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Neutrophil-to-Platelet Ratio in Patients with Ulcerative Colitis Treated with Infliximab or Vedolizumab: A Retrospective, Single-Center Study in Poland

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Statistical Analysis C
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Manuscript Preparation E
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Background: This retrospective study from a single center in Poland was undertaken to evaluate the clinical utility of neutrophil-to-platelet ratio in therapy of 35 ulcerative colitis (UC) patients with infliximab or vedolizumab.

Material/Methods: This study included 35 patients: 16 were treated with infliximab and 19 were treated with vedolizumab. Treatment response was evaluated using partial Mayo score. Treatment response was defined as a reduction of partial Mayo score of ≥3 points followed by a decrease of a minimum of 30% from the baseline, decrease in the rectal bleeding subscore of ≥1, or an absolute rectal bleeding subscore of 0 or 1. During the maintenance period, we diagnosed 13 patients with loss of response (LOR) (5 with infliximab and 8 with vedolizumab). The Mann-Whitney U test was performed to assess differences between the groups. Statistical significance was defined as $P<0.05$. The median was used to describe the value of the parameter. Analysis of the receiver operating characteristic (ROC) curve with the determination of area under the curve (AUC) was performed for the neutrophil-to-platelet parameter during the induction period.

Results: The median value of the neutrophil-to-platelet ratio for the treatment response group was lower than in the LOR group (median=13.18 and median=19.49, respectively). Calculation of AUC curve for neutrophil-to-platelet ratio during the induction period showed best sensitivity and specificity for values ≥32.511. There were no other significant findings.

Conclusions: Neutrophil-to-platelet ratio might be a promising biomarker of LOR in biologic therapy of UC. However, to fully prove this, further studies are needed.

Keywords: Colitis, Ulcerative • Neutrophils • Platelet Count

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Background

Ulcerative colitis (UC) is a chronic, diffuse, nonspecific inflammation of colonic mucosa with unknown etiology [1], with the natural course including periods of exacerbations and remissions [1]. Diagnosis of UC uses information obtained during medical interview, including persistent/recurrent bloody/mucous stools, family history, smoking, medications, and recent foreign travel [2]. The most important findings during physical examination are abdominal tenderness, weight loss, fever, and anemia [2]. Colonoscopy is a valuable tool for confirmation of UC, evaluation of its severity, monitoring effectiveness of treatment, and observation for possible development of colorectal cancer [3-6]. Non-endoscopic imaging examinations like abdominal ultrasound, computed tomography, or magnetic resonance imaging are used for pre- and post-treatment assessment of UC activity or confirmation of complications [7,8]. The current treatment strategy for UC is based on early induction of remission (endoscopic and clinical) by demonstrating mucosal healing and long-term maintenance therapy to prevent relapse [9]. The first-line treatment for low-risk patients with mild-to-moderate ulcerative proctitis or ulcerative proctosigmoiditis is mesalamine in the form of suppository/enemas [10,11]. Alternative therapy includes use of topical steroids in the form of suppository/enemas or foam preparation [10,12]. Patients who are unwilling or unable to tolerate topical medications can be treated with oral 5-aminosalicylates (5-ASA) (high-dose mesalamine is preferable, with sulfasalazine as an alternative) [10,13,14]. The first-line treatment for left-sided or extensive colitis with mild-to-moderate activity UC is with a combination of oral 5-ASA agent and rectal mesalamine, or sulfasalazine as an alternative option [13,14]. Failure to respond can be treated using 5-ASA with topical glucocorticoids; no response requires adding budesonide MMX to the existing regimen [15]. Lack of symptom improvement requires discontinuation of budesonide MMX and initiation of glucocorticoid therapy with prednisone [16]. Induction therapy among patients with moderate-to-severe UC should be personalized, and based on several factors, including risk of adverse effects, prior therapy for UC, patient preferences and characteristics, and a plan for long-term therapy [17]. Therapy with anti-tumor necrosis factor (TNF) drugs like infliximab is used to induce remission in such patients, with or without additional use of immunomodulators like azathioprine or methotrexate in case of intolerance to thiopurines [18-20]. Anti-integrin antibody agents like vedolizumab are usually preferred in induction of remission among patients with history of malignancy, higher risk of infections, or advanced age, because of gut-selection action [21,22]. Ustekinumab acts as an anti-interleukin 12/23 antibody agent and is a treatment option for moderate-to-severe UC, especially for patients who did not respond to other forms of treatment (mesalamine and/or glucocorticoids and/or immunosuppressants), but failure of prior anti-TNF treatment is not required [23]. Janus kinase (JAK) inhibitors (upadacitinib and tofacitinib) are approved to use in the United States as a subsequent therapy for patients not responding to anti-TNF drugs [23,24].

Recent findings regarding the use of several biomarkers in the clinical management of UC patients include markers of inflammatory response in the prediction of UC's prognosis [25], the activity of UC [1,9-11], or LOR [26]. Finding proper diagnostic biomarkers would enable development of easy, timesaving, and low-cost monitoring of disease without the need to perform endoscopic examinations, which are valuable tools, but are often contraindicated in severe cases and are burdened with the risk of dangerous complications [27].

The neutrophil-to-platelet ratio is a novel biomarker studied in monitoring the activity of UC [1] as well as in other diseases [28]. Neutrophils play a major role in the pathophysiology of UC due to their appearance in colonic mucosa [29] and the high prevalence of anti-neutrophil cytoplasmatic antibodies (ANCA) among UC patients [30]. Some research found platelets play a crucial role in UC, as a release of Interleukin 8 (IL-8) leads to chemoattraction of neutrophils [31], which together with excessive production of superoxide creates neutrophil-platelet aggregates related to the activity of disease [32].

This scientific paper describes the evaluation of the Neutrophil-to-platelet ratio in UC patients who underwent biologic therapy with infliximab and vedolizumab. Similar studies were already conducted for different biomarkers [26] or in Crohn's disease (CD) [33]. The reason for studying the neutrophil-to-platelet ratio is the assessment of its clinical utility in biologic therapy of UC, because to the best of our knowledge there have been no studies assessing its diagnostic value in this form of UC treatment. Additionally, biomarkers might be a useful, low-cost, and minimally invasive method of helping in monitoring treatment of UC.

Therefore, this retrospective study from a single center in Poland aimed to evaluate the neutrophil-to-platelet ratio in patients with UC treated with infliximab or vedolizumab.

Material and Methods

Ethics

Out local Bioethics Committee reviewed and approved our study (approval number APK.002.241.2021) for original data collection. The requirement for patient written informed consent was waived due to the retrospective analysis of routinely collected clinical data, as well as the commitment of the authors of the study to confidentiality and not to disclose personal data to unauthorized persons. The study was conducted in accordance with the Helsinki Declaration.

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Data source

To assess the neutrophil-to-platelet ratio, a retrospective analysis of clinical data of patients who underwent biologic therapy between January 2018 and November 2021 was conducted in our hospital.

Study design

Infliximab is a monoclonal anti-TNF-alpha antibody and was one of the first biologic drugs with approval for treatment of UC [34]. Vedolizumab is a recombinant, humanized monoclonal anti-alpha-4-beta-7 integrin, which specifically targets the gastrointestinal tract, and is approved for treatment moderate-to-severe UC [35].

Patients with moderate-to-severe activity of UC undergoing vedolizumab and infliximab treatment with the achievement of clinical response during the induction period were included in our study. Because of the lack of achieving clinical remission during the induction period, we decided to exclude 7 patients from the study. Dosages of infliximab and vedolizumab were administered according to the recommended regimen (5 mg/kg and 300 mg, respectively) at weeks 0, 2, and 6, and the maintenance dosage was every 8 weeks. UC was diagnosed clinically, endoscopically, and histopathologically. Demographic, clinical, and laboratory data were obtained from patients' electronic medical records. Measurement of neutrophils and platelets was conducted using the Sysmex XN 1500 hematology analyzer. Neutrophils and platelets were measured at the same stage of treatment. However, we did not compare pre- and post-treatment levels.

One week before the beginning of therapy all patients were examined by a physician and biochemical markers of systemic inflammation were measured using a blood test. Additionally, every patient was physically examined with a blood test, and response estimation was performed at week 2, week 6, and subsequently every 8 weeks thereafter. The neutrophil-to-platelet ratio was calculated by the division of differential count of neutrophils with the platelets divided by 1000 [1]. Patients were followed until the end of therapy.

UC activity was evaluated with the partial Mayo score, which is a scale used for noninvasive monitoring of UC activity, and is composed of 3 categories (stool frequency, bleeding, and physician's global assessment) rated from 0 to 3 points [36]. A partial Mayo score ≥7 was determined as severe UC, whereas a partial Mayo score ≥5 was defined as moderate-to-severe active UC [36]. Clinical relapse of UC with the need for optimization of dose of a biologic drug and/or use of additional drugs during the maintenance period was determined as LOR. The sustained response was classified as a lack of LOR over the follow-up duration [37]. Patients, who obtained clinical responses at the end of the induction phase (week 14) were classified as responders. Reduction of partial Mayo score of ≥3 points followed by a decrease of at least 30% from the baseline, and a decrease in the rectal bleeding subscore of ≥1, or an absolute rectal bleeding subscore of 0 or 1 was determined as treatment response [38]. Biopsy and histopathological examination, which is an evidence-based approach in assessing LOR in UC, were not used in our study.

Statistical Analysis

The median and the interquartile range (IQR) were used for continuous variables. The U Mann-Whitney rank-sum test for nonparametric independent variables was used to compare the differences between patients with sustained response and LOR. Probability value (*P* value) was utilized to assess statistical significance. A *P* value less than 0.05 was regarded as statistically significant. Receiver operating characteristics (ROC) curves were used to calculate the area under the ROC curve and to determine the correctness of the classifier (neutrophil-to-platelet ratio). Statistical analysis was performed using Statistica version 13 (TIBCO Software, Inc).

Results

Baseline Characteristic of the Study Population

Forty-two patients started biologic therapy at University Hospital in Białystok, Poland: 7 were excluded due to a primary lack of response, and 35 patients undergoing treatment with infliximab and vedolizumab (16 treated with infliximab and 19 with vedolizumab) were included in the study. All patients achieved remission during the induction phase of therapy. During the maintenance period, 13 patients were diagnosed with LOR (5 treated with infliximab and 8 with vedolizumab).

The baseline characteristics of the study population are presented in **Table 1**. No patients were diagnosed with malignant tumors. Three patients treated with infliximab and 4 treated with vedolizumab had comorbidities (3 patients diagnosed with hypertension, 2 had diabetes type 2, 1 had rheumatoid arthritis, and 1 had a history of ischemic stroke). None of the patients had cardiovascular symptoms.

Difference in Neutrophil-to-Platelet Ratio Between Responders and LOR Patients

Differences between populations of patients with sustained response and LOR are presented in **Table 2**. The neutrophil-to-platelet ratio in patients with LOR (median=19.41) was significantly higher than in patients with sustained response

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Table 1. General characteristics of the study group of ulcerative colitis patients treated with Infliximab or Vedolizumab. (Word 2016, Microsoft Office).

	All patients
Number of patients	35
Gender: male/female	27/8
Age at diagnosis, median (interquartile range)	28 (18-36) years
Age at start of therapy, median (interquartile range)	
Vedolizumab	23 (18-31) years
Infliximab	32 (21-38) years
Disease duration, median (interquartile range)	7 (4-10) years
UC location: proctitis/left-sided/pancolitis	2/15/18
Contaminant therapies, n%	
Immunomodulators	9 (25.7%)
Corticosteroids	6 (17.14%)
Mesalamine	21 (60%)
Sulfasalazine	2 (5.7%)
Partial Mayo score, median (interquartile range)	7 (6-8)
WBC (/μl), median (interquartile range)	7950 (6025-9380)
Platelet (×10^3/μl), median (interquartile range)	257 (221-301)
Neutrophils (×10^3/μl), median (interquartile range)	4.718 (3.217-5.55)
Hemoglobin (g/dl), median (interquartile range)	13.25 (11.7-14.8)
CRP (mg/l), median (interquartile range)	2.75 (1.2-6.4)
MPV (fl), median (interquartile range)	9.9 (9.3-10.8)
Neutrophil-to-platelet ratio, median (interquartile range)	17.98 (14.16-21.40)

UC – ulcerative colitis, WBC – white blood cells, CRP – C-reactive protein, MPV – mean platelet volume, μl – microliters, g/dl – grams per deciliter, mg/l – milligrams per liter, fl – femtoliters.

(median=13.62) (P<0.05). We observed significant differences in 14-week value of neutrophil-to-platelet ratio between patients with sustained response and LOR (P=0.007) (**Figure 1**). To assess the diagnostic usefulness of the neutrophil-to-platelet ratio, we used the ROC curve for 3 neutrophil-to-platelet ratios measured during the induction period (weeks 2, 6, 14) with area under the curve (AUC)=0.787, with a 95% confidence interval: (0.619, 0.954). The best cut-off value was 32.511 (sensitivity: 81.2%; specificity: 68.9%) (**Figure 2**). We also assessed ROC curves for week 2, 6, and 14 for neutrophils (**Figure 3**; AUC=0.556; 95% CI: 0.345-0.767) and WBC (**Figure 4**; AUC=0.502; 95% CI: 0.318-0.789). Due to the use of 2 different drugs, we constructed separate ROC curves for vedolizumab (**Figure 5**) and infliximab (**Figure 6**). Neutrophil-to-platelet ratio appears to be a better predictor of LOR for infliximab (AUC=0.873; 95% CI: 0.688-1) than vedolizumab (AUC=0.795; 95% CI: 0.559-1). To assess difference in remission among patients with concomitant therapy using steroids and steroid-free individuals we decided to construct 2 additional ROC curves (**Figures 7 and 8**, respectively).

Discussion

Our study results show that a high neutrophil-to-platelet ratio in the induction phase of the therapy is associated with a high risk of LOR in UC therapy with infliximab and vedolizumab. In addition, more patients were diagnosed with LOR using vedolizumab in comparison to infliximab.

Comparative study of the effectiveness of infliximab and vedolizumab in UC showed that more patients responded to induction with vedolizumab than infliximab, but clinical response after the induction period was comparable for both drugs [39]. Interestingly, a multi-center study from France found that more UC patients after failure to a first subcutaneous TNF drug achieved clinical remission with vedolizumab than with infliximab [40]. However, disease severity was significantly higher among patients treated with infliximab; therefore, there is still a need for more studies with 2 comparable groups of patients [40].

A potential explanation of our result is the role of neutrophils in the inflammatory process [41] as well as their ability to cause tissue damage in UC [42]. Pathological factors are also relevant, as the accumulation of neutrophils and formation of abscesses in the intestinal crypts play important roles in the pathogenesis of UC [43]. Additionally, removing activated granulocytes through apheresis has been well established as a therapeutic option in UC [44]. Platelets are also believed to play a significant role in mucosal inflammation due to their inflammatory functions associated with the modulation of other inflammatory cells or participating in the release of inflammatory mediators [45].

Only 1 previous study assessed the utility of neutrophil-to-platelet ratio in UC in monitoring disease activity with good

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Table 2. Differences between ulcerative colitis patients with sustained response and loss of response to Vedolizumab or Infliximab. (Word 2016, Microsoft Office).

	Sustained response	Loss of response	*P* value
Number of patients	22	13	
Gender: male/female	16/6	11/2	0.578
Age at diagnosis, median (interquartile range)	23 (18-35) years	30 (23-39) years	0.229
Age at start of therapy, median (interquartile range)			
Vedolizumab	25 (21-42) years	42 (30-58.5) years	0.033
Infliximab	37 (28-44) years	40 (40-54) years	0.583
Disease duration, median (interquartile range)	4 (3-11)	9 (8-15)	0.091
UC location: proctitis/left-sided/pancolitis	2/8/12	0/7/6	1
Contaminant therapies, n %			
Immunomodulators	3 (13.6%)	6 (46,.1%)	0.113
Corticosteroids	2 (9.1%)	4 (30.8%)	0.302
Mesalamine	11 (50%)	10 (76.9%)	0.191
Sulfasalazine	1 (4.5%)	1 (7.7%)	0.932
Partial Mayo score, median (interquartile range)	6 (5-7)	7 (6-8)	0.158
WBC (/µl), median (interquartile range)	7950 (6025-9380)	8460 (5647-9547)	0.749
Platelet ($\times 10^3$/µl), median (interquartile range)	257 (221-301)	241 (198-274)	0.215
Neutrophils ($\times 10^3$/µl), median (interquartile range)	4.718 (3.217-5.55)	4.334 (3.409-6.169)	0.853
Hemoglobin (g/dl), median (interquartile range)	13.25 (11.7-14.8)	14.3 (13.5-14.8)	0.098
CRP (mg/l), median (interquartile range)	2.75 (1.7-6.4)	2.6 (1-5.6)	0.625
MPV (fl), median (interquartile range)	9.9 (9.3-10.8)	10.1 (8.6-10.8)	0.624
Neutrophil-platelet ratio, median (interquartile range)	13.63 (11.85-17.01)	19.41 (16.88-21.67)	0.007

UC – ulcerative colitis, WBC – white blood cells, CRP – C-reactive protein, MPV – mean platelet volume, µl – microliters, g/dl – grams per deciliter, mg/l – milligrams per liter, fl – femtoliters.

correlation, sensibility, and specificity, especially with the mild and moderate activity of UC [1]. Similar studies were previously conducted for various types of cancer [46] and ischemic stroke [28]. Neutrophil-platelet score (NPS) showed a high correlation between CRP and albumin in breast, bladder, and prostate cancer, as well as worse outcomes in colorectal cancer [46]. Neutrophil-to-platelet ratio in ischemic stroke was found as a good 90-day survival marker [28].

Previously published research proved that the neutrophil-to-lymphocyte ratio (NLR) can be considered a prognostic factor for LOR in UC [26] and CD [47]. Both studies presented similar results with best NLR cut-off values of 4.488 (sensitivity: 78.6%, specificity: 78.3%) in UC and 4.068 (80% sensitivity and 87% specificity) in CD. Our research shows that the neutrophil-to-platelet ratio might be more valuable in monitoring LOR due to increased value during the induction phase, and the associated lower randomness observed in only 1 measurement, in comparison to NLR with an elevated pre-treatment level [26].

Risk factors of LOR in infliximab therapy are associated with low levels of the drug, high C-reactive protein (CRP), and the presence of specific antibodies [8,32,33]. Risk factors of LOR in vedolizumab therapy include previous anti-TNF therapy and high CRP [48].

The Mayo scale for the assessment of activity of UC, which was used in this study, is not a perfect tool because of subjective components that have strong impact on the score [49]. Number of loose stools, presence of blood in the stool, and abdominal pain are valuable elements of the Mayo scale, but physician global assessment is particularly sensitive to bias [49].

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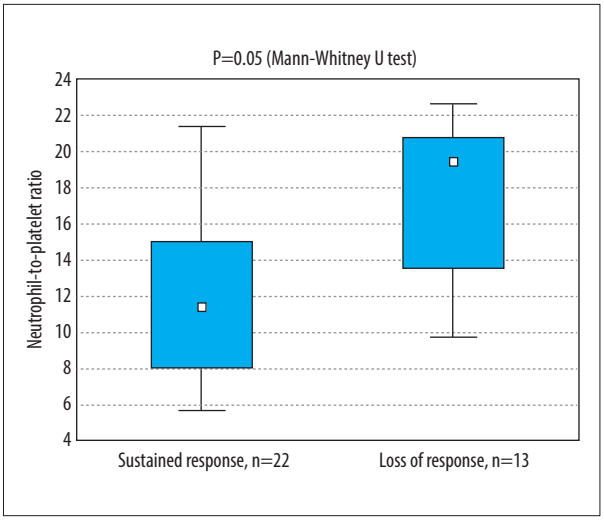

Figure 1. Box-plot comparison between average value of neutrophil-to-platelet ratio during the induction phase between patients with sustained response and loss of response to infliximab or vedolizumab. Small squares represent the median value. The figure was created using Statistica version 13 (TIBCO Software, Inc.).

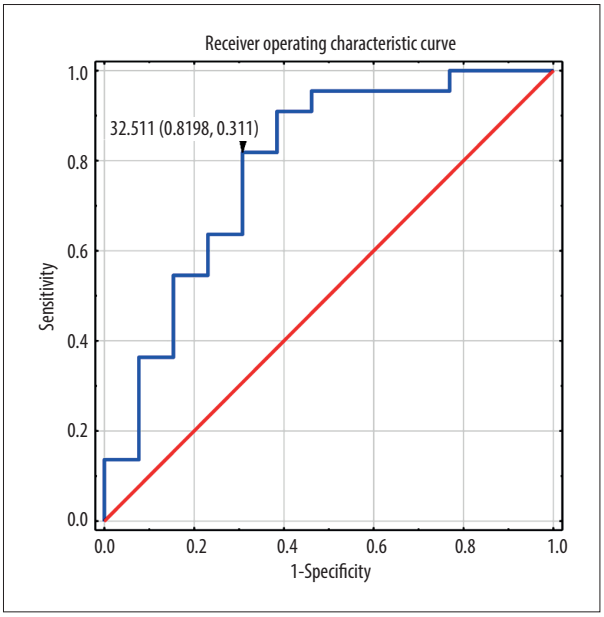

Figure 2. A receiver operating characteristic curve was used to analyze the predictive ability of neutrophil-to-platelet ratio value during the induction phase (weeks 2, 6, 14) in predicting loss of response with the best cut-off value of 32.511; AUC=0.787 (sensitivity: 81.2%; specificity: 68.9%; 95% CI: 0.619-0.954) AUC – area under the curve, CI – confidence interval. The figure was created using Statistica version 13 (TIBCO Software, Inc.).

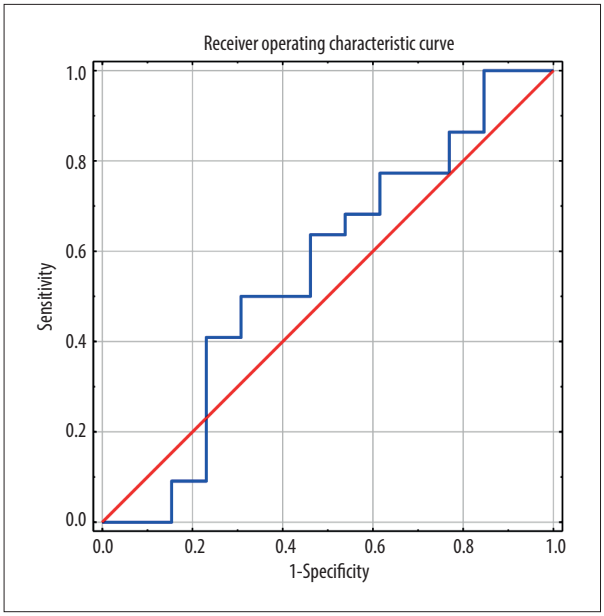

Figure 3. A receiver operating characteristic curve was used to analyze the predictive ability of neutrophil value during the induction phase (weeks 2, 6, 14) in predicting loss of response; AUC=0.556; 95% CI: 0.345-0.767 AUC – area under the curve, CI – confidence interval. The figure was created using Statistica version 13 (TIBCO Software, Inc.).

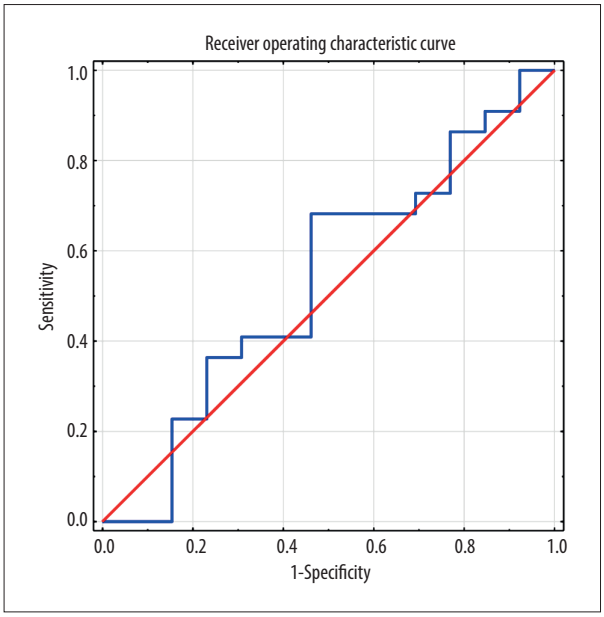

Figure 4. A receiver operating characteristic curve was used to analyze the predictive ability of white blood cell value during the induction phase (weeks 2, 6, 14) in predicting loss of response; AUC=0.502; 95% CI: 0.318-0.789; AUC – area under the curve, CI – confidence interval. The figure was created using Statistica version 13 (TIBCO Software, Inc.).

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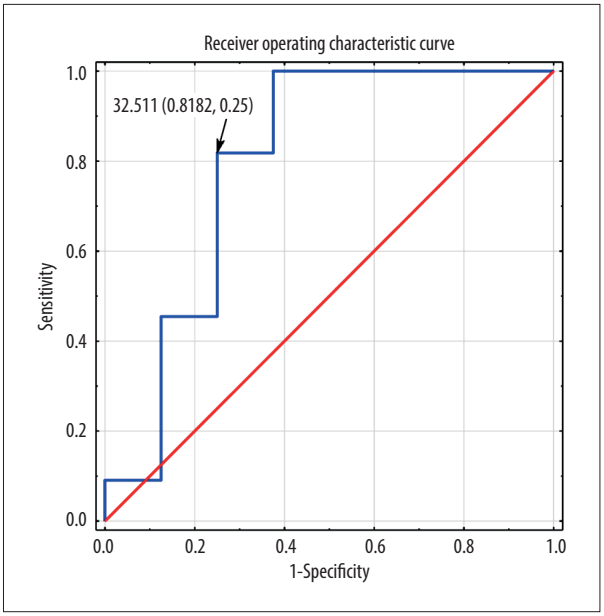

Figure 5. A receiver operating characteristic curve was used to analyze the predictive ability of neutrophil-to-platelet ratio in patients treated with vedolizumab during the induction phase (weeks 2, 6, 14); AUC=0.795; 95% CI: 0.559-1; AUC – area under the curve, CI – confidence interval. The figure was created using Statistica version 13 (TIBCO Software, Inc.).

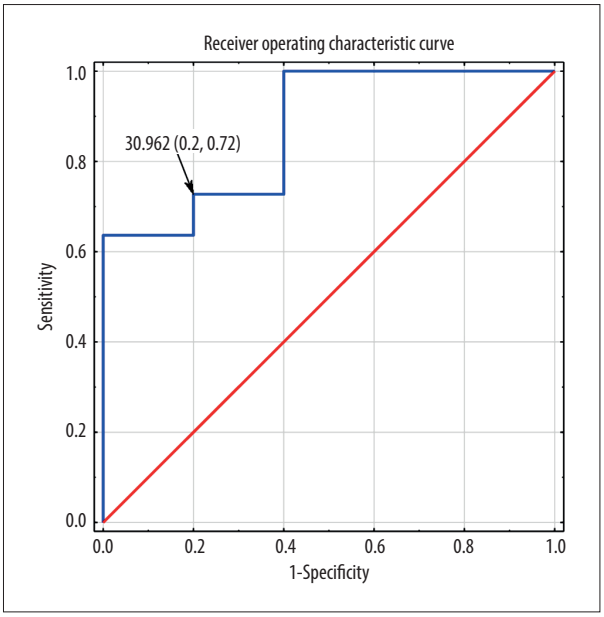

Figure 6. A receiver operating characteristic curve was used to analyze the predictive ability of the neutrophil-to-platelet ratio in patients treated with infliximab during the induction phase (weeks 2, 6, 14); AUC=0.873; 95% CI: 0.688-1; AUC – area under the curve, CI – confidence interval. The figure was created using Statistica version 13 (TIBCO Software, Inc.).

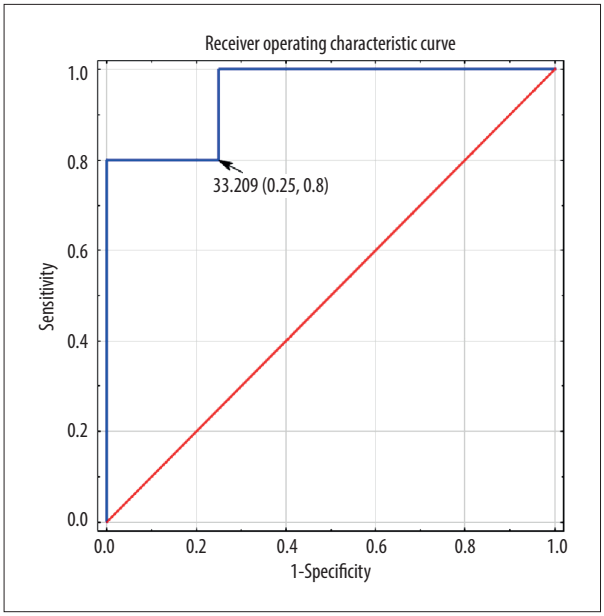

Figure 7. A receiver operating characteristic curve was used to analyze the predictive ability of the neutrophil-to-platelet ratio during the induction phase (weeks 2, 6, 14) for patients with steroid drugs as concomitant therapy during the induction phase with best cut-off value 33.209. AUC=0.95; 95% CI: 0.806-1; AUC – area under the curve, CI – confidence interval. The figure was created using Statistica version 13 (TIBCO Software, Inc.).

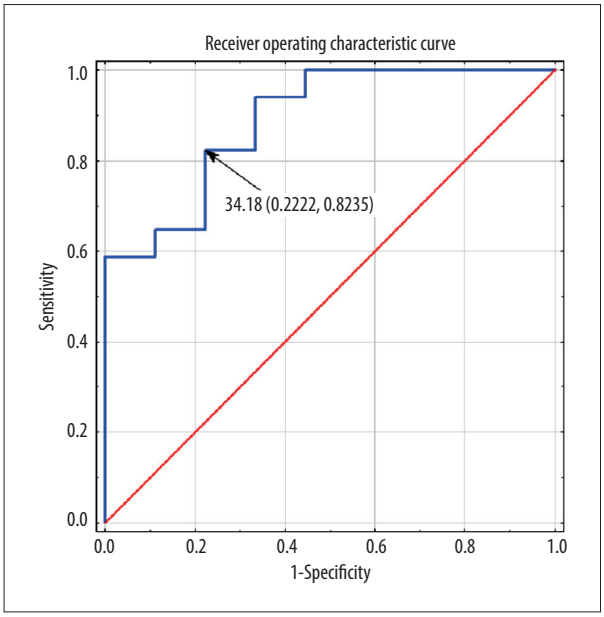

Figure 8. A receiver operating characteristic curve was created to analyze the predictive ability of the neutrophil-to-platelet ratio during the induction period (weeks 2, 6, 14) for steroid-free patients with best cut-off value 34.180. AUC=0,889; 95% CI: 0.76-1; AUC – area under the curve, CI – confidence interval. The figure was created using Statistica version 13 (TIBCO Software, Inc.).

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According to the current evidence-based approach, assessing activity of UC should be done using biopsy and histopathological examination, with the grade activity based on the most diseased fragment of the biopsy [50].

Limitations

First, we did not use biopsies and histopathological examination to determine activity of UC, which represents an evidence-based approach and are supported by current clinical guidelines. Second, we did not evaluate the neutrophil-to-platelet ratio before our patients underwent biologic therapy, as all data were analyzed retrospectively, so there is a need for prospective studies. Third, we only included a relatively small number of patients, who were additionally treated with 2 different drugs. Future studies assessing neutrophil-to-platelet ratio should include more patients, who will be treated using 1 biologic. Moreover, we could not exclude the influence of bacterial infection on the results due to the lack of routine measurement of procalcitonin. Our study could not measure the serum level of the drugs or drug-specific antibodies, which is also a crucial limitation of the study. To fully confirm the usefulness of the neutrophil-to-platelet ratio, further studies with larger sample sizes are needed, with the determinants of LOR mentioned above taken into account. In addition, blood parameters were counted using an automatic analyzer, which may have limited the measurement accuracy of the device.

Conclusions

Neutrophil-to-platelet ratio appears be a promising biomarker of LOR in biologic therapy of UC. However, to fully prove its clinical utility, further studies are needed.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original without duplication and have not been previously published in whole or part.

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