical evaluation

Anthropometric assessment included body mass index and waist circumference measurements. Blood pressure was measured after an adequate resting period under standardized conditions.

Fasting venous blood samples were analyzed for glucose, insulin, lipid parameters, liver enzyme levels, ferritin concentrations, and hematologic indices. Insulin resistance was calculated using the homeostasis model assessment formula.

Assessment of Carotid Intima–Media Thickness

CIMT measurements were performed by an experienced radiologist who was blinded to the participants' characteristics. High-resolution B-mode ultrasonography was used for vascular imaging. Bilateral measurements were obtained from the distal segment of the common carotid artery proximal to the bifurcation, and mean values were recorded.

Hemorheological Analysis

Whole blood and plasma viscosity measurements were obtained using a rotational viscometer at shear rates of 45 s^{-1} and 225 s^{-1}. Lower shear rates were considered representative of microcirculatory conditions.[11]

Statistical Analysis

All statistical analyses were conducted using SPSS software, version 25.0. Continuous variables were expressed according to their distribution characteristics. Between-group comparisons were performed using appropriate parametric or nonparametric statistical tests. Independent predictors of CIMT were evaluated using multivariable linear regression analysis. Statistical significance was defined as $p<0.05$.

The overall study design and analytical workflow are summarized in Figure 1.

Results

Compared with controls, patients with MASLD exhibited significantly greater waist circumference, systolic blood

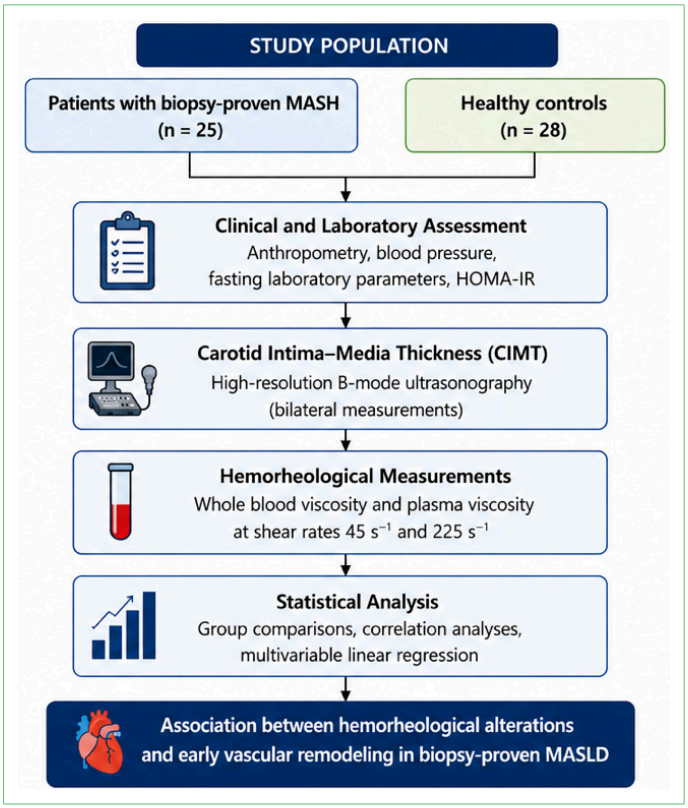


Figure 1. Study design and analytical workflow.
MASH: Metabolic dysfunction-associated steatohepatitis; MASLD: Metabolic dysfunction-associated steatotic liver disease; HOMA-IR: Homeostasis model assessment of insulin resistance

Table 1. Liver histology distribution according to Brunt classification

Histological feature	n (%)
Steatosis 5–33%	13 (52%)
Steatosis 33–66%	10 (40%)
Steatosis >66%	2 (8%)
Fibrosis F0	9 (36%)
Fibrosis F1	11 (44%)
Fibrosis F2	3 (12%)
Fibrosis F3	2 (8%)
Fibrosis F4	0

pressure, insulin resistance indices, liver enzyme levels, and ferritin concentrations (Table 2).

CIMT measurements were significantly higher in the MASLD group, suggesting the presence of early arterial wall remodeling (Fig. 2).

Whole blood viscosity values obtained at both shear rates were elevated in patients with MASLD, whereas plasma viscosity values were similar between the study groups (Table 3).

Multivariable regression analysis demonstrated that systolic blood pressure and waist circumference independently predicted CIMT values (Table 4). Hematocrit was identified as an independent determinant of whole blood viscosity (Table 5).

Table 2. Baseline clinical and laboratory characteristics of patients with biopsy-proven MASH and controls

Variable	MASH (n=25)	Controls (n=28)	p
Age (years)	44.12±9.57	39.14±12.32	0.110
Male sex, n (%)	16 (64)	13 (46)	0.200
BMI (kg/m^2)	29.70±5.00	26.32±4.93	0.170
Waist circumference (cm)	103.80±11.53	89.68±20.53	**0.003**
Systolic BP (mmHg)	132.40±15.68	116.61±19.10	**<0.001**
Diastolic BP (mmHg)	81.00±12.74	80.00±17.37	0.204
Hematocrit (%)	46.00±3.60	43.21±4.16	**0.013**
LDL cholesterol (mg/dL)	122.52±29.57	100.82±34.00	**0.017**
Insulin (µU/mL)	19.00±9.78	8.80±3.97	**<0.001**
HOMA-IR	4.61±2.16	1.93±0.91	**<0.001**
ALT (U/L)	57.92±38.93	18.25±7.65	**<0.001**
AST (U/L)	35.24±15.13	18.79±4.69	**<0.001**
Ferritin (ng/mL)	141.40±109.55	87.78±87.12	**0.026**

Values are presented as mean±SD or n (%). Statistically significant values are shown in bold (p<0.05). BMI: Body mass index; BP: Blood pressure; LDL: Low-density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HOMA-IR: Homeostasis model assessment of insulin resistance.

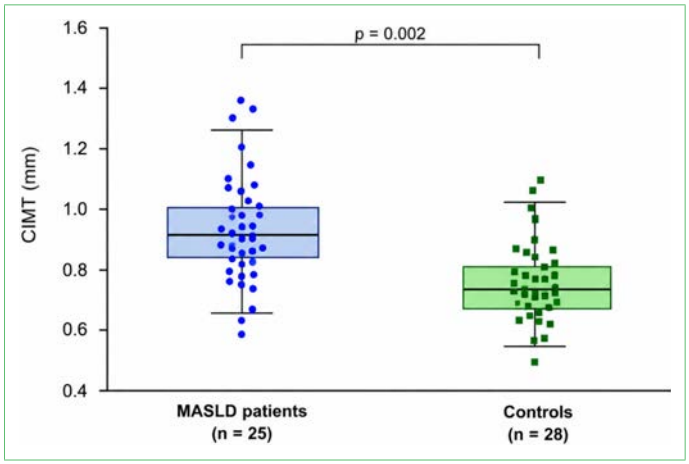


Figure 2. Comparison of carotid intima–media thickness between groups.
CIMT: Carotid intima-media thickness; MASLD: Metabolic dysfunction-associated steatotic liver disease

Discussion

The present study demonstrated increased carotid intima–media thickness and elevated whole blood viscosity values in patients with biopsy-confirmed MASLD. These findings indicate that vascular and hemorheological alterations may accompany metabolic liver disease even before overt cardiovascular events become clinically apparent.

Growing evidence suggests that MASLD contributes to accelerated vascular aging and subclinical atherosclerosis.[4–8] Consistent with previous reports, our study identified significantly

Table 3. Comparison of vascular and hemorheological parameters between groups

Parameter	MASH	Controls	p
CIMT (mm)	0.92±0.16	0.76±0.13	0.002
Whole blood viscosity – 45 s^{-1} (cP)	6.84±0.98	6.14±0.76	0.010
Whole blood viscosity – 225 s^{-1} (cP)	5.10±0.81	4.66±0.66	0.040
Plasma viscosity – 45 s^{-1} (cP)	1.79±0.23	1.73±0.23	0.631

Values are presented as mean±SD. CIMT: Carotid intima–media thickness; cP: Centipoise.

Table 4. Multivariable regression analysis identifying independent predictors of carotid intima–media thickness

Variable	β	Standardized β	p
Systolic BP	0.003	0.41	0.006
Waist circumference	0.002	0.35	0.018
Whole blood viscosity	NS	–	>0.05

Model R^2=0.42; Adjusted R^2=0.38; Model p<0.001; BP: blood pressure; β: Regression coefficient; R^2: Coefficient of determination

Table 5. Multivariable regression analysis identifying determinants of whole blood viscosity

Variable	β	Standardized β	p
Hematocrit	0.082	0.67	<0.001

Model R^2=0.58; Adjusted R^2=0.54; β: Regression coefficient; R^2: Coefficient of determination.

higher CIMT measurements in the MASLD group. Chronic inflammation, oxidative stress, endothelial dysfunction, insulin resistance, and metabolic imbalance may collectively contribute to vascular remodeling in these patients.[2,3,9,10]

A major strength of the present study is the histopathological confirmation of the disease. Many previous investigations relied primarily on imaging modalities or surrogate biochemical markers for diagnosis. Liver biopsy increases diagnostic precision and strengthens the reliability of the present findings.[8,12]

Whole blood viscosity was also significantly elevated in patients with MASLD. Increased viscosity may adversely affect endothelial physiology and microvascular blood flow.[9–11] However, viscosity-related variables did not remain independently associated with CIMT after adjustment for cardiometabolic risk factors. This finding suggests that hemorheological abnormalities may reflect systemic metabolic dysregulation rather than act as direct determinants of vascular structural change.

Several limitations should be considered when interpreting these findings. The cross-sectional design prevents causal interpretation, and the relatively modest sample size may have limited statistical power. In addition, residual confounding factors associated with metabolic risk cannot be fully excluded.

Conclusion

Patients with biopsy-confirmed MASLD demonstrated increased carotid intima–media thickness together with altered hemorheological characteristics. These findings support the concept that MASLD is associated with early vascular remodeling and increased cardiovascular risk.

Disclosure

Ethics Committee Approval: Ethics committee approval was obtained from Erciyes University Ethics Committee (Approval No: 373, Date: 12 February 2014).

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

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

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Research Article

Evaluation of Complication Development and Laboratory Data Between Diabetic Individuals Regularly Check-Ups and Diabetic Individuals Not Regularly Attending Check-ups at the Endocrinology and Metabolism Diseases Polyclinic of Necmettin Erbakan University Meram Faculty of Medicine Hospital

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Abstract

Objectives: Our intention is to assess the effects of routine control and diabetes education on diabetes-related complications, anthropometric measurements, and laboratory tests.

Methods: The research enrolled patients over 18 years of age who presented to the Endocrinology and Metabolic Diseases Outpatient Clinic, including both those undergoing regular control and those not undergoing regular control.

Results: Patients enrolled in this research were separated into two groups: those under irregular control and those under regular control. There were no remarkable discrepancies in the characteristics of the two groups. Those in the irregular monitoring group had a longer duration of diabetes (11.6±7.5 vs. 8.3±7.1, p<0.001). When evaluated in terms of diabetes-related complications and comorbidities, the irregular control group showed higher rates of diabetic foot, peripheral neuropathy, diabetic kidney disease, and coronary artery disease (p=0.002, p=0.001, p=0.001, and p=0.002, respectively).

Conclusion: The prevention of diabetes-related complications, illnesses, and deaths can be achieved through regular patient follow-up. Regular follow-up enables the early detection of alterations in HbA1c levels and allows for early intervention before glycemic control deteriorates; it also ensures that patients receive face-to-face information about diabetes and the risks of diabetes-related complications. Regular control also contributes to raising patient awareness about diabetes and improving dietary adherence.

Keywords: Diabetes-related complications, HbA1c, regular check-ups

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The number of diabetes cases worldwide is estimated at 828 million, corresponding to a global prevalence of 14%.[1] Type 2 diabetes (T2DM) accounts for 98% of all diabetes diagnoses.[2] The increase in childhood obesity raises concerns that the prevalence of diabetes will increase. Diabetes cases increased by 39% globally from 1990 to 2019.[3] Furthermore, one study showed increased rates of T2DM among young adults and adolescents.[4]

Diabetes is a chronic condition associated with decreased insulin secretion and impaired insulin activity. Chronic hyperglycemia associated with diabetes leads to dysfunction and failure in many organs over the long term. Abnormal blood glucose levels are caused by impaired insulin secretion in pancreatic islet β-cells or insulin resistance in insulin-sensitive tissues (the liver, muscles, and adipose tissue).[5] In type 2 DM, insulin resistance causes increased glucose release from the liver while reducing glucose uptake in adipose tissue and muscles. Additionally, β-cell dysfunction causes decreased insulin secretion and abnormal glucose levels.[6] Various studies have shown that both adolescents and adults lose approximately 80% of their pancreatic β-cell function before receiving a diagnosis of type 2 DM.[7,8]

Long-standing complications of diabetes can lead to organ dysfunction and limb amputation. Nephropathy causes kidney failure, while peripheral neuropathy can have serious consequences ranging from foot ulcers to amputation. Autonomic neuropathy causes sexual dysfunction and genitourinary, gastrointestinal, and cardiovascular symptoms. The incidence of atherosclerotic heart disease, peripheral artery disease, and cerebrovascular disease is increased in patients with diabetes. Hypertension and abnormalities in lipoprotein metabolism are also frequently found in individuals with diabetes.[9]

Diabetes mellitus (DM) is classified based on the pathogenic process leading to hyperglycemia. The two major classes of diabetes mellitus are called type 1 and type 2 diabetes. Both types are preceded by abnormal glucose homeostasis that worsens as the pathological processes progress.

Diabetes-related morbidity and mortality are associated with acute complications of diabetes (hypoglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemic state) and chronic microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (atherosclerosis) complications. The onset of type 2 diabetes is insidious, and diagnosis is often delayed. Consequently, diabetes-related complications may be present when a diagnosis is made.[10] The progression of these complications can be prevented by regulating glycemia, blood pressure, and fasting lipid levels. Laser treatment can be applied for advanced retinopathy, and ACE inhibitors (angiotensin-converting enzyme inhibitors) and ARBs (angiotensin receptor blockers) can be given for nephropathy. These interventions reduce the incidence of various diabetes-related complications, such as stroke, myocardial infarction (MI), end-stage renal disease, and limb amputation.[11]

The aim of this study is to examine the relationship between diabetes education, regular clinical check-ups at specific intervals, timely interventions, and the prevention of the onset and progression of diabetes-related complications in patients diagnosed with diabetes. Furthermore, laboratory tests, such as complete blood count, lipid profile, glycemic control, and renal function tests, as well as anthropometric measurements, such as body mass index (BMI), body weight, waist circumference, and hip circumference, will also contribute to this relationship.

Methods

Patient selection and study design

The study enrolled individuals aged 18 years and older who had been diagnosed with type 2 diabetes, had visited the Endocrinology and Metabolic Diseases Outpatient Clinic over a five-year period, and had sufficient recorded data, including both those attending regular follow-up and those not attending regular follow-up.

For patients with HbA1c≤7, those attending follow-up every 6 months or less frequently were included in the ordered check-ups group, whereas those attending check-ups at intervals of more than 6 months were included in the disordered check-ups group.

For patients with HbA1c>7, those attending follow-up every 3 months or less frequently were included in the ordered check-ups group, whereas those attending check-ups at intervals of more than 3 months were included in the disordered check-ups group.

It is recommended that patients with type 2 DM have their HbA1c checked every 3–6 months, their lipid profiles checked annually, and their kidney function tests (complete urinalysis and spot urine microalbumin/creatinine ratio) and liver function tests performed.

Patients whose check-up time was due and who had undergone these tests were reviewed.

The patients' age, sex, smoking status, duration of diabetes, comorbid diseases, and presence of type 2 DM complications (retinopathy, nephropathy, and neuropathy) were evaluated according to their medical histories and medications used.

BMI, body weight, waist circumference, and hip circumference were recorded as anthropometric values.

Patients with type 1 diabetes mellitus, pregnant women, and patients with insufficient data were excluded from the study.

Anthropometric and clinical measurements

BMI was calculated by dividing body weight in kilograms by the square of height in meters. Measurements were performed using methods recommended by the World Health Organization (WHO).

Blood pressure measurements were taken from the right brachial artery using a standard Erka-brand sphygmomanometer after the patient had rested in a seated position for at least 5 minutes before the examination.

Assessment of diabetes complications

The presence of diabetic retinopathy in patients was determined based on their medical histories. The presence of peripheral neuropathy was investigated. The presence of diabetic kidney disease was determined using the microalbumin/creatinine ratio in spot urine, the eGFR value [calculated using the MDRD (Modification of Diet in Renal Disease) formula], and the patients' medical histories.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Version 21.0 software package. Numerical variables are presented as the mean±standard deviation, while categorical variables are presented as counts and percentages. We checked the normality of the numerical values using the one-sample Kolmogorov–Smirnov test. To compare categorical data across groups, the chi-square test and Fisher's exact test were used. The independent-samples Student's t-test was used to compare numerical data that followed a normal distribution, while the Mann–Whitney U test was used for data that did not follow a normal distribution. A p-value of <0.05 was considered statistically significant.

Ethics Committee Approval

The study commenced after receiving approval from the Necmettin Erbakan University Faculty of Medicine Clinical Research Ethics Committee, dated January 19, 2018, and numbered 2018/1167. Written informed consents were obtained from patients who participated in this study.

Results

Clinical and demographic findings of all patients

The mean age of the 361 patients included in the study was 56.9±10.2 years (range, 32–80 years). Of the patients, 222 (61.5%) were female, and 139 (38.5%) were male. The mean body weight of the patients was 84.1±13.8 kg, and the mean BMI was 31.7±5.6 kg/m^2. Based on the mean BMI, the patients were classified as "obese." Based on BMI, 30 (8.3%) patients were classified as morbidly obese (BMI>40), 187 (51.8%) as obese (BMI, 30–40), and 114 (31.5%) as overweight (BMI, 25–30). Only 27 (7.4%) patients were found to be within the normal BMI range (BMI, 18–25). The mean BMI of female patients was 34.1±13.2 kg/m^2, and that of male patients was 29.3±4.5 kg/m^2 ($p<0.001$). The mean waist circumference of female patients was 104.3±14.1 cm, and that of male patients was 99.7±15 cm. The mean hip circumference of female patients was 117.2±13 cm, and that of male patients was 102±11.4 cm. The mean duration of diabetes was 9.5±7.4 years (range, 4 months–50 years). The patients' mean systolic blood pressure was 132.8±17.1 mmHg, and their mean diastolic blood pressure was 82.7±11.1 mmHg (Table 1).

Of the patients, 55 (15.2%) had coronary artery disease (CAD), 193 (53.5%) had hypertension (HT), 3 (0.8%) had peripheral artery disease (PAD), and 3 (0.8%) had a history of cerebrovascular events (CVA).

When the patients were evaluated for diabetes-related complications, 147 (40.7%) had diabetic kidney disease, 43 (11.9%) had diabetic retinopathy, 127 (35.2%) had diabetic neuropathy, 12 (3.3%) had diabetic foot, and 41 (11.4%) had a history of hypoglycemia. Regarding proteinuria levels, 117 (32.4%) had microalbuminuria, and 28 (7.8%) had overt proteinuria. Additionally, 39 (10.8%) patients had a history of urinary tract infection (UTI) (Table 2).

Of the patients, 107 (29.6%) were on a diet, 87 (24.1%) exercised, and 37 (10.2%) were smokers.

Regarding the diabetes medications used by the patients, 193 (53.4%) were taking oral antidiabetic drugs, 56 (15.5%) were receiving insulin, and 109 (30.1%) were receiving oral antidiabetic drugs plus insulin therapy. Three (0.8%) patients were not taking any medication.

Laboratory findings of all patients

The mean fasting plasma glucose (FPG) level of the patients was 157.8±66 mg/dL, the mean HbA1c level was 7.9±1.8%,

Table 1. Clinical and demographic findings of the patients

Parameters	Mean±SD
Age in years	56.9±10.2
Gender (F/M)	222/139
Diabetes duration (years)	9.5±7.4
Body weight (kg)	84.1±13.8
BMI (kg/m2)	31.7±5.6
Systolic blood pressure (mmHg)	132.8±17.1
Diastolic blood pressure (mmHg)	82.7±11.1

the mean total cholesterol level was 196.8±46.1 mg/dL, the mean LDL cholesterol level was 117±35.4 mg/dL, the mean HDL cholesterol level was 44.2±12.3 mg/dL, the mean creatinine level was 0.86±0.32 mg/dL, and the mean microalbumin/creatinine ratio in spot urine was 149.7±544.6 mg/g. Other laboratory findings are shown in Table 3.

Comparison of diabetes-related complications according to the diabetes medications used by the patients

Of the patients included in the study, 163 (45.2%) were receiving insulin therapy, while 198 (54.8%) were not receiving insulin therapy. When the patients were divided into two groups, those receiving insulin therapy and those not receiving insulin therapy, and diabetes-related complications were compared, the rates of diabetic neuropathy, diabetic retinopathy, diabetic kidney disease, hypoglycemia, and coronary artery disease were found to be significantly higher in the insulin-using group than in the other group (p<0.001, p<0.001, p=0.002, p=0.002, and p<0.001, respectively) (Table 4).

Table 2. Diabetes complication rates of patients

Parameters	n (%)
Retinopathy	43 (11.9)
Neuropathy	127 (35.2)
Diabetic kidney disease	147 (40.7)
Microalbuminuria	117 (32.4)
Overt proteinuria	28 (7.8)
Hypoglycemia	41 (11.4)
Diabetic foot	12 (3.3)

Table 3. Laboratory findings of the patients

Parameters	Mean±SD
APG (mg/dL)	157.8±66
HbA1C (%)	7.9±1.8
Total chol. (mg/dL)	196.8±46.1
LDL chol. (mg/dL)	117±35.4
HDL chol. (mg/dL)	44.2±12.3
Triglycerides (mg/dL)	187.3±136.3
Creatinine (mg/dL)	0.86±0.32
GFR (ml/min)	87.9±21.2
ALT (IU/mL)	24.5±17.3
Hemoglobin (g/dL)	13.6±1.6
WBC (µl)	8185±2064
Platelets (103/µl)	288±78.1
TSH (µIU/mL)	2.1±1.9
Microalbumin/creatinine in spot urine (mg/g)	149.7±544.6
Vitamin D (ng/mL)	13±9.8
Vitamin B12 (pg/ml)	408±330.4

APG: Admission plasma glucose; HbA1C: Hemoglobin A1C; LDL: Low-density lipoprotein; HDL: High-Density Lipoprotein; GFR: Glomerular filtration rate; ALT: Alanine transaminase; WBC: White blood count; TSH: Thyroid-stimulating hormone.

Comparison of the clinical and demographic findings of patients attending regular and irregular follow-ups

Patients enrolled in this research were separated into two groups: those attending regular follow-ups and those attending irregular follow-ups. A total of 222 (61.4%) patients attended regular follow-ups, while 139 (38.6%) attended irregularly. The groups were observed to be similar in terms of sex distribution, age, and diastolic and systolic blood pressure measurements. The mean duration of diabetes was longer in patients who attended irregular check-ups than in those who attended regular check-ups (11.6±7.5 vs. 8.3±7.1 years, p<0.001) (Table 5). The mean BMI of the group attending irregular health check-ups was 32.4±6.4 kg/m^2, while the mean BMI of the other group was 31.3±5 kg/m^2 (p=0.14). The mean body weight of the group attending irregular follow-up examinations was 87±16 kg, while the mean body weight of the other group was 82.2±11.9 kg (p=0.003). Waist circumference was greater in patients who attended irregular check-ups, but no difference was found between the groups in terms of hip circumference (105.4±15.7 vs. 100.7±13.7 cm, p=0.005) (Table 5).

Although there was no difference between the groups regarding exercise and smoking rates, the rate of dieting

Table 4. Comparison of diabetes complications according to the diabetes medications used by patients

Parameters	Insulin (n/%*)	Others (n/%*)	p
Diabetic retinopathy	35/%21.5	8/%4	**<0.001**
Diabetic kidney disease	80/%50	67/%34	**0.002**
Diabetic neuropathy	74/%45.4	53/%26.8	**<0.001**
Hypoglycemia	28/%17.2	13/%6.6	**0.002**
Diabetic foot	6/%3.7	6/%3	0.731
CAD	43/%26.4	12/%6.1	**<0.001**
PAH	2/%1.2	1/%0.5	0.591
STROKE	3/%1.8	0/%0	0.091
UTI	23/%14.6	16/%8.1	0.054

*: Percentage within the group. CAD: Coronary artery disease; PAH: Pulmonary arterial hypertension; STROKE: Symptoms, causes, types, and recovery; UTI: Urinary tract infection.

Table 5. Comparison of clinical and demographic findings of patients attending regular and irregular follow-up

Parameters	Regular (n=222)	Irregular (n=139)	p
Age	57.1±10.1	56.8±10.5	0.820
Gender (F/M)	142/80	80/59	0.223
Duration of diabetes (years)	8.3±7.1	11.6±7.5	**<0.001**
Body weight (kg)	82.2±11.9	87±16	**0.003**
BMI (kg/m2)	31.3±5	32.4±6.4	0.140
Waist circumference	100.7±13.7	105.4±15.7	**0.005**
Hip circumference	110.3±13.4	113.1±15.9	0.093
Systolic BP (mmHg)	132.2±16.7	133.7±17.8	0.669
Diastolic BP (mmHg)	82.4±10.9	83.3±11.4	0.579
Smoking (%)	8.6	12.9	0.181
Exercise (%)	26.1	20.9	0.255
Diet (%)	36.5	18.7	**<0.001**

BP: Blood pressure.

was higher in the group that attended regular follow-ups (36.5% vs. 18.7%, p<0.001) (Table 5).

When the groups were compared in terms of diabetes-related complications and comorbidities, diabetic kidney disease, diabetic foot, coronary artery disease, and diabetic neuropathy were more prevalent in the group with irregular attendance at follow-up visits (p=0.001, p=0.002, p=0.002, and p=0.001, respectively). There were no differences between the groups in the frequency of stroke, peripheral artery disease, hypertension, diabetic retinopathy, hypoglycemia, or a history of urinary tract infection (Table 6).

Table 6. Comparison of comorbid diseases and diabetic complications in patients who attended regular and irregular control

Parameters	Regular	Irregular	p
Diabetic retinopathy (n/%*)	21 / %9.5	22 / %15.8	0.176
Diabetic kidney disease (n/%*)	77 / %34.7	70 / %51.9	**0.001**
Diabetic neuropathy (n/%*)	63 / %28.4	64 / %46	**0.001**
Hypoglycemia	24 / %10.8	17 / %12.2	0.679
Diabetic foot	2 / %0.9	10 / %7.2	**0.002**
Hypertension	111 / %50	82 / %59	0.096
CAD	25 / %11.3	30 / %21.6	**0.002**
PAH	1 / %0.5	2 / %1.4	0.561
STROKE	0 / %0	3 / %2.2	0.056
UTI	19 / %8.6	20 / %14.9	0.065

*: Percentage within the monitoring group. CAD: Coronary artery disease; PAH: Pulmonary arterial hypertension; STROKE: Symptoms, causes, types, and recovery; UTI: Urinary tract infection.

Comparison of laboratory findings of patients attending regular and irregular follow-up

According to the comparison of laboratory parameters, the mean levels of FPG, urine microalbumin-to-creatinine ratio, HbA1c, and triglycerides were statistically significantly higher in patients attending irregular check-ups than in those attending regular check-ups (p<0.001, p=0.017, p<0.001, and p=0.023, respectively). Among individuals attending regular follow-up, the mean serum vitamin D level was higher than that in the other group (14.5±10.2 vs. 10.7±8.9, p=0.006). No remarkable disparities were found between the groups according to the other laboratory parameters evaluated (Table 7).

In the group attending regular check-ups, microalbuminuria was detected in 65 (31%) patients during spot urine evaluation, compared with 52 (39.7%) patients in the group attending irregular check-ups. Similarly, macroalbuminuria was detected in 12 (5.7%) patients in the group attending regular check-ups and 16 (12.2%) patients in the group attending irregular check-ups. The difference was significant (p=0.003) (Table 8).

Comparison of patients grouped according to follow-up duration

There was a significant difference in disease duration be-

Table 7. Comparison of laboratory findings of patients who attended check-ups regularly and irregularly

Parameters	Regular	Irregular	p
FPG (mg/dL)	132±35.2	198.7±81.3	**<0.001**
HbA1C (%)	7±1	9.5±1.9	**<0.001**
Total Chol. (mg/dL)	193.7±47.5	201.6±43.6	0.111
LDL Chol. (mg/dL)	114.8±35.3	120.4±35.4	0.149
HDL Chol. (mg/dL)	44.7±11.7	43.5±13.1	0.112
Triglycerides (mg/dL)	177±129.9	203.6±144.8	**0.023**
Creatinine (mg/dL)	0.82±0.23	0.91±0.44	0.051
GFR (ml/min)	89.1±18.6	86.1±24.7	0.214
ALT (IU/mL)	23.8±14.5	25.7±21.1	0.622
Hemoglobin (g/dL)	13.5±1.5	13.7±1.8	0.437
WBC (µl)	8043.4±1996.7	8412.9±2156.7	0.109
Platelets (103/µl)	288±79	288±76	0.999
TSH (µlU/mL)	2.1±1.7	2.2±2.3	0.873
Microalbumin/creatinine in spot urine (mg/g)	89.1±318.1	246.9±773	**0.017**
Vitamin D (ng/mL)	14.5±10.2	10.7±8.9	**0.006**
Vitamin B12 (pg/ml)	375.2±289	477.4±397.3	0.057

FPG: Fasting plasma glucose; HbA1C: Hemoglobin A1C; LDL: Low-density lipoprotein; HDL: High-Density Lipoprotein; GFR: Glomerular filtration rate; ALT: Alanine transaminase; WBC: White blood count; TSH: Thyroid-stimulating hormone.

tween the groups attending regular and irregular check-ups. To reduce the impact of this difference on the variables, patients were separated into four groups according to diabetes duration (Group 1=0–5 years, Group 2=6–10 years, Group 3=11–15 years, and Group 4=16–20 years). In each group, it was investigated whether there were differences between those attending regular and irregular follow-ups in terms of the parameters that were found to differ when all patients were evaluated. In all groups, the mean HbA1c level was significantly higher among patients attending irregular check-up visits. In the third group (11–15 years), the rates of diabetic kidney disease and neuropathy were significantly higher (p=0.029 and p=0.002, respectively), and in the fourth group (16–20 years), the frequency of diabetic neuropathy was significantly higher (p=0.021) among patients who did not attend check-up visits regularly (Tables 9–12).

Table 8. Comparison of albuminuria levels in patients who attended regular and irregular check-ups

Albuminuria level	Regular	Irregular	p
None	133 (%63.3)	63 (%48.1)	
Microalbuminuria	65 (%31)	52 (%39.7)	0.003
Macroalbuminuria	12 (%5.7)	16 (%12.2)	

Table 9. Comparison of patients with a diabetes duration of "0-5 years"

Parameters	Regular (n=101)	Irregular (n=33)	p
Diabetic retinopathy (n/%*)	3/%3	1/%3	0.968
Diabetic kidney disease (n/%*)	30/%29.7	11/%35.5	0.543
Diabetic neuropathy (n/%*)	27/%26.7	6/%18.2	0.322
Diabetic foot (n/%*)	1/%1	2/%6.1	0.150
CAD (n/%*)	8/%7.9	6/%18.2	0.096
HbA1C (%)	6.7±0.9	9.7±2.2	**<0.001**

*: Percentage within the monitoring group. CAD: Coronary artery disease; Hb1AC: Hemoglobin A1C.

Table 10. Comparison of patients with diabetes duration of "6-10 years"

Parameters	Regular (n=57)	Irregular (n=46)	p
Diabetic retinopathy (n/%*)	5/%8.8	6/%13	0.090
Diabetic kidney disease (n/%*)	22/%38.6	22/%48.9	0.297
Diabetic neuropathy (n/%*)	16/%28.1	19/%41.3	0.159
Diabetic foot (n/%*)	0/%0	3/%6.5	0.086
CAD (n/%*)	6/%10.5	7/%15.2	0.183
HbA1C (%)	7.3±0.9	9.4±1.9	**<0.001**

*: Percentage within the monitoring group.

Table 11. Comparison of patients with diabetes duration of "11-15 years"

Parameters	Regular (N=32)	Irregular (N=30)	p
Diabetic retinopathy (n/%*)	6/%18.8	6/%20	0.692
Diabetic kidney disease (n/%*)	12/%37.5	19/%65.5	**0.029**
Diabetic neuropathy (n/%*)	8/%25	19/%63.3	**0.002**
Diabetic foot (n/%*)	0/%0	3/%10	0.107
CAD (n/%*)	4/%12.5	10/%33.3	0.146
HbA1C (%)	7.2±1.2	9.3±1.5	**<0.001**

*: Percentage within the monitoring group. CAD: Coronary artery disease; Hb1AC: Hemoglobin A1C.

Table 12. Comparison of patients with diabetes duration of "16-20 years"

Parameters	Regular (N=23)	Irregular (N=18)	p
Diabetic retinopathy (n/%*)	2/%8.7	5/%27.8	0.083
Diabetic kidney disease (n/%*)	8/%34.8	11/%61.1	0.093
Diabetic neuropathy (n/%*)	7/%30.4	12/%66.7	**0.021**
Diabetic foot (n/%*)	1/%4.3	1/%5.6	1.000
CAD (n/%*)	5/%21.7	3/%16.7	0.109
HbA1C (%)	7.2±0.9	9.6±1.6	**<0.001**

* Percentage within the monitoring group. CAD: Coronary artery disease; Hb1AC: Hemoglobin A1C.

Discussion

In recent years, the significant increase in the diabetic patient population, the presence of important diabetes-related complications, and the substantial financial burden associated with diabetes have made diabetes mellitus a serious social problem. The prevention of diabetes-related complications, illnesses, and deaths can be achieved through regular patient follow-up. Regular follow-up enables the early detection of alterations in HbA1c levels and allows for early intervention before glycemic control deteriorates; it also ensures that patients receive face-to-face information about diabetes and the risks of diabetes-related complications.

Diabetes is a chronic condition. Doctors and diabetes educators have no influence over patients' daily lives or dietary control.

The American Diabetes Association (ADA) describes diabetes self-management education as the process of equipping individuals with the knowledge and skills necessary to manage their own care, handle crises, and implement lifestyle changes.[12,13] Diabetes health education is crucial for long-term success. Although only limited studies exist, it is thought that diabetes education can be cost-effective and improve outcomes.[14]

In a study involving 88 patients with diabetes, comprising a study group of 44 patients and a control group of 44 patients, diabetes education was provided to patients in the study group after the initial consultation, and they were followed up by telephone for 3 months. It was found that education and telephone follow-up reduced the values of various metabolic control variables, such as hemoglobin A1c, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and systolic blood pressure.[15]

In the study conducted by Anjana et al.[16], 1,798 patients with diabetes attending irregular check-ups and 1,783 patients with diabetes attending regular check-ups were retrospectively evaluated over a nine-year follow-up period. The irregularly followed group was found to have higher HbA1c, fasting plasma glucose, postprandial plasma glucose, total and LDL cholesterol, and triglyceride levels at each control visit than the regularly followed group.

Furthermore, this study observed that the glycemic load was twice as high in the group with irregular follow-up and that the risks of retinopathy and nephropathy were also increased. This study indicated that regular follow-up was associated with a favorable cardiovascular risk profile and a lower risk of developing retinopathy and nephropathy.

Kumar et al.[17] revealed a relationship between microvascular complications and triglyceride levels. Triglyceride levels and aging have been identified as independent risk factors for neuropathy. A study by Wiggin et al.[18] also showed a similar relationship between triglyceride levels and neuropathy.[19,20]

Other studies have also observed that patients with diabetic nephropathy have higher triglyceride levels.[21,22] Therefore, it is suggested that lipid-induced kidney damage may occur through the stimulation of TGF-β (transforming growth factor-beta), thereby inducing the production of reactive oxygen species that damage the glomerulus and glomerular glycocalyx.[23]

The association between hypertension and microvascular complications observed in other populations was also observed in the Thai population.[24,25] This study also demonstrated that advanced age and duration of diabetes are associated with microvascular complications in patients with T2DM.[26,27] However, in another study, no association was observed between the duration of diabetes and microvascular complications.[24]

Furthermore, large epidemiological studies have revealed the advantages of glycemic control in preventing complications.[28,29]

Timely assessment of HbA1c allows physicians to identify trends in disease progression and initiate corrective measures for glycemic control at the most appropriate time.[30]

Furthermore, reinforcing healthy behaviors through consultations with physicians, diabetes educators, dietitians, and exercise consultants at each visit can contribute to better glycemic control and a lower glycemic load in regularly monitored patients.[31]

Conclusion

As recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), a patient-centered approach is necessary for diabetes management. Preventing microvascular and macrovascular complications and ensuring a high quality of life for patients require not only good glycemic control but also the prevention of other controllable risk factors. Furthermore, the importance of lifestyle changes should be better explained to patients, and they should be encouraged to be more willing to adopt them. Therefore, patient education or an assessment of patient awareness regarding this issue is necessary at each follow-up appointment.

Disclosures

Ethics Committee Approval: The study commenced after receiving approval from the Necmettin Erbakan University Faculty of Medicine Clinical Research Ethics Committee, dated January 19, 2018, and numbered 2018/1167.

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

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Research Article

Effects of Parathyroidectomy on Renal Anemia in End-Stage Renal Disease

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Abstract

Objectives: This study aimed to assess postoperative changes in renal anemia parameters and erythropoietin-stimulating agent (ESA) requirements. The focus was on dialysis patients who underwent parathyroidectomy (PTx) for secondary hyperparathyroidism (SHPT).

Methods: This retrospective study included 22 dialysis patients who underwent PTx for SHPT. Demographic, biochemical, and hematological data were recorded preoperatively and at 1, 3, 6, and 12 months postoperatively. Changes in hemoglobin (Hgb), platelet (Plt) levels, and ESA doses were analyzed using appropriate parametric and nonparametric tests, and correlations between variables were assessed using Pearson's or Spearman's coefficients.

Results: The mean preoperative PTH level decreased from 2248±308 pg/mL to 468±165 pg/mL at 3 months ($p<0.001$). The mean Hgb level increased from 9.3±1.5 g/dL to 11.7±2.0 g/dL at 12 months ($p<0.05$). The ESA requirement decreased by 48%, from 22,500±13,000 IU/month to 11,700±10,400 IU/month ($p<0.05$). A moderate negative correlation was observed between increases in Hgb levels and decreases in ESA doses ($p<0.05$). In the subgroup with a biochemical response, the platelet count significantly increased at 12 months ($p<0.035$).

Conclusion: Parathyroidectomy enhances hematological parameters by increasing erythropoietin sensitivity in dialysis patients with SHPT. The reduction in ESA requirements and the increase in Hgb levels reflect improved postoperative erythropoiesis.

Keywords: Chronic kidney disease, erythropoietin resistance, erythropoiesis, parathyroidectomy, renal anemia, secondary hyperparathyroidism

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Many organ systems can be negatively affected by metabolic disorders that develop after chronic kidney disease (CKD).[1] Although various complications of the hematopoietic system develop, renal anemia is one of the most common and earliest-onset findings.[2,3] Multifactorial causes have been implicated in the development of anemia associated with CKD.[3,4] It has been suggested that many factors, including a shortened erythrocyte lifespan, chronic blood loss, increased erythropoiesis inhibitors, uremic toxins, iron and vitamin deficiencies, hemolysis, and hyperparathyroidism, contribute to anemia. Still, the most crucial factor is decreased erythropoietin production.[5,6] In these patients, elevated parathyroid hormone (PTH) levels have been shown to suppress bone marrow function, leading to osteitis fibrosa cystica and bone marrow fibrosis and thereby decreasing erythrocyte mass.[7–9] Additionally, a significant increase in hemoglobin levels and a decrease in ESA requirements were reported after parathyroidecto-

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my (PTx) in patients receiving dialysis treatment and using erythropoietin-stimulating agents (ESAs).[10]

Renal anemia not only reduces quality of life but can also lead to increased cardiovascular morbidity and mortality, as well as significant clinical problems.[11,12] Given these risks, the effectiveness of different approaches to anemia treatment in patients with CKD can directly determine prognosis.[12] Despite the importance of this issue, clinical data regarding changes in anemia parameters and their effects on erythropoietin sensitivity after PTx are limited. To address this gap, our study aimed to evaluate changes in renal anemia parameters and ESA doses during a 12-month follow-up of patients with CKD receiving dialysis treatment after PTx.

Methods

This study was approved by the İnönü University Health Sciences Non-Interventional Clinical Research Ethics Committee (Ethics Committee No. 2018-B17/18.09.2018). The study was conducted in accordance with the principles of the Declaration of Helsinki. In our study, we retrospectively analyzed patients with end-stage renal disease (ESRD) who underwent hemodialysis (HD) or peritoneal dialysis (PD) treatment in our clinic between January 2009 and December 2018. Patient data were retrieved from an electronic database. Patients with ESRD aged ≥18 years who underwent PTx for secondary or tertiary hyperparathyroidism, had renal anemia, and were using ESAs were included in the study. Anemia was diagnosed based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (hemoglobin <13.5 g/dL in men and <12 g/dL in women).[13] Transferrin, ferritin, B12, folate, and thyroid hormone levels were measured to rule out other causes of anemia, and patients with etiologies other than renal anemia were excluded from the study. Additionally, patients aged <18 years, those with a history of kidney transplantation before or after PTx, those with dialysis insufficiency, those with a diagnosis of malignancy, and those receiving immunosuppressive therapy for any reason were excluded. Dialysis adequacy was assessed using the Kt/V ratio, which is based on urea clearance (K), dialysis duration (t), and the patient's urea volume of distribution (V). Dialysis insufficiency was defined as Kt/V<1.2 in HD patients and Kt/V<1.7 in PD patients.

Patient demographics, dialysis duration, dialysis adequacy ratio, CKD etiology, and comorbidities were recorded. ESA doses, PTH, hemoglobin (Hgb), mean corpuscular volume (MCV), mean corpuscular hemoglobin content (MCH), platelet (Plt) levels, and ESA doses were measured before PTx and at 1, 3, 6, and 12 months after PTx. To ensure the standardization of ESA doses, the formula 1 µg darbepoetin alfa=200 IU epoetin alfa was used for patients receiving darbepoetin alfa. Patients who were converted from peritoneal dialysis to hemodialysis were evaluated based on their dialysis modality at the time of surgery. Additionally, transferrin, ferritin, B12, folic acid, and thyroid hormone levels were determined.

Statistical Analysis

Based on the sample size analysis, a minimum of 16 patients would be sufficient to achieve 95% confidence (α=0.05) and 80% power (β=0.20). The 22 patients included in the study exceeded this value, demonstrating that the sample had sufficient statistical power. Data are expressed as the mean±standard deviation or median (min–max). Normality was assessed using the Shapiro–Wilk test. The Mann–Whitney U test, dependent- and independent-samples t-tests, Wilcoxon and Kruskal–Wallis tests, one-way analysis of variance (ANOVA), and Pearson or Spearman correlation coefficients were used when appropriate. Statistical significance was accepted at $p<0.05$. Analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 22 patients were included in the study. Of these, a subgroup of 18 patients was defined based on the achievement of an adequate biochemical response at 1 month after PTx; specifically, four patients were excluded from the subgroup because their PTH levels remained above 300 pg/mL at that time point. Fifteen patients received HD, and seven received PD. No significant differences were found in pre- and post-PTx Hgb levels or ESA doses according to dialysis type ($p>0.05$) (Table 1).

Total PTx was performed in eight patients, total PTx plus autotransplantation in six, and subtotal PTx in eight. The mean preoperative PTH level was 2248±308 pg/mL. It dropped sharply in the first month after surgery, reaching its lowest level of 468±165 pg/mL by month 3, and remained stable thereafter. PTH declines were statistically significant at all follow-up points compared with preoperative values ($p<0.001$). The mean pre-PTx Plt count was 206±15/mm^3, rising to 249±22/mm^3 at month 12, but this increase was not significant ($p>0.05$). The mean pre-PTx Hgb level was 9.3±1.5 g/dL. It increased significantly during follow-up, reaching 11.7±2.0 g/dL at month 12 ($p<0.05$). ESA doses decreased from 22,500±13,000 U/month before surgery to 11,700±10,400 U/month at month 12. This 48% reduction was significant ($p<0.05$) (Table 2). A moderate negative correlation was found between the increase in Hgb levels after PTx and the decrease in ESA doses ($p<0.05$) (Fig. 1).

In the 18-patient subgroup, PTH levels remained significantly lower than preoperative values at all follow-up points

Table 1. Changes in Hgb and ESA doses by dialysis type (n=22)

Dialysis type	Parameter	Preoperative	1 month	3 months	6 months	12 months	p
PD (n=7)	Hgb (g/dL)	9.5±1.3	9.1±2.3	9.6±1.8	10.1±1.6	10.3±1.7	>0.05
	EUA (U/month)	24,000±13,000	13,000±17,000	15,000±13,000	14,000±12,000	10,000±10,000	
HD (n=15)	Hgb (g/dL)	9.1±1.5	9.9±1.5	11.0±1.8	11.3±2.1	12.0±1.9	>0.05
	EUA (U/month)	18,000±12,000	18,000±10,000	16,000±9,000	16,000±11,000	15,000±10,000	

Hgb: Hemoglobin; ESA: Erythropoiesis-stimulating agent; PD: Peritoneal dialysis; HD: Hemodialysis; EUA: Emergency use authorization.

(p<0.001). Platelet counts significantly increased at 12 months compared with pre-PTx values (p<0.035) and were higher at month 12 than at months 1, 3, and 6 (p<0.007, p<0.048, and p<0.016, respectively). Hgb levels were higher at months 3, 6, and 12 than before surgery (p<0.02, p<0.004, and p<0.001, respectively) but showed no significant change at month 1 (p>0.05). ESA doses decreased significantly at months 3, 6, and 12 after PTx (p<0.011, p<0.02, and p<0.003, respectively) (Table 3). There was no significant correlation between Hgb levels and ESA doses at months 1 and 12 (p>0.05), but there was a moderate negative correlation at months 3 and 6 (p<0.029 and p<0.014, respectively) (Fig. 2).

Discussion

Although medical treatment methods are primarily preferred for secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD), unresponsiveness can develop over time.[14,15] Therefore, PTx stands out as an effective treatment method for refractory cases.[14,15] In our study, patients with ESRD who underwent PTx due to SHPT unresponsive to medical treatment were examined. PTH levels decreased significantly in the early postoperative period. Postoperatively, PTH reached its lowest level in the first month and remained stable thereafter. A significant decrease in ESA requirements was observed in parallel with significant increases in Hgb levels at months 3, 6, and 12. Furthermore, a significant increase in Plt was observed at month 12 in the subgroup with a biochemical response. The negative correlation between Hgb levels and ESA doses suggests that PTx enhances the hematopoietic response by increasing erythropoietin sensitivity. Furthermore, the significant increase in Plt observed at 12 months

Table 2. Changes in PTH, Hgb, Plt and ESA doses before and after parathyroidectomy (n=22)

Timepoint	PTH (pg/mL, Mean±SD)	Hgb (g/dL, Mean±SD)	Plt (/mm³, Mean±SD)	ESA (U/month, Mean±SD)	p (PTH)	p (Hgb)	p (Plt)	p (ESA)
Preoperative	2248±308	9.3±1.5	206±15	22,500±13,000	—	—	—	—
1 mo	616±164	9.8±1.85	214±16	17,300±12,600	<0.001	>0.05	>0.05	>0.05
3 mo	468±165	10.6±1.95	215±12	15,000±12,600	<0.001	<0.02	>0.05	<0.003
6 mo	550±150	11.0±2.0	222±17	14,900±12,000	<0.001	<0.01	>0.05	<0.006
12 mo	642±172	11.7±2.0	249±22	11,700±10,400	<0.001	<0.01	>0.05	<0.001

PTH: Parathyroid hormone; Hgb: Hemoglobin; Plt: Platelet; ESA: Erythropoiesis-stimulating agent; SD: Standard deviation; mo: Month.

Table 3. Changes in PTH, Hgb, Plt counts and ESA doses before and after parathyroidectomy (n=18)

Timepoint	PTH (pg/mL, Mean±SD)	Hgb (g/dL, Mean±SD)	Plt (/mm³, Mean±SD)	ESA (U/month, Mean±SD)	p (PTH)	p (Hgb)	p (Plt)	p (ESA)
Preoperative	2248±308	9.4±1.4	213±81	21600±12800	–	–	–	–
1 mo	41±13	9.95±1.45	199±77	17200±12800	<0.001	>0.05	>0.05	>0.05
3 mo	70±27	10.5±1.8	218±57	14900±13300	<0.001	<0.02	>0.05	<0.011
6 mo	70±24	10.8±1.7	226±86	14800±12500	<0.001	<0.004	>0.05	<0.02
12 mo	66±27	11.6±1.8	260±108	11600±11000	<0.001	<0.001	<0.035	<0.003

PTH: Parathyroid hormone; Hgb: Hemoglobin; Plt: Platelet; ESA: Erythropoiesis-stimulating agent; SD: Standard deviation; mo: Month.

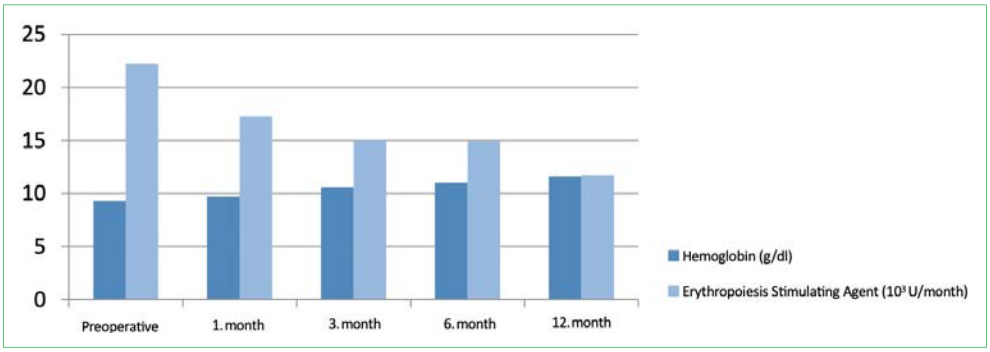


Figure 1. Relationship between hemoglobin levels and erythropoiesis -stimulating agent doses (n=22).

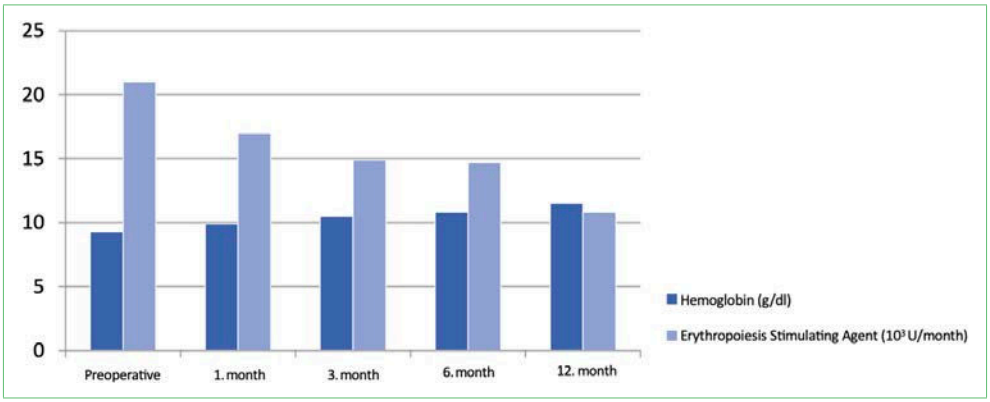


Figure 2. Relationship between hemoglobin levels and erythropoiesis-stimulating agent doses (n=18).

in the subgroup that developed a biochemical response supports the persistence of this effect at the hematological level. These findings demonstrate that PTx not only improves calcium-phosphorus balance but also positively impacts erythropoiesis dynamics, highlighting the systemic benefits of surgery.

The biochemical efficacy of PTx in treating SHPT, as evidenced by the achievement of target PTH levels, has been demonstrated in many studies.[14,15] In a study of 80 hemodialysis patients who underwent PTx, the preoperative median PTH level was 1239 pg/mL. This decreased to 11.2 pg/mL at postoperative month 1 and remained stable at 18.0 and 22.6 pg/mL at months 6 and 12, respectively (p<0.001).[15] Another study of 257 patients who underwent PTx for ESRD found a significant decrease in PTH levels, which remained stable until month 12.[14] In our study, in line with the literature, we observed a significant decrease in PTH levels at month 1 after surgery. These values remained stable from month 3 onward. The current findings show that PTx for SHPT in patients with ESRD can effectively control PTH levels. It also plays an important role in maintaining long-term biochemical balance. This significant and sustained reduction in PTH levels can be considered not only a biochemical success but also the underlying mechanism for improved hematological parameters.

Studies examining hematological parameters after PTx show that a decrease in PTH levels positively affects erythropoiesis and mineral-metabolic balance.[16–18] A study examining 81 cases of ESRD reported that although no significant increase in Hgb levels was found after PTx, ESA requirements decreased from 41.6 IU/kg/week to 10.3 IU/kg/week (p=0.008).[18] This study also found a statistically significant decrease in ESA use, particularly in patients with Hgb≤10 g/dL (OR: 20.1, 95% CI: 4.71–125, p<0.001) and transferrin saturation<25% (OR: 12.8, 95% CI: 2.51–129, p<0.001).[16] In another study examining 37 patients with ESRD and SHPT, serum PTH levels decreased from 1,871±236 pg/mL to 172±29 pg/mL (p<0.001) after PTx. In contrast, weekly erythropoietin doses decreased from 10,086±1,721 U to 3,514±620 U (p<0.05).[17] These results suggest that although some studies have not observed a significant increase in Hgb levels, substantial reductions in ESA doses improve erythropoiesis and increase erythropoietin sensitivity after PTx. Indeed, in our study, the preoperative ESA requirement of 22,500 IU/month decreased to 11,700 IU/month at 12 months, and Hgb levels increased

significantly from 3 months onward. Our study is one of the limited number of clinical studies demonstrating that reductions in ESA doses are sustained, the negative correlation between Hgb levels and ESA doses persists, and PTx enhances the functional response of erythropoiesis.

Fibroblast growth factor 23 (FGF-23) is an important factor in the development of anemia. It reduces erythropoietin production and receptor expression.[18] FGF-23 increases in CKD when phosphate levels rise and inhibits renal 1α-hydroxylase activity, leading to SHPT. High FGF-23 levels have been linked to resistant hyperparathyroidism. Conversely, patients with low levels respond better to calcitriol treatment.[19–21] After PTx, FGF-23 levels decrease significantly.[22] Although our study did not examine FGF-23 levels, we believe that PTx reduces FGF-23 levels. This reduction may remove its suppressive effect on erythropoietin, leading to increased Hgb levels and decreased ESA doses.

Studies examining changes in hematological parameters after parathyroidectomy (PTx) have reported varying results for platelet counts. For example, in a prospective study examining 29 patients with ESRD receiving HD, the platelet count was $17.8\pm4.8\times10^4/mm^3$ before PTx, $21.0\pm7.6\times10^4/mm^3$ at week 2, $20.2\pm5.0\times10^4/mm^3$ at month 3, and $21.2\pm6.2\times10^4/mm^3$ at month 12; this increase was reported to be statistically significant at all time intervals ($p<0.01$).[23] Similarly, another series of 11 patients reported that bone marrow function returned to normal after total PTx, with a positive effect on Plt.[24] In contrast, a prospective study examining 213 cases found that Plt was $202\times10^3/mm^3$ before PTx but decreased to $193\times10^3/mm^3$ at postoperative follow-up ($p=0.033$).[25] In our study, Plt levels increased in the postoperative period. We believe that the discrepancy in findings in the literature may be due to varying levels of bone marrow suppression in the preoperative period and individual differences in the rate of reversal of the chronic effects of PTH on the hematopoietic system.

Limitations

The relatively small number of patients and the retrospective design limit the generalizability of our results. Additionally, the absence of biomarker assessments, such as FGF-23, complicates conclusions about the mechanisms by which PTx improves hematological outcomes. Nevertheless, the completeness of the patient data, regular follow-up for 12 months after PTx, and assessment of both biochemical and hematological parameters are strengths. These findings significantly contribute to the literature on the long-term effects of PTx on the hematopoietic system and support future prospective studies.

Conclusion

PTx in patients with SHPT resistant to medical treatment can significantly reduce PTH levels. This leads to biochemical stabilization. The reduction in the negative effects of PTH on hematological parameters results in higher Hgb levels and lower ESA requirements. The current findings indicate that PTx improves the management of renal anemia in patients with chronic kidney disease (CKD). However, prospective studies evaluating more parameters and including larger patient groups are needed to confirm our results and clarify the mechanisms underlying its beneficial effects on anemia.

Disclosures

Ethics Committee Approval: This study was approved by the İnönü University Health Sciences Non-Interventional Clinical Research Ethics Committee (Ethics Committee No: 2018-B17).

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

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Research Article

Predictive Value of Development of Macroalbuminuria for Hypoglycemia in Patients with Type 2 Diabetes Mellitus

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Abstract

Objectives: The predictive role of macroalbuminuria in the development of hypoglycemia in patients with type 2 diabetes mellitus was investigated.

Methods: Ninety-two patients diagnosed with type 2 diabetes mellitus who presented to Çukurova University Faculty of Medicine between January 2014 and January 2015 were included in the study. At the beginning of the study, the glomerular filtration rate values of 92 patients with type 2 diabetes mellitus were calculated using creatinine levels. The study was designed as a single-blind study. There were 14 patients with proteinuria at the level of macroalbuminuria (stage IV diabetic nephropathy) in the study group (group 1) and 78 patients without proteinuria at the level of macroalbuminuria (stage I–III diabetic nephropathy) in the control group (group 2). Thyroid-stimulating hormone, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, C-peptide, and HbA1c levels were measured in all patients at baseline and at 6 months. If adrenergic symptoms of hypoglycemia developed together with a capillary glucose level below 70 mg/dL, or if a measurement below 55 mg/dL was obtained regardless of the presence of hypoglycemic symptoms, the episode was recorded as a hypoglycemic event.

Results: The study was completed with 70 patients, 12 of whom were in the first group and 58 of whom were in the second (control) group. Statistical analysis was performed using SPSS version 24 after the 6-month follow-up. Twenty-six hypoglycemic attacks occurred in the macroalbuminuria group (group 1), and 37 hypoglycemic attacks occurred in the control group (group 2). The Mann–Whitney U test was applied.

Conclusion: The presence of macroalbuminuria was found to be significant for the development of hypoglycemia at the $p<0.01$ level (Sig. [2-tailed]=0).

Keywords: Hypoglycemia, proteinuria, type 2 diabetes mellitus

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Diabetes mellitus is a metabolic disorder characterized by relative or absolute insulin deficiency and/or peripheral insulin resistance and affects multiple organ systems. The World Health Organization (WHO) and the American Diabetes Association (ADA) have established diagnostic criteria for diabetes and classified its subtypes to ensure standardization.[1,2] Although several subtypes have been described, most patients with diabetes are classified as having either type 1 or type 2 diabetes mellitus. Type 1 diabetes mellitus is characterized primarily by absolute insulin deficiency, whereas the pathophysiology of type 2 diabetes mellitus (T2DM) is dominated by peripheral insu-

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lin resistance. With the rapid worldwide rise in obesity as a major public health challenge, the prevalence of diabetes has also increased steadily. According to 2021 estimates, diabetes affects approximately 530 million people globally, corresponding to a prevalence of 10.5% among individuals aged 20–79 years.[3,4] Of these patients, the overwhelming majority have T2DM.[5]

Hypoglycemia is one of the acute complications of T2DM and may be life-threatening. In particular, hypoglycemia occurring during intensive glycemic control has been shown not only to cause neuroglycopenic symptoms but also to increase cardiovascular risk.[6] In a meta-analysis of 46 studies involving patients with T2DM, the prevalence of hypoglycemia was 45%, whereas the prevalence of hypoglycemia requiring medical assistance was 6%.[7] In patients with a reduced glomerular filtration rate (GFR), oral antidiabetic agents are routinely discontinued, and insulin doses are reduced in accordance with guideline recommendations because drug elimination is impaired. However, robust evidence regarding dose reduction is lacking in patients with diabetic nephropathy who retain a preserved GFR despite established renal injury. Recent studies have shown that renal gluconeogenesis accounts for approximately 20% of total endogenous gluconeogenesis and is impaired in chronic kidney disease.[8,9] Neuropathy is another common complication of diabetes. Proposed mechanisms include activation of the polyol pathway, increased nonenzymatic glycosylation, and microvascular injury involving the vasa nervorum, leading to neuronal damage. In addition to sensory neuropathy, patients with diabetes may also develop autonomic neuropathy, which may increase the risk of hypoglycemia by reducing hypoglycemia awareness, impairing glucagon release during hypoglycemia, and delaying gastric emptying.[10,11] In the present study, we investigated whether hypoglycemia occurs more frequently in patients with established diabetic nephropathy despite a preserved GFR.

Methods

Study Design and Patient Selection

This study examined whether macroalbuminuria is a risk factor for hypoglycemia in patients with T2DM who had macroalbuminuric-range proteinuria but preserved GFR.

Patients older than 65 years were excluded, as were those with baseline serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >35 IU/mL, uncontrolled hypertension, chronic inflammatory disease, chronic liver disease, chronic heart failure, rheumatic disease, inflammatory bowel disease, chronic infection, adrenal insufficiency, or risk factors for pituitary insufficiency. Risk factors for pituitary insufficiency included radiotherapy, cranial surgery, a relevant family history, and compatible biochemical findings. Patients with thyroid-stimulating hormone (TSH) levels outside the normal range were also excluded.

At baseline, patients with 24-hour urinary albumin excretion >300 mg/day were assigned to group 1 (macroalbuminuria; study group), whereas those with microalbuminuria or normoalbuminuria were assigned to group 2 (control group). Patients were followed according to the nutritional recommendations of the 2013 guideline of the Turkish Society of Endocrinology and Metabolism, together with self-monitoring of blood glucose tailored to the treatment regimen, ranging from three measurements per week to six measurements per day, depending on therapy.[12]

Capillary glucose values <70 mg/dL accompanied by adrenergic symptoms and values <55 mg/dL, irrespective of symptoms, were recorded as hypoglycemic events. Device standardization was performed monthly, telephone follow-up was conducted every 2 months, and in-person visits were scheduled at months 3 and 6. During clinic visits, HbA1c, blood urea nitrogen (BUN), creatinine, AST, ALT, sodium, and potassium levels were remeasured. In patients with dyslipidemia at baseline, lipid profiles were reassessed at month 6. Four patients whose medical treatment was changed because of adverse drug effects and two patients who underwent angiography followed by coronary intensive care monitoring because of coronary artery disease were excluded during follow-up. In addition, seven patients with elevated AST, ALT, or creatinine levels and nine patients who did not maintain regular follow-up were excluded. The final analysis included 12 patients in the macroalbuminuria group and 58 in the control group.

Collection of Blood and Urine Samples and Measurement Methods

Patients presented to the clinic after completing a 24-hour urine collection. Urinary albumin levels were measured using the Jaffe method and classified according to the Mogensen classification (Table 1).

Plasma glucose was measured in venous blood obtained after 12 hours of fasting using the glucose oxidase method. Follow-up HbA1c levels were measured by high-performance liquid chromatography, and the treatment target was an HbA1c level below 7%. The reference range for C-peptide was 1.1–3 ng/mL. The normal range for ALT and AST was 0–35 IU. Total cholesterol was measured using the Lieberman–Burchard method.

Table 1. Stages of diabetic nephropathy

Diabetic nephropathy	Characteristic	GFR	Albuminuria	Blood pressure	Time since diagnosis
Stage 1	Glomerular hyperfiltration	Increased	Absent	Normal-Increased	At diagnosis
Stage 2	Thickened basement membrane (silent stage)	Normal	Normal or <30 mg/day	Normal-Increased	5 years
Stage 3	Microalbuminuria	Normal	30-300 mg/day	Normal-Increased	5-15 years
Stage 4	Macroalbuminuria	Normal-Decreased	>300 mg/day	Hypertension	15-25 years
Stage 5	Uremia	Progressive decrease	Variable	Hypertension	25-30 years

GFR: Glomerular filtration rate.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).[13] Regression analysis and the Mann–Whitney U test were used for statistical evaluation.

Written informed consent was obtained from all participants. Patients were enrolled in a blinded manner. Ethical approval was granted by Çukurova University on December 2, 2016 (meeting no. 59).

Results

Demographic Characteristics, Biochemical Parameters, and Complications of the Study Population

Patients were divided into two groups: a control group (microalbuminuria–normoalbuminuria) and a macroalbuminuria group. Table 2 summarizes the demographic characteristics, biochemical parameters, and complications of the study population. The cohort comprised 43 women and 27 men, including 12 patients in the study group and 58 in the control group. The mean age of all participants was 54.7±7.7 years. The mean HbA1c and C-peptide levels were 7.4±1.6% and 2.5±1.1, respectively. The mean duration of diabetes was 8.8±6.8 years. A significant between-group difference was observed in diabetes duration (MVU=182.5, p=0.010), whereas no statistically significant difference was found in HbA1c or C-peptide levels (MVU=28.1, p=0.3).

We also evaluated neuropathy as an important clinical variable. Patients with electrophysiologically confirmed peripheral neuropathy accompanied by autonomic symptoms were considered positive. As expected, body mass index analysis showed that most patients were in the overweight or obese categories (Fig. 1). Ten patients had a normal body mass index, eight of whom had a first-degree family history of T2DM. Of the 28 patients classified as obese (BMI≥30), 20 were receiving insulin therapy.

Evaluation of Hypoglycemia and Related Conditions in the Study Groups

At least one hypoglycemic episode occurred in 10 of 12 patients in the macroalbuminuria group (Fig. 2), compared with 12 of 58 patients in the microalbuminuria–normoalbuminuria control group. Patients in the macroalbuminuria group experienced 26 hypoglycemic episodes, whereas 37 episodes occurred in the control group. Two episodes led to hospital presentation with neuroglycopenic symptoms, whereas all other episodes resolved after oral carbohydrate intake. No glucagon injection was

Table 2. Demographic characteristics, biochemical parameters, and complications of the study population (mean±SD)

	Group 1 (Macroalbuminuria)	Group 2 (microalbuminuria-normoalbuminuria)
Age (years)	56.1±6.0	54.4±8.1
Sex (F/M) (%)	7/5 (%58)	36/22 (%62)
BMI	3/12 (%25)	25/58 (%43.1)
Duration of diabetes (years)	13.8±7.8	7.7±6.1
Glucose (mg/dL)	146±11.5	135±8.4
HbA1c (%)	7.5±1.1	7.4±1.7
C-peptide	2.0±0.8	2.6±1.2
Diabetic neuropathy n (%)	6 (%50)	15 (%25.8)
Oral antidiabetic therapy		
Pioglitazone	2/12 (%16.6)	8/58 (%13.7)
Metformin	11/12 (%91.6)	56/58 (%96.5)
Secretagogue	2/12 (%16.6)	28/58 (%48.2)
Insulin therapy		
Intensive	2/12 (%16.6)	4/58 (%6.8)
Basal	1/12 (%8.3)	10/58 (%17.2)
Mixed	3/12 (%25)	2/58 (%3.4)

SD: Standard deviation.

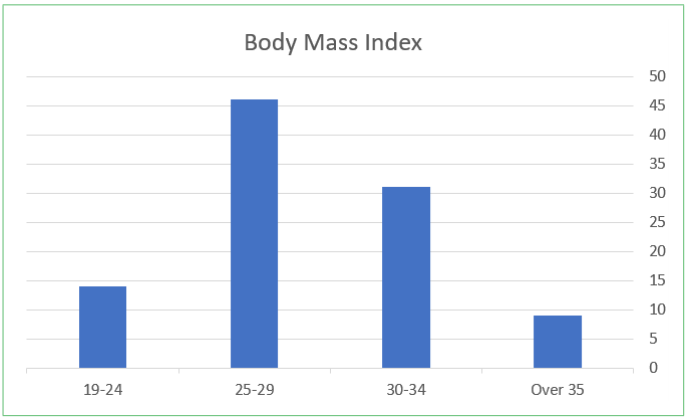


Figure 1. Distribution of body mass index among participants.

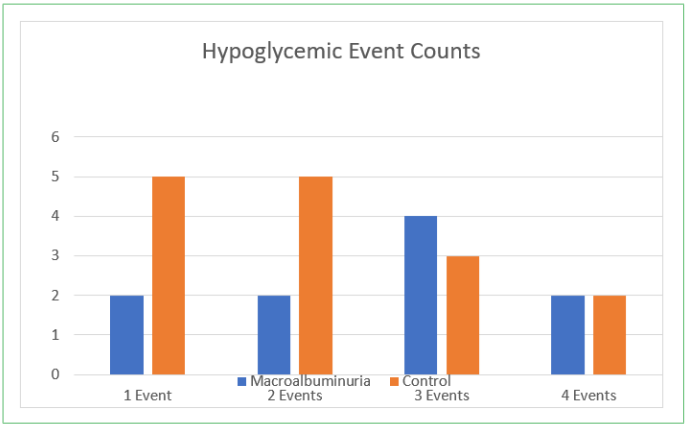


Figure 2. Frequency of hypoglycemia in the case and control groups.

administered during any episode, and only one of the 70 patients carried glucagon. No hospitalization occurred because of hypoglycemia. None of the episodes was associated with alcohol use. According to patient histories, all events were related to dietary nonadherence or exercise. Because of the limited sample size and nonhomogeneous distribution, parametric tests were not applied; instead, the Mann–Whitney U test was used. The presence of macroalbuminuria was significantly associated with the development of hypoglycemia at the $p<0.01$ level (Sig. [2-tailed]=0). Overall, hypoglycemic episodes occurred significantly more frequently in the macroalbuminuria group than in the control group.

Correlation analysis was performed to examine the relationship between hypoglycemic episodes and HbA1c levels. A strong positive association was observed ($r=0.482$, $p<0.001$), indicating that hypoglycemic episodes occurred more frequently in patients with higher HbA1c levels.

In logistic regression analysis, bolus insulin use was associated with hypoglycemia (OR, 3.7; $R^2=0.54$; $p<0.01$), and basal insulin use was likewise associated with hypoglycemia (OR, 2.9; $R^2=0.40$; $p<0.01$).

Discussion

Previous studies have partly clarified the etiology and pathophysiological mechanisms of hypoglycemia in patients with T2DM. Vigorous exercise, escalation of antidiabetic therapy, inadequate food intake, progressive decline in GFR, and delayed renal insulin clearance have all been identified as common causes.[14] Hypoglycemia is associated with both adrenergic and neuroglycopenic manifestations. Adrenergic symptoms include tremor, cold sweating, palpitations, hunger, and paresthesia, whereas neuroglycopenic symptoms include headache, dizziness, speech difficulty, weakness, and confusion. Our study was based on the hypothesis that the progression of diabetic nephropathy may impair renal gluconeogenesis and reduce the availability of substrates for both hepatic and renal gluconeogenesis during the proteinuric stage.

Our findings indicate that macroalbuminuria is associated with a higher frequency of hypoglycemia. No significant association was observed between hypoglycemia and neuropathy or the use of secretagogue agents. Only a limited number of studies have evaluated the relationship between macroalbuminuria and hypoglycemia. This paucity may reflect the multifactorial nature of hypoglycemia in diabetes, substantial interindividual variability in response to insulin secretagogues, frequent polypharmacy due to comorbid conditions, and marked variation in treatment adherence. In addition, adherence to medical nutrition therapy and exercise is inherently difficult to monitor, which complicates the design and conduct of such studies. Furthermore, the number of patients with preserved GFR despite macroalbuminuria is relatively small. The most comparable study is the 2013 prospective study by Yun et al.[15], which evaluated the relationship between macroalbuminuria and hypoglycemia. In that study, the mean follow-up duration was 10.2 years, and severe hypoglycemia developed in 111 of 878 patients. Severe hypoglycemia was defined as an event requiring glucose administration by another person or hospital presentation. By contrast, because our study had a shorter follow-up period, we used closer glucose monitoring and a more sensitive definition of hypoglycemia, recording glucose values <55 mg/dL and values <70 mg/dL when accompanied by adrenergic or neuroglycopenic symptoms. Unlike Yun et al.[15], we limited the upper age to 65 years because of concerns regarding creatinine-based GFR estimation in older adults. We also excluded patients using mixed insulin and analyzed basal and bolus insulin as separate variables. In our clinic, hypoglycemia is particu-

larly common among patients receiving mixed insulin, and many such episodes are related to dietary nonadherence in individuals using two or three daily doses. In the study by Yun et al.[15], diabetic neuropathy was not considered, and insulin therapy was assessed as a single variable without distinction by duration of action. However, lipid profiles and fasting C-peptide levels were monitored more regularly in that study at 3- to 6-month intervals. Cox proportional hazards regression analysis identified advanced age ($p<0.001$), insulin use ($p<0.001$), macroalbuminuria ($p<0.001$), and sulfonylurea use ($p<0.003$) as significant predictors.

The frequency of hypoglycemia increased with increasing HbA1c levels. Adherence to exercise recommendations appeared partial, whereas adherence to medical nutrition therapy appeared poorer. It is therefore plausible that both hypoglycemic episodes and elevated HbA1c levels arose from the same underlying factor, namely dietary nonadherence. Patient reports supported this interpretation, as many described clinical histories linking hypoglycemia to failure to follow dietary recommendations. Similarly, in an observational study of T2DM, Zhao et al. reported an increase in hypoglycemia-related hospitalizations with higher HbA1c levels.[16]

In the systematic review by Pratiwi et al.[17], autonomic neuropathy was identified as an important risk factor for hypoglycemia. In our study, however, no significant relationship was found between neuropathy and hypoglycemia. This discrepancy may be attributable to the limited sample size and short follow-up duration.

The main limitations of this study include the small sample size, the inability to fully meet guideline-recommended standards for blood glucose monitoring, only partial adherence to diet and exercise recommendations, and reliance on patient self-reports for the accuracy of these data.

Conclusion

In conclusion, in patients with type 2 diabetes mellitus, the presence of macroalbuminuria was associated with a higher frequency of hypoglycemic episodes. By contrast, no increased risk of hypoglycemia was observed in association with diabetic neuropathy, pioglitazone use, or secretagogue use (glinides and sulfonylureas). Insulin use was significantly associated with hypoglycemic episodes, and all recorded events were linked to dietary nonadherence.

Taken together with current molecular evidence, our findings suggest that patients who develop macroalbuminuria may remain at increased risk of hypoglycemia even when GFR is preserved.

Disclosures

Ethics Committee Approval: Ethics committee approval was obtained from Çukurova University Faculty of Medicine Ethics Committee on December 2, 2016, with meeting number 59.

Informed Consent: Informed consent forms were obtained from all patients participating in the study.

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

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Research Article

Prognostic Value of the Neutrophil-to-Lymphocyte and Lymphocyte-to-Monocyte Ratios and Their Association with the International Prognostic Index in Patients with Diffuse Large B-Cell Lymphoma

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Abstract

Objectives: We assessed the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) at diagnosis, their correlations with the International Prognostic Index (IPI), and their impact on survival in patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab-based regimens.

Methods: We retrospectively analyzed 139 patients with DLBCL at a single center between 2008 and 2019. Optimal cutoffs were determined by ROC analysis, survival was assessed using the Kaplan–Meier method, and independent predictors were identified using Cox regression analysis.

Results: The optimal cutoffs were 2.90 for NLR and 2.40 for LMR. Both NLR≥2.90 and LMR<2.40 were associated with significantly shorter overall survival (OS) and progression-free survival (PFS) ($p<0.05$). NLR correlated positively with IPI ($r=0.205$, $p=0.021$), whereas LMR correlated negatively ($r=-0.272$, $p=0.001$). In multivariate analysis, ECOG performance status, serum albumin, and NLR independently predicted OS; ECOG performance status, serum albumin, and bone marrow involvement independently predicted PFS. NLR showed the highest discriminatory ability for mortality among NLR, LMR, IPI, and R-IPI.

Conclusion: NLR≥2.90 independently predicts poor OS in DLBCL and may complement existing prognostic indices as an inexpensive marker of host immunity.

Keywords: Diffuse, large B-cell, lymphocytes, lymphoma, monocytes, neutrophils, prognosis; survival analysis

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Lymphomas are a family of malignancies arising from cells of the immune system. Among these, non-Hodgkin lymphomas (NHLs) constitute a biologically diverse category. They are among the leading hematological cancers worldwide. Within this group, diffuse large B-cell lymphoma (DLBCL) is the dominant type, accounting for approximately one-quarter to one-third of NHL diagnoses in industrialized regions.[1] The 1-year survival rate without treatment is approximately 50%. However, modern treatment regimens make the disease curable in a significant proportion of cases.

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Since its introduction in 1993, the International Prognostic Index (IPI) has served as the principal risk-assessment tool in DLBCL and is based on five clinical parameters: patient age, disease stage according to the Ann Arbor classification, serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status, and the number of extranodal involvement sites.[2] The advent of the anti-CD20 monoclonal antibody rituximab substantially altered survival expectations in CD20-expressing lymphomas and called into question the prognostic separation provided by the original index.[3] To address this, a Revised IPI (R-IPI) was developed and demonstrated better risk discrimination among individuals receiving rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[4]

Although improved, IPI-based systems are limited to clinical and tumor-related variables and overlook the contributions of immune competence and the surrounding tumor milieu—two elements increasingly appreciated as key factors in lymphoma pathobiology.[5] Inflammatory infiltrates within neoplastic tissue exert dual effects, fostering or restraining malignant growth depending on their composition.[6,7] Lymphocyte populations contribute to antineoplastic surveillance via cytotoxic mechanisms,[8] whereas macrophages derived from peripheral monocytes may shift toward a tumor-promoting phenotype that supports disease progression and helps the tumor evade immune control.[9] In addition, high neutrophil counts and persistent inflammation can further sustain malignancy through the release of protumorigenic cytokines.[10]

NLR and LMR, calculated directly from standard complete blood counts, collectively summarize systemic inflammatory activity and adaptive immune capacity. Unfavorable values of these indices have been associated with poor outcomes in various solid malignancies.[11–13] Data suggest a similar prognostic effect in DLBCL.[14,15] However, reported findings remain inconsistent. Questions persist regarding the most informative thresholds and the additional value these markers may provide compared with IPI or R-IPI, particularly when examined in single-institution cohorts receiving rituximab-containing treatment.

Our study aimed to investigate the prognostic significance of pretreatment NLR and LMR values. Other objectives of our study included examining their associations with IPI and R-IPI, evaluating their relationships with the initial therapeutic response, and exploring their independent contributions to OS and PFS in a DLBCL population managed with rituximab-containing chemotherapy.

Methods

Study Design And Patients

Adults aged 18 years and older who were diagnosed with biopsy-confirmed DLBCL at the Hematology Clinic of XXX Hospital between January 2008 and May 2019 were included in the study. Records were reviewed retrospectively. Individuals with an ongoing infection, known HIV positivity, liver cirrhosis or advanced liver disease, a history of another malignancy, or prior exposure to anti-inflammatory, immunosuppressive, or monoclonal antibody agents administered for indications unrelated to the index lymphoma were excluded from the study. A final sample of 139 patients was obtained after applying these criteria. Ethical approval was obtained from the University of Health Sciences, İzmir Bozyaka Training and Research Hospital Institutional Ethics Committee (approval no. 05, dated May 22, 2019), and all procedures were performed in accordance with the principles outlined in the Declaration of Helsinki.

Data Collection and Definitions

Basic demographic information, clinical characteristics, laboratory test results, chemotherapy regimens, response assessments, and follow-up outcomes were obtained from the hospital records. These included age, sex, frequency of B symptoms, ECOG score, hemoglobin level, absolute neutrophil, lymphocyte, and monocyte counts, platelet count, LDH, C-reactive protein (CRP), and albumin concentration. All calculations were performed using the hospital laboratory's limits of normality. NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. LMR was calculated as the ratio of lymphocytes to monocytes.

Staging followed the revised Ann Arbor system, as updated by the Lugano consensus, with whole-body 18F-FDG PET/CT used as the principal modality and contrast-enhanced cervical, thoracic, and abdominal CT serving as an alternative when PET/CT could not be performed.[16] Marrow infiltration was evaluated by single-sided iliac crest biopsy, PET/CT imaging, or a combination of both. Immunohistochemical classification into germinal-center versus non-germinal-center subtypes using the Hans algorithm was feasible in 62 cases.[17] IPI and R-IPI risk scores were derived for every patient following the original methodology.[2,4]

Treatment and Response Evaluation

Each patient was treated with a protocol that included rituximab. Initial treatment consisted of three R-CHOP cycles (n=15), six to eight R-CHOP cycles (n=82), six R-CHOP cycles followed by eight rituximab maintenance doses (n=10),

R-CVP (n=3), or the attenuated R-mini-CHOP variant (n=4), in conjunction with involved-field radiotherapy. Twenty-five patients initiated rituximab-based treatment. However, they were unable to complete the planned course of treatment because of adverse effects or early death. Therapeutic response was assessed by PET/CT or contrast-enhanced CT and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), according to the revised Lugano framework.[16] Those showing primary refractoriness or relapse who were eligible for autologous hematopoietic stem cell transplantation were referred to a specialized transplant unit.

Overall survival (OS) was measured as the time from diagnosis to death from lymphoma or its treatment or to the date of the last clinical contact. Disease-free survival (PFS) was calculated as the time from diagnosis to objectively documented progression, relapse after complete remission, or lymphoma-related death. Eleven patients whose causes of death were unrelated to lymphoma were excluded from the survival models. This left 128 patients for time-to-event calculations. Vital status information was cross-validated using the national death registry.

Statistical Analysis

All computations were carried out using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA). Numerical variables were summarized either as the mean with standard deviation or as the median with range, depending on distributional characteristics determined by the Kolmogorov–Smirnov and Shapiro–Wilk tests; categorical data were reported as counts with percentages. Between-group testing employed Student's t-test or the Mann–Whitney U test for numerical data, whereas categorical comparisons relied on the chi-square test. Survival estimates were generated using Kaplan–Meier curves and compared using the log-rank test. The most informative NLR and LMR cut-off points for predicting all-cause mortality were obtained from ROC analysis by maximizing the Youden index (J=-sensitivity+specificity−1). Spearman's coefficient was used to assess correlations between the two ratios and the IPI score. Covariates reaching statistical significance in univariate Cox analysis were carried forward into multivariable Cox proportional hazards models using the enter method to identify independent predictors of OS and PFS. Statistical significance was defined as a two-tailed $p<0.05$.

Results

Patient Characteristics

The mean age of the analysis cohort was 59.1±14 years. The mean follow-up period was 30.5 months (range, 1–138 months). Of the 139 individuals observed, 76 were male and 63 were female. More than half (53.2%) were over 60 years of age. B symptoms were reported by 42.4%, and 51.1% had an ECOG score of 2 or higher. Advanced-stage disease (Ann Arbor III–IV) was present in 64% of cases, and 64% had involvement of at least one extranodal region. Bone marrow infiltration was documented in 13.6%. Of the 62 patients with evaluable immunohistochemistry, 82.3% were classified in the non-germinal center category according to the Hans algorithm. According to the IPI, the risk distribution was 28.1% low risk, 20.9% low-to-moderate risk, 30.2% high-to-moderate risk, and 20.9% high risk. Detailed baseline data are presented in Table 1.

Treatment Response and Survival

Of the 139 patients, 100 (71.9%) successfully completed the planned first-line treatment regimen. Of the remaining

Table 1. Demographic profile, clinical features, and laboratory findings at baseline among the 139 study patients with diffuse large B-cell lymphoma

Characteristic	n	%
Age, years - mean ± SD	59.1±14	
Age, years - median (range)	61 (18-85)	
> 60 years	74	53.2
Sex - male	76	54.7
B symptoms present	59	42.4
ECOG performance status 2-4	71	51.1
Ann Arbor stage III-IV	89	64.0
Extranodal involvement ≥ 1 site	89	64.0
≥ 2 extranodal sites	36	25.9
Bone marrow involvement	19	13.6
Elevated LDH	69	49.6
Elevated CRP (> 5 mg/L)	96	69.1
Albumin < 3.5 g/dL	25	18.0
Non-germinal center subtype (Hans, n=62)	51	82.3
IPI - low risk (0-1)	39	28.1
IPI - low-intermediate (2)	29	20.9
IPI - high-intermediate (3)	42	30.2
IPI - high (4-5)	29	20.9
R-IPI - very good (0)	11	7.9
R-IPI - good (1-2)	57	41.0
R-IPI - poor (3-5)	71	51.1

CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; R-IPIÇ: Revised International Prognostic Index; SD: Standard deviation.

patients, 25 (18%) died during treatment or before response assessment. The others either did not initiate treatment or refused treatment. Response outcomes were distributed as follows: 55.4% complete response (CR), 3.6% partial response (PR), 0.7% stable disease (SD), and 12.2% progressive disease (PD). After excluding 11 cases of death due to non-lymphoma causes, 128 patients were included in the survival analyses. Five-year overall survival (OS) reached 58.2%, and 3-year disease-free survival (PFS) reached 52%; the median OS was 83.1 months (95% CI, 87–118), and the median PFS was 69.4 months (95% CI, 63.1–90.6).

In univariate analyses, the presence of B symptoms, an ECOG score of 2–4, involvement of multiple extranodal sites, bone marrow infiltration, and a serum albumin level below 3.5 g/dL were associated with shorter overall survival (OS) and/or disease-free survival (PFS), whereas age, sex, hemoglobin, LDH, CRP, and Hans-defined cell of origin were not associated with these outcomes. Risk stratification according to the IPI or R-IPI yielded statistically significant stratification for both endpoints ($p \leq 0.007$). Five-year OS rates for the four IPI strata (low, low-to-moderate, high-to-moderate, and high) were 76.4%, 61.8%, 57.9%, and 30.3%, respectively. When the shortened treatment regimen (three R-CHOP cycles plus radiotherapy) was compared with the standard six- to eight-cycle R-CHOP approach, no significant difference was found in overall survival (OS) or disease-free survival (PFS) ($p=0.786$ and $p=0.427$, respectively). Initial treatment response was strongly associated with overall survival. Three-year overall survival was 89.3% after complete response (CR), 80% after partial response (PR), and only 13.3% after progressive disease (PD) ($p<0.001$).

NLR Cutoff, Correlations, and Survival

Through ROC analysis, an NLR threshold of 2.90 emerged as the optimal value for discriminating mortality, providing 86% sensitivity, 50% specificity, an AUC of 0.674, and $p=0.001$ (Fig. 1). The proportion of patients exceeding this cutoff was 89 of 139 (64%). The ratio showed a direct correlation with the IPI score ($r=0.205$, $p=0.021$), as well as with a poorer initial response ($r=0.263$, $p=0.004$). Compared with their counterparts, individuals with NLR≥2.90 had higher proportions of ECOG≥2, elevated LDH and CRP levels, low albumin levels, and higher IPI/R-IPI categories (all $p<0.05$); the two NLR groups were similar in terms of age, sex, B symptoms, extranodal involvement, marrow status, stage, and Hans subtype (Table 2).

Five-year OS reached 81% when NLR remained below 2.90 but fell to 45.8% above that threshold (median OS, 116.2 vs. 65.7 months; $p<0.001$). Likewise, 3-year PFS was 66.2% versus 44.7% across the two strata (median PFS, 92.8 vs. 57.7 months; $p=0.006$) (Fig. 2).

LMR Cutoff, Correlations, and Survival

For LMR, the optimal cutoff point obtained by ROC analysis was 2.40, with a sensitivity of 69%, specificity of 56%, AUC of 0.630, and $p=0.032$. Fifty-one of 128 patients (42.1%) fell below this value. The ratio showed an inverse relationship with the IPI score ($r=-0.272$, $p=0.001$) and a positive correlation with the response category ($r=0.210$, $p=0.048$). Values below the 2.40 threshold were significantly associated with ECOG≥2, two or more extranodal sites, high LDH levels, hypoalbuminemia, and high-risk IPI/R-IPI categories (Table 3).

The 5-year overall survival rate was 45% in patients with an LMR value below 2.40 and 67.3% in those with a value greater than or equal to 2.40 (median overall survival, 66.7 months vs. 94.9 months; $p=0.019$). The 3-year progression-free survival rate was similarly 38.6% versus 61.2% (median progression-free survival, 53.6 months vs. 66.4 months; $p=0.022$) (Fig. 3).

Multivariate Analysis and Comparison of Prognostic Markers

Univariate Cox modeling identified ECOG score, number of extranodal regions, serum albumin, IPI, R-IPI, NLR, and LMR as factors significantly associated with OS. For PFS, the corresponding factors were B symptoms, ECOG score, bone marrow infiltration, albumin, IPI, R-IPI, NLR, and LMR (Table 4). In the multivariate model for OS, three variables retained their independent prognostic significance. These variables were ECOG performance status (HR, 4.17; 95% CI, 2.04–

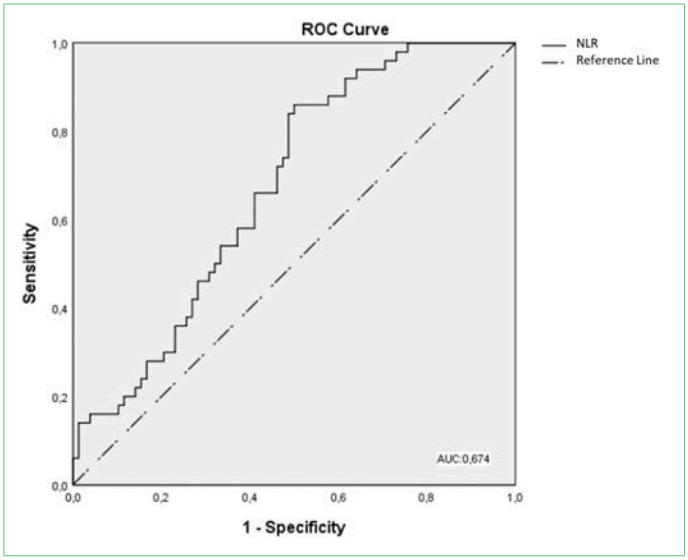


Figure 1. ROC curves illustrating the discriminative thresholds for NLR (AUC 0.674) and LMR (AUC 0.630) in predicting all-cause mortality among patients with diffuse large B-cell lymphoma.

Table 2. Distribution of patient features stratified by neutrophil-to-lymphocyte ratio (NLR) category (threshold 2.90)

Characteristic	NLR < 2.90 (n=50) n (%)	NLR ≥ 2.90 (n=89) n (%)	OR (95% CI)	p
Age > 60 years	24 (52.2)	42 (51.2)	0.96 (0.47-1.98)	0.917
Male sex	25 (54.3)	44 (53.7)	1.97 (0.47-2.01)	0.940
B symptoms	18 (39.1)	39 (47.6)	1.41 (0.68-2.94)	0.357
ECOG 2-4	15 (32.6)	49 (59.8)	3.07 (1.44-6.55)	0.003
≥ 2 extranodal sites	7 (15.2)	24 (29.3)	2.31 (0.91-5.87)	0.075
Bone marrow involvement	5 (10.9)	14 (17.1)	1.69 (0.57-5.03)	0.344
Advanced stage (III-IV)	27 (58.7)	56 (68.3)	1.52 (0.72-3.21)	0.275
Elevated LDH	16 (34.8)	47 (57.3)	2.52 (1.19-5.32)	0.014
Elevated CRP	26 (56.5)	61 (74.4)	2.23 (1.04-4.80)	0.038
Albumin < 3.5 g/dL	2 (4.3)	19 (23.2)	6.64 (1.47-29.95)	0.006
IPI high-intermediate/high	17 (37.0)	49 (59.8)	2.53 (1.20-5.33)	0.013
R-IPI poor	17 (37.0)	49 (59.8)	2.53 (1.20-5.33)	0.013

CI: Confidence interval; CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; OR: Odds ratio; R-IPI: Revised International Prognostic Index.

8.54; p<0.001), serum albumin (HR, 2.19; 95% CI, 1.07–4.49; p=0.032), and NLR≥2.90 (HR, 3.00; 95% CI, 1.26–7.14; p=0.013). Independent predictors of PFS were ECOG performance status (HR, 6.03; 95% CI, 3.02–12.04; p<0.001), albumin (HR, 2.33; 95% CI, 1.16–4.66; p=0.017), and bone marrow involvement (HR, 3.59; 95% CI, 1.48–8.72; p=0.005). NLR and LMR did not retain their independent significance in this model.

Direct ROC comparison of the four prognostic markers for mortality discrimination produced AUC values of 0.680 for NLR, 0.616 for LMR, 0.664 for IPI, and 0.634 for R-IPI; therefore, NLR offered the greatest discriminatory capacity among the tested indices (Fig. 4).

Discussion

In a single-center retrospective DLBCL series of 139 patients managed with rituximab-based protocols, baseline NLR and LMR values were associated with overall survival (OS) and disease-free survival (PFS), followed IPI risk categories, and reflected the quality of response to first-line treatment. After accounting for classical prognostic variables, NLR≥2.90 emerged as an independent predictor of OS, along with poor ECOG performance status and hypoalbuminemia, whereas LMR failed to maintain its independence in the adjusted model. Specifically, direct comparison among the four indices revealed that NLR had greater discriminatory power for mortality than IPI, R-IPI, or LMR.

There is increasing evidence that systemic inflammation, immune capacity, and the microenvironment surrounding malignant cells collectively influence lymphoma behavior. Considering all these effects, these ratios can be observed to have a biological basis for their prognostic importance. Neutrophils contribute to an environment that promotes

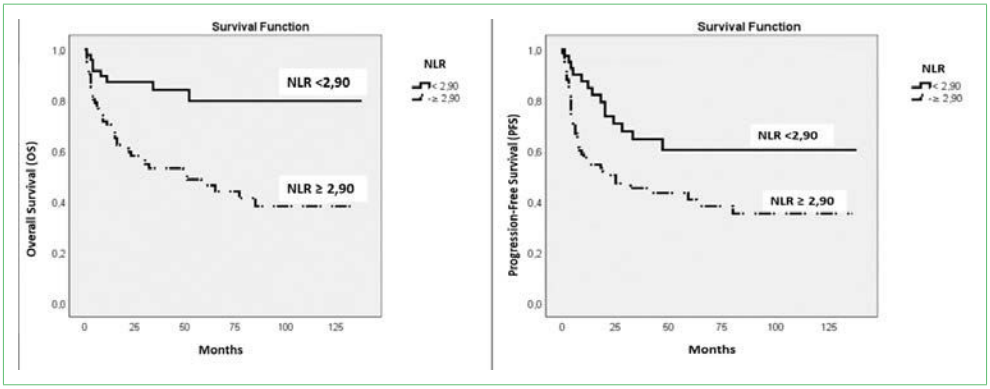


Figure 2. Kaplan-Meier estimates for overall survival (panel A) and progression-free survival (panel B), stratified by an NLR threshold of 2.90.

Table 3. Distribution of patient features stratified by lymphocyte-to-monocyte ratio (LMR) category (threshold 2.40).

Characteristic	LMR < 2.40 (n=51) n (%)	LMR ≥ 2.40 (n=77) n (%)	OR (95% CI)	p
Age > 60 years	27 (52.9)	39 (50.6)	1.10 (0.54-2.23)	0.799
Male sex	29 (56.9)	40 (51.9)	1.22 (0.60-2.49)	0.385
B symptoms	28 (54.9)	29 (37.7)	2.02 (0.98-4.14)	0.055
ECOG 2-4	32 (62.7)	32 (41.6)	2.37 (1.15-4.90)	0.019
≥ 2 extranodal sites	17 (33.3)	14 (18.2)	2.25 (1.00-5.12)	0.049
Bone marrow involvement	8 (15.7)	11 (14.3)	1.12 (0.41-3.00)	0.827
Advanced stage (III-IV)	37 (72.5)	46 (59.7)	1.78 (0.83-3.83)	0.137
Elevated LDH	33 (64.7)	30 (39.0)	2.87 (1.38-5.99)	0.004
Elevated CRP	37 (72.5)	50 (64.9)	1.43 (0.66-3.09)	0.366
Albumin < 3.5 g/dL	17 (33.3)	4 (5.2)	9.13 (2.85-29.19)	<0.001
IPI high-intermediate/high	34 (66.7)	32 (41.6)	2.81 (1.35-5.88)	0.005
R-IPI poor	34 (66.7)	32 (41.6)	2.81 (1.35-5.88)	0.005

CI: Confidence interval; CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: Lactate dehydrogenase; OR: Odds ratio; R-IPI: Revised International Prognostic Index.

tumor formation through the release of mediators, including IL-10, TNF-α, and vascular endothelial growth factor.[10] Lymphocytes directly drive antitumor cytotoxic activity.[8] Circulating monocytes, after recruitment, can transform into tumor-associated macrophages, which reduce antitumor responses and aid neoplastic progression.[9] In this context, an increased NLR together with a decreased LMR reasonably reflects an imbalance that promotes inflammation rather than effective adaptive immunity, thereby supporting tumor formation.

Our cohort's NLR threshold of 2.90 falls within the spectrum reported in previous DLBCL studies. Although a Mayo Clinic group led by Porrata established a cutoff point of 3.5, analyses by Wang and Spassov determined values of 2.81 and 3.01, respectively, both validating NLR as an independent predictor of OS.[14,18,19] Higher thresholds, ranging from 4.35 to 5.54, have been identified elsewhere. In these studies, NLR retained significance only at the univariate level. Such differences may reflect variations in cohort composition, treatment exposure, and the definitions used for survival endpoints.[20,21] This methodological variability explains the differing multivariate outcomes reported in the literature. It also underscores the need for prospective validation using uniform threshold criteria.

The LMR threshold of 2.40 that we observed is comparable to the value of 2.60 reported by Rambaldi and colleagues, whose work positioned LMR as an independent determinant of both OS and PFS in patients with DLBCL receiving

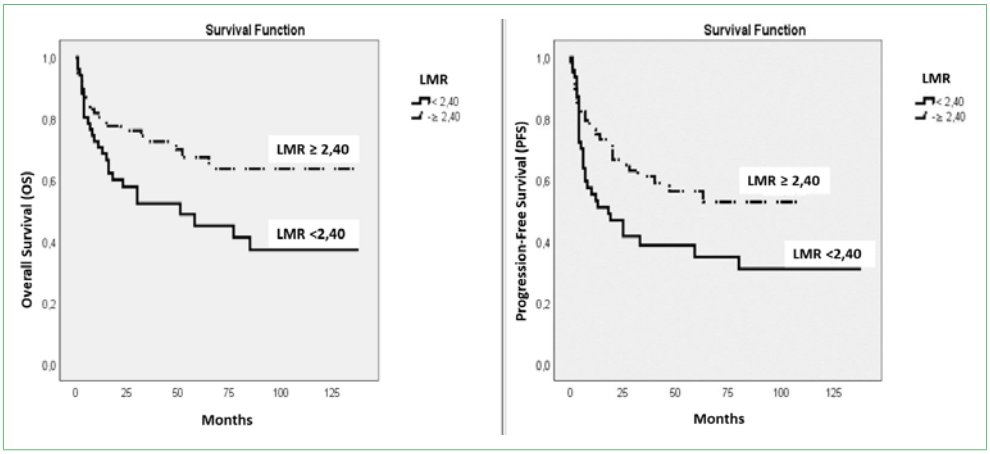


Figure 3. Kaplan-Meier estimates for overall survival (panel A) and progression-free survival (panel B), stratified by an LMR threshold of 2.40.

Table 4. Cox proportional hazards modeling, univariate and multivariable results for factors related to overall survival (OS) and progression-free survival (PFS)

	Univariate OS HR (95% CI), p	Multivariate OS HR (95% CI), p	Univariate PFS HR (95% CI), p	Multivariate PFS HR (95% CI), p
B symptoms	1.69 (0.97-2.96), 0.065	-	2.02 (1.20-3.41), 0.009	1.40 (0.81-2.41), 0.229
ECOG 2-4	4.96 (2.53-9.71), <0.001	4.17 (2.04-8.54), <0.001	5.98 (3.21-11.15), <0.001	6.03 (3.02-12.04), <0.001
≥ 2 extranodal sites	1.90 (1.05-3.43), 0.033	1.44 (0.69-3.00), 0.327	1.38 (0.77-2.46), 0.281	0.64 (0.30-1.37), 0.248
Bone marrow involvement	1.61 (0.78-3.34), 0.199	-	2.07 (1.06-4.04), 0.032	3.59 (1.48-8.72), 0.005
Albumin < 3.5 g/dL	2.81 (1.51-5.22), 0.001	2.19 (1.07-4.49), 0.032	2.66 (1.48-4.77), 0.001	2.33 (1.16-4.66), 0.017
IPI high-int./high	2.32 (1.29-4.18), 0.005	-	2.27 (1.32-3.89), 0.003	-
NLR ≥2.90	4.18 (1.88-9.30), <0.001	3.00 (1.26-7.14), 0.013	2.29 (1.23-4.26), 0.009	1.04 (0.51-2.13), 0.911
LMR <2.40	1.92 (1.10-3.35), 0.022	0.73 (0.36-1.49), 0.391	1.80 (1.07-3.02), 0.026	0.89 (0.46-1.71), 0.727

CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IPI: International Prognostic Index; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio. Covariates without univariate significance were not carried forward to multivariable modeling (denoted). The adjusted multivariable models incorporated ECOG score, ≥ 2 extranodal sites, albumin level, B symptoms, marrow involvement, NLR, and LMR.

rituximab-based regimens.[22] In our cohort, LMR was significantly associated with OS and PFS in univariate testing but lost its independent role after multivariable adjustment, suggesting that LMR is heavily influenced by tumor burden and other coexisting prognostic factors. Consistent with this observation, Ji and coworkers demonstrated that an LMR/LDH composite outperformed LMR alone in multivariable settings, supporting the rationale that combined indices integrating immunity and tumor burden may provide superior prognostic resolution.[23]

This study offers several distinctive features beyond reinforcing previous observations. First, rituximab-based treatment was uniformly administered at a single institution. This minimized variability in clinical management. Second, non-lymphoma-related deaths were excluded from the survival analyses. This made the prediction of disease-specific outcomes more sensitive. Third, a simultaneous direct ROC comparison of NLR, LMR, IPI, and R-IPI was performed in the cohort. It objectively ranked NLR as having the highest discriminatory power. These findings are consistent with previous suggestions that integrating immune-related parameters into established clinical scores can improve risk stratification in the modern rituximab-treated population.[2,4]

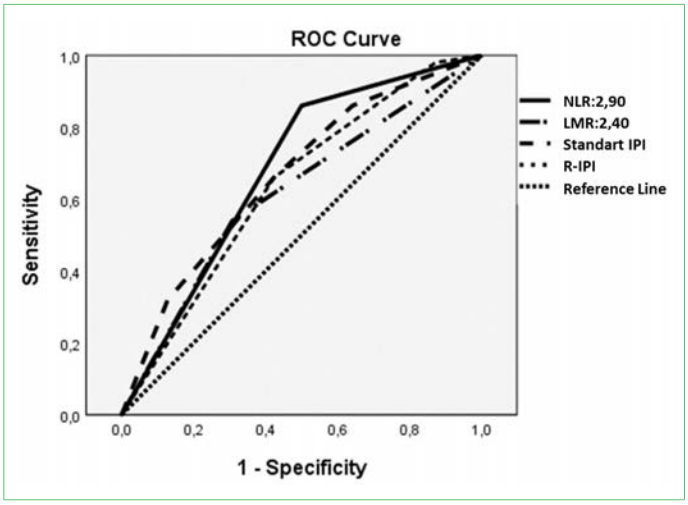


Figure 4. Head-to-head ROC comparison of NLR, LMR, IPI, and R-IPI for predicting all-cause mortality.

The findings further validate the prognostic weight of traditional clinical variables. A poor ECOG score, advanced IPI-defined disease, involvement of multiple extranodal regions, bone marrow infiltration, and low serum albumin levels were all associated with worse outcomes. Hypoproteinemia, an integral reflection of both nutritional reserve and chronic inflammatory burden, remained independently associated with both OS and PFS, mirroring observations from previously published series.[24] Notably, Hans-based immunohistochemical classification (germinal center origin and non-germinal center origin) was not associated with survival in our cohort. The limited number of cases for which immunohistochemical data were available (n=62) and reliance on the Hans surrogate, instead of gene expression profiling, which remains the reference standard but is rarely accessible in daily practice, may be the underlying reasons for this unfavorable finding.[17]

Some limitations should be considered. Because the analysis was retrospective and limited to a single center, generalizability is naturally restricted. Comprehensive cell-of-origin assessment for the entire cohort and FISH-based detection of double- or triple-hit rearrangements were not available, which prevented specific subgroup analyses. Bone marrow sampling was largely unilateral, increasing the possibility of underestimating bone marrow involvement. In addition,

NLR and LMR show demographic variability in healthy populations, reinforcing the need for population-specific normative ranges.[25] Finally, the discriminatory performance of both ratios in predicting individual mortality was only moderate (AUC range, 0.61–0.68). This suggests that they are best viewed as complementary to, rather than replacements for, established prognostic tools.

Despite these constraints, NLR and LMR remain inexpensive and widely accessible parameters that provide prognostic information at essentially no incremental laboratory expense. Embedding them within the IPI/R-IPI framework in larger multicenter prospective studies, potentially together with tumor-burden surrogates such as LDH or β2-microglobulin, could refine existing risk-prediction models and help identify patients who might benefit from intensified treatment strategies or earlier enrollment in clinical investigations.

Conclusion

In a DLBCL population managed with rituximab-inclusive protocols, baseline NLR≥2.90 and LMR<2.40 were both associated with higher IPI risk, a poorer first-line response, and shorter overall survival (OS) and disease-free survival (PFS). NLR emerged as an independent predictor of OS, along with ECOG performance status and serum albumin, and demonstrated the strongest discriminatory capacity for mortality among the indices examined. Because both ratios are readily obtainable from routine laboratory data, they can be easily integrated into daily risk assessment in conjunction with IPI-based scoring; however, prospective multicenter studies are needed to validate these results.

Disclosures

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences, İzmir Bozyaka Training and Research Hospital Institutional Ethics Committee (approval no. 05, dated May 22, 2019), and all procedures were performed in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: Individual patient consent was waived by the Ethics Committee due to the retrospective nature of the study.

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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