ORIGINAL PAPERS

Red cell distribution width-to-platelet count ratio is a promising predictor of functional bowel disease

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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.** Hemogram parameters are not only diagnostic tools in haematological diseases, but their role in inflammatory conditions is also important. One of these haematological markers is a derived index, the so-called red cell distribution width-to-platelet count ratio (RPR). The role of RPR has been well established in various inflammatory conditions.
Objectives. In the present study, we aimed to observe the RPR levels of patients with functional bowel disease (FBD), which is also considered as an inflammatory process, and to compare this to the healthy population.
Material and methods. Patients diagnosed with FBD according to Rome IV criteria were included as the study group. Healthy volunteers were enrolled as control subjects. Patients with any form of anaemia or haematological disorders or inflammatory diseases were excluded. Age, gender and hemogram parameters were obtained from institutional databases. The data of the study and control groups was compared.
Results. 158 subjects were enrolled in the study; 87 in the FBD group and 71 in the control group. The RPR of the FBD and control groups were 7% (2%) and 5% (1%), respectively. The difference in RPR between the FBD and control groups was statistically significant ($p = 0.008$). A RPR value higher than 6% has a 70% sensitivity and 52% specificity in detecting FBD. There was a significant and positive correlation between RPR levels and the presence of FBD ($r = 0.22$, $p = 0.007$).
Conclusions. We suggest that elevated RPR levels could yield potential diagnostic benefits in the diagnosis of FBD. However, prospective studies with a larger population are needed to confirm our results.
Key words: erythrocyte indices, blood platelets, inflammation.

Background

Hemogram parameters have gained the attention of scientist in recent years. Both diagnostic potential in haematological diseases and predictive role in inflammatory condition of hemogram parameters make them the subject of recent studies in literature. One of these haematological markers is a derived index, the so-called red cell distribution width-to-platelet count ratio (RPR). RPR has been associated with various clinical conditions in medical literature. These conditions include rheumatoid arthritis, autoimmune hepatitis, cardiovascular morbidities, mortality of burned patients and acute pancreatitis [1–5].

Functional bowel disease (FBD) is characterised by abdominal discomfort and pain, a change in bowel habits and flatulence. Interactions between mucosal immunity and microbiological gut flora, infections and inflammation are three possible mechanisms of the development of functional bowel disease [6–9]. Since it affects nearly one third of the world population, it could not be classified as a rare condition [10]. Therefore, FBD imposes an enormous burden on healthcare systems and makes up a large proportion of hospital visits [11].

An association between inflammatory markers and one of the functional bowel diseases, irritable bowel syndrome (IBS), has been well established in literature [12, 13].

Objectives

There is strong evidence of a correlation between FBD and inflammation; therefore, in the present study, we aimed to observe the RPR levels of patients with FBD and to compare this to the healthy population.

Material and methods

Study design and setting

Patients visiting the outpatient internal medicine clinics of our institution with a diagnosis of FBD between January 2020 and April 2021 were enrolled in the present retrospective analysis. The institutional ethics committee approved the study (approval no: 2021-141). Rome IV criteria were used in the establishment of FBD. These subjects were grouped in the FBD group, while healthy volunteers visiting the institutional outpatient internal medicine clinics for a routine check-up were grouped as the control group. Patients with any kind of anaemia or haematological disorders, inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, with recent infectious diseases, with cancer, type 2 diabetes mellitus, chronic renal insufficiency and advanced heart failure were excluded.

Table 1. General characteristics of the study groups				
		FBD	Control	*p*
		X^2		
Sex	Men (*n*, %)	27 (31%)	31 (43%)	0.15
	Women (*n*, %)	60 (69%)	40 (57%)	
		mean ± SD		
Age (years)		41 ± 14	41 ± 11	0.85
HB (g/dL)		14 ± 1.1	14.2 ± 1	0.18
HTC (%)		42 ± 3	42 ± 3	0.38
MCV (fL)		87 ± 4	87 ± 4	0.95
		Median (IQR)		
WBC (k/mm³)		7 (2.8)	7.6 (2.5)	0.17
PLT (k/mm³)		235 (72)	256 (80)	0.08
RDW (%)		16 (1.2)	15.7 (1)	**0.03**
RPR (%)		7 (2)	5 (1)	**0.008**

Laboratory analyses

Age, gender and hemogram parameters including white blood cell count (WBC), haemoglobin (HB), haematocrit (HTC), mean erythrocyte volume (MCV), erythrocyte distribution width (RDW) and platelet count (PLT) were obtained from institutional databases. A RPR value was calculated by division of RDW by PLT.

All haematological analyses were carried out within 15 minutes after drawing of blood samples into sterile tubes containing a constant amount of EDTA. The LH 780 automatic analyser (Beckman Coulter Inc., Brea, CA, USA) was used in hemogram analyses. The study variables of FBD and control groups were compared.

Statistical analyses

SPSS software (SPSS 15.0; SPSS Inc., Chicago, IL, USA) was used in statistical analyses. Normality of the study variables was conducted using the Kolmogorov-Smirnov test. Either the independent samples *t*-Test (for variables with normal distribution) or the Mann-Whitney U test (for variables without normal distribution) were used in the comparison of parametric variables. These variables were expressed either as mean ± standard deviation (variables with normal distribution) or median (IQR) (variables without normal distribution). Comparison of non-parametric variables were carried out with the X^2 test and were expressed as numbers and percentage. The sensitivity and specificity of RPR in determining FBD were analysed with the ROC curve test. The correlation between FBD and RPR was analysed with the Spearman's correlation analysis. When the *p*-value was lower than 5%, it was considered statistically significant.

Results

158 subjects were enrolled to the study; 87 in the FBD group and 71 in the control group. 27 (31%) were men and 60 (69%) were women in the FBD group, and 31 (43%) were men and 40 (57%) were women in the control group. Gender was not statistically different between the study groups (*p* = 0.15). The mean age of the FBD and control groups were 41 ± 14 years and 41 ± 11 years, respectively (*p* = 0.85). The WBC (*p* = 0.17), HB (*p* = 0.18), HTC (*p* = 0.38), MCV (*p* = 0.95) and PLT (*p* = 0.08) levels of the FBD and control groups were not statistically different. The RDW of the FBD group was higher than that of the control group (*p* = 0.03).

The RPR of the FBD and control groups were 7% (2%) and 5% (1%), respectively. The difference in RPR between the FBD and control groups was statistically significant (*p* = 0.008). Table 1 shows the data of the study groups.

A RPR value higher than 6% has 70% sensitivity and 52% specificity in detecting FBD (AUC: 0.63, *p* = 0.008, 95% CI: 0.53–0.72). Figure 1 shows the sensitivity and specificity of RPR in detecting FBD.

There was a significant and positive correlation between RPR levels and the presence of FBD (*r* = 0.22, *p* = 0.007).
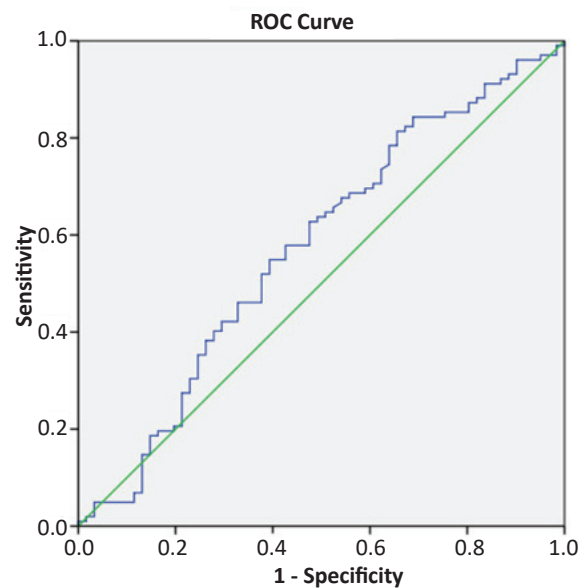

Figure 1. Sensitivity and specificity of RPR in detecting FBD

Discussion

The present study showed that RPR is a reliable and sensitive marker of FBD. Moreover, we showed that RPR has a significant positive correlation with the disease and has high sensitivity and considerable specificity in selecting patients with FBD.

Inflammatory diseases have been reported to be associated with elevated RPR levels in recent literature. Taefi et al. found increased RPR levels in subjects with chronic hepatitis, and they also concluded that the degree of fibrosis was better correlated with the RPR than MELD score [14]. Subsequently, fibrosis in patients with chronic hepatitis C was found to be associated with blood RPR levels in a study by Karagöz et al. in 2016 [15]. Not only fibrosis in chronic hepatitis but also in non-alcoholic fatty liver disease has been reported to be correlated with blood RPR levels [16]. Moreover, RPR was suggested to be correlated with the severity of primary biliary cirrhosis [17]. In another study, RPR has been suggested as a diagnostic and follow-up tool in pa-

tients with patent ductus arteriosus [18]. Increased RPR yields potential diagnostic or prognostic benefits in systemic lupus erythematosus [19], colorectal cancer [20], myocardial infarction [21], breast cancer [22] and acute traumatic brain injury [23]. All of these conditions are associated with subtle or prominent levels of inflammatory burden. Since FBD is also associated with inflammatory response in the microvasculature of the bowel, increased RPR in FBD is not a surprising finding.

The association between inflammation and functional bowel disease is well established. There are numerous studies in literature that report upon the correlation between inflammation and irritable bowel syndrome, a type of FBD [12, 13, 24]. Moreover, there is evidence that chronic, low-grade inflammation at the microscopic level in the bowel of patients with FBD accompanies the disease [25]. Inflammatory cytokines, such as, interleukin-6 and interleukin-8, were also found to be increased in patients with irritable bowel disease [26]. This evidence suggests that inflammation may be somewhat involved in the pathogenesis of FBD. Since RPR is a novel inflammatory marker, it is increased in FBD, another inflammatory condition.

Overlap syndrome of inflammatory bowel disease and FBD (especially irritable bowel syndrome) has been reported in recent studies. A recent meta-analysis suggested that 40% of patients with inflammatory bowel disease experience symptoms of FBD [27]. Subsequently, Gracie et al.'s study supported those findings in this meta-analysis [28]. Bowel functions and intestinal permeability are suggested to be altered by ongoing, chronic inflammation in inflammatory bowel disease and irritable bowel syndrome, thus causing similar symptoms in these conditions [29]. Histological examination of the intestinal biopsy materials of patients with inflammatory bowel disease and irritable bowel syndrome reveal a common pathology – increased permeability of the intestines [29]. This data suggests that inflammation could be a triggering factor in irritable bowel syndrome, a type of FBD, as in inflammatory bowel disease. Increased RPR in FBD could be also explained by this phenomenon.

Limitations of the study

The present study has two important limitations. The design of the study was retrospective, which could cause selection bias. Control of the accompanied factors is also difficult in a retrospective analysis. The second possible limitation could be the small size of study cohort. However, to the best of our knowledge, this is the first study in literature that showed a significant association between FBD and blood RPR levels.

Conclusions

We think that elevated RPR levels could yield potential diagnostic benefits in the diagnosis of FBD. However, prospective studies with a larger population are needed to confirm our results.

References

1. Derviševic A, Muhic A, Začiragic A, et al. Red blood cell distribution width-to-platelet ratio inversely correlates with indicators of disease activity status in rheumatoid arthritis patients. *Rom J Intern Med* 2021; 59(2): 180–186, doi: 10.2478/rjim-2020-0044.
2. Li X, Xu H, Gao P. Red Blood Cell Distribution Width-to-Platelet Ratio and Other Laboratory Indices Associated with Severity of Histological Hepatic Fibrosis in Patients with Autoimmune Hepatitis: A Retrospective Study at a Single Center. *Med Sci Monit* 2020; 26: e927946-1–e927946-10, doi: 10.12659/MSM.927946.
3. Zhu X, Li G, Li S, et al. Neutrophil-to-lymphocyte ratio and red blood cell distribution width-to-platelet ratio predict cardiovascular events in hemodialysis patients. *Exp Ther Med* 2020; 20(2): 1105–1114, doi: 10.3892/etm.2020.8756.
4. Angulo M, Moreno L, Aramendi I, et al. Complete Blood Count and Derived Indices: Evolution Pattern and Prognostic Value in Adult Burned Patients. *J Burn Care Res* 2020; 41(6): 1260–1266, doi: 10.1093/jbcr/iraa091.
5. Arora S, Patro S, Nath P et al. Red cell distribution width(RDW) to platelet ratio (RPR): A novel marker in early prediction of severity of Acute Pancreatitis. *JAPI* 2020; 68: 88.
6. Camilleri M, Katzka DA. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. Genetic epidemiology and pharmacogenetics in irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol* 2012; 302(10): G1075–G1084, doi: 10.1152/ajpgi.00537.2011.
7. Guarner F, Malagelada JR. Gut flora in health and disease. *Lancet* 2003; 361: 512–519, doi: 10.1016/s0140-6736(03)12489-0.
8. Törnblom H, Lindberg G, Nyberg B, et al. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. *Gastroenterology* 2002; 123: 1972–1979.
9. Spiller RC. Postinfectious irritable bowel syndrome. *Gastroenterology* 2003; 124: 1662–1671.
10. Hungin AP, Whorwell PJ, Tack J, et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther* 2003; 17(5): 643–650, doi: 10.1046/j.1365-2036.2003.01456.x.
11. Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. *J Gastrointestin Liver Dis* 2006; 15(3): 237–241.
12. Aktas G, Alcelik A, Tekce BK, et al. Red cell distribution width and mean platelet volume in patients with irritable bowel syndrome. *Prz Gastroenterol* 2014; 9: 160–163, doi: 10.5114/pg.2014.43578.
13. Aktas G, Duman T, Atak B, et al. Irritable bowel syndrome is associated with novel inflammatory markers derived from hemogram parameters. *Fam Med Prim Care Rev* 2020; 22(2): 107–110.
14. Taefi A, Huang CC, Kolli K, et al. Red cell distribution width to platelet ratio, a useful indicator of liver fibrosis in chronic hepatitis patients. *Hepatol Int* 2015; 9: 454–460, doi: 10.1007/s12072-015-9638-9.
15. Karagöz E, Tanoğlu A, Ülçay A, et al. Mean platelet volume and red cell distribution width to platelet ratio for predicting the severity of hepatic fibrosis in patients with chronic hepatitis C. *Eur J Gastroenterol Hepatol* 2016; 28(7): 744–748, doi: 10.1097/MEG.0000000000000647.
16. Zhou WJ, Yang J, Zhang G, et al. Association between red cell distribution width-to-platelet ratio and hepatic fibrosis in nonalcoholic fatty liver disease: a cross-sectional study. *Medicine* 2019; 98: e16565, doi: 10.1097/md.0000000000016565.
17. Wang H, Xu H, Wang X, et al. Red Blood Cell Distribution Width to Platelet Ratio is Related to Histologic Severity of Primary Biliary Cirrhosis. *Medicine* 2016; 95: e3114, doi: 10.1097/md.0000000000003114.
18. Özer Bekmez B, Tayman C, Büyüktiryaki M, et al. A promising, novel index in the diagnosis and follow-up of patent ductus arteriosus: red cell distribution width-to-platelet ratio. *J Clin Lab Anal* 2018; 32(9): e22616, doi: 10.1002/jcla.22616.

19. Xie S, Chen X. Red blood cell distribution width-to-platelet ratio as a disease activity-associated factor in systemic lupus erythematosus. *Medicine* 2018; 97: e12342, doi: 10.1097/md.0000000000012342.

20. Bilgin B, Sendur MAN, Hizal M, et al. Prognostic effect of red cell distribution width-to-platelet ratio in colorectal cancer according to tumor stage and localization. *J Cancer Res Ther* 2019; 15(1): 54–60, doi: 10.4103/jcrt.JCRT_624_17.

21. Celık T, Balta S, Demır M, et al. Predictive value of admission red cell distribution width-platelet ratio for no-reflow phenomenon in acute ST segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Cardiol J* 2016; 23: 84–92, doi: 10.5603/CJ.a2015.0070.

22. Takeuchi H, Abe M, Takumi Y, et al. Elevated red cell distribution width to platelet count ratio predicts poor prognosis in patients with breast cancer. *Sci Rep* 2019; 9: 3033, doi: 10.1038/s41598-019-40024-8.

23. Ge X, Zhu L, Li W, et al. Red Cell Distribution Width to Platelet Count Ratio: A Promising Routinely Available Indicator of Mortality for Acute Traumatic Brain Injury. *J Neurotrauma* 2022; 39(1–2): 159–171, doi: 10.1089/neu.2020.7481.

24. Atak BM, Erkus E, Duman TT, et al. Mean Platelet volume to platelet and red cell distribution width to platelet ratios in Irritable Bowel Syndrome. *Exp Biomed Res* 2018; 1: 60–63.

25. Ng QX, Soh AYS, Loke W, et al. The role of inflammation in irritable bowel syndrome (IBS). *J Inflamm Res* 2018; 11: 345–349, doi: 10.2147/JIR.S174982.

26. Clarke G, Quigley EM, Cryan JF et al. Irritable bowel syndrome: towards biomarker identification. *Trends Mol Med* 2009; 15(10): 478–489, doi: 10.1016/j.molmed.2009.08.001.

27. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2012; 107: 1474–1482, doi: 10.1038/ajg.2012.260.

28. Gracie DJ, Williams CJ, Sood R, et al. Negative Effects on Psychological Health and Quality of Life of Genuine Irritable Bowel Syndrome-type Symptoms in Patients with Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2017; 15(3): 376–384, doi: 10.1016/j.cgh.2016.05.012.

29. Vivinus-Nébot M, Frin-Mathy G, Bzioueche H, et al. Functional bowel symptoms in quiescent inflammatory bowel diseases: role of epithelial barrier disruption and low-grade inflammation. *Gut* 2014; 63: 744–752, doi: 10.1136/gutjnl-2012-304066.

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