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Original Article

Mean platelet volume as an indicator of persistent organ failure in acute pancreatitis

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Abstract: Aim: Mean platelet volume (MPV) serves as a biomarker of platelet activation. Increased level of MPV is associated with uncontrolled and systemic infection and is correlated to sepsis severity, which is commonly observed in patients with acute pancreatitis (AP). AP patients with persistent organ failure (POF) show an extremely high mortality rate. The association underlying MPV and POF in AP has not been characterized. Methods: We conducted a retrospective cohort study of adult patients who presented within 72 hours from symptom onset of AP at our center between January 2015 and January 2016. Demographic parameters on admission, organ failure assessment, laboratory data and in-hospital mortality were compared between patients with and without POF. Uni-and multi-variate logistic regression analyses were utilized to evaluated the predictive ability of MPV. Results: A total of 156 consecutive AP patients, including 29 with POF, were included. Compared to patients without POF, patients with POF showed a significantly higher value of MPV on admission (11.54 ± 1.49 vs. 9.68 ± 1.38 fl; $P < 0.001$). After multivariate logistic analysis, MPV > 12 fl remained an independent risk factor for POF (Hazard ratio 8.41, 95% confident interval: 1.51-46.77; $P = 0.015$). A MPV value of 12 fl predicted POF with an area under the curve (AUC) of 0.823, a sensitivity with 44.8% and specificity with 90.6%, respectively. Conclusion: Our results indicate that MPV on admission is independently associated with POF in AP and may serve as a potential prognostic factor.

Keywords: Mean platelet volume, acute pancreatitis, persistent organ failure

Introduction

Acute pancreatitis (AP) is an inflammatory disorder featured by local and systemic immuno-inflammation, with a procedure observed clinically from local pancreatitis through the systemic inflammatory response, organ dysfunction and death. Most patients suffer from a mild, self-limiting inflammatory derangement, but the remaining ones will develop a severe disease associated with local or systemic complications and/or organ failure (OF) [1]. According to 2012 revised Atlanta classification for AP, severe AP (SAP) has been redefined as AP with persistent organ failure (OF lasts more than 48 hours) with a mortality rate of 20-50% [2-6]. Rapid assessment of disease severity is pivotal for the determination of therapeutic strategy since effective treatment could significantly decrease mortality of patients with severe pancreatitis [7, 8].

As one of platelet indices, increased level of MPV serves as a biomarker of platelet activation. Once the production of platelet count is decreased, immature platelets are activated and become bigger, and the values of MPV increase. An association between platelet volume and inflammatory cytokines (such as thrombopoietin, interleukin-3 and interleukin-6) is observed by several researchers. These mediators regulate megakaryocyte ploidy, resulting in the generation of larger platelets [9-11]. The relationship between MPV and disease severity in AP was evaluated by Beyazit et al. They found that compared with healthy individuals, patients with AP showed a significantly decreased level of MPV [12]. Beyazit et al. for revealed that compared with healthy individuals, patients with AP showed a significantly decreased level of MPV [10]. Mimidis et al. found that MPV values detected upon symptom onset were significantly lower than that after disease remission [13]. On the contrary, Akbal et al. investigated the levels of MPV at onset and remission in 24 AP patients, but no difference was found between symptom onset and remission [11].

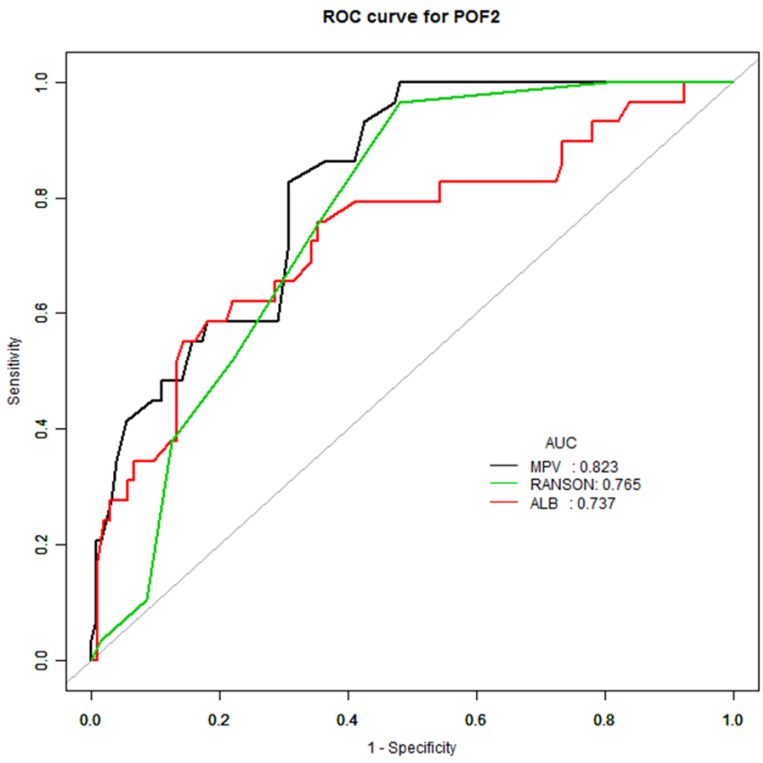

Figure 1. Receiving operator curve of MPV, albumin and Ranson score on admission in predicting POF.

However, the relationship between MPV and incidence of POF in the AP pathophysiology has not been elucidated yet. The main aim of our study was to evaluate the value of MPV upon presentation of hospital in correlation with the incidence of POF in AP.

Materials and methods

Patient selection

We conducted a retrospective study of patients with AP admitted to the Pancreatic Disease Institute of Wuhan Union Hospital between January 2015 and January 2016. Diagnosis of AP was based on clinical findings based on the presence of two or more of the following three criteria: 1) abdominal pain consistent with AP; 2) serum amylase and/or lipase elevation ≥ three times the upper limit of normal; and/or 3) contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) or abdominal ultrasonography findings characteristic of AP [2]. The exclusion criteria included any of the following: 1) the time from abdominal pain onset to hospital admission ≥ 72 hours; 2) age younger than 18 years; 3) pancreatitis induced by trauma; 4) chronic pancreatitis; and 5) unavailable laboratory measurements or medical records (**Figure 1**).

Laboratory data were obtained from the blood screening test at hospitalization. Patient's electronic medical records and paper charts were reviewed by one independent physician for information on demographics, physiologic variable, and disease severity. The study was conducted according to the principles of the Declaration of Helsinki. Informed consent for individual patient was not obtained since all data were retrieved retrospectively from the laboratory test information system without additional blood samples or laboratory analysis. The ethics review board of Wuhan Union Hospital approved this study.

Definitions

Disease severity was determined according to the revised 2012 Atlanta classification (2). OF was diagnosed when the following cutoffs were exceeded: 1) cardiovascular failure if systolic blood pressure was < 90 mmHg despite fluid replacement; 2) respiratory failure if the ratio of PaO_2/FiO_2 was < 300 mmHg; and 3) renal failure if serum creatinine was ≥ 1.9 mg/dl. POF was identified if OF lasts for more than 48 h. PNec was defined as appearance of pancreatic parenchymal and/or peripancreatic necrosis on CECT images [3].

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (SPSS Inc, Chicago IL, USA). Continuous variables are presented as means and standard derivation (SD). Categorical data are reported as number (frequency). Student's *t* test and Mann-Whitney *U* test were used to evaluate the differences in baseline characteristics between two groups. Multiple group comparisons were performed using the Chi-square test for categorical variables and the Kruskal-Wallis test for continuous data. Univariate anal-

Table 1. Basic characteristic of AP patients according to MPV level (cut-off: 12 fl)

	All patients	MPV ≤ 12.0 fl	MPV > 12.0 fl	*P*-value
No.	156	131	25	
Age, years	46.81 ± 14.50	46.76 ± 14.28	47.04 ± 15.94	0.987
Male gender	85 (54.5%)	67 (51.1%)	18 (72.0%)	0.055
Daily drinker	58 (37.2%)	45 (34.4%)	13 (52.0%)	0.094
Current smoker	70 (44.9%)	53 (40.5%)	17 (68.0%)	0.011
Etiology				0.322
Biliary	82 (52.6%)	69 (52.7%)	13 (52.0%)	
Alcohol	32 (20.5%)	24 (18.3%)	8 (32.0%)	
Hyperlipidemia	27 (17.3%)	25 (19.1%)	2 (8.0%)	
Idiopathic	15 (9.6%)	13 (9.9%)	2 (8.0%)	
Outcomes				
POF	30 (19.2)	16 (12.2%)	13 (52.0%)	< 0.001
ICU stay > 7 days	32 (20.5%)	21 (14.5%)	11 (44.0%)	< 0.001
In-hospital mortality	9 (5.8%)	5 (3.8%)	4 (16.0%)	0.037

Abbreviations: AP, acute pancreatitis; MPV, mean platelet volume; POF, persistent organ failure.

Table 2. Types of POF and the corresponding in-hospital mortality

	POF	In-hospital mortality
Solitary POF	21	3 (14.3%)
Respiratory	21 (100.0%)	3 (14.3%)
Renal	0 (0.0%)	0 (0.0%)
Cardiovascular	0 (0.0%)	0 (0.0%)
Multiple POF	8	6 (75.0%)
Respiratory + renal	5 (62.5%)	3 (60.0%)
Respiratory + cardiovascular	1 (12.5%)	1 (100.0%)
Respiratory + cardiovascular + renal	2 (25.0%)	2 (100.0%)

Abbreviations: POF, persistent organ failure.

ysis was performed using log-rank test. All variables with statistically significant prognostic value in univariate analysis were selected for further multivariate analysis. Multivariate analysis was undertaken with a Cox regression model. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) are presented. Receiver-operator characteristic (ROC) curves were constructed to evaluate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the parameters in predicting POF. A *P* value < 0.05 was considered a statistically significant difference.

Results

Patients

A total of 156 patients with confirmed AP were included in this study. Baseline characteristics of these patients according to MPV values (cut off: 12 fl) are presented in **Table 1**. Compared to patients with normal MPV (n = 131), patients with elevated MPV (n = 25) show significantly higher incidences of developing POF (52.0% vs. 12.2%; P < 0.001), longer intensive care unit (ICU) stay (44.0% vs. 14.5%; P < 0.001) and higher in-hospital mortality (16.0% vs. 3.8%; P = 0.037). Overall, 29 patients were identified with POF. There were 21 patients developing solitary POF (all of respiratory system). Multiple POF was observed in 8 patients (5 of lung and kidney, 1 of lung and heart, and 2 of lung, kidney and heart). During hospitalization, 9 patients with POF died with an overall mortality of 5.8%. No death was observed in patients without POF (**Table 2**).

Comparison between patients with and without POF

Compared to patients without POF, patients with POF were older, had higher rates of in-hospital mortality and longer ICU stay. The level of albumin was significantly lower, while the values of MPV, white blood count, hematocrit, glucose, urea and creatinine were statistically higher in those with POF. No statistical significance was found regarding platelet count and aspartate aminostransferase between two groups (**Table 3**).

MPV as an independent prognostic factor for POF

In order to further investigate the association between MPV and incidence of POF, we used multivariate Cox regression model. Since the levels of urea and creatinine were used in the definition of POF, they should not be utilized in neither uni- nor multi-variate analysis. Univariate analysis suggested white blood count,

Table 3. Clinical data of the patients with and without POF

	Non-POF	POF	*P*-value
No.	127	29	
Age, years	46.66 ± 13.73	47.45 ± 17.65	0.987
Male gender	68 (53.5%)	17 (58.6%)	0.620
Daily drinker	45 (35.4%)	13 (44.8%)	0.345
Current smoker	56 (44.1%)	14 (48.3%)	0.683
Pre-existing co-morbidity	41 (32.3%)	10 (34.5%)	0.829
Etiology			0.119
Biliary	72 (56.7%)	10 (34.5%)	
Alcohol	22 (17.43%)	10 (34.5%)	
Hyperlipidemia	21 (16.5%)	6 (20.7%)	
Idiopathic	12 (9.4%)	3 (10.3%)	
Laboratory data			
White blood count, $\times 10^9$/L	11.64 ± 4.36	18.65 ± 11.02	< 0.001
Hematocrit, %	40.40 ± 5.27	43.52 ± 7.59	0.009
Platelet count, $\times 10^9$/L	196.14 ± 64.18	182.28 ± 77.98	0.359
Serum glucose, mmol/L	7.51 ± 2.91	12.15 ± 8.21	< 0.001
Aspartate aminostransferase, U/L	95.44 ± 144.22	108.55 ± 105.50	0.645
Albumin, g/L	37.34 ± 5.68	32.18 ± 6.35	< 0.001
Serum urea, mmol/L	4.64 ± 2.01	9.43 ± 5.42	< 0.001
Serum creatinine, μmol/L	64.99 ± 23.29	159.19 ± 123.83	< 0.001
MPV, fl	9.68 ± 1.38	11.54 ± 1.49	< 0.001
Ranson score	3.07 ± 1.90	4.76 ± 1.50	< 0.001
Outcomes			
ICU stay > 7 days	14 (11.0%)	17 (58.6%)	< 0.001
In-hospital mortality	0 (0.0%)	9 (31.0%)	< 0.001

Abbreviations: MPV, mean platelet volume; POF, persistent organ failure.

serum glucose, serum albumin, MPV and Ranson score correlated significantly with the incidence of POF. As white blood count and serum glucose were not independent of Ranson score, they were excluded from multi-variate analysis. Due to the small number of patients with POF, we decided to only include 3 parameters (serum albumin, MPV and Ranson score) in multi-variate model. After multi-variate adjustment, serum albumin < 32 g/L (HR: 6.41, 95% CI 1.29, 31.88; P = 0.023) and MPV > 12 fl (HR: 8.41, 95% CI 1.51, 46.77; P = 0.046) were identified as independent prognostic factors for POF (**Table 4**).

Table 5 showed the prognostic value of these predictors. MPV > 12 fl detected upon admission had an area under curve (AUC) of 0.823 (95% CI: 0.751-0.895), with a sensitivity of 44.8%, specificity of 90.6%, PPV of 87.8%, and NPV of 82.1%. The optimal threshold was 1.97 mmol/L. The AUC of serum albumin and Ranson score were 0.737 (95% CI: 0.625-0.849) and 0.765 (95% CI: 0.688-0.842), respectively. It turned out that MPV was superior to other simple predictors and severity scores in predicting POF in AP.

Discussion

In this retrospective work, we sought to examine the correlation between MPV and incidence of persistent organ failure in patients with acute pancreatitis. Our results showed that MPV detected upon admission was significantly lower in AP patients with POF compared with non-POF. Furthermore, MPV was revealed as an independent risk factor for the development of POF. The predicting value of MPV was superior to severity scores such as SIRS and Ranson, and other single severity-predicting parameters.

The relationship between MPV and disease severity in AP was evaluated by Beyazit et al. They found that compared with healthy individuals, patients with AP showed a significantly decreased level of MPV. The overall accuracy of MPV in predicting severe AP (according to the mGPS) was 72.7% with a sensitivity and specificity of 70.6% and 73.9% [12]. Initial MPV values were lower than remission values in all patients with AP. MPV values were higher than initial values in remission period in patients both of groups. MPV was lower in non-biliary AP group than biliary AP group that can be an indicator of early-onset infection [14]. In a study of 54 AP patients, Mimidis et al. found that MPV values detected upon symptom onset were significantly lower than that after disease remission (9.1 vs. 9.8 fL) [13]. The relationship between MPV and disease severity in AP was evaluated by Beyazit et al. They found that compared with healthy individuals, patients with AP showed a significantly decreased level of MPV. Using a cut-off value of 7.85 fL for MPV, the

Table 4. Uni- and multi-variate logistic regression analyses of risk factors for POF

Univariate analysis	Hazard ratio (95% CI)	*P*-value
Age ≥ 60 years	1.63 (0.65, 4.13)	0.299
Male gender	0.81 (0.36, 1.84)	0.621
Daily drinker	1.48 (0.65, 3.35)	0.347
Current smoker	1.18 (0.53, 2.66)	0.683
Pre-existing co-morbidity	1.10 (0.47, 2.59)	0.819
White blood count > 12×10^9/L	4.68 (1.86, 11.77)	0.001
Hematocrit > 43%	2.19 (0.96, 4.97)	0.062
Platelet count < 100×10^9/L	3.55 (0.75, 16.81)	0.111
Serum glucose > 7.1 mmol/L	3.29 (1.29, 8.39)	0.013
Serum albumin < 32 g/L	6.96 (2.77, 17.48)	< 0.001
MPV > 12 fl	9.72 (3.56, 26.54)	< 0.001
Ranson score ≥ 4	5.73 (2.27, 14.44)	< 0.001
Multivariate analysis	Hazard ratio (95% CI)	*P*-value
Serum albumin < 32 g/L	6.41 (1.29, 31.88)	0.023
MPV > 12 fl	8.41 (1.51, 46.77)	0.015
Ranson score ≥ 4	6.29 (1.10, 35.97)	0.059

As white blood count and serum glucose were not independent of Ranson score, they were excluded from multi-variate analysis. Abbreviations: CI, confidence interval; MPV, mean platelet volume.

Table 5. Receiving operator curve analysis of MPV, albumin and Ranson score in diagnosing POF

	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
MPV > 12 fl	0.823 (0.751-0.895)	0.448	0.906	0.878	0.821
Albumin < 32 g/L	0.737 (0.625-0.849)	0.552	0.857	0.516	0.874
Ranson score ≥ 4	0.765 (0.688-0.842)	0.758	0.646	0.328	0.921

Abbreviations: AUC: area under the curve; CI: confidence intervals; MPV, mean platelet volume; NPV: negative predictive value; POF, persistent organ failure; PPV: positive predictive va.

overall accuracy in predicting severe AP (according to the mGPS and CTSI scores) was 72.7% with a sensitivity and specificity of 70.6% and 73.9% [10]. Akbal et al. investigated the levels of MPV at onset and remission in 24 AP patients, but no difference was found between onset and remission (8.6 vs. 8.5 fL) [11]. The findings can be explained by small number of patients included in the study, and long storage time of blood samples before the measurements.

MPV reflects the average size of platelets, which is valuable since increased volume and size of platelets may occur in conjunction with inflammatory or thrombotic conditions [40016]. Elevated MPV may occur as a result of either increased production or destruction of platelets, and changes in MPV are influenced by immune mediators, (such as tumor necrosis factor-a, interleukin [IL]-1, and IL-6), and growth hormones that affect platelet production and megakaryocyte proliferation [15, 16]. Activated platelets are enlarged and contain many vasoactive and prothrombic factors that aggravate systemic inflammation and endothelial dysfunction [17, 18]. More so, MPV is not elevated in local infections, so increased MPV is associated with uncontrolled and systemic infection and is correlated to sepsis severity [19]. Severe sepsis and septic shock are also involved in activation of platelets, as are unusual changes in the coagulation system. Although the mechanisms underlying thrombocytopenia in sepsis are unclear, impairments in central platelet production and peripheral overconsumption and/or destruction have been proposed as causes of thrombocytopenia [19].

Azab et al. suggested that a relatively higher MPV in conjunction with a low platelet count reflects increased activity and aggregation of platelets [20]. Herbert et al. reported that a higher immature platelet fraction is associated with the severity of sepsis as part of the ongoing inflammatory process involved in sepsis [21]. Previous studies have described MPV as a useful independent factor in identifying the severity of sepsis, coronary artery disease including myocardial infarction, cerebrovascular diseases, arterial and venous thrombosis, and chronic inflammatory disorders including inflammatory bowel disease, ankylosing spondyloarthritis, and rheumatoid arthritis [22].

POF, the main cause of early death within the first 2 weeks of disease onset, develops in

10%-20% of AP patients, with a mortality rate between 20% and 50% [2, 3]. The ability to assess AP patients at risk for developing persistent organ failure early in hospitalization is critical, both for triaging patients to the appropriate grade of care and for designing appropriate medical treatment and intervention [23]. A lot of invasive or non-invasive methods, including biochemical parameters, radiological imaging modalities and severity scores have been utilized for predicting POF in patients with AP. In a systemic review for prospective studies evaluating predictors of POF within 48 h of admission, the Japanese Severity Score and the Bedside Index of Severity in Acute Pancreatitis (BISAP) were identified as the best predictors [24]. But these scores were too complex to calculate immediately. Another study used a head-to-head comparison between the Ranson, Glasgow, APACHE II and the BISAP scoring systems and found that the best classifier at 48 h of admission for predicting POF in patients with AP was the Glasgow score [25]. Mounzer et al. [23] compared several existing clinical scoring systems to predict POF in patients with AP. They found that these scores showed modest accuracy (AUC at admission of 0.6 to 0.8 in both the training and the validation cohorts) and seemed to have reached their maximal efficacy.

However, no previous study has investigated the association between MPV and incidence of POF in AP. Therefore, to our knowledge, this study is the first time to show that the increase of MPV is significantly associated with increased risk of POF in acute pancreatitis.

There are several limitations of the present study. First of all, as this is an observational study, the causality role of MPV and POF in AP, however, requires to be investigated further in a prospective validation study. Second, we only examined one time measurements. Therefore, this study did not address the problem of intra-individual variation in MPV value.

Conclusion

Our present study implies that MPV on admission is independently associated with POF in AP. We suggest that MPV is a valuable tool for a rapid assessment of POF in patients with AP.

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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