The utility of platelet, mean platelet volume, and red cell distribution width in the diagnosis of active Crohn's disease and intestinal tuberculosis

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ABSTRACT

الأهداف: تقييم التشخيص المساعد في عدد الصفائح الدموية، ومتوسط حجم الصفائح، ونطاق توزيع الخلايا الحمراء في المرضى الذين يعانون من مرض داء كرون النشط والسل المعوي مقارنة مع أعراض مرض القولون العصبي.

الطريقة: أجريت هذه الدراسة في قسم أمراض الجهاز الهضمي، مستشفى جونجان، جامعة وولان، وولان، الصين. اشتملت الدراسة على 68 مريض يعانون من مرض داء كرون النشط، 35 مع مرض السل المعوي و22 بدون أعراض الأمراض السابقة قاموا بالتطوع. حيث تمت الدراسة والتحقق من فحص الدما لروتيني المتضمن لكريات الدم البيضاء، كريات الدم الحمراء، عدد الصفائح الدموية، حجم الصفائح الدموية المتوسطة، وعرض توزيع كريات الدم الحمراء.

النتائج: مرض داء كرون النشط ومرض السل المعوي قاما بزيادة كريات الدم البيضاء، عدد الصفائح الدموية، رفع عرض توزيع كريات الدم الحمراء، وخفض حجم الصفائح الدموية المتوسطة ($p>0.05$، على الترتيب). ظهرت علاقة طردية بين مستوى عدد الصفائح الدموية مع البروتين المتفاعل C ومعدل ترسيب كريات الدم الحمراء في كلا المرضين، و علاقة عكسية بين حجم الصفائح الدموية المتوسطة مع البروتين المتفاعل C ومعدل ترسيب كريات الدم الحمراء فقط في مرض داء كرون النشط ($p>0.05$، على الترتيب). كان توزيع كريات الدم الحمراء هو الأفضل في التنبؤ بكل من مرض داء كرون النشط والسل المعوي على حد سواء (OR = 2.390 و= OR 2.338). كان تصرف عدد الصفائح الدموية أفضل كمؤشر لمرض داء كرون النشط. ومع ذلك، فإن حساسية ونوعية عدد الصفائح الدموية، حجم الصفائح الدموية المتوسطة، أو عرض توزيع كريات الدم الحمراء كانت منخفضة.

خاتمة: في تشخيص كلا المرضين على حد سواء، عدد الصفائح الدموية وحجم الصفائح الدموية المتوسطة، وكذلك عرض توزيع كريات الدم الحمراء–الأحادية أو المتحدة– قدمت قيمة معينة وجديرة باهتمام الأطباء، في حين أنها كانت لا تزال تكميلية ولا يمكن أن تحل محل البروتين المتفاعل C ومعدل ترسيب كريات الدم الحمراء.

Objectives: To evaluate the diagnostic utility of platelet count (PLT), mean platelet volume (MPV), and red cell distribution width (RDW) in patients with active Crohn's disease (CD) and intestinal tuberculosis (ITB).

Methods: This study was conducted in the Department of Gastroenterology, Zhongnan Hospital of Wuhan University, Wuhan, China. Sixty-eight patients with active CD, 35 with ITB, and 22 as control group were recruited. Blood routine test including white blood cell, red blood cell, PLT, MPV, RDW, and so forth was investigated.

Results: Patients with active CD and ITB have increased PLT and RDW (both $p<0.001$), and decreased MPV ($p=0.002$). The RDW performed preferably in predicting both active CD (odds ratio [OR]=2.390, $p=0.007$), and ITB (OR=2.338, $p=0.017$), and had better diagnostic value (area under the receiver operating characteristics curve [AUC] - 0.812; $p<0.001$) than CRP (AUC - 0.716; $p=0.007$) and ESR (AUC - 0.804; $p<0.001$) in ITB diagnosis.

Conclusion: Among the laboratory markers, RDW not only possessed the favorable capability to predict active CD, but also showed outstanding predicting capability, and good diagnostic value in ITB.

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The pathogenesis of Crohn's disease (CD) remains unknown, and the diagnosis and judgment of active CD is still a challenge for physicians to treat this disease. A combination of symptoms, laboratory examinations, and endoscopy with histology is commonly applied to make the diagnosis, assess severity, and predict the outcomes of disease.[1] An ideal marker should be easy and rapid to perform, cheap, and reproducible for the evaluation of activity of the disease. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) has been widely used and highlighted in the judgment of activity of inflammation diseases, and is recognized as the best laboratory marker for active CD. However, it is still far from ideal.[2] Blood routine tests, which include white blood cells (WBC), red blood cells (RBC), platelet count (PLT), and so forth is the most common laboratory indices for clinical use. However, it is also considered as an easily neglected detection in clinics. Studies on platelets in inflammatory bowel disease (IBD) have been put into execution. It is shown that platelet count (PLT) increase has been observed, and it plays a crucial role in hypercoagulable state of IBD, which results in a high probability of microvascular thrombosis and microcirculation dysfunction.[3,4] Moreover, other type of platelets, such as reticulated platelets was also stated as a significant marker for ulcerative colitis.[3] Mean platelet volume (MPV), a parameter related to platelet function, refers to the average size of platelets, and can reflect changes both in the platelet stimulation and production rate. Kapsoritakis et al[5] proposed that MPV is significantly reduced in active IBD, and is negatively correlated with the known activity markers, such as WBC count, CRP, and ESR. However, a study did not find this parameter useful in differentiating the disease activity.[6] The reason for MPV decrease may be correlated with thrombopoiesis disturbance in the early stages of systemic inflammatory processes.[5] Red cell distribution width (RDW), a laboratory measure of the heterogeneity of erythrocyte size, is usually used in the differential diagnosis for clinical physicians. Although RDW value is highlighted in iron deficiency rather than in chronic disease, RDW is potentially correlated with immunologic activity and chronic inflammatory diseases. One pilot study reported that RDW could be applicable to differentiate between CD and ulcerative colitis (UC).[7] A study showed that high RDW values are significantly correlated to alternated CRP and ESR levels.[8] Moreover, the association between increased RDW and active IBD was evident in IBD patients with and without anemia.[9] Tuberculosis is quite common in developing countries, and intestinal tuberculosis (ITB) is the sixth most common extrapulmonary tuberculosis.[10] The ITB presents with diverse clinical manifestations and mimics clinical entities of CD. Differentiation between ITB and CD is still a crucial challenge.[11] In the present study, we investigated whether PLT, MPV, and RDW could be useful in the diagnosis of CD or ITB compared with irritable bowel syndrome (IBS) as control, and then analyzed, and compared the utility of these markers compared with CRP and ESR. In addition, we examined whether these markers could be helpful to differentiate active CD and ITB.

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Methods. Sixty-eight patients with active CD hospitalized at the Department of Gastroenterology, Zhongnan Hospital of Wuhan University, Wuhan, China from January 2010 to January 2012 were included in the current respective study. Patients with the coexistence of other severe systemic or infectious diseases were excluded. The patients with active CD were diagnosed by clinical, endoscopic, radiological, histopathological means on the basis of the diagnostic criteria.[12] The selection of active CD patient was according to the simplified Crohn's Disease Activity Index (HBI).[13] The CD patients with HBI >4 were defined as active CD. Simultaneously, 35 patients with ITB, and 22 patients with IBS diarrhea (IBS-D) were collected in Zhongnan Hospital of Wuhan University. The diagnosis of ITB was according to radiology, endoscopy, pathology and diagnostic treatment of anti-tuberculosis drugs. The diagnosis of IBS-D was according to the guidelines.[14] All subjects were unrelated people in Hubei province without history of IBD, immune, ischemia, or radiation diseases. All patients and controls have never received any medication such as aspirin, oral contraceptives, nonsteroidal anti-inflammatory drugs, or oral anticoagulants, which can cause platelet or coagulation, and fibrinolytic abnormalities during the last 8 weeks before blood sampling. The ethics committee of Zhongnan Hospital of Wuhan University approved the study. Written consent was obtained from all subjects. Fasting blood samples were obtained from all subjects. Samples for blood routine test were collected into sterile vacuum tubes within ethylenediaminetetraacetic acid (EDTA) tripotassium salt, while samples for

ESR and CRP were collected into tubes containing sodium citrate. Blood routine test, ESR, and CRP were determined using automatic devices.

The statistical analysis was conducted with Statistical Package for Social Sciences version 13 for Windows (SPSS Inc, Chicago, IL, USA). Measurement data were presented as mean ± standard deviation or mean rank, and numeration data are expressed as number of cases. Chi-square test was used for categorical variables. Laboratory indices normally distributed were analyzed with a t-test for 2 independent samples, or one-way analysis of variance (ANOVA, Welch) for 3 independent samples, and the variables abnormally distributed were managed with Mann Whitney test, or Kruskal Wallis test instead. Spearman correlative analysis was performed to detect the relationship among these markers. Binary logistic regression was used to determine the association of markers and disease. The diagnostic utility was evaluated by means of receiver operating characteristics (ROC) curve analysis. Optimal cut-off value, as well as the sensitivity, specificity, Youden index, and diagnostic accuracy of indices were calculated as well. The overall performance was expressed in terms of the area under the ROC curve (AUC) with 95% confidence interval (CI). All calculated *p*-values were 2-sided, and a $p<0.05$ was considered significant.

Results. ***Demographic profiles and laboratory markers of patients.*** As shown in **Table 1**, patients with ITB and active CD were younger than IBS patients. Active CD and IBS seemed to have longer disease duration than ITB hospitalized. The distribution of ITB showed that 17.1% had ileal, 54.3% had colonic, and 28.6% had ilea-colonic involvement. The clinical findings in active CD were as follows: 50% ileitis, 32.4% colitis, and 17.6% ileocolitis. Furthermore, ITB and active CD had lower albumin concentration ($p<0.001$), increased WBC ($p=0.003$), and PLT count ($p<0.001$), increased RDW ($p<0.001$), and decreased MPV ($p=0.002$). Active CD was more apt to get anemia ($p=0.005$) compared with ITB (**Table 2**). However, no significant difference was found in the markers above between active CD and ITB (data not shown).

Relationship between MPV, RDW, PLT and other disease indices. Based on Spearman correlative analysis,

Table 1 - Demographic and clinical characteristics of patient's included in a study at the Department of Gastroenterology, Zhongnan Hospital of Wuhan University, Wuhan, China.

Variables	Control group (n=22)	Intestinal tuberculosis (n=35)	Crohn's disease (n=68)
Age, years	55.9 ± 15.7	36.0 ± 14.9	35.5 ± 12.9
Gender			
M	12	19	43
F	10	16	25
Duration of disease (months)	37.6 ± 63.0	16.0 ± 29.3	38.3 ± 45.7
Localization of the disease, n(%)			
Ileitis	N/A	6 (17.1)	34 (50.0)
Colitis	N/A	19 (54.3)	22 (32.4)
Ileocolitis	N/A	10 (28.6)	12 (17.6)

Table 2 - Comparison analysis of laboratory values of patient's included in a study at the Department of Gastroenterology, Zhongnan Hospital of Wuhan University, Wuhan, China.

Markers	Control group (n=22)	Intestinal tuberculosis (n=35)	Crohn's disease (n=68)	*P*-value
Albumin (g/dL)	42.6 ± 3.6	36.4 ± 7.7	36.3 ± 5.9	<0.001*¶
CRP (mg/L)	N/A	41. 6 ± 51.0	27.4 ± 31.2	0.381†
ESR (mm/h)	N/A	28.4 ± 22.1	31.3 ± 26.9	0.712†
RBC ($\times10^{12}$/L)	4.2 ± 0.6	4.2 ± 0.6	3.8 ± 0.7	0.005*¶
WBC ($\times10^{9}$/L)	5.0 ± 1.2	7.4 ± 3.4	6.5 ± 2.8	0.003*¶
PLT ($\times10^{9}$/L)	186.7 ± 44.1	294.1 ± 141.2	308 ± 113.0	<0.001*¶
MPV (%CV)	10.4 ± 2.5	8.8 ± 2.4	8.4 ± 1.6	0.002*¶
RDW (fL)	13.7 ± 1.1	15.9 ± 2.6	16.0 ± 3.4	<0.001*¶

*Kruskal Wallis test, †Mann Whitney test, ¶significant difference. CRP - C-reactive protein, ESR - erythrocyte sedimentation rate, RBC - red blood cells, WBC - white blood cells, PLT - platelet count, MVP - mean platelet volume, RDW - red cell distribution width

Table 3 - Binary regression analysis for independent markers in active Crohn's disease and intestinal tuberculosis of patient's included in a study at the Department of Gastroenterology, Zhongnan Hospital of Wuhan University, Wuhan, China.

Markers	Crohn's disease versus control group		Intestinal tuberculosis versus control group	
	Odd ratio (95% CI)	*P*-value	Odd ratio (95% CI)	*P*-value
Platelet count	1.013 (0.998-1.027)	0.086	1.001 (0.982-1.020)	0.916
Mean platelet volume	0.742 (0.472-1.165)	0.194	0.769 (0.507-1.166)	0.216
Red cell distribution width	2.390 (1.269-4.502)	0.007*	2.338 (1.161-4.706)	0.017*
C-reactive protein	1.025 (0.989-1.063)	0.177	1.013 (0.981-1.046)	0.422
Erythrocyte sedimentation rate	1.157 (1.003-1.336)	0.046*	1.192 (0.997-1.425)	0.054

in both active CD and ITB, PLT was significantly positively correlated with CRP (r=0.361, p<0.001and r=0.349, p=0.008) and ESR (r=0.601, p<0.001 and r=0.550, p<0.001). However, MPV showed negative correlation with CRP (r=-0.369, p<0.001) and ESR (r=-0.340, p=0.001) only in active CD. Moreover, the correlation between RDW and ESR was remarkable in both diseases (r=0.296, p=0.005; r=0.307, p=0.020). Notably, the relationship among PLT, MPV and RDW appeared significant in both diseases (p=0.001 or p< 0.001). Casually, it was shown that the level of albumin in patients with both diseases was obviously correlated with PLT (r=-0.592, p<0.001 and r=-0.431, p=0.001), MPV (r=0.434, p<0.001and r=0.417, p=0.001) and RDW (r=-0.380, p<0.001and r=-0.301, p=0.023).

Correlation between MPV, RDW, PLT, and disease compared with CRP and ESR. Binary logistic regression analysis (**Table 3**) showed that RDW behaved as a favorable independent marker in predicting both active CD and ITB (OR=2.390, p=0.007 and OR=2.338, p=0.017), as compared to CRP (OR=1.025, p=0.177 and OR=1.013, p=0.422) and ESR (OR=1.157, p=0.046 and OR=1.192, p=0.054). However, compared with CRP and ESR, PLT (OR=1.013, p=0.086 and OR=1.001, p=0.916) and MPV (OR=0.742, p=0.194 and OR=0.769, p=0.216) performed lower value in detecting the 2 diseases.

Comparison of diagnostic value of MPV, RDW, PLT, and CRP, as well as ESR. The diagnostic value of MPV, RDW, and PLT between active CD and IBS was conducted, and the results are presented in **Figure 1**. Based on the ROC curve, it was shown that PLT (AUC - 0.848; p<0.001) behaved better as an indicator for active CD, compared with CRP (AUC - 0.691; p=0.007) and ESR (AUC - 0.844; p<0.001). Meantime, value of RDW (AUC - 0.812; p<0.001) seemed better than CRP (AUC - 0.716; p=0.007) and ESR (AUC - 0.804; p<0.001) in ITB diagnosis. A PLT cut-off value of 247.5 x 10^9/L had a sensitivity of 70.59%, and a specificity of 90.9% in detecting active CD. A RDW cut-off value of 14.45% had a sensitivity of 74.29%, and a specificity of 86.36% in detecting ITB. In

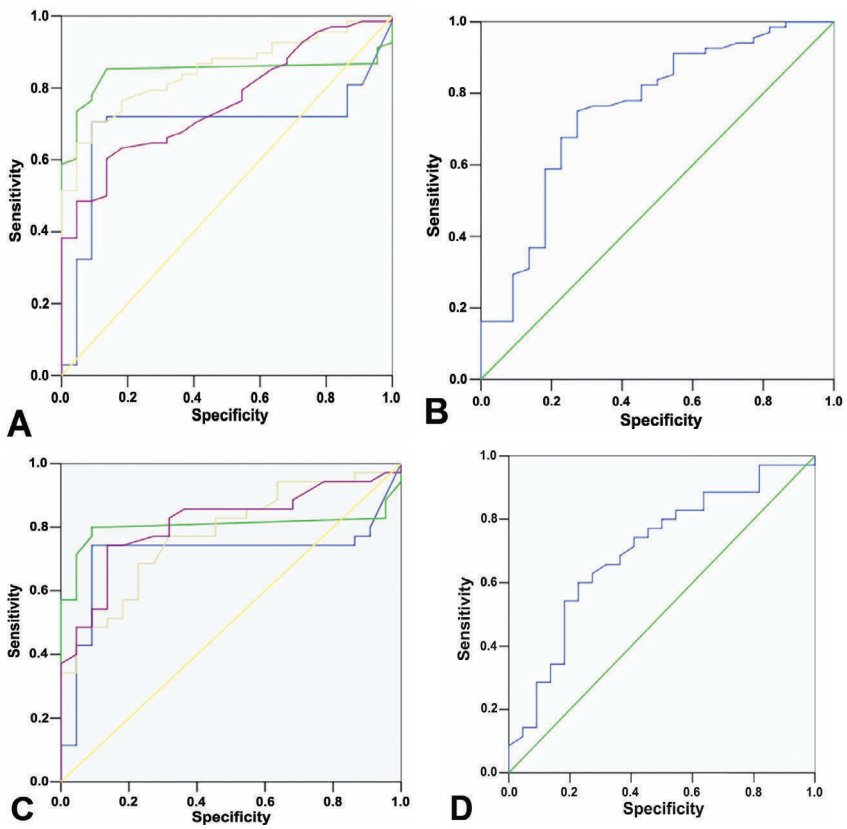

Figure 1 - Receiver operating characteristics (ROC) curves for markers in active Crohn's disease diagnosis showing: **A**) platelet count (PLT) (area under the ROC curve [AUC] - 0.848, p<0.001) (gold), red cell distribution width (RDW) (AUC - 0.759, p<0.001))(purple), C-reactive protein (CRP) (AUC - 0.691, p=0.007) (blue), erythrocyte sedimentation rate (ESR) (AUC - 0.844, p<0.001) (green); **B**) mean platelet volume (MPV) (AUC - 0.753, p<0.001) (blue); and for markers in intestinal tuberculosis diagnosis: **C**) PLT (AUC - 0.779, p<0.001) (gold), RDW (AUC - 0.812, p<0.001) (purple), CRP (AUC - 0.716, p=0.007) (blue), ESR (AUC - 0.804, p<0.001) (green); and **D**) MPV (blue) (AUC - 0.701, p=0.011).

differentiating ITB and active CD without significant difference, all the markers showed little diagnostic value (data not shown).

Discussion. In this retrospective study, we found increased level of PLT and RDW, as well as decreased MPV in patients with both active CD and ITB. We also detected RDW did best in predicting both diseases as markers individually. Meanwhile, PLT in active CD, as well as RDW in ITB owned the largest AUC as diagnostic markers. The CRP is one of the most vital indications for acute phase in humans, which is a pentameric protein, composed of 5 monomers. It increased in most IBD, whereas CD is correlated with a strong CRP response, and UC has only a modest to absent CRP response.[2] The ESR is also considered as an important laboratory index in IBD, but it would be affected by the plasma concentration, and on the number and size of RBC. Moreover, ESR will increase along with age. Tests for CRP and ESR have been used to assess inflammatory processes and predict the course of IBD progression.[15] In our study, we found that CRP and ESR were both higher in active CD and ITB compared with IBS. We also discovered that CRP and ESR displayed good sensitivity, and specificity as a diagnostic indicator.

In terms of diagnosis of CD, it was reported that the elevated PLT was correlated with disease severity and serum orosomucoid level.[3] The reason for increase of PLT in IBD was unclear and the possible explanation was the nonspecific responses to inflammation.[3] In comparison with lots of studies for platelet count in IBD, there was little investigation with regard to PLT in ITB. As evidenced in our study, we demonstrated the existence of increased number of platelet though the reason, for which was not clear. Based on our results, we also found PLT displayed the significant predominance as an indicator of active CD, and its value of AUC was even beyond CRP and ESR. The PLT, as a diagnostic marker showed sensitivity (70.59%), specificity (90.9%), and Youden index (0.615), and overall accuracy (75.55%), equaling to those of CRP but lower than ESR. Thus, our findings suggested that PLT should be made account of in differentiating active CD and IBS. Nonetheless, the predicting value of PLT (OR=1.013, p=0.086) was much lower than CRP and ESR. In a word, PLT displayed favorable diagnostic value but cannot replace other examinations.

The MPV, an easily overlooked marker in IBD, is significantly reduced in active inflammatory bowel disease and is negatively correlated with the known inflammatory bowel disease activity markers and the platelet activation products.[5] In our study, the finding that MPV decreased in active CD was in line with previous reports.[3,16] Platelet volume was reported to correlate with platelet function and was influenced by inflammation.[3] The reason for the decreased MPV in IBD remains unclear. Some authors speculated that reduced MPV was attributed to the consumption of large activated platelets in the intestinal vasculature.[3] Others proposed that the platelets' life length in IBD was normal and consumption of thrombocytes was minimal.[3] Besides, Kapsoritakis et al[5] demonstrated that the disturbance of thrombopoiesis was involved in the descendent MPV. According to our results, we also discovered the reduced MPV in ITB. As far as we know, there are few articles targeting MPV in ITB though some reports noticed MPV in pulmonary tuberculosis.[17] More researches with big sample can be carried out to confirm and explain our results of MPV in ITB. As a diagnostic marker in inflammatory bowel disease, MPV was paid increasing attention in recent years. One study showed that level of MPV reduced in UC, particularly in patients with active UC. Decreased MPV may be an indicator for increased disease activity in patients with UC.[18] Another study based on 56 patients with CD demonstrated MPV was statistically significantly reduced during clinical relapse compared with clinical remission.[19] Recently, researchers detected that MPV behaved well in diagnosis of determination of CD and healthy control but was useless in discriminate disease activity.[16] However, our findings that MPV behaved inferiorly in either predicting or diagnosing active CD than ESR or CRP did not approve the important value of MPV as a diagnostic marker in active CD or ITB.

The RDW reflects the variability in the size of circulating red blood cells and is routinely reported by automated laboratory equipment used to perform complete blood counts. The association between increased RDW and active IBD was evident in IBD patients with and without anemia.[7] Consistently, we discovered the level of RDW in the present study appeared higher in active CD than in control. The mechanism is unknown. An elevation in the RDW may occur in conditions of ineffective red cell production (iron deficiency, B12 or folate deficiency, and hemoglobinopathies), increased red cell destruction (hemolysis), or after blood transfusions.[20] As for the results of logistic regression analysis, we found RDW presented higher odds ratio than either CRP or ESR did, which suggested dramatic value of RDW in predicting active CD. There was also evidence showed that RDW was better than CRP and ESR in predicting activity of CD.[9] Meantime, it was shown in ROC curve analysis that RDW had larger AUC than CRP did. All the results above-mentioned indicated the notable value

of RDW in the prediction and diagnosis of active CD. This marker deserves more attention and research.

According to our research, we discovered the increased RDW in ITB. Although the specificity and sensitivity of RDW was lower than CRP and ESR, the odds ratio and AUC of this marker appeared highest in the five markers. To our knowledge, there was little research focusing on RDW in ITB, and the mechanism of the increased RDW was not clear. We firstly demonstrated the existence of elevated RDW and the prominent predicting value of RDW in ITB. RDW should be attached importance to for clinicians in the diagnosis of ITB. This study can be repeated with a larger sample to prove our discovery and the mechanism deserves explored.

Based on the Spearman correlation analysis in active CD and ITB, we detected the relationship between the 3 markers, such as PLT, MPV, or RDW, and the known disease activity indices (ESR or CRP). The significant correlation of them indicated the importance of the 3 markers in inflammation, and may suggest a link between the 3 markers and the inflammatory course itself. For one with a history of mild abdominal pain or diarrhea, the presence of normal screening laboratory values often implicated functional disorder (for example, irritable bowel syndrome) as a cause of symptoms and precludes additional diagnostic testing. Thus, we considered that the choice of patients with IBS as controls was appropriate in our research.

There are some limitations in our study, patients that come to be hospitalized could not be controlled by us, and not all of the IBS-D patients are willing to get common inflammatory biomarkers, such as ESR and CRP as they cannot afford it, and the age disparity may affect the result, but we also could conclude that the high prevalence of old-aged IBS-D, while active CD showed 2 peak in the age.

In conclusion, our study demonstrated the increased PLT and RDW, as well as the decreased MPV in active CD and ITB. As a cheap and convenient laboratory indicator, except for possessing the capability to predict active CD, RDW showed outstanding predicting capability and good diagnostic value in ITB, and merits more concern, as well as, investigated in depth.

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