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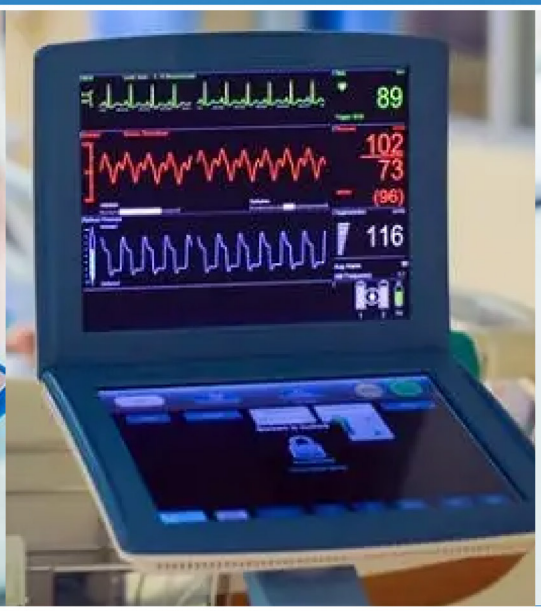

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CONTENTS

Volume: 4 Issue: 2 Year: 2026

ORIGINAL ARTICLES

REVIEW

LETTER TO THE EDITOR

The Intercontinental Journal of
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Original Article

Assessment of systemic inflammatory and immune biomarkers and alterations in calcium and parathyroid hormone in hemodialysis patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Chronic systemic inflammation and mineral metabolism disturbances are prevalent in hemodialysis (HD) patients. The presence of type 2 diabetes mellitus (T2DM) may further exacerbate inflammatory burden and disrupt calcium-parathyroid hormone (Ca-PTH) homeostasis. This study aimed to perform a comparative assessment of systemic and immune-inflammatory indices together with Ca-PTH levels in HD patients with and without T2DM, to assess the impact of diabetes on these parameters.

Methods: This retrospective multicenter study included 211 maintenance HD patients, including 97 with T2DM and 114 without diabetes. Inflammatory and immune-related indices, including the PIV, SIRI, SII, NLR, PLR, LMR, NMR, MPVLR, MHR, SII/albumin ratio, and CRP/albumin ratio were evaluated together with hematological parameters, biochemical markers, and mineral metabolism parameters.

Results: SIRI, PIV, MHR, IMA, and monocyte concentrations were notably elevated in the T2DM group compared to their non-diabetic counterparts ($p<0.05$). ROC analysis showed modest discriminatory performance for SIRI (AUC=0.586) and PIV (AUC=0.583), with PIV demonstrating 71% sensitivity at a cut-off value of 25.28. In contrast, serum calcium and PTH levels were lower in the T2DM group, with calcium exhibiting the negative association among the studied parameters. SIRI and PIV were positively associated with leukocyte-related inflammatory markers, whereas calcium and PTH correlated with hemoglobin, hematocrit, potassium and phosphorus.

Conclusion: In hemodialysis patients, T2DM may be associated with an increased systemic inflammatory burden and a relative suppression of the Ca-PTH axis. Lower calcium and PTH levels could potentially reflect alterations in mineral metabolism and may be suggestive of a tendency toward adynamic bone disease. These observations may highlight the potential value of integrating inflammatory indices with Ca-PTH parameters to better characterize diabetes-associated inflammatory activity and disturbances in mineral metabolism in this patient population.

Keywords: Diabetes, hemodialysis, systemic inflammatory and immune indices, parathyroid hormone, calcium, mineral metabolism

INTRODUCTION

Maintenance hemodialysis (HD) cohorts are increasingly defined by a striking prevalence of type 2 diabetes mellitus (T2DM), an overarching comorbidity that imposes a multifaceted cardiovascular, metabolic, and psychosocial strain.[1] The survival of diabetic dialysis patients is significantly worse than that of dialysis patients without diabetes.[2] Cohort studies conducted in HD populations have reported that approximately 45-74% of HD patients have diabetes, and diabetes has been shown to be associated with a higher comorbidity burden and an approximately 72% increased risk of mortality.[1] Systemic inflammation serves as a pivotal mechanistic link in the underlying pathophysiology of both HD and T2DM. In HD patients, contact between blood and dialysis membranes promotes platelet adhesion and activation, contributing to chronic subclinical inflammation and immune dysregulation.[3,4] Platelet activation represents one of the earliest steps in the inflammatory cascade observed in HD patients and triggers multiple events that lead to chronic subclinical inflammation and immune dysfunction. Notably, platelet activation is considered a central mechanism that initiates chronic low-grade inflammation and contributes to immune system dysregulation in this population.[3-5] In HD patients, dysfunction has been demonstrated in both the innate and adaptive immune systems. This condition is characterized by impaired anti-inflammatory responses, including reduced synthesis of IL-10 and caspase-8, as well as T-cell abnormalities such as a reduction in $CD73^+$ T-cell subsets.[5,6] Alterations in innate immune cells, such as neutrophils and monocytes, as well as adaptive immune components including T and B lymphocytes, are partly associated with exposure to uremic toxins and repeated extracorporeal blood circulation. These changes are positively associated with systemic inflammation,

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increased susceptibility to infections, and an elevated risk of cardiovascular complications.[4,5,7] In particular, the accumulation of uremic toxins, which is common in HD patients, increases leukocyte activity and promotes inflammation.[7] Chronic low-grade inflammation is both a driver and a consequence of diabetes, particularly T2DM, and is closely linked to oxidative stress and metabolic dysfunction. Sustained inflammation in diabetes mellitus is linked to insulin resistance and increased glucose concentrations, which is evidenced by elevated levels of inflammatory biomarkers.[8] In addition, chronic hyperglycemia and insulin resistance observed during the diabetic process lead to the pathological accumulation of advanced glycation end products (AGEs) in tissues, thereby disrupting bone homeostasis. This metabolic dysfunction suppresses bone turnover by inhibiting osteoblastic activity and limits the physiological adaptive capacity of the parathyroid gland in response to altered homeostatic demands.[9,10]

In this context, in this context, the present study aimed to assess the effect of T2DM on inflammatory status among individuals undergoing HD by analyzing systemic inflammatory and immune-inflammatory indices, together with calcium (Ca) and parathyroid hormone (PTH) levels.

METHODS

Ethics

This study was conducted with the approval of the Kırıkkale University Ethics Committee for Non-interventional Researches (Date: 14.05.2025, Decision No: 2025.05.07). Permission to access clinical data was granted by Private Ankara Balgat Dialysis Center. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This retrospective, multicenter study include.d 211 patients receiving maintenance HD who were followed at the Department of Internal Medicine, Kırıkkale University Faculty of Medicine, and the Private Ankara Balgat Dialysis Center between January 2020 and January 2025. According to diabetes status, patients were categorized into two groups: those with T2DM (n=97) and those without diabetes (n=114). The study included patients with a confirmed diagnosis of T2DM and a disease duration of at least 10 years, all of whom were diagnosed with diabetic nephropathy based on hospital records. The mean age of the study population was 62.7±11 years. All participants were receiving maintenance HD due to end-stage kidney disease with a glomerular filtration rate (GFR) of 15 ml/min/1.73 m^2 or lower. The diagnosis of T2DM was established in accordance with the criteria of the American Diabetes Association (ADA).

In this study, inflammatory and immune-related indices-including the Pan-Immune-Inflammation Value (PIV), Systemic Immune-inflammation Index (SII), Systemic Inflammation Response Index (SIRI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-monocyte ratio (NMR), mean platelet volume-to-lymphocyte ratio (MPVLR), monocyte-to-high-density lipoprotein cholesterol ratio (MHR), SII/albumin ratio, and CRP/albumin ratio were evaluated. Hematological parameters included leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, plateletcrit, hemoglobin, hematocrit, and mean platelet volume (MPV). Biochemical markers comprised C-reactive protein (CRP), ferritin, ischemia-modified albumin (IMA), high-density lipoprotein cholesterol (HDL-C), non-HDL cholesterol, alanine aminotransferase (ALT), and albumin. Parameters related to electrolyte and mineral metabolism, including PTH, sodium (Na), potassium (K), Ca, and phosphorus (P), were also recorded. Patient demographics and laboratory datasets were compiled retrospectively by accessing medical archives.

Inclusion and Exclusion Criteria

Patients aged 18 years or older were eligible for inclusion, were receiving maintenance HD for end-stage kidney disease (GFR≤15 ml/min/1.73 m^2), had been on regular HD for at least 6 months.

Patients were excluded if they had been receiving HD for less than 6 months; had an active infection, sepsis, or any acute inflammatory condition at the time of blood sampling; had a known malignancy or active autoimmune or rheumatologic disease; were pregnant; had missing key clinical or laboratory data that could compromise the reliability of the analyses; or were younger than 18 years of age. Patients with severely impaired glycemic control or acute critical conditions were excluded from the study.

Statistical Analyses

All data analyses were conducted with IBM SPSS Statistics for Windows (version 27.0; IBM Corp., Armonk, NY, USA). Normality of the data was examined using the Shapiro-Wilk test. According to the distribution characteristics, intergroup differences were analyzed using the Student's t-test for normally distributed variables or the Mann-Whitney U test for non-normally distributed variables. The discriminative ability of inflammatory biomarkers was evaluated using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was used to assess diagnostic accuracy. The optimal cut-off valuewas determined using the Youden index (sensitivity+specificity-1) to identify the point that provided the best balance between sensitivity and specificity.

Correlations among variables were examined using either Pearson or Spearman correlation tests, as appropriate. Statistical significance was defined as a two-tailed p value of less than 0.05.

RESULTS

Hematological and Inflammatory Parameters

A statistically significant difference in monocyte counts was observed between the groups (p=0.045). In contrast, no statistically significant differences were detected in leukocyte, neutrophil, lymphocyte, platelet counts, plateletcrit, hemoglobin, hematocrit, or MPV (p>0.05), (**Table 1**). Regarding inflammatory and immune-related indices, significant differences in PIV, SIRI, and MHR were observed between the groups (p=0.044, p=0.040, and p=0.004, respectively). However, no significant differences were found for SII, NLR, PLR, LMR, NMR, MPVLR, or the ratios of SII/albumin and CRP/albumin (p>0.05), (**Table 2**).

Table 1. Hematological, biochemical, and mineral metabolism parameters in hemodialysis patients with T2DM

Categories/parameters	HD with T2DM (mean±SD/IQR)	HD (mean±SD/IQR)	p
Gender (female)	46 (47.4%)	44 (38.6%)	0.21
Gender (male)	51 (52.6%)	70 (61.4%)	
Hematological parameters (mean±SD)			
Leukocyte (10^3/μL)	6.95±2.1	6.56±2.2	0.14
Neutrophil (10^3/μL)	4.71±1.7	4.32±1.7	0.12
Lymphocyte (10^3/μL)	1.44±0.5	1.37±0.5	0.37
Monocyte (10^3/μL)	0.67±0.4	0.58±0.2	0.045*
Platelet (10^3/μL)	198.3±67.6	194.9±56.1	0.69
Plateletcrit (%)	0.64±3.4	0.25±0.1	0.24
Hemoglobin (g/dl)	11.36±1.6	11.36±1.7	0.97
Hematocrit (%)	34.67±6.4	35.09±6.4	0.64
MPV (fL)	11.12±1.1	10.96±1.0	0.30
Biochemical markers (median (IQR))			
CRP (mg/L)	10.3 (5.4-23.2)	9.6 (4.6-16.6)	0.35
Ferritin (ng/ml)	618 (400-760.2)	732 (514-851.5)	0.29
IMA (ABSU)	0.711 (0.595-0.818)	0.619 (0.507-0.753)	0.044*
HDL-C (mg/dl)	40 (29-46)	38.50 (34-44.2)	0.20
non-HDL-C (mg/dl)	139 (120.7-179.2)	136 (120.5-172.7)	0.92
ALT (U/L)	14 (11-18.7)	13 (9-17.2)	0.55
Alb (g/dl)	3.7 (3.4-3.9)	3.7 (3.5-4)	0.51
Mineral metabolism			
PTH (pg/ml) (median (IQR))	198.5 (110.2-309)	203.5 (129.7-406.7)	0.007*
Na (mEq/L) (mean±SD)	137.8±3.1	138.2±4.2	0.45
K (mEq/L) (mean±SD)	5.13±0.8	5.28±0.8	0.18
Ca (mg/dl) (mean±SD)	8.34±0.8	8.74±0.9	0.002*
P (mg/dl) (mean±SD)	5.12±1.4	5.18±1.4	0.77

T2DM: Type 2 diabetes mellitus, IQR: Interquartile range, SD: Standard deviation, MPV: Mean platelet volume, CRP: C-reactive protein, Ferritin: Ferritin, IMA: Ischemia-modified albumin. HDL-C: High-density lipoprotein cholesterol, ALT: Alanine aminotransferase, Alb: Albumin, PTH: Parathyroid hormone, Na: Sodium, K: Potassium, Ca: Calcium, P: Phosphorus (IQR; 25th-75th percentile)

Table 2. Comparison of inflammatory indices between groups

Parameter	HD with T2DM median (IQR)	HD median (IQR)	p
PIV	34 (21.40-62.58)	26.9 (14.03-61.21)	0.044*
SII	647.8 (413.21-909.02)	586.7 (366.74-976.95)	0.20
SIRI	2.03 (1.38-3.15)	1.6 (1.16-2.51)	0.040*
NLR	3.14 (2.42-4.50)	3.2 (2.40-4.49)	0.13
PLR	143.9 (104.34-192.75)	138.6 (112.88-190.60)	0.63
LMR	2.14 (1.56-3.26)	2.3 (1.80-3.28)	0.39
NMR	8.6 (5.24-10.69)	7.4 (5.85-9.44)	0.40
MPVLR	8.03 (6.26-11.13)	7.8 (6.37-10.36)	0.45
MHR*	0.020 (0.010-0.020)	0.010 (0.010-0.020)	0.004*
SII/Alb ratio	170.5 (104.10-229.00)	159.9 (98.46-258.75)	0.89
CRP/Alb ratio	2.6 (1.68-5.10)	2.4 (1.16-3.99)	0.22

T2DM: Type 2 diabetes mellitus, IQR: Interquartile range, PIV: Pan-Immune-Inflammation Value, SII: Systemic Immune-inflammation Index, SIRI: Systemic Inflammation Response Index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, NMR: Neutrophil-to-monocyte ratio, MPVLR: Mean platelet volume-to-lymphocyte ratio, MHR: Monocyte-to-high-density lipoprotein cholesterol ratio. Data are presented as median (IQR; 25th-75th percentile)

The diagnostic performance evaluation demonstrated that SIRI and PIV were significantly elevated in the diabetic group (p<0.05). The AUC values for SIRI (0.586) and PIV (0.583) indicated a modest but significant discriminatory capacity for identifying diabetic status. Specifically, PIV showed a sensitivity of 71% at a cut-off value of 25.28, suggesting screening potential. Correlation analysis revealed that both PIV and SIRI were significantly and positively associated (p<0.001) with neutrophil and leukocyte (WBC) counts, as well as with NLR and SII, while showing a highly significant inverse correlation with LMR (p<0.001).

Biochemical Markers and Mineral Metabolism

A statistically significant difference in IMA concentrations was identified between the groups (p=0.044), whereas no significant differences were observed for CRP, ferritin, HDL-C, non-HDL-C, ALT, or albumin (p>0.05). Notably, PTH and serum Ca levels differed significantly between the groups (p=0.007 and p=0.002, respectively), being significantly lower in the diabetic group. No significant differences were detected in sodium, potassium, or phosphorus levels (p>0.05), (**Table 1**).

Receiver operating characteristic (ROC) analyses and curves are presented in **Table 3** and **Figure**. ROC curve analysis suggested that Ca might serve as a negative predictor for T2DM (**Table 3**). This finding suggests that decreased Ca levels may be inversely associated with T2DM occurrence. In the present cohort, the observed relationship between lower PTH and Ca levels and an increased prevalence of T2DM may reflect a complex interplay between Ca homeostasis and glucose metabolism. Correlation analysis showed that PTH was positively correlated with LMR (p<0.001), hematocrit (p=0.001), hemoglobin (p=0.016), phosphorus (p<0.001), and potassium (p=0.015). Similarly, serum Ca levels were significantly and positively associated with hematocrit (ρ=0.205, p=0.003) and phosphorus (ρ=0.182, p=0.008), (**Table 4**).

DISCUSSION

The pathophysiological framework of both HD and T2DM is inextricably tied to systemic inflammation. In the present study, the T2DM subgroup exhibited substantially higher values for SIRI, PIV, MHR, IMA, and monocytes, whereas a physiological suppression was observed in Ca and PTH levels when compared with their non-diabetic counterparts. Consistent with our findings, previous studies have identified SIRI as a independent prognostic marker in diabetic HD patients. Elevated SIRI levels were associated with an approximately fourfold increase in mortality risk, and a SIRI-based predictive model has been proposed as a valuable tool for clinical risk stratification in this population.[11,12] There is a limited number of studies evaluating the MHR in diabetic HD patients. However, findings from related populations support our results. In a study conducted among patients with diabetic nephropathy, the association between MHR and disease severity was evaluated in the subgroup with severe albuminuria, and MHR levels were found to be significantly elevated.[13] The PIV index has not previously been examined in HD patients with T2DM. In contrast, earlier research demonstrated significantly higher SII and PIV levels in female HD patients compared with their male counterparts.[14] The PIV index, which integrates neutrophil, monocyte, platelet, and lymphocyte counts, reflects both inflammatory activation and immune dysregulation.[15] In patients undergoing HD, the presence of T2DM may further increase PIV levels due

Table 3. ROC analysis of biomarkers for T2DM in hemodialysis patients

Variable	AUC (95% CI)	p-value	Cut-off	Sensitivity (%)	Specificity (%)
SIRI	0.586 (0.509-0.663)	0.028	2.01	49.5	67.5
PIV	0.583 (0.505-0.661)	0.036	25.29	71.0	49.6
Parathormone	0.420 (0.341 - 0.498)	0.04	46.50	97.9	8.3
Calcium	0.382 (0.307-0.457)	0.002	6.80	96.9	3.5

ROC: Receiver operating characteristic, T2DM: Type 2 diabetes mellitus, AUC: Area under the curve, CI: Confidence interval, PIV: Pan-Immune-Inflammation Value, SII: Systemic Immune-inflammation Index, SIRI: Systemic Inflammation Response Index

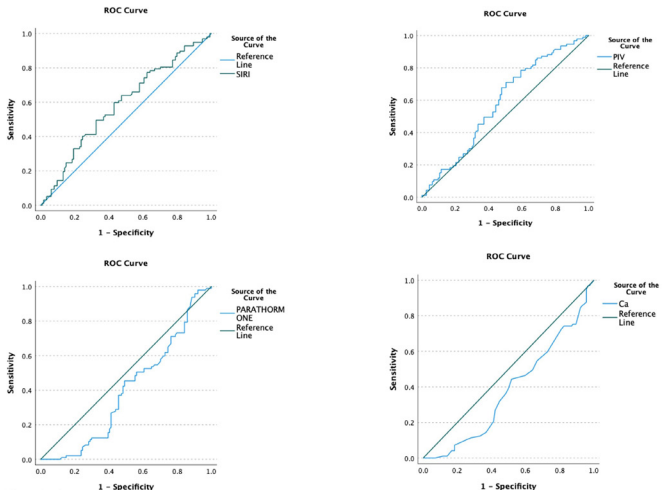

Figure. ROC curve analyses

ROC: Receiver operating characteristic

to possibly driven by intensified systemic inflammation, endothelial impairment, and oxidative stress.

Although not identical to the population included in the present study, similar outcomes have been reported in studies involving patients with diabetic nephropathy, where monocyte levels were significantly higher compared with healthy controls.[16] These results support the hypothesis that monocyte-mediated inflammatory pathways may contribute to the inflammatory milieu observed in diabetic kidney disease and HD patients with T2DM.

Diabetes mellitus is well known to exert detrimental effects on both innate and acquired immune responses, leading to significant immune dysfunction.[17] Hyperglycemia and AGEs in diabetes increase the release of monocytes from the bone marrow and prolong their survival in circulation.[18] In the literature, non-classical pro-inflammatory monocytes ($CD14^{+}CD16^{+}$) have been reported to be increased particularly in patients with diabetic nephropathy.[16]

Recent evidence indicates that when diabetes and chronic kidney disease coexist, monocytes undergo epigenetic and metabolic reprogramming, resulting in a pro-inflammatory phenotype through a mechanism referred to as "trained immunity." Hyperglycemia-induced metabolic stress and AGEs affect hematopoietic stem cells and myeloid progenitors, thereby increasing the production of pro-inflammatory monocytes and promoting a persistent inflammatory response in these cells.[19,20] Furthermore, the chronic inflammatory milieu associated with uremia and HD alters monocyte functional properties and contributes to persistent activation of the innate immune response.[7,17] In our study, the pronounced increase in monocyte levels in T2DM patients undergoing HD may be attributable to impaired chemotactic receptor function, which may limit the migration of these cells from the vascular compartment to tissues, thereby prolonging their persistence in circulation. In addition, chronic inflammation may promote immune aging (immunosenescence), further contributing to the accumulation of circulating monocytes. Indeed, it has been reported that immunosenescence in chronic kidney disease

Table 4. Correlation analysis of inflammatory and biochemical parameters

Parameters	SIRI	Monocyte	PIV	MHR	Ca++	PTH	NLR	SII	CRP	Alb
SIRI	1	.628** (<.001)	.400** (<.001)	.437** (<.001)	-.088 (.204)	-.359** (<.001)	.685** (<.001)	.735** (<.001)	.134 (.052)	-.066 (.338)
Monocyte	.628** (<.001)	1	.061 (.384)	.745** (<.001)	.003 (.968)	-.219** (.002)	.464** (<.001)	.001 (.988)	.107 (.122)	-.002 (.980)
PIV	.400** (<.001)	.061 (.384)	1	.017 (.811)	-.244** (<.001)	-.114 (.10)	.523** (<.001)	.488** (<.001)	.866** (<.001)	.052 (.458)
MHR	.437** (<.001)	.745** (<.001)	.017 (.811)	1	.014 (.836)	-.138 (.050)	.396** (<.001)	.341** (.002)	-.130 (.060)	-.112 (.108)
Ca++	-.088 (.204)	.003 (.968)	-.244** (<.001)	.014 (.836)	1	.146* (.040)	-.020 (.777)	-.120 (.082)	-.097 (.161)	.330** (<.001)
PTH	-.319** (<.001)	-.219** (.002)	-.124 (.076)	-.138 (.050)	.146* (.040)	1	-.246** (<.001)	-.201** (.004)	-.032 (.647)	.134 (.055)
NLR	.685** (<.001)	.464** (<.001)	.523** (<.001)	.396** (<.001)	-.020 (.777)	-.246** (<.001)	1	.832** (<.001)	.288** (<.001)	-.144* (.042)
SII	.735** (<.001)	.001 (.988)	.488** (<.001)	.341** (.002)	-.120 (.082)	-.201** (.004)	.832** (<.001)	1	.081 (.241)	.041 (.563)
CRP	.134 (.052)	.107 (.122)	.866** (<.001)	-.130 (.060)	-.097 (.161)	-.032 (.647)	.288** (<.001)	.081 (.241)	1	-.026 (.713)
Alb	-.066 (.338)	-.002 (.980)	.052 (.458)	-.112 (.108)	.330** (<.001)	.134 (.055)	-.144* (.042)	.041 (.563)	-.026 (.713)	1

SIRI: Systemic Inflammation Response Index, PIV: Pan-Immune-Inflammation Value, MHR: Monocyte-to-high-density lipoprotein cholesterol ratio, Ca: Calcium, PTH: Parathyroid hormone, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic Immune-Inflammation Index, CRP: C-reactive protein, Alb: Albumin

leads to the accumulation of functionally altered but highly pro-inflammatory monocyte and macrophage populations in the circulation.[21] This phenomenon may reflect the presence of an "aged" immune cell pool characterized by reduced tissue infiltration capacity but increased inflammatory activity, which may represent an important mechanism underlying the chronic inflammatory state observed in diabetic HD patients. In the present study, lower Ca and PTH levels observed in HD patients with T2DM may be associated with adynamic bone disease, a condition characterized by low bone turnover that is frequently reported in diabetic patients with chronic kidney disease.[22] Chronic hyperglycemia, accumulation of AGEs, and insulin resistance may suppress osteoblast function, thereby reducing bone turnover and impairing the physiological responsiveness of the parathyroid gland.[9] Consistent with this mechanism, previous studies have reported lower PTH levels and a higher prevalence of low bone turnover patterns in diabetic nephropathy patients.[10]

The present study demonstrates that SIRI (AUC: 0.586, p=0.028) and PIV (AUC: 0.583, p=0.036) exhibit statistically significant but modest discriminatory performance for identifying T2DM status. Although SIRI achieved a specificity of 67.5% at a cut-off value of 2.01 and PIV showed a sensitivity of 71.0%, the proximity of their lower confidence intervals to the 0.50 threshold indicates that their clinical applicability should be interpreted with caution.

In contrast, parathormone (AUC: 0.420) and Ca (AUC: 0.382) demonstrated limited diagnostic performance, suggesting a weak inverse association with T2DM rather than meaningful predictive utility. Given their suboptimal AUC values and particularly the low specificity observed for Calcium, these markers do not currently satisfy the criteria for independent clinical biomarkers in this setting.

Overall, these findings should be considered preliminary evidence of altered mineral metabolism in the diabetic nephropathy rather than definitive diagnostic indicators, and they warrant validation in larger, adequately powered prospective cohorts.

Limitations

This study's retrospective design limited our ability to fully adjust for confounding factors like medication history and comorbidities via multivariable analysis. Although HbA1c was not recorded, it is often a suboptimal marker in HD patients due to altered erythrocyte turnover. To minimize these constraints, we applied strict inclusion criteria, including a T2DM history of ≥10 years and a stable dialysis vintage of ≥ 6 months. Future prospective studies are required to validate the independent predictive value of these markers.

CONCLUSION

As a result, HD patients with T2DM exhibit a complex biochemical profile characterized by elevated SIRI and PIV levels, as well as a decline in Ca and PTH concentrations. Although SIRI and PIV showed statistically significant but modest discriminatory performance, their diagnostic utility necessitates cautious interpretation. Furthermore, the inverse patterns observed for Ca and PTH suggest a potential suppression of the mineral bone axis possibly reflecting low bone turnover states such as adynamic bone disease within the context of diabetic nephropathy. Collectively, these findings provide preliminary evidence of a link between systemic inflammation and altered mineral metabolism. Further high-powered, prospective studies are essential to validate these associations and to clarify their prognostic significance in the diabetic nephropathy population.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Kırıkkale University Ethics Committee for Non-interventional Researches (Date: 14.05.2025, Decision No: 2025.05.07).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: FBA; Design: FBA; Control: FBA, HÖ; Data Collection and/or Processing: FBA, HÖ; Analysis and/or Interpretation: FBA; Literature Review: FBA; Article Writing: FBA; Critical Review: FBA, HÖ.

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Original Article

Clinical determinants of recurrent hospitalisations in patients presenting to the emergency department with acute exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

Aims: This study aimed to identify the clinical and laboratory determinants of recurrent hospitalisations within one year among patients admitted to hospital via the emergency department due to acute exacerbation of chronic obstructive pulmonary disease (COPD). Particular emphasis was placed on evaluating the potential contribution of inflammatory indices derived from routine laboratory tests in predicting the risk of recurrent admissions.

Methods: This retrospective observational study included a total of 117 patients who were hospitalised with a diagnosis of acute exacerbation of COPD during the predefined study period. Patients were categorised into two groups according to the occurrence of recurrent hospitalisation during the one-year follow-up period. Sociodemographic characteristics, clinical variables, requirement for intensive care, use of long-term oxygen therapy (LTOT) at home, and routine laboratory parameters were recorded. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP)-to-albumin ratio (CAR), Systemic Immune-inflammation Index (SII), and the CALLY (CRP-albumin-lymphocyte) index were calculated. Between-group comparisons were performed using appropriate parametric and non-parametric statistical tests.

Results: Of the 117 patients included in the study, 50 (42.7%) experienced recurrent hospitalisations during the follow-up period, whereas 67 patients (57.3%) had no recurrent admissions. The proportion of male patients was significantly higher in the recurrent hospitalisation group compared with the non-recurrent group (78.0% vs. 41.8%; p<0.001). No significant difference was observed between the groups in terms of age (71.78±9.08 vs. 72.37±9.92 years; p=0.738). The need for intensive care during the index admission was more frequent in patients who subsequently developed recurrent hospitalisation (38.0% vs. 20.9%; p=0.042). However, no statistically significant differences were identified between the groups regarding the presence of pneumonia or length of hospital stay. The use of LTOT was significantly more common among patients with recurrent admissions. Among laboratory parameters, lower arterial pH (p=0.025) and higher partial pressure of carbon dioxide (PCO_2) levels (p=0.011) were significantly associated with recurrent hospitalisation. While no significant differences were observed between the groups in terms of NLR and PLR, the CAR (p=0.027), SII (p=0.038), and CALLY (p=0.008) indices were found to be significantly associated with recurrent admission.

Conclusion: Recurrent hospitalisations following acute exacerbation of COPD appear to be more closely associated with disease severity, chronic physiological burden, and a multidimensional inflammatory response rather than with age or simple haematological ratios alone. Composite inflammatory indices, particularly CAR, SII, and CALLY, may contribute to the early identification of patients at high risk of readmission. Such an approach could facilitate closer post-discharge surveillance and the implementation of targeted care strategies in this vulnerable population.

Keywords: Patient readmission, chronic obstructive pulmonary disease, acute exacerbation, biomarkers

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) remains a major cause of morbidity and mortality worldwide and constitutes an increasing clinical and economic burden. Severe exacerbations requiring hospitalisation not only increase short-term mortality but are also associated with accelerated decline in pulmonary function, significant deterioration in quality of life, and increased healthcare utilisation in the long term.[1]

Previous studies have demonstrated that hospital readmission rates following COPD exacerbations are particularly high within the first 30-90 days and during the first year of follow-up. In the Readmission After COPD Exacerbation (RACE) study, readmission rates within the first 30 and 90 days after a severe exacerbation were reported to be notably high.[1] Similarly, Chen et al.[2] showed that patients with a history of acute exacerbation within the preceding year had a 4.086-fold

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higher risk of rehospitalisation compared with those without such a history. These recurrent admissions represent an increased risk of complications and deterioration in quality of life for patients, a substantial workload for healthcare professionals, and a significant economic burden for healthcare systems. Accordingly, predicting and preventing recurrent hospitalisations in patients with COPD should be regarded as one of the key objectives of contemporary clinical practice.

In addition to clinical and sociodemographic factors such as age, sex, comorbidities, and the use of long-term oxygen therapy (LTOT) at home, laboratory parameters are also known to play a role in determining the risk of recurrent hospitalization.[3-5] A large-scale meta-analysis conducted in Asian countries, which demonstrated high readmission rates among patients with COPD, reported that risk factors for recurrent hospitalisation may vary according to geographical and ethnic differences.[4] Given the central role of inflammation in the pathogenesis of COPD, inflammatory biomarkers derived from routine laboratory tests have attracted increasing attention in recent years. Indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP)-to-albumin ratio (CAR), Systemic Immune-inflammation Index (SII), and the CALLY (CRP-albumin-lymphocyte) index offer potential advantages in clinical practice due to their ability to reflect systemic inflammation, wide availability, and low cost.

Although existing studies have demonstrated that these laboratory parameters and indices may be associated with the severity of COPD exacerbations, mortality, and short-term outcomes, their role in predicting recurrent hospitalisations remains unclear.[6-8] The Hospital Readmission Reduction Program (HRRP), implemented in the United States, aimed to reduce COPD-related readmissions; however, post-implementation data indicated that the impact was limited, largely due to the heterogeneity and multifactorial nature of the underlying risk factors.[9] Moreover, considerable heterogeneity exists among findings derived from different healthcare centres and patient populations.[10] Therefore, more comprehensive and methodologically robust investigations are warranted in this field. Each additional well-designed study may contribute to the existing body of evidence and help to address the current uncertainties in the literature.

In this study, it is aimed to identify the clinical and laboratory determinants of recurrent hospitalisations occurring within one year among patients admitted via the emergency department due to acute exacerbation of COPD. By comprehensively evaluating sociodemographic characteristics, clinical variables, routine laboratory parameters, and inflammatory indices derived from these parameters, we hypothesised that early identification of patients at high risk of readmission may be feasible, thereby contributing to the development of more effective follow-up strategies and preventive interventions.

METHODS

Ethics

This study was conducted with the approval of the Bozok University Ethics Committee for Non-interventional Clinical Researches (Date: 05.11.2025, Decision No: 2025-GOKAEK-2519_05.11.2025_684). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This single-centre, retrospective, observational study was conducted through a review of medical records of patients who were admitted to hospital via the Emergency Department of Yozgat City Hospital due to acute exacerbation of COPD. Patients aged 18-100 years who presented to the emergency department between 1 January 2024 and 29 February 2024 and were hospitalised with a diagnosis of acute exacerbation of COPD based on clinical, laboratory, and radiological findings were included in the study. As this was a retrospective study, no formal sample size calculation was performed. All consecutive patients who met the inclusion criteria during the study period were included in the analysis. Patients with respiratory failure attributable to causes other than COPD, those with incomplete medical records, individuals who were documented to have died within the one-year follow-up period, and those residing abroad or outside the city were excluded from the study.

All patients were followed for a period of one year from the date of their index admission. Any subsequent hospitalisations occurring within this period due to acute exacerbation of COPD were defined as recurrent admissions.

Patient data were obtained from the hospital electronic medical record system and archived patient files. As information on smoking status and post-discharge treatment adherence could not be obtained from patient records, these variables were not included in the study.

The following variables were recorded for each patient:

- **Sociodemographic data:** Age and sex
- **Clinical data:** Comorbidities, requirement for intensive care at the index admission, use of LTOT at home, and the total number of hospitalisations and intensive care admissions within one year. No comorbidity index was used in the present study, as the analysis focused on the association between each individual comorbid condition and recurrent hospitalization rather than on the overall comorbidity burden.
- **Laboratory parameters:** Complete blood count values measured at admission (white blood cell count, lymphocyte count, neutrophil count, platelet count, and haemoglobin level), biochemical parameters (urea, creatinine, estimated glomerular filtration rate [eGFR], albumin, sodium, potassium, chloride, and blood glucose), arterial blood gas parameters (pH, partial pressure of carbon dioxide [pCO_2], partial pressure of carbon dioxide [pO_2], arterial oxygen saturation [SaO_2], and bicarbonate [HCO_3^-]), as well as CRP, procalcitonin, troponin, and D-dimer levels.

Based on these laboratory data, the following inflammatory indices were calculated:

- **NLR:** Neutrophil count/lymphocyte count
- **PLR:** Platelet count/lymphocyte count
- **CAR:** CRP-to-albumin ratio
- **SII:** Platelet count×neutrophil count/lymphocyte count
- **CALLY index:** Albumin×lymphocyte count/CRP

Statistical Analysis

The data were performed using SPSS for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed variables were compared using the Independent Samples t-test, whereas non-normally distributed variables were analysed using the Mann-Whitney U test or the Kruskal-Wallis test, as appropriate. For correlation analyses, Pearson's correlation coefficient was applied to variables with normal distribution, and Spearman's rank correlation coefficient was used for variables that were not normally distributed. Categorical variables were compared using the Chi-square test; Fisher's exact test was employed when the expected cell count was less than 5. A p-value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 117 patients (67 men and 50 women) were evaluated within the scope of the study. Recurrent hospitalisation during the follow-up period was identified in 50 patients (42.7%), whereas 67 patients (57.3%) had no recurrent admissions. In the recurrent hospitalisation group, 39 patients (78.0%) were male and 11 (22.0%) were female. In contrast, among patients without recurrent admission, 28 (41.8%) were male and 39 (58.2%) were female. The difference in sex distribution between the groups was statistically significant (p<0.001) (Table 1).

Table 1. Demographic characteristics according to recurrent hospitalisation status

Variable	Overall (n=117)	No readmission (n=67)	Readmission (n=50)	p-value
Age (years), mean±SD	72.12±9.53	72.37±9.92	71.78±9.08	0.741
Sex, n (%)				<0.001
Male	67 (57.3)	28 (41.8)	39 (78.0)	
Female	50 (42.7)	39 (58.2)	11 (22.0)	

SD: Standard deviation

With respect to age distribution, the overall mean age was 72.12±9.53 years. The mean age was 71.78±9.08 years in the recurrent hospitalisation group and 72.37±9.92 years in the non-recurrent group. No statistically significant difference was observed between the groups in terms of age (p=0.741) (Table 1).

Among the 50 patients with recurrent hospitalisation, a total of 122 readmissions occurred within one year, of which 57 required intensive care unit (ICU) admission.

In the comparison of comorbid conditions between the groups, a history of cerebrovascular disease (CVD) was found to be more prevalent in the non-recurrent hospitalisation group than in the recurrent group (17.9% vs. 4.0%), and this difference was statistically significant (p=0.022). No statistically significant differences were observed between the groups with respect to other comorbidities, including atrial fibrillation, Alzheimer's disease, arrhythmia, dementia, diabetes mellitus, hyperlipidaemia, hypertension, coronary artery disease, chronic kidney disease, heart failure, and pulmonary thromboembolism (all p>0.05) (Figure 1).

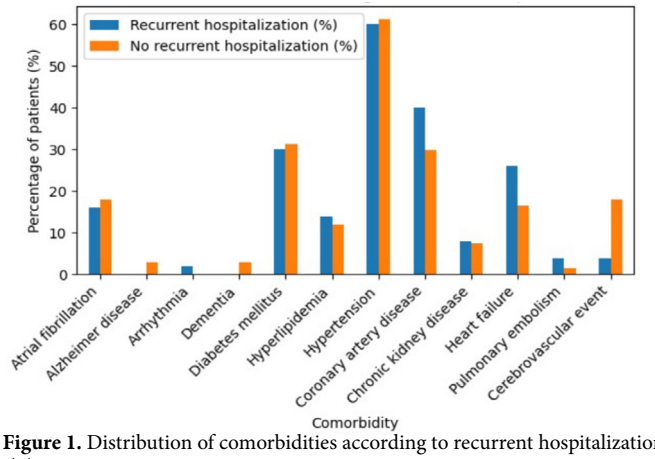

Figure 1. Distribution of comorbidities according to recurrent hospitalization status

In the comparison of clinical characteristics, the use of LTOT at home was identified in 33 of 50 patients (66.0%) in the recurrent hospitalisation group, compared with 18 of 67 patients (26.9%) in the non-recurrent group. This difference was statistically significant (p<0.001). Overall, 51 patients were receiving LTOT at home, whereas 66 patients were not (Table 2, Figure 2).

Table 2. Comparison of clinical characteristics according to recurrent hospitalisation status

Variable	Recurrent hospitalization (n=50)	No recurrent hospitalization (n=67)	p-value
Home oxygen therapy, n (%)	33 (66.0)	18 (26.9)	<0.001
ICU requirement at index admission, n (%)	19 (38.0)	14 (20.9)	0.042
Pneumonia, n (%)	31 (62.0)	46 (68.7)	0.453
Length of hospital stay (mean±SD)	10.54±6.4	9.52±6.17	0.358

ICU: Intensive care unit, SD: Standard deviation

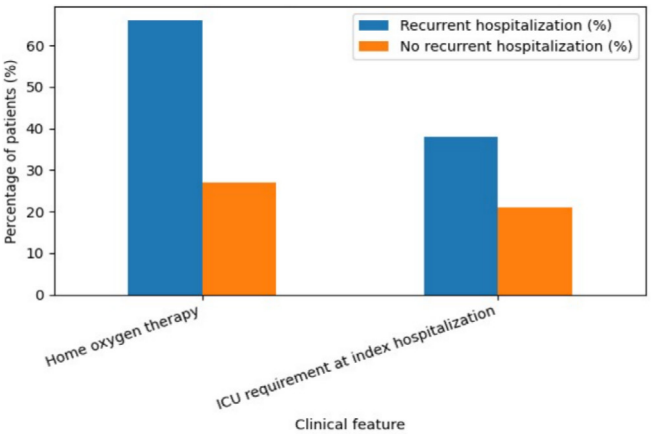

Figure 2. Clinical features significantly associated with recurrent hospitalization
ICU: Intensive care unit

When the units of admission during the index hospitalisation were evaluated, 33 patients were admitted to the ICU, whereas 84 patients were managed in the general ward without requiring intensive care. The need for ICU admission at the initial hospitalisation was observed in 19 patients (38.0%) in the recurrent hospitalisation group and in 14 patients (20.9%) in the non-recurrent group. This difference between the groups was statistically significant (p=0.042) (Table 2, Figure 2).

The presence of pneumonia was identified in 31 patients (62.0%) in the recurrent group and in 46 patients (68.7%) in the non-recurrent group, with no statistically significant difference between the groups (p=0.453) (Table 2). Among the 33 patients who required ICU admission at the index hospitalisation, 15 (45.5%) were readmitted to the ICU within one year.

Regarding the length of stay at the initial admission, the mean duration was 10.54±6.4 days in patients with recurrent hospitalisation and 9.52±6.17 days in those without recurrent admission. No statistically significant difference was found between the groups in terms of length of stay (p=0.358) (Table 2).

In the evaluation of laboratory parameters, patients with recurrent hospitalisation demonstrated a more pronounced acid-base disturbance and ventilatory burden. In this group, pCO_2 levels were significantly higher compared with patients without recurrent admission (52.81±15.32 mmHg vs. 47.14±15.67 mmHg; p=0.011), and correspondingly, arterial pH values were significantly lower (7.37±0.06 vs. 7.38±0.08; p=0.025). Additionally, patients in the recurrent hospitalisation group exhibited higher potassium levels (4.62±0.55 mmol/L vs. 4.38±0.57 mmol/L; p=0.010) and lower haemoglobin levels (14.61±2.22 g/dl vs. 13.32±2.37 g/dl; p=0.003) (Table 3). HCO_3^- levels tended to be higher in the recurrent hospitalisation group, demonstrating borderline statistical significance (p=0.051).

Table 3. Parameters demonstrating statistically significant differences between groups

Parameter	Recurrent hospitalization	No recurrent hospitalization (n=67)	p-value
Potassium (K)	4.62±0.55	4.38±0.57	0.010
pH	7.37±0.06	7.38±0.08	0.025
pCO_2 (mmHg)	52.81±15.32	47.14±15.67	0.011
Hemoglobin (g/dl)	14.61±2.22	13.32±2.37	0.003
Procalcitonin (ng/ml)*	48.54 (0.01-24.94)	66.81(0.01-99.25)	0.004
CRP (mg/L)*	50.29 (0.38-299.00)	65.50 (0.57-239.00)	0.016
Troponin (ng/L)*	50.00 (3.70-516.00)	64.94 (4.10-1324.00)	0.018

CRP: C-reactive protein, pCO2: Partial pressure of carbondioxide, * As the data were not normally distributed, the Mann-Whitney U test was used. Data are presented as mean rank (minimum-maximum)

Conversely, procalcitonin, CRP, and troponin levels were significantly higher in the non-recurrent hospitalisation group. As the variables were not normally distributed, the Mann-Whitney U test was used for comparisons and the mean ranks were 66.81 versus 48.54 for procalcitonin (p=0.004), 65.50 versus 50.29 for CRP (p=0.016), and 64.94 versus 50.00 for troponin (p=0.018), respectively. These findings suggest a more pronounced acute inflammatory and cardiac stress response among patients who did not subsequently develop recurrent admissions (Table 3). No statistically significant differences were observed between the groups with respect to the remaining biochemical and haematological parameters (all p>0.05).

In the comparison of inflammatory indices, CAR and SII values were found to be significantly higher in the non-recurrent hospitalisation group (Table 4). CAR and SII were significantly higher in patients without recurrent hospitalization than in those with recurrent hospitalization (CAR mean rank: 64.99 vs. 50.97, p=0.027; SII mean rank: 64.63 vs. 51.46, p=0.038). In contrast, the CALLY index was significantly higher in the recurrent hospitalisation group compared with the non-recurrent group (mean rank: 68.50 vs. 51.91; p=0.009) (Table 4). No statistically significant differences were observed between the groups with respect to NLR and PLR (p=0.074 and p = 0.101, respectively) (Table 4).

Table 4. Comparison of inflammatory indices between groups

Index	Recurrent hospitalization (n=50)	No recurrent hospitalization (n=67)	p-value
NLR	52.55 (1.3-82.5)	63.81 (1.4-153.2)	0.074
PLR	53.04 (65-1175)	63.45 (36-2360)	0.101
CAR	50.97 (0.09-78.68)	64.99 (0.14-71.67)	0.027
SII	51.46 (310-19388)	64.63 (293-41202)	0.038
CALLY	68.50 (0.01-13.80)	51.91 (0.01-9.12)	0.008

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CAR: C-reactive protein-to-albumin ratio, SII: Systemic Immune-inflammation Index, CALLY: C-reactive protein-albumin-lymphocyte index, As the data were not normally distributed, the Mann-Whitney U test was used. Data are presented as mean rank (minimum-maximum)

ROC curve analysis was performed to evaluate the discriminatory performance of laboratory parameters and inflammatory indices for recurrent hospitalization. The AUC values were 0.642 for potassium, 0.372 for pH, 0.633 for pCO_2, 0.644 for hemoglobin, 0.346 for procalcitonin, 0.372 for CRP, 0.371 for troponin, 0.383 for CAR, 0.387 for SII, and 0.640 for CALLY index. None of the evaluated parameters demonstrated strong discriminatory performance.

Binary logistic regression analysis was performed to identify independent predictors of recurrent hospitalization (Omnibus test: χ^2=46,981, p<0.001, Cox & Snell R^2=0.333; Nagelkerke R^2=0.447, Hosmer-Lemeshow test p=0.072 and accuracy 80,2%). Among the variables included in the model, only sex and LTOT use were identified as independent predictors of recurrent hospitalization. Male sex was associated with a significantly increased risk of recurrent hospitalization (OR: 4.38, 95% CI: 1.50-12.82, p=0.007), while LTOT use was also independently associated with higher risk (OR: 5.47, 95% CI: 1.86-16.06, p=0.002). Other variables, including potassium, pH, pCO_2, hemoglobin, procalcitonin, CRP, troponin, CAR, SII, and CALLY index, were not found to be independently associated with recurrent hospitalization (p>0.05 for all).

DISCUSSION

The present study demonstrated that recurrent hospitalisation within one year after acute exacerbation of COPD was frequent and was observed in 42.7% of the cohort. Recurrent hospitalisation was more common among male patients and was significantly associated with LTOT use at home and ICU requirement at the index admission, suggesting that baseline disease severity and respiratory reserve play a central role in readmission risk. In addition, patients with recurrent hospitalisation had lower pH and higher pCO_2 and HCO_3^- levels, indicating a greater chronic ventilatory burden. Although NLR and PLR did not differ significantly between groups, CAR, SII, and CALLY showed significant differences, suggesting that composite inflammatory and nutritional indices may provide additional insight beyond simple cellular ratios. In addition, ROC curve analysis demonstrated that none of the evaluated laboratory parameters or inflammatory indices showed strong discriminatory performance for predicting recurrent hospitalization. Consistently, multivariate logistic regression analysis identified only male

sex and LTOT use as independent predictors, while other laboratory and inflammatory markers were not independently associated with readmission. These findings suggest that recurrent hospitalization risk in COPD is more strongly driven by clinical indicators of disease severity rather than by individual laboratory parameters.

Numerous epidemiological studies have reported that COPD-related hospitalisations predominantly occur in individuals over 65 years of age and are more common in men. However, it has also been noted that the sex gap has gradually narrowed in recent years, partly due to increasing smoking prevalence among women and the impact of environmental exposures.[11] In this context, the higher proportion of male patients observed in the recurrent hospitalisation group in our study is consistent with the existing literature. Greater cumulative tobacco exposure, occupational risk factors, and diagnosis at more advanced stages of disease in men have been suggested as potential contributors to an increased risk of readmission.[3,10,11]

In our cohort, the readmission rate exceeded 40% within the first year, and patients who were readmitted experienced a mean of 2.44 recurrent hospitalisations per year. These findings indicate that recurrent hospitalisation remains a clinically important problem following severe COPD exacerbation. Numerous studies have reported that readmission rates following COPD exacerbations are particularly high within the first year. In the RACE study, both short- and intermediate-term readmission rates after a severe exacerbation were shown to be notably elevated.[1] Similarly, Chen et al.[2] demonstrated a significantly increased risk of rehospitalisation among patients with a history of exacerbation within the preceding year. Furthermore, systematic reviews and meta-analyses have indicated that readmission rates in COPD may range between 30% and 50%, varying according to patient characteristics, healthcare systems, and duration of follow-up.[4,10,12]

Conversely, some studies have reported lower readmission rates, particularly in centres where structured discharge planning, early follow-up programmes, and integrated care models have been implemented.[13] These discrepancies may be explained by heterogeneity in patient selection, comorbidity burden, access to healthcare services, and follow-up strategies. Accordingly, the relatively high rates of recurrent hospitalisation and intensive care requirement observed in our cohort support the notion that the burden following COPD exacerbation remains substantial in real-world settings, underscoring the need for more effective risk stratification and follow-up strategies in this patient population.

The relationship between COPD and comorbidities is complex. Several systematic reviews and cohort studies have demonstrated that cardiovascular and metabolic comorbidities-such as heart failure, coronary artery disease, and diabetes mellitus-may increase the risk of recurrent hospitalization.[3,4,10] In contrast, the finding in our study that the presence of a prior CVD was associated with a lower risk of readmission is relatively uncommon in the literature. Some reports suggest that patients with a history of CVD are often subject to closer clinical surveillance and are more frequently enrolled in multidisciplinary care programmes, which may contribute to reduced readmission rates.[13] However, the literature remains inconsistent, with some studies reporting increased risk related to neurological comorbidities,[12] whereas others found no independent association between prior CVD and recurrent admission.[14] The lower rate of recurrent hospitalisation observed among patients with prior CVD in our cohort may plausibly be related to closer follow-up and more structured integrated care; however, confirmation of this association requires larger cohorts and prospective study designs.

In the present study, the significantly higher likelihood of recurrent hospitalisation among patients receiving LTOT at home is consistent with findings reported in the literature. In the systematic review by Chow et al.,[3] LTOT use was identified as being associated with an increased risk of readmission, a relationship largely attributed to more advanced disease stages and more severe clinical phenotypes. Similarly, large-scale cohort studies have reported higher rates of exacerbation and rehospitalisation among patients using LTOT; however, these studies emphasised that the observed association likely reflects underlying disease severity and comorbidity burden rather than a direct effect of the therapy itself.[15,16]

On the other hand, some studies have demonstrated that LTOT, when implemented in appropriately selected patients and combined with structured post-discharge follow-up programmes, may contribute to a reduction in readmission rates. In particular, LTOT integrated with planned discharge support and close outpatient monitoring has been reported to exert a protective effect.[12,13] In this context, the association observed in our study between LTOT use and recurrent hospitalisation should be interpreted not as a direct adverse effect of oxygen therapy itself, but rather as a marker of advanced disease stage and greater clinical severity.

The higher rate of ICU requirement at index admission among patients who subsequently developed recurrent hospitalisation suggests that the risk of readmission may be closely related to the initial clinical severity of the exacerbation. Severe COPD exacerbations requiring ICU monitoring have been emphasised as markers of a more fragile post-discharge phenotype and have been consistently reported among major predictors of readmission risk.[10,17] Meta-analyses have also identified ICU requirement as a surrogate marker of severe disease and adverse follow-up outcomes.[12] In the meta-analysis by Njoku et al.,[10] patients requiring ICU support or mechanical ventilation during index admission were categorised as the highest-risk group for both 30-day and 1-year recurrent ICU need after discharge. Another study estimated that approximately one in every five to six COPD patients admitted to the ICU would require ICU readmission within one year.[18]

In contrast, the absence of a significant association between pneumonia and recurrent hospitalisation in our cohort is consistent with literature indicating that pneumonia is more strongly linked to acute-phase mortality and short-term clinical deterioration rather than serving as a consistent predictor of long-term readmission risk.[19]

Likewise, the similar length of stay observed between groups suggests that hospitalisation duration alone may have limited predictive value for recurrent admission. A large U.S. cohort study reported an association between longer individual hospital stays and 30-day readmission; however, this was interpreted as reflecting disease severity and comorbidity burden rather than a direct causal relationship. At the institutional level, mean length of stay was not significantly associated with readmission rates, and the weak relationship

observed appeared to be shaped primarily by post-discharge care processes and patient characteristics.[20] A separate systematic review and meta-analysis similarly identified length of stay as a potential source of heterogeneity but not as a consistently independent risk factor across studies.[12]

Evaluation of laboratory findings in our study suggests that recurrent hospitalisation may be more strongly associated with chronic physiological burden and impaired respiratory reserve rather than the magnitude of the acute inflammatory response. Higher pCO_2 and lower pH values in the recurrent group are consistent with previous reports linking hypercapnia and gas exchange impairment to adverse outcomes and increased readmission risk after severe COPD exacerbation.[3,8,12,18] A large national guideline-based study conducted in Turkiye likewise identified hypercapnia and severe hypoxaemia as important predictors of readmission after exacerbation.[21] Furthermore, studies assessing the predictive value of haematological parameters have emphasised that isolated laboratory values generally demonstrate limited discriminatory capacity and should instead be interpreted as markers of underlying chronic disease burden.[22]

Conversely, the higher CRP and procalcitonin levels observed in the non-recurrent group may indicate a more prominent acute infectious trigger during the index event in these patients. The literature suggests that elevated CRP and procalcitonin levels during acute exacerbation are associated with short-term clinical deterioration; however, their ability to predict long-term readmission risk remains inconsistent.[6,23,24] Contemporary clinical guidelines similarly recommend the use of these biomarkers primarily for guiding acute management decisions rather than for long-term risk stratification.[21]

Taken together, these findings suggest that raw laboratory parameters may not directly determine readmission risk but rather reflect the biological distinction between acute inflammatory activation and chronic respiratory burden. Rehospitalisation dynamics appear to be shaped within a multidimensional clinical framework, consistent with systematic reviews emphasising that laboratory markers should be interpreted within appropriate clinical context.[12]

Additionally, elevations in troponin levels during acute COPD exacerbations have been associated with cardiac stress and systemic burden, correlating with adverse short-term outcomes.[25] In our study, the observation that CAR and SII were higher in the non-recurrent group may indicate that acute inflammatory and cardiovascular stress was more pronounced at the index admission in these patients, whereas those who later developed recurrent hospitalisations may have exhibited a lower-grade but more persistent biological burden. Evidence regarding troponin remains heterogeneous; notably, a UK cohort study reported that elevated troponin levels during acute exacerbation were associated with both major adverse cardiac events and a higher 90-day risk of COPD readmission.[25]

Regarding inflammatory indices, NLR and PLR did not differ significantly between groups, whereas CAR, SII, and CALLY demonstrated statistically meaningful differences. These findings suggest that composite indices reflecting inflammation, immune response, and nutritional status may provide greater discriminatory value for recurrent hospitalisation risk than simple cellular ratios alone.

Although NLR and PLR have been linked to exacerbation severity, mortality, and short-term outcomes in previous studies, their predictive value for 6-12 month readmission remains inconsistent.[6,7] In the meta-analysis by Ruan et al.,[12] the impact of inflammatory markers on readmission was described as heterogeneous, with simple ratios such as NLR and PLR showing limited predictive utility for long-term rehospitalisation. Similarly, the systematic review by Njoku et al.[10] reported that these ratios were not consistently validated as independent predictors of readmission across studies. These findings support the absence of significant differences in NLR and PLR in our cohort.

In contrast, the significant differences observed in CAR, SII, and CALLY indices suggest that recurrent hospitalisation risk may be linked to more integrated biological processes. CAR, which simultaneously reflects systemic inflammation and nutritional status, has been associated with adverse clinical outcomes in several chronic diseases, including COPD. In a meta-analysis involving Asian populations, Lin et al.[4] reported stronger associations between CRP-based composite indices and both readmission and mortality. Similarly, Alqahtani et al.[17] noted that evaluating systemic inflammation alongside negative acute-phase reactants such as albumin provides more meaningful prognostic information than CRP or leukocyte count alone.

SII and CALLY, incorporating multiple parameters such as neutrophils, lymphocytes, platelets, CRP, and albumin, represent more comprehensive indices that have only recently been introduced into COPD research. In a 12-month readmission study, Zhang et al.[8] demonstrated that such multi-component inflammatory indices outperformed conventional haematological ratios in predicting rehospitalisation. Although some reports suggest that these indices may primarily reflect acute-phase prognosis and have limited long-term predictive value, our findings indicate that they may be particularly useful in identifying high-risk patient profiles.[3,10]

Limitations

The single-center and retrospective design of this study limits the generalizability of the findings. Inflammatory markers were measured at only a single time point, precluding the assessment of temporal dynamic changes and their relationship with disease progression. Therefore, multicenter, prospective studies with long-term follow-up are required to validate these findings. Socioeconomic factors (such as income level, educational status, social support, and treatment adherence) were not systematically recorded and thus could not be incorporated into the analyses. Finally, although the sample size was sufficient for the primary analyses, it may have limited the statistical power to detect smaller effect sizes, particularly for secondary endpoints and subgroup analyses. Despite these limitations, the study provides clinically meaningful insights into the association between inflammatory and cardiac biomarkers and recurrent hospitalizations, and may serve as a foundation for future prospective, multicenter investigations.

CONCLUSION

Readmission following acute exacerbation of COPD is a common and clinically significant outcome, affecting nearly half of patients within the first year. In this study, readmissions in patients admitted for acute exacerbation of COPD were more closely associated with disease severity, multidimensional

inflammatory processes, and chronic physiological burden, independent of age and several conventional clinical parameters. The predominance of male sex among patients with recurrent admissions, the higher frequency of ICU requirement during the index hospitalization, and the greater use of home oxygen therapy suggest that this patient group represents a more vulnerable clinical phenotype in the post-discharge period.

Laboratory findings further indicate that chronic ventilatory impairment, reflected by hypercapnia and acid-base imbalance, may be more closely associated with recurrent hospitalisation than markers of acute inflammatory response. In contrast, composite inflammatory indices -particularly CAR, SII, and CALLY- demonstrated greater discriminatory value compared with simpler ratios such as NLR and PLR, highlighting the importance of integrating inflammation, immune response, and nutritional status into risk assessment.

In light of these findings, incorporating multidimensional inflammatory indices and clinical markers of disease severity into routine clinical assessment may facilitate early identification of patients at high risk for recurrent hospitalization in COPD. Early recognition of this high-risk subgroup may enable closer post-discharge monitoring and targeted care strategies, thereby potentially reducing the overall hospital burden. Further large-scale, prospective studies are warranted to validate these findings and to establish their clinical applicability.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Bozok University Ethics Committee for Non-interventional Clinical Researches (Date: 05.11.2025, Decision No: 2025-GOKAEK-2519_05.11.2025_684).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: İA; Design: İG; Control: İA, İG; Data Collection and/or Processing: İA; Analysis and/or Interpretation: İG; Literature Review: Article Writing: İG, İA; Critical Review: İG, İA.

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Original Article

Prevalence of *demodex* spp. in patients with chronic blepharitis and rosacea in a state Hospital in Kırıkkale

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ABSTRACT

Aims: *Demodex* spp. are ectoparasites that are believed to play a role in the pathogenesis of various dermatological and ocular diseases. This study aimed to determine the prevalence of *Demodex* spp. in patients with chronic blepharitis and rosacea and to contribute to the existing epidemiological data.

Methods: This study was conducted between December 2019 and December 2025 and included 40 patients with chronic blepharitis, 40 patients with rosacea, and 40 healthy controls. Eyelash samples were collected from patients with blepharitis, whereas skin samples from the cheek and forehead were obtained from patients with rosacea. All samples were examined under light microscopy using 10× and 40× objectives.

Results: *Demodex* spp. were detected in 47.5% of patients with blepharitis and 62.5% of patients with rosacea. The overall positivity rate was 55% (44/80) in the patient group and 12.5% (5/40) in the control group, representing a statistically significant difference ($p<0.001$). Fisher's exact test also confirmed this significant association ($p<0.001$). Patients with blepharitis and rosacea had significantly higher odds of *Demodex* positivity compared with controls (OR=8.56, 95% CI: 3.04-24.09). *Demodex* positivity appeared to be more common in older age groups. In patients with blepharitis, positivity was more frequent in males.

Conclusion: *Demodex* spp. positivity was significantly higher in patients with chronic blepharitis and rosacea than in healthy controls. These findings suggest that *Demodex* spp. may contribute to the pathogenesis of inflammatory ocular and dermatological diseases.

Keywords: Blepharitis, rosacea, *Demodex* spp., age, gender

INTRODUCTION

Demodex mites are common ectoparasites found on human skin. Two species have been identified in humans: *Demodex* folliculorum (*D. folliculorum*) and *Demodex brevis (D. brevis)*. While *D. folliculorum* primarily inhabits hair follicles, *D. brevis* resides in deeper sebaceous and meibomian glands.[1]

Although *Demodex* mites may be present in healthy individuals, increased mite density has been associated with several dermatological conditions, including acne vulgaris, perioral dermatitis, pustular folliculitis, pityriasis folliculorum, papulopustular rosacea, granulomatous rosacea, and chronic blepharitis.[2,3]

Chronic blepharitis is a recurrent inflammatory disorder affecting the eyelid margins and is frequently encountered in ophthalmology practice. Common symptoms include redness, burning, itching, crusting, and debris accumulation at the base of the eyelashes.[4] The etiology of blepharitis is multifactorial and may involve bacterial infections, meibomian gland dysfunction, dermatological diseases, and parasitic infestations.[5]

Rosacea is a chronic inflammatory skin disease that predominantly affects the central facial region and may also involve the eyes. Ocular rosacea may present with blepharitis, conjunctivitis, and keratitis and is considered an important cause of ocular surface disease.[6,7]

Demodex mites are generally present in low densities on healthy skin; however, under favorable conditions, they may proliferate and trigger inflammatory responses.[8] Therefore, investigating the relationship between *Demodex* spp., blepharitis, and rosacea may contribute to improved diagnostic and therapeutic approaches.

The aim of this study was to determine the prevalence of *Demodex* spp. in patients diagnosed with chronic blepharitis and rosacea in a state hospital in Kırıkkale and to compare the findings with those of healthy controls.

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METHODS

Ethics

This study was conducted with the approval of the Clinical Researches Ethics Committee of Kırıkale University (Date: 19.02.2019, Decision No: 02/04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants prior to their inclusion in the study.

This study included 40 patients with blepharitis (17 females, 23 males), 40 patients with rosacea (35 females, 5 males), and 40 healthy controls (17 females, 23 males).

Chronic blepharitis was diagnosed based on ophthalmologic examination findings, including eyelid margin erythema, crusting, irritation, itching, and chronic inflammatory changes of the eyelid margin. Rosacea was diagnosed by dermatological evaluation according to characteristic clinical findings such as persistent facial erythema, papules, pustules, and telangiectasia.

Patients with active systemic inflammatory diseases, immunosuppressive conditions, or concomitant dermatological or ocular infections were excluded from the study. In addition, patients with a known history of recent antiparasitic treatment were excluded when such information was available in the medical records.

Eyelash samples were collected from patients with blepharitis under biomicroscopic examination. At least two eyelashes from both the upper and lower eyelids were removed and examined under light microscopy at 40× and 100× magnification.[9]

For patients with rosacea, samples were obtained from the cheek and forehead using the standardized skin surface biopsy (SSSB) technique with cyanoacrylate adhesive. Samples were examined under 400× and 1000× magnification, and a density of ≥5 mites/cm² was considered positive.[10]

Samples from the control group were collected using the same procedures. Eyelash samples were obtained from control subjects assigned to the eyelash examination subgroup, whereas skin samples were collected from individuals in the skin sampling subgroup using the SSSB technique. The control group consisted of healthy individuals aged 18-65 years without clinical findings of blepharitis or rosacea.

Statistical Analysis

The data were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using Pearson's Chi-square test and Fisher's exact test when appropriate. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated to evaluate the association between *Demodex* positivity and the study groups. A p value of <0.05 was considered statistically significant.

RESULTS

Among the 40 patients diagnosed with chronic blepharitis, *Demodex* spp. was detected in 47.5% (n=19). Of these patients, 63% (n=12) were male and 37% (n=7) were female, with a mean age of 61.4 years. *Demodex* positivity was highest among male patients aged 56-70 years (**Table 1**). No parasites were detected in patients aged 18-29 or 30-40 years.(**Figure**)

Table 1. Distribution of *Demodex* spp. positivity by age group and gender (%) in patients with blepharitis

Age-group	Female n (%)	Male n (%)
18-29	0 (0)	0 (0)
30-40	0 (0)	0 (0)
41-55	1 (14.2)	3 (25)
56-70	3 (42.8)	5 (41.6)
≥70	3 (42.8)	4(33.3)
Total	7 (100)	12(100)

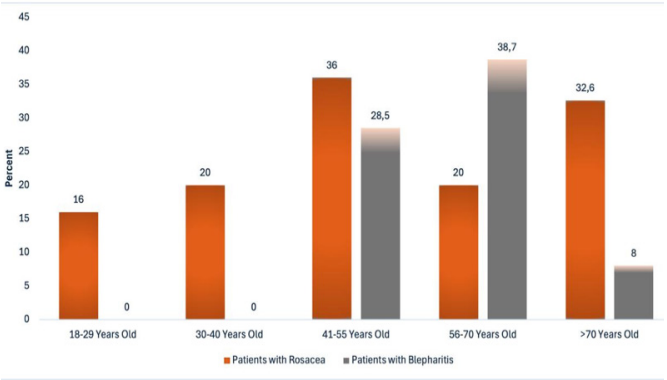

Figure. Percentage dstrbuton by age groups of patents wth blepharts and rosacea n whom *Demodex* spp were detected

Among the 40 patients with rosacea, the mean age was 47.0 years, and 62.5% (n=25) tested positive for *Demodex* spp. The highest positivity rate (36%) was observed in female patients aged 41-55 years (**Table 2**). Additionally, four patients with rosacea and positive *Demodex* findings also had concurrent blepharitis.

Table 2. Distribution of *Demodex* spp. positivity by age group and gender (%) in patients with rozacea

Age grouup	Female n (%)	Male n (%)
18-29	2 (9)	1(33.3)
30-40	6 (27.2)	0 (0)
41-55	9 (41)	0 (0)
56-70	4(18.1)	1 (33.3)
≥70	1 (4.5)	1 (33.3)
Total	22 (100)	3 (100)

In the control group, *Demodex* positivity was detected in 12.5% (n=5). Among the 20 skin-sample controls, 11 were female and 9 were male; *Demodex* positivity was detected in one female and two male patients. In the eyelash-sample control subgroup, there were 6 female and 14 male patients, and one female and one male patient tested positive.

A statistically significant difference was found between the patient group (44/80; 55%) and the control group (5/40; 12.5%) (χ^2=19.93; p<0.001). Fisher's exact test also confirmed this significant association (two-tailed p<0.001). The odds of Demodex positivity were significantly higher in patients with blepharitis and rosacea compared with controls (OR=8.56, 95% CI: 3.04-24.09).

These findings indicate that *Demodex* infestation is significantly more prevalent in patients with blepharitis and rosacea than in healthy individuals and may be associated with these inflammatory conditions.

DISCUSSION

Blepharitis is a chronic inflammatory condition of the eyelid margins characterized by itching, burning, redness, and scaling. Its etiology is multifactorial and includes bacterial infections, viral agents, *Demodex* infestation, meibomian gland dysfunction, and inflammatory skin diseases.[11-13]

Chronic blepharitis and rosacea are common inflammatory disorders in which *Demodex* spp. have increasingly been investigated as potential contributing factors. In the present study, *Demodex* positivity was significantly higher in patients with chronic blepharitis and rosacea compared with healthy controls. In addition, Demodex prevalence increased with age in both patient groups.

Previous studies conducted in different countries have reported *Demodex* positivity rates ranging from 42% to 90% in patients with blepharitis and rosacea.[14,15,20-22] Studies from Turkiye have similarly demonstrated a higher prevalence of *Demodex* in symptomatic patients compared with healthy individuals.[9,16-19] Our findings are generally consistent with the literature and support a possible association between Demodex infestation and inflammatory ocular and dermatological disorders.

In patients with blepharitis, *Demodex* positivity was more frequent in males, whereas rosacea-associated positivity was more common in females. The increased prevalence observed in older age groups may be associated with age-related alterations in immune response, sebaceous gland activity, and skin barrier function. However, the relationship between *Demodex* infestation, age, and gender remains multifactorial and may also be influenced by environmental and individual factors.

Increased dermal vascularity, altered immune response, and follicular inflammation in rosacea may facilitate *Demodex* proliferation. Similarly, in chronic blepharitis, mites may contribute to inflammation through mechanical obstruction of follicles and increased bacterial colonization. Nevertheless, because of the cross-sectional design of this study, a causal relationship cannot be established.

From a clinical perspective, evaluation for Demodex spp. may be useful in selected patients with persistent symptoms or treatment-resistant blepharitis and rosacea. Identification of *Demodex* infestation may help guide targeted antiparasitic treatment approaches in appropriate clinical settings.

Limitations

This study has several limitations. First, the sample size was relatively small and the study was conducted at a single center, limiting generalizability. Second, the cross-sectional design does not allow causal interpretation. Third, species-level differentiation between *Demodex folliculorum* and *Demodex brevis* was not performed. Finally, limited statistical adjustment for potential confounding factors may have affected the findings.

CONCLUSION

As a result, *Demodex* spp. positivity was significantly higher in patients with chronic blepharitis and rosacea compared with healthy controls. These findings suggest a possible association between *Demodex* infestation and inflammatory ocular and dermatological disorders. Larger prospective studies are needed to clarify the clinical significance of *Demodex* spp. and their role in disease progression.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Clinical Researches Ethics Committee of Kırıkale University (Date: 19.02.2019, Decision No: 02/04).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: ANV, ZEG, EY, YÇ; Design: ZEG, ANV, EY, YT; Control: ZEG, ANV; Data Collection and/or Processing: ANV, EY, YT; Analysis and/or Interpretation: ZEG, ANV; Literature Review: EY, YT, ZEG, ANV; Article Writing: ZEG, ANV, EY, YT; Critical Review: All Authors.

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Review

The relationship between inflammatory parameters and disease severity in patients with active ulcerative colitis

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ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by relapsing and remitting mucosal inflammation with variable clinical severity. Accurate evaluation of disease activity is essential for treatment optimization, monitoring therapeutic response, and preventing long-term complications. Although endoscopic assessment remains the gold standard for determining mucosal inflammation, its invasive nature and limited practicality for repeated evaluation have increased interest in noninvasive inflammatory biomarkers. Recent evidence has demonstrated that several hematological and biochemical inflammatory parameters may reflect both clinical and endoscopic disease activity in UC. Acute phase reactants such as C-reactive protein (CRP) and serum albumin, along with inflammatory indices derived from the complete blood count-including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), Systemic Immune-inflammation Index (SII), and Aggregate Index of Systemic Inflammation (AISI), have shown potential utility in predicting inflammatory burden and disease severity. In addition, fecal calprotectin (FCP) has emerged as one of the most valuable noninvasive biomarkers because of its strong association with mucosal inflammation and endoscopic disease activity. The Montreal classification system also provides a standardized framework for assessing disease extent and clinical severity in UC. Growing evidence suggests that extensive colitis and severe disease activity are associated with elevated levels of inflammatory biomarkers and lower serum albumin concentrations. This review summarizes the current literature regarding the relationship between inflammatory biomarkers and disease severity in active UC and discusses the clinical utility, advantages, and limitations of these parameters in evaluating inflammatory activity and predicting endoscopic disease severity.

Keywords: Ulcerative colitis, inflammatory biomarkers, C-reactive protein, albumin, fecal calprotectin, endoscopic activity

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory intestinal disease characterized by persistent inflammation of the colonic mucosa and progressing through periods of flare-ups and remissions throughout its clinical course.

The disease typically begins in the rectum and progresses proximally, and its clinical manifestations can range from limited mucosal involvement to severe fulminant colitis.[1,3] In the current approach to UC treatment, the goal is not limited to merely controlling clinical symptoms but also includes achieving mucosal healing, reducing disease-related complications, and sustainably preserving patients' quality of life.[4] In this regard, the reliable assessment of disease activity is of great importance for effective treatment planning and the management of the clinical follow-up process.

Although endoscopic examination is still considered the gold standard for assessing mucosal inflammation, its invasive nature, high cost, and potential negative impact on patient comfort, impose limitations on routine follow-up.[5,7] For this reason, in recent years, research and clinical interest in noninvasive inflammatory biomarkers that can be used to assess disease activity have increased significantly.

THE PATHOPHYSIOLOGY OF INFLAMMATION IN ULCERATIVE COLITIS

In the pathogenesis of ulcerative colitis, it is believed that genetic predisposition, changes in the gut microbiota, and dysregulation of immune response mechanisms act in concert.[8-12] In particular, an increase in the proinflammatory cytokine response and the massive migration of neutrophils into the intestinal mucosa are recognized as primary pathophysiological mechanisms in the development of inflammatory tissue damage. The systemic inflammatory response causes significant changes in various hematological and biochemical markers; these parameters can be used as auxiliary biomarkers.[10,11]

GENERAL CHARACTERISTICS OF INFLAMMATORY BIOMARKERS

Inflammatory biomarkers are defined as measurable laboratory parameters that provide information regarding

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the presence, severity, and systemic manifestations of inflammation. In inflammatory bowel diseases, these markers serve as important clinical tools for assessing disease activity, monitoring treatment response, and predicting potential relapses.[5]

The main advantages of these biomarkers are that they are non-invasive, easily accessible in routine clinical practice, and can be repeatedly measured. However, because they can be influenced by infections, malignancies, and other concomitant systemic inflammatory processes, they may have limited diagnostic accuracy in indicating disease activity when evaluated alone.[5,23]

ACUTE-PHASE REACTANTS AND ALBUMIN

Among the most commonly used systemic inflammation markers in patients with UC are C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). CRP is an acute-phase reactant synthesized in hepatocytes in response to proinflammatory cytokines, particularly interleukin-6, and exhibits a rapid increase in serum levels during active inflammatory processes.[5,23]

Serum albumin is considered a negative acute-phase reactant; during active inflammation, serum levels may decrease due to increased vascular permeability, intestinal protein loss, and changes in hepatic protein synthesis.[22] Additionally, low albumin concentrations have been reported in various studies to be associated with severe disease activity, inadequate response to biologic therapy, and increased risk of colectomy.[28-31]

Recent studies have demonstrated that the C-reactive protein-to-albumin ratio (CAO) may more effectively reflect systemic inflammatory burden and show a significant association with disease activity.[14,25]

INFLAMMATORY INDICES DERIVED FROM COMPLETE BLOOD COUNTS

Inflammatory indices derived from complete blood counts are among the biomarkers that have garnered increasing attention in recent years for assessing UC activity.

The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), Systemic Immune-inflammation Index (SII), and aggregate index of systemic inflammation (AISI) are among the most frequently evaluated inflammatory parameters in this context.[15-21]

Neutrophils are among the primary cellular components of the active inflammatory response and play a significant role in the development of mucosal tissue damage. In contrast, a relative decrease in lymphocyte count may be interpreted as an indicator of systemic stress and the inflammatory response. Therefore, it has been reported that an increase in the NLR may be associated with disease activity in patients with UC.[15,16] Since platelet activation also plays a significant role in the inflammatory process, it has been reported PLR values increase during active disease periods.[16,17] Additionally, newer-generation inflammatory indices, such as the SII and AISI, are considered biomarkers that may reflect the systemic inflammatory burden more comprehensively.[17-21]

FECAL CALPROTECTIN AND ENDOSCOPIC ACTIVITY

Fecal calprotectin (FCP) is considered a noninvasive biomarker that reflects neutrophilic inflammation in the intestinal mucosa. Particularly in patients with ulcerative colitis, it is widely used in clinical practice to monitor disease activity.[13] In a study by Liu et al.,[24] it was reported that FCP levels possess high sensitivity in detecting active inflammation and can be considered one of the reliable biomarkers for predicting endoscopic disease activity. Additionally, it was demonstrated that FCP levels increase significantly as the severity of mucosal inflammation increases; therefore, it was emphasized that this marker could provide significant clinical contributions in evaluating treatment response and monitoring mucosal healing.[13,24]

However, the use of FCP also has some important limitations. FCP levels may also increase in various clinical conditions such as infectious enterocolitis,the use of nonsteroidal anti-inflammatory drugs, and gastrointestinal malignancies, which may reduce its diagnostic value.[24] Furthermore, differences in measurement methods and a lack of standardization are among the other important factors limiting its use in clinical practice.[13]

MONTREAL CLASSIFICATION AND CLINICAL ACTIVITY

The Montreal Classification was developed to standardize the clinical characteristics of inflammatory bowel diseases and is currently widely used, particularly in UC and Crohn's disease.[34] This classification system has become one of the most widely used classification systems in clinical practice.[34] This classification system was developed in accordance with the recommendations of an expert working group established at the 2005 Montreal World Gastroenterology Congress; it aims to provide a more objective assessment of disease extent, clinical activity, and disease prognosis.[34] Additionally, it offers significant clinical advantages by providing a common terminology in clinical research and to helping predict disease prognosis. According to the Montreal classification, the clinical classification for UC is not limited to the description of anatomical involvement but also encompasses the prediction of the disease's biological behavior, potential treatment needs, and the risk of long-term complications.[34] In this regard, the classification system is structured around two core components: disease extent and disease severity.

In the Montreal classification system, the extent of UC is divided into three primary anatomical patterns of involvement: ulcerative proctitis (E1), left-sided colitis (E2), and extensive colitis/pancolitis (E3). In the E1 subgroup, inflammation is limited to the rectum, and the clinical presentation frequently features rectal bleeding, mucus-containing stools, and tenesmus. In this patient group, the systemic inflammatory response typically has a milder course, and a significant elevation in inflammatory biomarkers may not always be detected.[34] Due to the limited anatomical distribution, it has been reported that response rates to topical treatments are higher and the long-term prognosis is generally better in most cases.

In the E2 subgroup, inflammation extends as far as the splenic flexure, and involvement of the rectum, sigmoid colon, and descending colon is observed. In this patient group, clinical

symptoms such as increased bowel movement frequency, hematochezia, abdominal pain, and fecal urgency may manifest more prominently. As the disease spreads, elevations may be observed in systemic inflammation markers such as CRP and erythrocyte sedimentation rate; concurrently, increases may also be detected in hematological inflammatory indices.[34] In the form of diffuse colitis or pancolitis classified as E3, inflammation extends as far as the proximal splenic flexure. The Montreal classification notes that this pattern of involvement is associated with a more severe disease course.[34] In cases of extensive colitis, severe diarrhea, weight loss, fever, anemia, and a pronounced systemic inflammatory response are observed more frequently. In addition, the need for hospitalization, the use of biologic agents, the need for colectomy, and the risk of developing colorectal cancer are also higher in this patient group. Studies have shown that inflammatory parameters such as CRP, erythrocyte sedimentation rate, NLR, PLR, and SII are significantly elevated in patients with extensive colitis. In contrast, serum albumin levels may decrease in parallel with the increase in inflammatory burden. The Montreal classification evaluates not only the anatomical spread of the disease but also the level of clinical activity. In this classification, clinical disease activity is defined in four distinct categories: remission (S0), mild activity (S1), moderate activity (S2), and severe disease (S3).[34] Patients in the clinical remission phase are generally asymptomatic, and inflammatory biomarkers are often within normal limits. In the presence of mild activity, the daily frequency of bowel movements is generally four or fewer, and no signs of systemic toxicity are observed. In moderate disease, there is an increase in bowel movement frequency, and mild signs of systemic inflammation may accompany this.

Severe UC is defined within the Montreal classification as daily bloody bowel movements of at least six times accompanied by signs of systemic toxicity.[34] In this patient group, signs of systemic inflammation such as tachycardia, fever, anemia are frequently observed; additionally, severe inflammatory activity is associated with increased CRP levels, a decrease in serum albumin concentration, and elevated hematological inflammatory indices.

In addition, the risk of developing serious complications such as toxic megacolon, intestinal perforation, and the need for emergency surgery also increases significantly.

The Montreal Classification Working Group has emphasized that the clinical behavioral characteristics of UC should also be evaluated over time.[34] It has been noted that clinical parameters such as the duration of remission, frequency of relapse, and a persistently active course are important determinants of prognosis. However, due to insufficient data, an independent behavior-based classification system has not been established. Nevertheless, it has been reported that, particularly in cases with a chronic active course, inflammatory biomarkers remain persistently elevated and the systemic inflammatory burden becomes more pronounced.

CONCLUSION

In patients with ulcerative colitis, inflammatory biomarkers provide important clinical data for assessing disease activity. It has been reported that CRP, serum albumin, fecal calprotectin, and inflammatory indices derived from complete blood counts exhibit significant changes according to disease activity.

However, none of the currently available biomarkers alone is sufficiently capable of accurately reflecting disease activity.

Therefore, inflammatory parameters must be interpreted holistically in conjunction with clinical findings, endoscopic evaluations, and histopathological examinations. It is increasingly recognized that easily accessible, noninvasive, and low-cost inflammatory indices are becoming important as clinical tools, particularly in predicting endoscopic activity.

ETHICAL DECLARATIONS

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Letter to the Editor

Bridging the gaps in multimorbidity care: reforming disease-specific guidelines in internal medicine

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Dear Editor,

The recent release of the 2026-2029 Polypharmacy Guidance by the Scottish Government underscores growing international recognition of medication-related harm and treatment burden in patients with complex chronic disease. Similarly, successive updates to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines continue to refine disease-specific targets while acknowledging the challenges of coexisting conditions. Yet despite these contemporary efforts, clinical practice guidance remains predominantly structured around single-disease frameworks. This ongoing reliance on siloed guideline architecture highlights a persistent gap between evolving policy attention to polypharmacy and the structural realities of multimorbidity in clinical care.

Multimorbidity-defined as the coexistence of two or more chronic conditions-has become the prevailing clinical reality in internal medicine. A recent systematic review in The Lancet Healthy Longevity confirmed the high global prevalence of multimorbidity and associated polypharmacy among adult and older populations.[1] Despite this epidemiologic shift, most clinical practice guidelines (CPGs) remain disease-specific. This structural mismatch between guideline architecture and patient complexity generates cumulative therapeutic burden, conflicting recommendations, and increased risk of adverse events.

Guideline development traditionally emphasizes internal validity derived from randomized controlled trials; however, patients with multimorbidity are frequently excluded from such studies, limiting external validity. A 2024 systematic review evaluating multimorbidity guidelines reported substantial methodological and reporting limitations, particularly inadequate incorporation of patient preferences and treatment burden assessment.[2] Furthermore, efforts to translate siloed disease-specific recommendations into integrated clinical decision-support systems highlight interoperability challenges. The CAREPATH study illustrates the structural difficulty of operationalizing fragmented guidelines within multimorbidity management platforms.[3] These limitations are therefore embedded not only in clinical reasoning but also in guideline design itself.

Clinical conflict is evident in the management of hypertension in patients with coexisting diabetes mellitus and chronic kidney disease. While angiotensin-converting enzyme inhibitors are recommended for nephroprotection and blood pressure control, layering glucose-lowering agents and additional renin-angiotensin-aldosterone system modifiers increases risks of hyperkalemia, acute kidney injury, and hemodynamic instability. Moreover, strict glycemic targets (e.g., lower HbA1c thresholds) and intensive blood pressure goals recommended within separate disease-specific guidelines may not account for frailty, limited life expectancy, or competing risks; when applied cumulatively, these targets can increase hypoglycemia, orthostatic hypotension, falls, and hospitalization-paradoxically elevating morbidity and mortality in multimorbid patients. The cumulative application of separate guidelines often necessitates complex medication regimens, intensive monitoring, and increased treatment burden-defined as the workload of healthcare imposed on patients and its impact on well-being.

Progress is further constrained by conceptual ambiguity in multimorbidity assessment. Systematic reviews demonstrate substantial heterogeneity in evaluation methods, including simple disease counts, severity-weighted indices, and drug-based metrics.[4,5] Without standardized operational definitions and assessment frameworks, risk stratification and harmonization of recommendations remain inconsistent. From a practical clinical standpoint, while simple disease counts offer ease of use, severity-weighted indices-particularly when integrated into electronic health systems-are better positioned to capture prognostic complexity and should form the basis of future standardization efforts in routine care.

To align guidelines with contemporary clinical realities, several reforms warrant consideration: development of multimorbidity-specific clinical pathways targeting common disease clusters; incorporation of treatment burden and polypharmacy risk metrics; emphasis on functional status and quality-of-life outcomes alongside disease-specific targets; and structural formatting of recommendations to facilitate digital interoperability across specialties. Existing frameworks such

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as the Beers Criteria and the STOPP/START criteria provide structured approaches to identifying potentially inappropriate prescribing, while the NICE Multimorbidity Guideline (NG56) emphasizes individualized care and deprescribing principles; however, these tools remain variably implemented and are not systematically embedded within most disease-specific guideline architectures. Importantly, these reforms do not replace disease-specific guidelines but contextualize them within patient-centered, complexity-informed frameworks.

Multimorbidity is no longer an exception but the norm in internal medicine practice. Persisting with siloed guideline architecture risks perpetuating polypharmacy, therapeutic conflict, and fragmented care. Future guideline updates should explicitly integrate multimorbidity frameworks to ensure that evidence-based medicine remains responsive to the realities of complex patients.

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