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Irritable bowel syndrome is associated with novel inflammatory markers derived from hemogram parameters

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that is associated with sub-clinical inflammation. Some hemogram parameters are thought to be novel inflammatory markers.
Objectives. We aimed to study novel inflammatory markers derived from hemograms and to compare them to those in healthy subjects.
Material and methods. The platelet distribution width (PDW), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) of patients with IBS were gathered from a database and compared to those in a healthy population.
Results. The PLR of the IBS group (144 ± 50%) was higher than the PLR of the control group (111 ± 32%; $p < 0.001$). The PDW of the IBS group (16.3 [1%]) was higher than the PDW of the control group (15.4 [2.4%]; p < 0.001). The NLR of the IBS group (2.2 [1.1%]) was higher than the NLR of the control group (1.8 [0.7%]; $p < 0.001$). The MLR of the IBS group (0.25 [0.14%]) was higher than the MLR of the control group (0.2 [0.12%]; $p < 0.001$).
Conclusions. We think that PDW, NLR, PLR, and MLR could all serve as diagnostic tools for IBS. Although the diagnosis of IBS is based on history and clinical findings, the simplicity and low cost of these hemogram tests could provide laboratory support in establishing a diagnosis, especially in suspected cases.
Key words: irritable bowel syndrome, inflammation, blood platelets.

Background

Irritable bowel syndrome (IBS) is a chronic functional bowel disease [1]. The severity of the disease varies widely; it can even be disabling. The prevalence of the disease is about 11.2% [2]. A diagnosis of IBS is established according to the Rome IV criteria, with the symptoms of recurrent abdominal pain while defecating or alterations in stool frequency or form [3]. Although there should be no biochemical or structural pathologies in order to make a diagnosis of IBS, recent data suggest that it may not be a single disease nor only a somatosensory condition [1]. The interrelation between mucosal immune cells and microorganisms of the gut flora, infection, and inflammation are suggested as the causes of IBS symptoms [4, 5].

Numerous indicators derived from routine hemogram tests have been suggested as novel markers of inflammation in inflammatory conditions. Of these, red cell distribution width (RDW) and mean platelet volume (MPV) have been shown to be higher in subjects with IBS compared to healthy individuals [6]. Some other hemogram parameters, including platelet distribution width (PDW), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), have also been suggested as inflammatory predictors in certain diseases, such as type 2 diabetes mellitus, cardiac conditions, thyroiditis, chronic obstructive pulmonary disease, familial Mediterranean fever, various cancers, osteoporosis, osteoarthritis, and rheumatoid arthritis [7–20].

Objectives

The data in the literature suggest a relationship between IBS and inflammatory markers. Therefore, we hypothesized that PDW, NLR, PLR, and MLR were associated with IBS. For this purpose, we compared the hemogram parameters of IBS patients to those in healthy volunteers.

Material and methods

Study design and setting

Our institution's medical records from December 2016 to July 2019 were retrospectively analyzed after the approval of the directory board was obtained.

The study protocol was approved by the Ethics Committee.

Study population

Patients diagnosed with IBS according to the Rome IV criteria were enrolled as the IBS group. Subjects that were defined as

healthy in routine check-ups in the outpatient internal medicine clinic were enrolled as a control group. Subjects with accompanying psychiatric disorders, cardiac conditions, diabetes mellitus, chronic kidney disease, cancer, active infection, or inflammatory conditions were excluded from the study. Patients being treated with aspirin, subjects with a history of recent surgery, or trauma within the previous six months were also excluded.

Laboratory analysis

Hemogram tests were performed within 10 minutes of venous blood samples being drawn into hemogram tubes containing an anticoagulant. The complete blood count analyses were performed in an LH 780 automatic analyzer (Beckman Coulter Inc., Brea, CA, USA). The manufacturer's original kits were used in the laboratory analyses.

The age and gender of the study population were recorded. The white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, hemoglobin (Hb) and hematocrit (Htc) values, mean corpuscular volume (MCV), platelet count (PLT), and PDW values of the study population were obtained from patients' files and from the medical database of our institution. The NLR, PLR, and MLR were calculated by simple division of the neutrophil count, PLT count, and monocyte count by the lymphocyte count, respectively.

Statistical analysis

Statistical analyses were carried out with SPSS software (SPSS 15.0; SPSS Inc., Chicago, IL, USA). The comparison of categorical variables in the study groups was done by a chi-squared test and are expressed as percentages. Variables with and without normal distribution were compared with the independent sample t-test and the Mann–Whitney U-test, respectively. Variables with and without normal distribution are expressed as mean ± standard deviation and median (interquartile range), respectively. A binary logistic regression analysis model was used for the role of PDW and NLR in determining the presence of IBS independently of other variables, such as age and gender. A p-value lower than 0.05 was considered to be statistically significant.

Results

The data of 215 patients with IBS who were admitted to the internal medicine clinic of the institution between December 2016 and July 2019 were screened. Of those patients, 76 were not enrolled in the study because they had one or more of the comorbidities mentioned above; an additional 30 were excluded because they were being treated with aspirin, and another 22 were excluded because of a recent surgery. The remaining 87 patients were enrolled in the IBS group. The control subjects consisted of 61 healthy subjects.

The median age of the IBS and control groups were 40 (26) and 38 (13) years, respectively (p = 0.73). There were 27 (31%) men and 60 (69%) women in the IBS group, while there were 26 (43%) men and 35 (57%) women in the control group (p = 0.15).

The levels of WBC (p = 0.17), Hb (p = 0.20), Htc (p = 0.38), MCV (p = 0.95), and PLT (p = 0.99) were not statistically different between the study groups. The PLR of the IBS group (144 ± 50%) was higher than the PLR of the control group (111 ± 32%). This difference was statistically significant (p < 0.001). Similarly, the PDW of the IBS group (16.3 [1%]) was higher than the PDW of the control group (15.4 [2.4%]) (p < 0.001). The NLR of the IBS group (2.2 [1.1%]) was higher than the NLR of the control group (1.8 [0.7%]). This difference between the study groups was statistically significant (p < 0.001). Similarly, the MLR of the IBS group (0.25 [0.14%]) was higher than the MLR of the control group (0.2 [0.12%]) (p < 0.001).

In binary logistic regression analysis, adjusted for age and gender, the Nagelkerke R square of the model was 0.512, and a 0.1-point increase in PDW significantly increased the rate of IBS threefold (OR: 3; 95% CI: 0.204–0.531; p < 0.001). Moreover, a 0.1-point increase in NLR level increased the incidence of IBS twofold (OR: 2; 95% CI: 0.253–0.934; p = 0.03).

Table 1 shows the characteristics and laboratory data of the study cohort.

Table 1. General characteristics and laboratory data of the study cohort		IBS group	Control Group	p
Gender	women (n, %)	60 (69%)	35 (57%)	0.15
	men (n, %)	27 (31%)	26 (43%)	
Median (IQR)				
Age (years)		40 (26)	38 (13)	0.73
WBC (k/mm³)		7,000 (2,880)	7,590 (2,450)	0.17
Hb (g/dL)		14 (2)	14.1 (1.4)	0.20
PDW (%)		16.3 (1)	15.4 (2.4)	**< 0.001**
NLR (%)		2.2 (1.1)	1.8 (0.7)	**< 0.001**
MLR (%)		0.25 (0.14)	0.2 (0.12)	**< 0.001**
Mean ± SD				
Htc (%)		41.6 ± 3.2	42 ± 3	0.38
MCV (fL)		87 ± 4	87 ± 4	0.95
PLT (k/mm³)		259,000 ± 62,000	259,000 ± 60,000	0.99
PLR (%)		144 ± 50	111 ± 32	**< 0.001**

Discussion

The main outcome of the present study is that novel inflammatory markers – PDW, NLR, PLR, and MLR – were higher in patients with IBS.

The variation in size of circulating platelets is measured by PDW in routine hemogram tests. Increased PDW suggests anisocytosis. In order to cover a larger surface area, platelets tend to change shape during activation; thus, the PDW of the platelets increases during activation [21]. Platelets develop pseudopodia during activation, which also results in an elevation in PDW. In general, PDW was considered to be a better indicator of platelet activation than MPV [21].

The role of PDW in various diseases has been studied in the literature. Some authors observed PDW in patients with diabetic retinopathy, a chronic inflammatory process, and found that the PDW level of these subjects was significantly higher than among the healthy controls [22]. High PDW levels were considered to be a prognostic factor for mortality by Rechcinski et al., who reported a correlation between elevated PDW and mortality in subjects with acute coronary syndrome [23]. Moreover, PDW was found to be higher in patients with ST-segment elevation myocardial infarction than that of the subjects with stable coronary heart disease [15]. In another report, a significant elevation in PDW in subjects with coronary heart disease and positive angiographic findings was found in comparison to those without positive angiographic findings [24]. PDW was not only associated with coronary heart disease, but also with type 2 diabetes mellitus. Some researchers have reported elevated PDW levels in subjects with type 2 diabetes mellitus compared to the PDW of healthy population [16, 25]. PDW was evaluated in a retrospective analysis in patients with sepsis, and higher PDW levels were found in deceased sepsis patients than in surviving patients [26]. Diabetes mellitus type 2, coronary artery disease, and sepsis are all characterized by engagement of inflammatory pathways in their pathogenesis. Similarly, IBS is closely related with inflammation [5]. Therefore, the higher PDW levels and

other inflammatory predictors derived from the hemograms of subjects with IBS in the present study could be a consequence of underlying inflammation. Higher PDW levels increased the presence of IBS threefold in our study.

There are many reports in the literature that concluded there is an association between NLR and inflammatory conditions. Increased NLR was suggested as an inflammatory marker which is as effective as C-reactive protein in patients with rheumatoid arthritis [27]. In another study, the authors reported that an elevated NLR level could predict the severity of mucosal disease in ulcerative colitis [28]. Furthermore, Han et al. found that high NLR levels were correlated with the severity of acute pancreatitis [29]. High NLR levels were noted during attacks in patients with Familial Mediterranean Fever [30]. These data suggest that increased NLR could be one of the inflammatory indices in certain diseases that are associated with inflammation. In accordance with reports in the literature, we reported elevated NLR levels in patients with IBS compared to that of the controls. Inflammation induces an increase in neutrophil count and a decrease in lymphocyte count, so NLR increases in such conditions. An increase in NLR increased the presence of IBS twofold in our study.

The correlation between PLR and sepsis is well-established, both in adults and in pediatric patients [31, 32]. Moreover, its role in rheumatologic diseases has also been studied. In a Chinese study, it was reported that PLR was higher in subjects with rheumatoid arthritis than in healthy controls [18]. PLR was suggested to have predictive value for vasculitis in Takayasu arteritis in another report [33]. The increased PLR levels in the IBS patients we found in our study is similar to the data in the literature. While inflammation stimulates platelet production, it also cause a decrease in lymphocyte count; all together cause an elevation in PLR levels.

The MLR was studied in various diseases characterized by inflammation. In a recent study in osteoarthritis, the authors suggested that MLR was an independent predictor of knee osteoarthritis [19]. Higher MLR levels were reported in patients with epithelial ovarian cancer than in the control subjects [34]. Moreover, MLR was significantly higher in patients with active tuberculosis compared to healthy subjects in a study from China [35]. Since the reports in the literature pointed out an MLR elevation in inflammatory conditions, the increased MLR in IBS found in our study is not surprising.

The relatively small study population and its retrospective nature are two limitations of our report. However, this is the first study in the literature to report an association between IBS and the hemogram markers NLR, PLR, MLR, and PDW.

Conclusions

We think that PDW, NLR, PLR, and MLR could all serve as diagnostic tools in IBS. Although the diagnosis of IBS is based on history and clinical findings, the simplicity and low cost of these hemogram tests could provide laboratory support in establishing a diagnosis, especially in suspected cases.

References

1. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol* 2016; 1: 133–146.
2. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 2012; 10: 712–721.
3. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology* 2016; 150: 1393–1407.
4. Guarner F, Malagelada JR. Gut flora in health and disease. *Lancet* 2003; 361: 512–519.
5. Camilleri M, Katzka DA. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. Genetic epidemiology and pharmacogenetics in irritable bowel syndrome. *Am J Physiol* 2012; 302: G1075–G1084.
6. Aktas G, Alcelik A, Tekce BK, et al. Red cell distribution width and mean platelet volume in patients with irritable bowel syndrome. *Gastroenterol Rev* 2014; 9: 160–163.
7. Aktas G, Sit M, Dikbas O, et al. Elevated neutrophil-to-lymphocyte ratio in the diagnosis of Hashimoto's thyroiditis. *Rev Assoc Med Bras* 2017; 63: 1065–1068.
8. Paliogiannis P, Fois AG, Sotgia S, et al. The neutrophil-to-lymphocyte ratio as a marker of chronic obstructive pulmonary disease and its exacerbations: a systematic review and meta-analysis. *Eur J Clin Inv* 2018; 48: e12984.
9. Duman TT, Aktas G, Atak BM, et al. Neutrophil to lymphocyte ratio as an indicative of diabetic control level in type 2 diabetes mellitus. *Afr Health Sci* 2019; 19: 1602–1606.
10. Uslu AU, Deveci K, Korkmaz S, et al. Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? *BioMed Res Int* 2013; 2013: 185317, doi: 10.1155/2013/185317.
11. Guthrie GJ, Charles KA, Roxburgh CS, et al. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol* 2013; 88: 218–230.
12. Fu H, Qin B, Hu Z, et al. Neutrophil- and platelet-to-lymphocyte ratios are correlated with disease activity in rheumatoid arthritis. *Clin Lab* 2015; 61: 269–273.
13. Atak B, Aktas G, Duman TT, et al. Diabetes control could through platelet-to-lymphocyte ratio in hemograms. *Rev Assoc Med Bras* 2019; 65: 38–42.
14. Kokcu A, Kurtoglu E, Celik H, et al. May the platelet to lymphocyte ratio be a prognostic factor for epithelial ovarian cancer? *Asian Pac J Cancer Prevent* 2014; 15: 9781–9784.
15. Cetin M, Bakirci EM, Baysal E, et al. Increased platelet distribution width is associated with ST-segment elevation myocardial infarction and thrombolysis failure. *Angiology* 2014; 65: 737–743.
16. Atak BM, Duman TT, Aktas G, et al. Platelet distribution width is associated with type 2 diabetes mellitus and diabetic nephropathy and neuropathy. *Nat J Health Sci* 2018; 3: 95–98.
17. Zaccardi F, Rocca B, Pitocco D, et al. Platelet mean volume, distribution width, and count in type 2 diabetes, impaired fasting glucose, and metabolic syndrome: a meta-analysis. *Diabetes Metab Res Rev* 2015; 31: 402–410.
18. Chen Q, Chen DY, Xu XZ, et al. Platelet/lymphocyte, lymphocyte/monocyte, and neutrophil/lymphocyte ratios as biomarkers in patients with rheumatoid arthritis and rheumatoid arthritis-associated interstitial lung disease. *Med Sci Monit* 2019; 25: 6474–6481.
19. Gao K, Zhu W, Liu W, et al. Diagnostic value of the blood monocyte-lymphocyte ratio in knee osteoarthritis. *J Int Med Res* 2019; 47(9): 4413–4421.
20. Gao K, Zhu W, Liu W, et al. The predictive role of monocyte-to-lymphocyte ratio in osteoporosis patient. *Medicine* 2019; 98: e16793, doi: 10.1097/MD.0000000000016793.

21. Vagdatli E, Gounari E, Lazaridou E, et al. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. *Hippokratia* 2010; 14: 28–32.
22. Ji S, Ning X, Zhang B, et al. Platelet distribution width, platelet count, and plateletcrit in diabetic retinopathy: a systematic review and meta-analysis of PRISMA guidelines. *Medicine* 2019; 98: e16510, doi: 10.1097/MD.0000000000016510.
23. Rechcinski T, Jasinska A, Forys J, et al. Prognostic value of platelet indices after acute myocardial infarction treated with primary percutaneous coronary intervention. *Cardiol J* 2013; 20: 491–498.
24. Ihara A, Kawamoto T, Matsumoto K, et al. Relationship between hemostatic factors and the platelet index in patients with ischemic heart disease. *Pathophysiol Haemost Thromb* 2006; 35: 388–391.
25. Jindal S, Gupta S, Gupta R, et al. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. *Hematology* 2011; 16: 86–89.
26. Orak M, Karakoc Y, Ustundag M, et al. An investigation of the effects of the mean platelet volume, platelet distribution width, platelet//lymphocyte ratio, and platelet counts on mortality in patents with sepsis who applied to the emergency department. *Nigerian J Clin Pract* 2018; 21: 667–671.
27. Chandrashekara S, Mukhtar Ahmad M, Renuka P, et al. Characterization of neutrophil-to-lymphocyte ratio as a measure of inflammation in rheumatoid arthritis. *Int J Rheum Dis* 2017; 20: 1457–1467.
28. Akpinar MY, Ozin YO, Kaplan M, et al. Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio predict mucosal disease severity in ulcerative colitis. *J Med Biochem* 2018; 37: 155–162.
29. Han C, Zeng J, Lin R, et al. The utility of neutrophil to lymphocyte ratio and fluid sequestration as an early predictor of severe acute pancreatitis. *Sci Rep* 2017; 7: 10704, doi: 10.1038/s41598-017-10516-6.
30. Basaran O, Uncu N, Celikel BA, et al. Assessment of neutrophil to lymphocyte ratio and mean platelet volume in pediatric familial Mediterranean fever patients. *J Res Med Sci* 2017; 22: 35, doi: 10.4103/1735-1995.202140.
31. Shen Y, Huang X, Zhang W. Platelet-to-lymphocyte ratio as a prognostic predictor of mortality for sepsis: interaction effect with disease severity-a retrospective study. *BMJ Open* 2019; 9: e022896, doi: 10.1136/bmjopen-2018-022896.
32. Can E, Hamilcikan S, Can C. The value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio for detecting early-onset neonatal sepsis. *J Pediatr Hematol Oncol* 2018; 40: e229–e232.
33. Pan L, Du J, Li T, et al. Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio associated with disease activity in patients with Takayasu's arteritis: a case-control study. *BMJ Open* 2017; 7: e014451, doi: 10.1136/bmjopen-2016-014451.
34. Cao Y, Ni X, Wang Y, et al. Clinical and prognostic significance of combined plasma fibrinogen concentrations and the monocyte-to--lymphocyte ratio in patients with ovarian cancer. *Ann Transl Med* 2019; 7: 242, doi: 10.21037/atm.2019.04.78.
35. Wang W, Wang LF, Liu YY, et al. Value of the ratio of monocytes to lymphocytes for monitoring tuberculosis therapy. *Can J Infect Dis Med Microbiol* 2019; 2019: 3270393, doi: 10.1155/2019/3270393.

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