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Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio as biomarkers in Crohn's disease

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ABSTRACT

Purpose The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been identified as potential inflammatory markers in Crohn's disease (CD). This study aimed to evaluate the diagnostic value and prognostic significance of these two indices in identifying and assessing relapses in CD.

Methods This was a prospective study involving 56 controls and 56 patients with CD, 32 of whom were in relapse. The data collected included clinical characteristics, a blood count, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) in all patients, and an assessment of the relapse in the cases. Statistical analysis of the relationship of NLR and PLR with other markers of inflammation and relapse was performed.

Results The mean age was 37.8 years [16-59] with a sex ratio of 1.55. There was a significant difference in NLR (p=0.049) and PLR (p<0.001) between the two groups. There was a significant correlation between CRP and NLR (p=0.002) and also with PLR (r=0.234, p=0.01), The correlation between NLR and total white blood cell count was significant p<0.0001. In the ROC curve analysis, the PLR cut-off =144.32 (sensitivity 67%, specificity 76%) for the NLR cut-off =2.37 (sensitivity 62%, specificity 75%). On the other hand, the NLR and PLR were significantly higher in patients in relapse, but without any significant difference.

Conclusion NLR and PLR are good discriminatory markers between cases and controls; they are elevated in relapse patients but not significantly.

Keywords Crohn's disease, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, Biomarkers

INTRODUCTION

Crohn's disease (CD) has been the subject of several major studies and is attracting growing interest in the field of research because of its increasing frequency [1] and because of its complexity and complications. Being a progressive disease with a natural history, it can lead to very disabling complications with a high morbidity and mortality rate. This body of evidence underlines the importance of early diagnosis. Of all the diagnostic criteria: clinical, endoscopic, and morphological, biology seems to be lagging considerably because to date there is no discriminatory work-up for the diagnosis of Crohn's disease. Current biological markers, such as CRP and ESR, have limited specificity in detecting intestinal inflammation specially for the small intestine. Fecal calprotectin is a more accurate biomarker; however, its routine use remains restricted due to high costs and limited accessibility. This leads us to study other indices which would be more accessible to the clinician and the patient and which could serve as useful markers of systemic inflammation. A high NLR is associated with active disease, severe flares, and potential complications like fistulas or strictures. Similarly, an elevated PLR correlates with increased disease severity, a higher risk of thrombosis, and potential need for surgery. Both markers are easily obtainable from a routine blood test and can complement CRP and fecal calprotectin for disease monitoring. While not specific to CD, they provide a cost-effective tool for assessing inflammation and treatment response. In this context, the aim was to study the value of neutrophil-to-lymphocyte ratios and platelet-to-lymphocyte ratios between patients with Crohn's disease and control subjects, and the discriminatory impact of these indices on disease activity.

MATERIAL AND METHOD

Study population and design

A prospective observational bicentric case-control study carried out at the Douera and Blida University Hospital during all year long 2023. The study focused on 56 patients with CD diagnosed on the basis of clinical, biological, endoscopic, histological, and imaging data. The control group consisted of 56 patients in apparent good health. The Vienna classification was used to classify cases according to phenotype and location.

The inclusion criteria were any patient, of either sex, with CD aged 16 or over; the non-inclusion criteria were any patient aged under 16, pregnant women, and patients with other inflammatory diseases or pathologies that influence the biological work-up.

Collection of demographic, clinical, and paraclinical data

The following data were collected after careful questioning, a clinical examination, and a biological check-up: age, sex, BMI, tobacco intoxication, hemoglobin, neutrophil, lymphocyte, platelet, ESR, and CRP levels. Blood samples were taken in tubes containing different anticoagulants depending on the parameter being analyzed: EDTA for the CBC and heparin for the biochemical tests (CRP).

CD relapse was assessed by the Harvey Bradshaw score, a score of less than five points is generally considered to represent clinical remission, and the duration of the disease was calculated per year.

STATISTICAL ANALYSIS

The statistical analysis of the results of our study was carried out using IBM SPSS (Statistical Package for the Social Sciences) version 26.0.

The formula used to calculate the statistical power in your study is derived from the power formula for a two-sample independent t-test. The number of subjects was more than sufficient, with power for both markers greater than 96.3%

The distribution normality of all quantitative parameters was assessed using the Kolmogorov-Smirnov test. Categorical variables were compared using the chi-square test. For continuous variables, Student's T-test was applied to normally distributed data, while non-parametric data were analyzed using the Mann-Whitney U test.

The Pearson test was used to study the correlation between the biological parameters.

The NLR and PLR indices were tested using the ROC curve (receiver operating characteristic) to define the cut-off points. The air under the curve (AUC) was calculated. The Youden index was used to define cut-off values for each of these three markers, with an estimate of sensitivity (Se), specificity (Sp), and sensitivity (Se).

A two-tailed significance threshold of 5% was applied, with p-values <0.05 deemed statistically significant.

RESULTS

1. Demographic, biological, and descriptive data of patients

112 patients, 56 with Crohn's disease and 56 without (controls) participated in the whole study. The cases were divided into two categories according to disease activity: patients in relapse (32 cases) and those in remission (24 cases). In both categories of our population, the sex ratio was 1.55 (M/F).

The mean age of the population was 37.8 years [16-59], 35.9 ± 12 years for cases, and 37.8 ± 13.7 years for controls. 85.8% of patients were under 50 years of age.

The mean BMI in the cases was significantly lower (23.22 ± 4.26 vs 24.8 ± 3.7 Kg /m2, p<0.04). 17.9% of cases were thin compared with only 3.6% of controls. 21.4% of the cases were smokers but there was no significant difference with the controls.

Biologically, there was a significant difference in hemoglobin, lymphocyte, and platelet levels, but not in neutrophil levels.

The mean duration of Crohn's disease was 5.0±4.4 years, with a predominance of the structuring form (46.4%). The location of the disease was as follows: ileal 37.5%, colonic 26.8%, ileocolic 35.7%. Table 1 summarises the

epidemiological, clinical, and biological characteristics of our two groups.

2. Comparison of NLR and PLR ratio and main factors of inflammation between patients and controls

When we compared inflammation markers and indices between the two groups, we noted that in our patients there was no significant difference between the ESR of the two groups, unlike CRP (15. 89 ± 34.31 vs 2.16 ± 1.69, p=0.0001), NLR (2.8 ±1.5 vs 2.1 ± 1, p=0.049) and PLR (193.68 ± 89.62 vs 124.05 ± 40.60, p< 0.001) where the difference was significant (Table 2).

There was also a significant correlation between CRP and NLR (r=0.351, p=0.002) and also with PLR (r=0.234, p=0.01), although this result was not found with ESR where the correlation was not significant.

A significant correlation was observed between NLR and total leukocyte count (p<0.0001).

The ROC curve analysis showed greater precision for the PLR ratio with a cut-off of 144.32, sensitivity of 67%, and specificity of 76% (AUC: 0.74) than for the NLR index with a cut-off of 2.37, sensitivity of 62%, and specificity 75% (AUC: 0.65) (Figure 1).

3. Comparison of NLR, PLR, and other blood factors between active and remission CD

We also wanted to look for factors that could discriminate between patients in relapse and patients in remission. Our analysis revealed that ESR, CRP, hemoglobin, and neutrophil levels were significantly elevated in patients experiencing a relapse. Although NLR (3.06 ±1.48 vs 2.52 ±1.46) and PLR (209.53 ±103.09 vs 172.55 ±63.79) were also elevated, the differences did not reach statistical significance (Table 3)

DISCUSSION

Crohn's disease is a chronic inflammatory disease of multifactorial origin. Its diagnosis is based on well-established clinical, endoscopic, and morphological elements. The contribution of biology in this pathology is not very contributory, as is the case for ESR and CRP, which increase during active CD, but lack specificity and sensitivity when it comes to chronic inflammation [2]. Other factors appear to be more specific, such as fecal calprotectin, but this is still relatively expensive for routine use. This study aimed to use indices such as NLR and PLR to help with diagnosis, assessment of the relapse, and follow-up, as these two indices are inexpensive, reproducible, and accessible to all patients.

Although the role of neutrophils in CD is unclear, they are one of the essential mediators of innate immunity, and it appears that lymphocyte function is severely impaired in CD [3]. In practical terms, the NLR has been used in several studies, including gastric and colonic cancer, acute coronary syndrome, and acute pancreatitis [4-7].

Our findings reinforce the potential utility of hematological indices in CD diagnosis; however, their clinical application in monitoring disease activity remains debated, in our study, both the NLR and PLR indices were significantly higher in patients with CD compared with controls. These results confirm those of several studies reported in the literature, firstly, concerning the NLR index in the meta-analysis by Langley B.O [8] where: Ahmad et al (p < 0.05) [9], Chen et al (p =0.034) [10] and Feng et al (p<0.01) [11] had the same findings, which confirms our suggestion that these ratios may be discriminative in the diagnosis of CD. We then determined a cut-off by ROC curve analysis, which was 2.37, sensitivity 62%, specificity 75%, very comparable to that of Chen et al, which was 2.85 (69.2% sensitivity, 76.2% specificity) [10], Feng et al. 2.72 (68.3% sensitivity, 75.9% specificity) [11] and Gao et al. 2.13 (82.7% sensitivity, 76.9% specificity, 80.9%) [12].

Secondly, concerning the PLR index, the study by Carrillo-Palau, M [13] recently published in 2023 carried out on patients with IBD, found a significant difference between cases (n=197) and controls (n= 208) and a p<0.001.

The correlation between NLR and CRP in our series between subjects and controls was highly significant, as was also found in the study by the same authors, namely Feng et al. CRP (rs = 0.39, p < 0.01) and Gao et al. (rs = 0.327, p < 0.001).

Secondly, we wanted to see whether these two indices discriminated between patients with relapsing CD and patients in remission, and we found that the NLR and PLR indices were significantly higher in patients with relapsing CD, but not significantly so. The results in the literature are discordant on this subject and depend on the scores used to assess the clinical relapse. In studies using the same assessment score as our series (Harvey Bradshaw score), such as Acarturk et al [14], Xu et al [15], and Gold et al [16], the link was significant, whereas, in other studies using other activity scores such as the Cronh disease activity index (CDAI), no significant link was found between the NLR and disease flare-up in Gao et al. nor between the PLR of IBD carriers and a clinical flare-up in the paper by Carrillo-Palau, M

CONCLUSION

The contribution of the NLR and PLR indices in Crohn's disease is useful given their accessibility, low cost, and reproducibility, but they can be classed as complementary markers, although not sufficient on their own to make a diagnosis . In our study, they discriminate between cases and controls and correlate well with CRP. On the other hand, they lose their significance in the follow-up and evaluation of the relapse, which makes their use in this case unnecessary. We suggest using these indices only in the initial diagnosis, subject to other, larger studies.

Limitations: A larger sample would be required to obtain more detailed and perhaps more significant results in terms of the link between the two indices and clinical relapse.

Although they were minimal, a study of the subgroup of patients on immunosuppressants would have been useful.

Analysis of the contribution of other indices to endoscopic relapse

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This article has been made according to the STROBE Statement of case-control studies

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Figure 1 : ROC curve analysis for NLR and PLR between cases ans controls

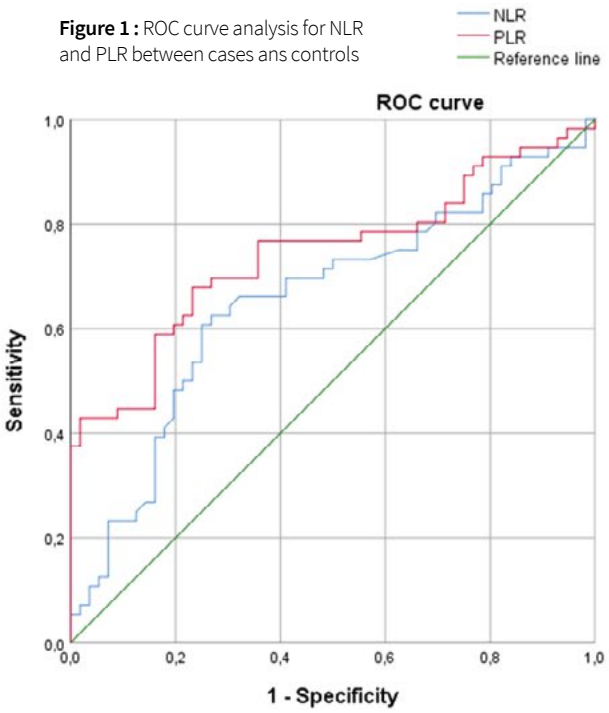

Tableau 1 : Caracteristics of patients and controls

	Crohn disease (n=56)	Control groupe (n=56)	*p*
Age (Years)	35.9 ± 12	37.8 ± 13.7	NS
Male (%)	60,7%	60,7%	NS
Body mass index (Kg	23,2 ± 4,3	24.8 ± 3.7	<0,04
Smoking (%)	21,4	17,9	NS
Hemoglobin (g/dl)	12,6 ± 2	13,7 ± 1,5	0,002
Neutrophiles (10^3 / u	4.8 ± 2	4.3 ±1.7	0.12
Lymphocyte (10^3 / u	2,0 ± 1.1	2.2 ± 0.6	0.005
Platelets (10^3 / uL)	313,1 ±86,8	254,1 ±55,9	0,0001
CRP (Mg/l)	15.89±34.31	2.16 ±1.69	0,0001
ESR (mm/h)	20,21±22,83	10,57±7,44	0,43
CD Activity (%)	32 (57,1%)	-	-
CD Duration (Years)	5,0 ± 4,4	-	-
CD Location (%)		-	-
A1 (Ileal)	21(37,5%)	-	-
A2 (Colonic)	15(26,8%)	-	-
A3 (Ileocolonic)	20(35,7%)	-	-
A4 (Upper intestinal	(0%)	-	-
CD Behavior (%)		-	-
B1 (Inflammatory)	14 (25%)	-	-
B2 (Structuring)	26(46,4%)	-	-
B3 (Penetrating)	16(28,6%)	-	-

CD : Crohn disease ; NS: non-significant

Tableau 2 : Comparaison of NLR and PLR ration with main factors of inflammation between patients and controls

	Crohn disease (n=56)	Control group (n=56)	*p*
NLR	2,8 ± 1,5	2,1 ± 1,0	0,049
PLR	193,7± 89,6	124,1± 40,6	< 0,001
ESR	20.2± 22.8	10.6± 7,4	0.43
CRP	15.9 ± 34.3	2.2 ± 1.7	0.0001

NLR: neutrophil-lymphocyte ratio; PLR : platelets-lymphocyte ratio ; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate

Tableau 3 : Comparaison of NLR, PLR and others bloods factors between active and remission CD

	CD Active (n=32)	CD Remission (n=24)	*p*
Hemoglobin (g/dl)	11.9± 1.9	13.5 ±1.8	0.003
Neutrophile (10^3 / uL)	5.2 ± 1.9	4.3 ± 2.0	0.023
Lymphocyte (10^3 / uL)	2.1± 1.3	1.9± 0.6	0.7
Platelets (10^3 / uL)	328.3 ±91.8	293.0± 77.0	0.134
NLR	3,1 ±1,5	2,5 ±1,5	0,101
PLR	209,5 ±103,1	172,6 ±63,8	0,188
ESR	28.4 ±25.9	9.3± 11.2	0.001
CRP	25.1 ±43.7	4,0± 4.2	0.0001

CD: Crohn's disease; NLR: neutrophil-lymphocyte ratio; PLR : platelets-lymphocyte ratio ;CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NS: non-significant