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Research paper

A low mean platelet volume indicates active inflammatory bowel disease; a sensitive model in resource poor settings

CHKA Fernando[1], SHA Williams[2], YJ Costa[1], D Moratuwagama[2], TD Warnakulasuriya[2], AP de Silva[2], R Wickremasinghe[2]

Key words: inflammatory bowel disease, mean platelet volume, Crohn's disease, ulcerative colitis, inflammatory markers, clinical activity index score

Abstract

Aim: To examine whether the mean platelet volume (MPV) can be used as an indicator of active inflammatory bowel disease (IBD).

Methods and Materials: A descriptive cross-sectional study was conducted on hundred patients with IBD (61 ulcerative colitis (UC), 29 Crohn's disease (CD)) of both genders (female: male; 67:33). Disease activity was assessed with clinical activity indices. Samples were taken for full blood count (FBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) from all participants. The correlation between the MPV and clinical disease activity index scores were examined. The cutoff point of MPV to differentiate active disease was obtained from ROC curve analysis.

Results: MPV was negatively correlated with disease activity index scores of UC and CD. Simple clinical colitis activity index (SCCAI) and Crohn's disease activity index (CDAI), respectively (MPV vs SCCAI; r= (-0.590), P< 0.001 and MPV vs CDAI; r= (-0.674), P<0.001). MPV predicted IBD activity best as compared to ESR, CRP, white cell count (WBC), platelet count (PLT) and absolute neutrophil count (ANC). In this study MPV was inversely correlated with all tested covariates in the total IBD group and two subgroups (UC and CD) except the platelet count in CD group.

Conclusion: MPV is a low-cost, sensitive indicator to assess IBD activity.

Introduction

UC and CD together comprise inflammatory bowel diseases which are characterised by a remitting and relapsing course[1]. They are common causes of gastrointestinal diseases and affected individuals have a notably impaired quality of life[2].

Breakdown of tolerance against commensal microflora is a principal factor involved in the pathogenesis of IBD[1]. Although, the incidence and prevalence of IBD in Sri Lanka are lower compared to the West, they are comparable to the rates reported from Asia. UC is commoner than CD, nevertheless CD appears to be increasing[3,4].

Disease activity of IBD is typically assessed by using a combination of indices, laboratory investigations, endoscopy and histopathological findings[5]. In general, clinical activity of UC is measured by a simple clinical colitis activity index (SCCAI), whereas Crohn's disease activity index (CDAI) is used to assess CD activity. The laboratory tests are usually confined to acute phase reactants such as CRP, fibrinogen and serum ferritin. Increased ESR, elevated platelet counts and WBC due to neutrophilia are also considered as markers of active inflammation.

No specific test to determine IBD disease activity has been discovered yet. Several recent studies on IBD have focused on non-invasive or micro-

[1]*Colombo North Teaching Hospital, Ragama, Sri Lanka.*

[2]*Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka.*

Correspondence: Dr. CHKA Fernando

E-mail: chkafernando@gmail.com

invasive sensitive markers to detect IBD activity[6]. A laboratory biomarker of objective assessment of active IBD should ideally yields a rapid and accurate result at minimum cost[7]. This would relieve the psychological and financial burden on patients as well as make less of a financial impact on low-income countries.

Even though platelets act as the main constituent of primary haemostasis, there is evidence to suggest that it plays a significant role in inflammation[8]. At sites of inflammation, platelets undergo structural changes and secrete cytokines. As a result, platelets become smaller in size with a consequent reduction in the MPV. For this reason, it has been assumed that MPV is a sensitive indicator of the inflammatory response. Although MPV has been studied as a useful indicator of IBD activity[9], contradictory results have been reported[10].

We investigated whether MPV is useful to differentiate between active and dormant IBD. We also studied whether MPV is correlated with universal markers of inflammation in active and inactive states of IBD.

Materials and methods

This descriptive cross-sectional survey was carried out in an adult medical unit and the gastroenterology follow up clinic at the Colombo North Teaching Hospital, Ragama, (CNTH-Ragama) Sri Lanka, from May 2014 to December 2015.

A total of one hundred (100) subjects were enrolled in the study after obtaining informed written consent. Patients of both genders (female: male; 67: 33) with IBD, treated as in-patients or out-patients were recruited.

The study group was divided into two subgroups. One subgroup comprised 69 patients diagnosed with UC and the other comprised 31 patients diagnosed with CD. Demographic and clinical information were obtained and recorded by the main investigator by administering an interviewer administered questionnaire. Disease activity of UC and CD were assessed using the clinical activity indices of the SCCAI and the CDAI respectively[11,12]. SCCAI was scored as: remission (0-4); active (5-20) and CDAI was scored as: remission (0-150) and active (150-600). FBC including MPV, platelet count, WBC and ANC, CRP and ESR were assayed in all subjects.

The FBC was analyzed using a Beckman Coulter automated analyzer that used an impedance technique. The machine was calibrated with standardized material. Quality control samples were run twice a day and quality control charts were maintained. The samples were analyzed in duplicate by a medical laboratory technologist and the mean platelet volume of the two readings was taken. ESR and CRP were assayed by the Westergren method and the immunoturbidimetry method, respectively, according to standard laboratory practice. Descriptive data were presented as median ± inter-quartile range (IQR). As MPV was not normally distributed, the Spearman's rank correlation coefficient was used to examine associations between MPV, disease activity indices and other inflammatory markers. The non-normally distributed quantitative measurements were compared using the Mann Whitney U statistic. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values of MPV that best differentiate active and dormant IBD. The role of other inflammatory markers in predicting active IBD was assessed using a similar approach. All statistical analyses were performed using IBM SPSS statistics (version 22). The overall accuracy was calculated by adding true-positive and true-negative test results divided by all test results. Ethical approval for the study was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Kelaniya. Permission to conduct the study was obtained from the Director of the Colombo North Teaching Hospital, Ragama and consultants of the adult medical units where the study was conducted. All subjects were recruited in to the study after informed written consent was obtained.

Results

The median (IQR) age of the IBD cohort was 44.50 years (34.25-58.00 years) and the median (IQR) duration of disease was 45.21 months (36.00-120.00 months). There were no statistically significant differences in age (p=0.053) and

duration of disease (p=0.116) between patients with UC and CD. The sex distribution and disease activity status in both subgroups were similar (p=0.572) (Table 1). We compared the medians of markers of inflammation; CRP, ESR, WBC, ANC, platelet count and MPV between active and inactive IBD patients.

The MPV was significantly lower in patients with active disease than in patients with inactive disease among the total IBD cohort, and the UC and CD groups separately (p<0.001 in all).

CRP, ESR, WBC, ANC and platelet counts were significantly greater in those with active disease compared to patients with inactive disease in both UC and CD groups as well as the total IBD group (p<0.05 in all).

Table 2 gives the Spearman rank correlation coefficients between clinical disease activity scores and inflammatory markers. MPV was negatively correlated with both SCCAI [r= (-0.590); p<0.001] and CDAI [r= (-0.674); p<0.001]. WBC count and ANC were not significantly correlated with CDAI score (p=0.062 and p=0.087, respectively). Platelet count was not correlated with the SCAAI score (p=0.067). Spearman correlation analysis illustrates that MPV was significantly negatively correlated with all other inflammatory markers; CRP, ESR, platelet count, WBC count and absolute neutrophil count. MPV was not correlated with the platelet count (r=0.154, P=0.207) in patients with CD.

The ability of MPV and other markers in differentiating active IBD patients from patients with dormant disease was examined.

The cutoff values of the all markers with sensitivities greater than 80% and the highest sensitivities were tabulated. (Table 3) (Figure1) The respective specificities varied between 60% and 90%. When the cut off value of MPV was 7.05, the sensitivity and specificity for active IBD were 80.4% and 88.9%, respectively (area under the curve (AUC): 0.885) at this cutoff value of MPV, the overall accuracy was 85%. For CRP, a cutoff value of 25.5 mg/dL gave a sensitivity of 80.4% and a specificity of 77.8% (AUC: 0.886); for ESR a cutoff value of 33.5 mm/hr gave a sensitivity of 87.0% and a specificity of 74.3% (AUC: 0.853). At the above cut off values of CRP and ESR the overall accuracy was 79% and 80%, respectively. Of all the markers, the area under the curve (AUC) for MPV was the highest (88.5%).

Table 1. Demographic characteristics of the IBD cohort

	Total IBD patients (n=100) Median (IQ range)	**Ulcerative Colitis (n=69) Median (IQ range)**	**Crohn's disease (n=31) Median (IQ range)**	**Test statistic (p-value)**
Age (years)	44.5 (34.25-58.00)	46.00 (37.5-8.00)	39.00 (25.00-6.00)	810.0 (0.053)*
Disease duration (months)	45.21 (36.00-120.00)	72.00 (36.00-38.00)	48.00 (24.00-8.00)	859.0 (0.116)*
Gender (M: F number of participants)	33:67	24:45	9:22	0.320(0.572)†
Disease activity (Active: Inactive number of participants)	46:54	30:39	15:16	0.570 (0.450)†

IQ range; interquartile range, *Mann Whitney U statistic, †Chi square, M; male, F; female

Table 2. Spearman rank correlation coefficients between disease activity scores and inflammatory markers

	UC (SCAAI score)		CD (CDAI score)	
	r	***P***	***r***	***P***
MPV	-0.590	<0.001	-0.675	<0.001
CRP	0.535	<0.001	0.586	<0.001
ESR	0.581	<0.001	0.620	<0.001
WBC count	0.527	<0.001	0.345	0.062
Absolute Neutrophil count	0.566	<0.001	0.318	0.087
Platelet count	0.221	0.067	0.421	0.020

r – spearman correlation coefficient, P – significance

Table 3. Receiver operating characteristic (ROC) curve analysis of MPV and other inflammatory markers in the diagnosis of active and inactive IBD

Marker	Cut off	Sensitivity value	Specificity (%)	AUC	Accuracy (%)
MPV (fL)	7.05	80.4	88.9	0.885	85
	7.15	82.6	85.2		84
	7.25	84.8	83.3		84
CRP (mg/dL)	23.0	84.8	72.2	0.866	78
	24.5	80.4	75.9		78
	25.5	80.4	77.8		79
ESR (mm/hr)	33.5	87.0	74.3	0.853	80
	34.5	84.3	75.9		80
	37.5	82.6	77.8		80
WBC ($x10^3$/cumm)	8850	82.6	64.8		73
	8950	80.4	66.7		73
	9050	80.4	70.4		75
ANC ($x10^3$/cumm)	5865	82.6	75.9	0.820	79
	5897.5	80.4	75.9		78
	5950.5	80.4	77.8		79
PLT ($x10^5$/cumm)	248.5	82.6	46.3	0.835	63
	255.0	82.6	48.1		64
	263.0	80.4	50.0		64

AUC – area under the curve

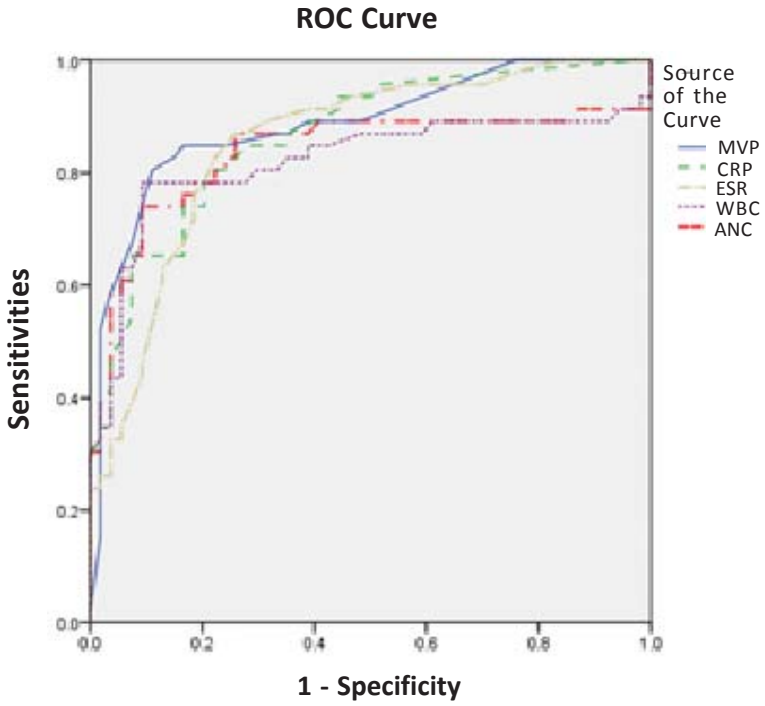

Figure 1. Receiver operating characteristic (ROC) curves in IBD cohort.

Discussion

IBD is characterized by a remitting and relapsing course[1]. Therefore, early detection of relapse with a simple, widely available, low-cost blood test will ensure patients an appropriate, timely and effective therapy. Furthermore, it could significantly improve the quality of life and life expectancy of the patients by reducing morbidity and mortality. In routine practice, endoscopy and histopathological diagnosis are used for investigating a relapse. These are invasive procedures that cause much discomfort to the patients. Current trends in the management of patients with IBD are focused on finding a gold standard, that is perfect for diagnosing and detecting an early relapse[13]. However, such an investigation is yet to be found.

MPV correlates with the degree of platelet activation. Our results show that MPV is negatively correlated with disease activity of UC and CD patients. We have demonstrated that MPV is a reliable and cost-effective marker in differentiating active disease states of IBD from its inactive form. Inflammatory markers such as CRP, ESR, WBC with ANC and platelet count are positively correlated with IBD disease activity.

This study has revealed that MPV is inversely correlated with all inflammatory markers in the total IBD group; CRP [r= (-0.594), p<0.001], ESR [r= (-0.503), p<0.001], WBC [r= (-0.443), p<0.001], ANC [r= (-0.455), p<0.001] and platelet count [r= (-0.302), p=0.002]. In the UC group, MPV was significantly negatively correlated with CRP [r= (-0.773), p<0.001], ESR [r= (-0.668), p<0.001], WBC [r= (-0.501), p=0.004] and ANC [r= (-0.467), p=0.008] but not with the platelet count [r= (-0.714), p<0.001]. Likewise, in the CD group MPV was significantly negatively correlated with CRP [r= (-0.502), p<0.001], ESR [r= (-0.446), p<0.001], WBC [r= (-0.440), p<0.001] and ANC [r= (-0.154), p<0.001] but not with the platelet count [r= (-0.154), p=0.207].

The results of this study while being comparable with results reported in some earlier studies, also contradict results reported in other studies. Kapsoritakis AN et al. reported that MPV is significantly lower in patients with active UC and CD as compared to those in the dormant state. They also showed that MPV was negatively correlated with other markers of inflammatory response and the by-products of platelet activation (β-thromboglobulin and platelet factor 4) similar to the results we have presented here[14].

Song Liu et al. demonstrated lower MPV levels in CD patients in a prospective study, conducted with 61 CD patients and 50 healthy controls in 2011. They observed statistically significantly lower MPV levels in the study cohort (CD) than in the control group (9.55 ± 0.168 fL vs. 11.1 ± 0.160 fL, P<0.0001). At the optimal cutoff of MPV (10.35 fL) the sensitivity and specificity were 78.7% and 74.0% respectively (AUC: 0.8303) and the overall accuracy of MPV in detecting CD patients was 76.6%[15].

Douda et al., analyzing MPV in 56 patients with active and inactive CD, reported a decrease in MPV in patients with active disease[16]. Investigating 36 patients with CD, Zubcevic et al. reported that MPV is associated with increased disease activity; they also reported an increased CRP in relapsed CD patients[17]. Kayhan and colleagues using the Truelove-Witts criteria to measure disease activity reported unchanged reticulated platelet counts in both active and inactive UC patients (P=0.998). Interestingly, in the same study cohort, MPV was negatively correlated with platelet count (r=-0.542, p=0.030)[18].

Results of some previous studies are contradictory to our results. Tayyibe et al. reported that there was no significant difference in the MPV, in all 3 groups; UC, CD and healthy subjects, irrespective of the level of disease activity in study cohort. Tayyibe and colleagues assessed a total of 200 individuals including 50 UC, 50 CD and 100 disease free subjects. MPV and CRP values of all three groups were compared. However, the final analysis did not show any association between MPV and IBD activity except a negative correlation between MPV and CRP in patients with active CD (r=-0.527; P=0,009)[10].

Most of the results of studies carried out to assess the usefulness of ESR, CRP, platelet count and WBC with ANC in IBD as markers of inflammatory response are consistent with the results of our study. These routine inflammatory markers are positively correlated with active IBD and clinical colitis activity indices as reported in our study[13,14].

Sensitivity, specificity and overall accuracy above 80% in predicting active disease was only seen with MPV. ESR, CRP and ANC were the next best parameters to predict the active state of the disease. Ozturk ZA et al. have reported that at a MPV cutoff value of 8.2 fL, active and inactive UC and CD can be differentiated with sensitivities of 60.0% and 56.25%, respectively and 77.5% specificity in both conditions[19]. The MPV levels recommended by both Song Liu et al.15 and Ozturk ZA et al[19]. were higher (10.35 fL and 8.2 fL respectively) than what was found in our study. In this study active and inactive disease could be differentiated with an overall accuracy of 85%, sensitivity of 80.4% and specificity of 88.9% among the IBD patients with a MPV cutoff value of 7.05 fL.

This study had some limitations. In the first place, if the sample size had been larger with equal numbers of patients in UC and CD the results would have been more comparable. Secondly, MPV and other inflammatory markers could have also been compared with other non-invasive methods; namely fecal calprotectin, fecal lactoferrin and neutrophil elastase. Therefore MPV should not be considered a stand-alone test for monitoring the disease activity. Thirdly, a negative impact from a descriptive cross-sectional study towards the final analysis cannot be neglected.

Conclusion

To conclude, our study showed that, MPV is reduced in patients with active UC and CD. Therefore, decreased MPV is a non-invasive sensitive indicator for increased disease activity in patients with UC and CD, particularly useful in resource poor settings.

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Authorship

CHKA Fernando involved in the study conception, interviewing, acquisition of data and manuscript preparation.

Authors AP de Silva, SHA Williams, YJ Costa and D Moratuwagama supervised the study and corrected the manuscript.

R Wickremasinghe and TD Warnakulasuriya carried out the data analysis.

Authors believe that manuscript represents honest work and take the full responsibility of the published material.

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Authors declare that there is no conflict of interest.

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