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Prognostic relationship between immature granulocyte ratio and ulcerative colitis activation

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Abstract

To aimed to determine the non-invasive predictive value for ulcerative colitis (UC) patients. This study aimed to investigate the relationship between colonic involvement, C-reactive protein (CRP) levels, and immature granulocyte (IG) proportions in patients with active UC. The study sought to establish the potential utility of immature granulocytes (IG) as a marker of disease activity. A retrospective study was conducted on UC patients followed between June 2022 and January 2023. Patients with active UC were included, and their demographic data, medical histories, biochemical findings, and outcomes were recorded. Exclusion criteria included patients under 18, those not followed up due to UC flares, those without confirmed UC, and those with incomplete data. The Mayo endoscopic score was used to assess disease severity. Statistical analysis was performed using SPSS version 27. A total of 121 patients were included, with 16 in remission. Patients were classified into Group 1 (Mayo score 1-2) and Group 2 (Mayo score 3). Significant differences were found in colonic involvement patterns between the groups. Group 1 had a higher percentage of IGs than Group 2. A receiver operating characteristic (ROC) analysis assessed the diagnostic accuracy of IG% and IG count. Both showed significant diagnostic value, with AUCs of 0.652 and 0.647, respectively. The study found that IG levels were not significantly associated with disease activity as measured by the Mayo score in UC patients. Ferritin levels were elevated in patients with severe disease. Further research is needed to explore the role of IGs and other biomarkers in UC management.

Keywords: Immature granulocyte, ulcerative colitis, inflammation

Introduction

The utility of immature granulocytes (IGs) as inflammatory markers in a range of medical conditions has been established, offering valuable insight into disease activity and severity. In rheumatoid arthritis (RA), there is a significant correlation between the IG count and percentage and disease activity indices such as DAS28, CDAI, and SDAI, as well as traditional inflammatory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [1,2]. This indicates that IGs could serve as rapid, inexpensive, and readily accessible markers for monitoring RA disease activity and potentially assist in diagnosis. Similarly, in acute pelvic inflammatory disease (PID), IG levels were significantly higher in severe cases compared to mild/moderate cases and controls, demonstrating their utility in assessing disease severity and the potential need for surgical intervention [3].

It is well established that inflammation is a key factor in the exacerbations of ulcerative colitis (UC), a form of inflammatory bowel disease (IBD). The occurrence of exacerbations in UC can be influenced by a number of factors, including environmental conditions and the presence of infections. Although seasonal variations have been demonstrated to be associated with UC flare-ups, the strength of this correlation is relatively modest, indicating that other factors may play a significant role in the inflammatory process in UC [4,5]. Infections caused by Edwardsiella tarda (which is a relatively

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obscure bacterium) may precipitate acute exacerbations of UC, underscoring the necessity of identifying and managing infectious agents to control inflammation. The pathogenesis of UC involves an amplified acute inflammatory response to bacterial stimuli, characterised by increased vascular responses and infiltration of neutrophils and CD4 lymphocytes, which are not primarily cytokine-driven. This exaggerated inflammation can be modulated by medications such as 5-aminosalicylic acids, which help normalise the inflammatory response [6]. Furthermore, psychological factors, diet, and medication adherence are being investigated for their potential roles in symptom flare-ups and inflammation, with ongoing studies aiming to identify specific risk factors [7].

The objective of our study is to evaluate the relationship between the pattern and extent of colonic involvement, CRP levels, and the proportion of immature granulocytes in the blood in patients with active UC. Furthermore, we aim to demonstrate the potential use of this ratio as a marker during disease activation.

Material and Methods

This study was conducted retrospectively on patients with UC who were followed up between June 2022 and January 2023 at a tertiary medical school hospital, following the approval of the ethics committee. The study population comprised patients aged 18 and above who experienced an ulcerative UC flare-up during the specified period, as identified through the hospital information management system. The demographic data, medical histories, biochemical findings, and outcomes of the patients included in the study were recorded. Patients under the age of 18, those who were not followed up due to an UC flare-up, those who were found not to have UC during follow-up, and those whose complete data could not be accessed through the hospital information management system were excluded from the study. Patient follow-ups are shown in Figure 1.

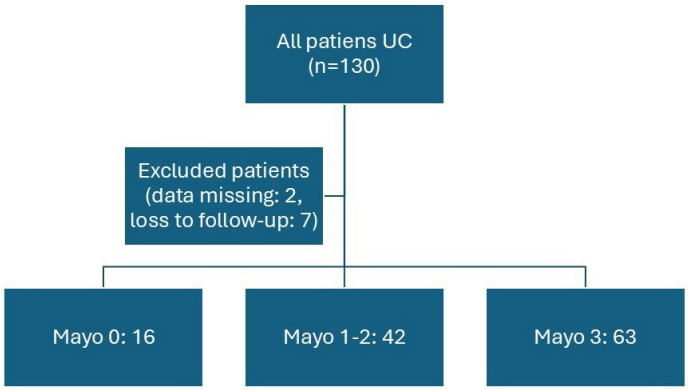

Figure 1. Flowchart

This study was carried out in accordance with the rules of the Declaration of Helsinki with the permission received from the Akdeniz University Faculty of Medicine Non-Interventional Clinical Studies Ethics Committee (No: 549, date: 02.08.2023).

Endoscopic Mayo score

The Mayo endoscopic score is a measure employed for the assessment of the severity of UC. The objective of this evaluation is to ascertain the disease status based on findings observed during endoscopic examinations. The Mayo endoscopic score is assigned a grade on a scale of 0 to 3, with parameters including mucosal erythema, pseudopolyps, bleeding, and ulcerations. The score is defined as follows: A score of 0 indicates a normal mucosal appearance, while a score of 1 denotes mild mucosal erythema. A score of 2 is indicative of marked erythema, loss of vascular pattern, fragility, and erosions, and a score of 3 signifies the presence of spontaneous bleeding and deep ulcerations. The Mayo endoscopic score is employed in clinical research to evaluate disease severity, thereby facilitating the modification of disease management and treatment plans as required [8].

Statistical Analysis

Following the creation of a database comprising the findings identified in the study, the data were subjected to analysis using the statistical software package SPSS version 27 (IBM Corporation, Armonk, USA). Subsequently, the data were classified, and frequency and percentage values were employed to describe categorical variables, while distribution analysis was conducted for numerical variables. Numerical data that followed a normal distribution were presented as mean ± SD, while those that did not were presented as median (interquartile range). Parametric tests were employed for the comparison of numerical data with a normal distribution, whereas the Mann-Whitney U test was used for non-normally distributed numerical data. The relationship between independent variables was evaluated through Receiver Operating Characteristic (ROC) analysis. The relationship between independent variables was assessed through multiple linear regression analysis. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 121 patients were included in the study, with 16 patients (13.2%) found to be in remission. Patients with a Mayo score of 1-2 were classified as Group 1, while those with a Mayo score of 3 were classified as Group 2. No significant difference was observed in age groups or gender distribution between the groups. However, a significant difference was noted in the patterns of UC involvement ($p = 0.017$). The prevalence of distal colitis and pancolitis was markedly elevated in Group 2. A comparison of the demographic data of the groups is presented in Table 1 for the reader's convenience. The mean percentage of immature granulocytes in Group 1 was 0.59 ± 0.091%, while in Group 2, it was 0.42 ± 0.074%. This difference was found to be statistically significant ($p = 0.008$), with Group 1 exhibiting a higher percentage of immature granulocytes. A comparison of the complete blood count and biochemical parameters at the time of admission between the groups is provided in Table 2 for reference.

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Table 1. Demographic data

Variables	Group 1 (n = 42)	Group 2 (n = 63)	p-Value
Female (n, %)	20 (47.6%)	19 (30.2%)	0.054
Age (mean ± SD)	47.16 ± 14.29	47.63 ± 14.38	0.807
Diagnose Age (mean ± SD)	40.78 ± 14.38	40.65 ± 13.71	0.947
Coronary artery disease (n, %)	5 (11.9%)	10 (15.9%)	0.195
Diabetes mellitus (n, %)	5 (11.9%)	9 (14.3%)	0.219
Hypertension (n, %)	11 (26.2%)	11 (17.5%)	0.108
Malignite (n, %)	2 (4.8%)	3 (4.8%)	0.354
Sicca (n, %)	2 (4.8%)	2 (3.2%)	0.352
Ankylosing spondylitis (n, %)	3 (7.1%)	3 (4.8%)	0.283
Asthma (n, %)	2 (4.8%)	4 (6.3%)	0.319
Hyperlipidemia (n, %)	2 (4.8%)	7 (11.1%)	0.221
Drugs (n, %)			
Convansional	32 (76.2%)	41 (65.1%)	0.160
Biological	10 (23.8%)	22 (34.9%)	
UC type (n, %)			
Proctitis	11 (26.2%)	4 (6.3%)	
Distal Colitis	11 (26.2%)	21 (33.3%)	0.017
Colitis, left side	6 (14.3%)	3 (4.8%)	
Extensive colitis	4 (9.5%)	12 (19%)	
Pancolitis	10 (23.8%)	23 (36.5%)	

UC: ulcerative colitis

Table 2. Comparison of biochemical values

Variables	Group 1 (n = 42)	Group 2 (n = 63)	p-value
Hemoglobine (mean ± SD)	12.93 ± 2.26	12.42 ± 1.96	0.233
WBC (mean ± SD)	8.34 ± 3.18	8.77 ± 2.89	0.472
Neutrophil (mean ± SD)	5.49 ± 2.94	5.75 ± 2.52	0.634
Lymphocyte (mean ± SD)	2.00 ± 0.86	2.09 ± 0.89	0.626
Monocyte (mean ± SD)	0.58 ± 0.24	0.67 ± 0.35	0.052
Eosonophile (median, IQR)	0.15 (0.20)	0.16 (0.23)	0.666
Basophile (mean ± SD)	0.04 ± 0.02	0.05 ± 0.03	0.458
%Ig (median, IQR)	0.4 (0.3)	0.3 (0.46)	0.008
Ig (median, IQR)	0.04 (0.03)	0.03 (0.03)	0.010
CRP (median, IQR)	4.24 (14.43)	5.4 (13.69)	0.729
Albumine (mean ± SD)	33.43 ± 16.34	34.37 ± 15.23	0.507
Ferritin (mean ± SD)	47.85 ± 46.89	71.60 ± 85.17	0.022
ALT (mean ± SD)	21.12 ± 23.69	16.83 ± 8.44	0.073
AST (mean ± SD)	22.64 ± 19.85	17.13 ± 6.51	0.029
Platelets (mean ± SD)	305.40 ± 105.84	323.65 ± 111.83	0.225

AST: Aspartate amino transferase, ALT: Alanine aminotransferase, CRP: C Reactive protein

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A ROC analysis was conducted to assess the diagnostic accuracy of the percentage and count of immature granulocytes (IG) in the groups classified according to the Mayo criteria. The area under the curve (AUC) for IG% was found to be 0.652 (p = 0.004), with a cut-off value of 0.35%. The AUC for IG count was 0.647 (p = 0.006), with a cut-off value of 0.035 (Table 3, Figure 2).

In Group 1, 32 patients (76.2%) were undergoing conventional therapy, while 10 patients (23.8%) were receiving biological agents. In Group 2, 41 patients (65.1%) were undergoing conventional therapy, while 22 patients (34.9%) were receiving biological agents. No significant difference was observed between the groups with respect to the types of medications utilized (p = 0.160). The median IG% value was 0.3 (0.3) for patients undergoing conventional therapy and 0.4 (0.35) for those receiving biological agents, with no statistically significant difference between the two groups (Figure 3, p = 0.384). The median IG count for patients undergoing conventional therapy was 0.03 (0.03), while for those receiving biological agents, it was 0.04 (0.04), with no significant difference observed between the two groups (Figure 2, p = 0.50).

Table 3. ROC analysis

Variables	AUC ± SD	p-value	Cut-off	Sensitivity	Specificity
IG%	0.652 ± 0.053	0.004	0.35	66.7%	66.1%
IG count	0.647 ± 0.054	0.006	0.035	59.5%	62.9%

ROC: Receiver Operating Characteristic, IG: immature granulocytes

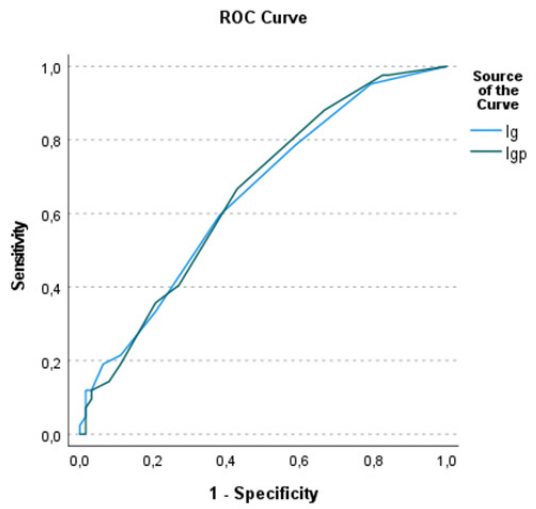

Figure 2. Receiver Operating Characteristic (ROC) analysis

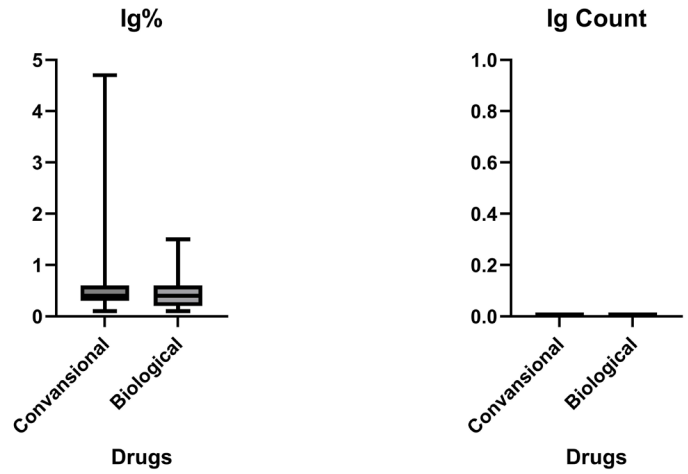

Figure 3. Comparisons of immature granulocytes according to drug groups used

Discussion

UC is a disease that is characterised by complex inflammatory processes, which often necessitate the utilisation of immunomodulatory agents in its management. The objective of our study was to investigate the potential of immature granulocytes, which have recently been identified through complete blood count, in identifying this immune structure. It was observed that the concentration of ferritin, an acute-phase reactant, was markedly elevated in patients classified as Mayo-3, indicative of severe disease activation, in comparison to patients in the Mayo 1-2 class. It is noteworthy that immature granulocytes, another marker of inflammation, exhibited a significantly higher prevalence in patients with a Mayo 1-2 classification in comparison to those within the Mayo-3 class.

In clinical trials, the Mayo Clinical Score, which includes subscores for rectal bleeding, stool frequency, physician's global assessment, and endoscopy, is a commonly used method for describing the clinical status of patients with UC. However, the high placebo response rates and variability in these trials present a challenge that requires the use of sophisticated modelling techniques to accurately predict outcomes [9]. Furthermore, while inflammatory markers such as IL-6 and IL-10 have been linked to cognitive outcomes in other conditions, their efficacy in predicting cognitive decline in the general population remains uncertain, underscoring the complexity of inflammation's role across different diseases [10]. While the Mayo score is indicative of disease progression, studies in the literature have demonstrated that inflammation also increases in parallel. In the present study, however, no correlation was observed between the complete blood count findings and the Mayo score. Instead, it was found that the rise in ferritin, an acute-phase reactant, was a result of the increased inflammation.

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Ferritin is widely acknowledged as an acute-phase reactant, with a pivotal function in a multitude of physiological and pathological processes. As an acute-phase reactant, ferritin levels may increase in response to various stressors, including inflammation, infection, and other forms of physiological challenge. This phenomenon reflects the body's intrinsic mechanism to sequester iron and limit its bioavailability to pathogens, thereby preserving the functionality of immune cells [11]. Elevated ferritin levels have been linked to increased disease severity and the development of complications such as skin thickening and vital organ involvement in conditions including systemic sclerosis and other inflammatory and non-inflammatory states [12]. It is established that inflammation causes an increase in ferritin levels, a finding that was corroborated by our study, which demonstrated that the Mayo-3 group exhibited significantly elevated ferritin levels in comparison to the Mayo 1 and 2 groups. It is hypothesised that this increase is due to heightened inflammation.

It has been previously demonstrated that IGs increase in inflammatory conditions. For example, studies by Doğan and Gürleyen in acute appendicitis [13], Ünal et al. in cholecystitis [14], Korkut et al. in ischemic stroke [15], and Bedel et al. in intracerebellar haemorrhages [16] have demonstrated that IGs are significant indicators. As evidenced in the existing literature, IGs are typically elevated in conjunction with inflammation. However, in our study, while we observed an increase in ferritin levels with rising Mayo scores, indicative of inflammation, changes in IGs were not reflected in the complete blood count. Instead, a significant decrease in IG values was noted. This discrepancy may be attributed to the specific treatment agents used in managing UC, which might affect IG levels differently from ferritin in the context of inflammation management.

Limitations

It should be noted that our study is subject to several limitations. Given that it was conducted retrospectively, it would be beneficial to plan future studies prospectively and implement them in a multi-centre format in order to minimise data loss and enhance the robustness of the findings.

Conclusion

The presentation of inflammation is a complex mechanism, particularly in cases where immunomodulatory therapies are applied. In such contexts, a complete blood count may prove an ineffective method for monitoring inflammatory conditions. For diseases such as UC, endoscopic assessment of the colon has been demonstrated to be a more effective method for identifying and evaluating inflammation.

Ethical Approval
This study was carried out in accordance with the rules of the Declaration of Helsinki with the permission received from the Akdeniz University Faculty of Medicine Non-Interventional Clinical Studies Ethics Committee (No: 549, date: 02.08.2023).

Patient Consent
This retrospective study was conducted after obtaining the necessary ethics committee approval. Due to the retrospective nature of the study, informed consent from the patients was not required.

Conflict of Interest
The authors confirm the absence of any conflicts associated with this work.

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