International Journal of Advances in Medicine
Chalodiya K et al. Int J Adv Med. 2020 Dec;7(12):1830-1835
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20205043

Original Research Article

Correlation of plasma fibrinogen and mean platelet volume in patients of sepsis to the severity of sepsis and its outcome

Ketan Chalodiya[1], Arun Bahulikar[1], Vrushali Khadke[1], Deepak Phalgune[2]*

[1]Department of Medicine, Poona Hospital and Research Centre, Pune, Maharashtra, India
[2]Department of Research, Poona Hospital and Research Centre, Pune, Maharashtra, India

Received: 08 October 2020
Accepted: 09 November 2020

***Correspondence:**
Dr. Deepak Phalgune,
E-mail: dphalgune@gmail.com

ABSTRACT

Background: The prognostic value of mean platelet volume (MPV) and plasma fibrinogen level in terms of survival in patients with sepsis and septic shock is still incompletely documented. The aim of the present study was to find a correlation between MPV and plasma fibrinogen with the severity of sepsis and mortality.
Methods: Three hundred eleven patients having quick sequential organ failure assessment score 2/3, systolic blood pressure ≤100 mmHg, respiratory rate ≥22/minute and altered mentation <15 (Glasgow coma scale) were included for this prospective observational study. Acute physiology and chronic health evaluation (APACHE) II score, MPV on days one and four, fibrinogen on days one and seven were tested. The number of days of intensive care unit (ICU), and hospital stay, in-hospital mortality was recorded. Categorical and continuous variables were tested using the chi-square test/Fisher's exact test and analysis of variance/Kruskal-Wallis H test respectively.
Results: The mean plasma fibrinogen at day one and day seven was significantly higher in patients who had septic shock and in expired patients. The mean MPV at day four was significantly higher in patients who expired compared to those who survived. The mean MPV on day four was significantly higher compared to the mean MPV at day one in patients who expired.
Conclusions: Fibrinogen level at admission is the predictor of mortality in patients with sepsis or septic shock. An increase in MPV was strongly correlated with mortality and can be used as a prognostic indicator.

Keywords: Platelet volume, APACHE II score, Sepsis, Mortality, Serum fibrinogen

INTRODUCTION

Sepsis is the leading cause of mortality in critically ill patients. Delay in diagnosis and treatment often results in rapid progression to circulatory collapse, multiple organ failure and eventually death. The incidence of severe sepsis and septic shock has increased over the past 30 years. Approximately two-thirds of the cases occur in patients with significant underlying illness.[1] Sepsis-related incidence and mortality rates increase with age and pre-existing co-morbidity. The mortality rates of these conditions are 25 to 80%, depending on the illness severity, the number of occurrences and the severity of organ failure.[1,2] Hence, early detection of progressive severe sepsis and/or septic shock will not only be useful for risk stratification in allocating resources, but also helpful in monitoring treatment efficacy and disease progress.

The diagnosis of sepsis is difficult because clinical signs of sepsis are subtle and overlap with other non-infectious causes of systemic inflammation. These signs include tachycardia, leukocytosis, tachypnoea and pyrexia, which are collectively termed systemic inflammatory response syndrome (SIRS). SIRS is common in trauma, surgery and hypoxic injuries. Though microbiological cultures were used to document infections, they cause substantial time delay, lack sensitivity and specificity.[3]

The pro-inflammatory response to sepsis leads to activation of the coagulation system with concurrent inhibition of anticoagulant mechanisms and fibrinolysis.[4] Consequently, fibrinolytic and fibrinogen products are consumed; so, disseminated intravascular coagulation occurs in forms of thrombus and bleeding.[5] MPV is a machine-calculated measurement of the average size of platelets found in blood and is typically included in blood tests as part of the complete blood count. It is considered as an indirect marker for acute thrombocytopenia. There are high MPV levels in destructive thrombocytopenia and low MPV levels in hypo proliferative thrombocytopenia.[6]

MPV and plasma fibrinogen are very useful to provide critical information quickly for SIRS and sepsis. The prognostic value of MPV and plasma fibrinogen level in terms of survival in patients with sepsis and septic shock and their relation to other inflammatory markers such as white blood cell count, C-reactive protein (CRP) and procalcitonin is still incompletely documented. Conflicting reports have surfaced regarding the usefulness of MPV and plasma fibrinogen as a prognostic marker in severe sepsis. The aim of the present study was to find the correlation between MPV and plasma fibrinogen with the severity of sepsis and outcome.

METHODS

This prospective observational study was conducted between July 2017 and October 2018 in Poona hospital and research center, Pune, India. After approval from the scientific advisory committee (letter No. RECH/SAC/2017-18/294) and institutional ethics committee (letter No. RECH/EC/2017-18/369), written informed consent was obtained from all the patients. Patients aged more than 18 years having quick sequential organ failure assessment score 2/3, systolic blood pressure ≤100 mmHg, respiratory rate ≥22/minute and altered mentation <15 (Glasgow coma scale) were included. Pregnant or lactating women, patients having known platelet disorder (immune thrombocytopenic purpura, essential thrombocytosis), acute coronary syndrome, cerebrovascular attack, recently thrombolysed, active gastrointestinal bleeding, malignancy and coagulation defect were excluded from this study.

Detailed clinical history and examination findings were noted for each patient. Sepsis was diagnosed in patients with either positive blood culture (viral, bacterial, fungal culture) or raised serum procalcitonin (>2 ng/ml). For disease severity assessment, APACHE II score were determined according to the worst values within the initial 24 hours of hospital admission. Septic shock was defined as suspected/documented infection, vasopressor therapy needed to maintain mean arterial pressure ≥65 mmHg and serum lactate level >2.0 mmol/l despite adequate fluid resuscitation. Hemogram, serum creatinine, arterial blood gas, serum lactate, MPV on days one and four, serum fibrinogen on days one and seven, total cholesterol, total bilirubin, CRP and serum albumin were tested for all the patients. Venous blood samples for laboratory counts were collected from all the patients in tubes containing ethylene diamine tetra acetic acid and analyzed with an Advia 2120 hematology analyzer (Siemens healthcare diagnostics, Deerfield, IL) within 30 minutes of sample collection. The normal reference range for plasma fibrinogen level and MPV in our hospital laboratory is 180 to 350 mg/dl and 9.3 to 12.1 fL respectively. The number of days of ICU stay, number of days in the hospital, in-hospital mortality, cure, or discharge were recorded.

The primary outcome measures were to correlate the levels of plasma fibrinogen and MPV with the severity of sepsis and mortality. The secondary outcome measures were to correlate the severity of sepsis with the duration of ICU and hospital stay and mortality. On the basis of a previously published study, a sample size of 311 patients was calculated by formula with 80% power and 5% probability of type I error to reject a null hypothesis.[7,8]

Statistical analysis

Data collected were entered in excel 2007 and analysis of data was done using statistical package for social sciences for windows, version 20.0 from IBM corporation, Armonk, NY, USA. The data on categorical variables are shown as n (% of cases) and the data on continuous variables are presented as mean and standard deviation (SD). The inter-group comparison of the distribution of categorical variables was done using the chi-square test or Fisher's exact test. The statistical significance of the inter-group difference of means of continuous variables was tested using analysis of variance (ANOVA) technique with post-Hoc Bonferroni's correction for multiple group comparisons. The underlying normality assumption was tested before subjecting the study variables to ANOVA. Non-parametric data on continuous variables (duration of ICU stay and hospital stay) are presented as the median with inter-quartile range (IQR). The statistical significance of difference across two or more variables of non-parametric data was tested using the Kruskal-Wallis H test. The p values of less than 0.05 were considered to be statistically significant.

RESULTS

Of 311 cases studied, 208 (66.9%) patients were males and 103 (33.1%) patients were females. Sixty-seven (21.5%), 54 (17.4%), 35 (11.3%), and 155 (49.8%) had no sepsis, sepsis, severe sepsis and septic shock respectively. Of 244 patients of sepsis, 54, 23, 159 and eight patients had serum procalcitonin >2 ng/ml, viral, bacterial and fungal culture-positive respectively. Of 311 cases, 50 (16.1%) died within four days; 93 (29.9%) died within seven days and a total number of 126 patients died during the study period.

The incidence of sepsis was significantly higher in patients who were >60 years of age, whereas there was

no statistically significant difference in the incidence of sepsis between male and female patients (Table 1). The mean APACHE II score was significantly higher in patients who had severe sepsis and septic shock. There was no statistically significant difference in mean MPV on day one and day four according to the severity of sepsis. The mean plasma fibrinogen on day one and day seven was significantly higher in patients who had septic shock. There was no statistically significant difference in the median duration of ICU and hospital stay according to the severity of sepsis. The incidence of mortality was significantly higher in patients who had septic shock (Table 2).

Table 1: Age and gender distribution according to sepsis.

Variables	No sepsis, n=67 (%)	Sepsis, n=244 (%)	Total, n=311 (%)	P value
Age group (in years)				
≤30	10 (26.3)	28 (73.7)	38 (100.0)	0.001*
31-40	19 (41.3)	27 (58.7)	46 (100.0)	
41-50	12 (17.9)	55 (82.1)	67 (100.0)	
51-60	20 (26.3)	56 (73.7)	76 (100.0)	
61-70	2 (4.5)	42 (95.5)	44 (100.0)	
>70	4 (10.0)	36 (90.0)	40 (100.0)	
Gender				
Male	44 (21.2)	164 (78.8)	208 (100.0)	0.812**
Female	23 (22.3)	80 (77.7)	103 (100.0)	

*Fisher's exact test was used, **Chi square test was used

Table 2: Outcome measures according to the severity of sepsis.

Variables	Severity of sepsis				P value
	No sepsis (n=67)	Sepsis (n=54)	Severe sepsis (n=35)	Septic shock (n=155)	
Mean APACHE II, score ± SD	28.2±8.2	30.9±6.2	34.5±7.5	33.7±7.9	0.001*
Mean MPV					
Day 1 ± SD, (n=311)	9.7±0.8	9.8±0.7	9.8±0.6	9.4±0.9	0.999*
Day 4 ± SD, (n=261)	10.1±0.7	9.8±0.7	10.0±0.6	10.1±0.7	0.999*
Mean plasma fibrinogen					
Day 1 ± SD, (n=311)	461.8±153.8	441.5±100.6	461.6±124.2	519.2±163.0	0.010*
Day 7 ± SD, (n=218)	452.0±80.6	453.3±69.2	474.8±88.8	535.7±116.3	0.001*
Median duration of ICU stays in days (IQR)	3.0 (3-7)	4.0 (3-5)	6.0 (4-11)	5.0 (3-8)	0.338**
Median duration of hospital stays in days (IQR)	9.0 (2-30)	9.0 (4-21)	11.0 (5-20)	9.0 (1-60)	0.719**
Incidence of mortality (%)					
Died	20 (29.9)	11 (20.4)	10 (28.6)	85 (54.8)	0.001***
Discharged from hospital	47 (70.1)	43 (79.6)	25 (71.4)	70 (45.2)	

*Analysis of variance (ANOVA) with post-Hoc Bonferroni's test was used, ** Kruskal-Wallis H test was used, ***Chi square test was used, SD-standard deviation, MPV- mean platelet volume, ICU- intensive care unit, IQR- interquartile range, APACHE II-acute physiology, age, chronic health evaluation II.

Table 3: Mean MPV and plasma fibrinogen in survivors and non-survivors.

Variables	Survivor group (n=185)	Expired group (n=126)	P value
Mean MPV			
Day 1 ±SD	10.0±0.7	9.1±0.8	0.001*
Day 4 ±SD	9.9±0.6	10.2±0.6	0.001*
Intra-group comparison p value	0.095	0.001	**
Mean plasma fibrinogen (mg/dl)			
Day 1 ±SD	425.1±70.8	565.4±185.4	0.001*
Day 7 ±SD	471.1±66.2	566.1±163.3	0.001*
Intra-group comparison p value	0.001	0.327	**

* Unpaired 't' test was used, ** Paired 'test' was used, SD- standard deviation, MPV- mean platelet volume

The mean MPV on day one was significantly lower in the expired group of patients compared with the survived group of patients whereas the mean MPV on day four was significantly higher in the expired group of patients compared with the survived group of patients. The mean MPV on day four was significantly higher compared with the mean MPV at the day one in the expired group of patients. The mean plasma fibrinogen on day one and day seven was significantly higher in the expired group of patients compared with the survived group of patients. The mean fibrinogen on day seven did not differ significantly compared with the mean fibrinogen on day one in the expired group of patients, whereas the mean fibrinogen on day seven was significantly higher compared with the mean fibrinogen on day one in the survived group of patients (Table 3). The mean ± SD of APACHE II score among survived (n=185) and expired (n=126) was 31.0±7.0 and 34.0±8.6 respectively which was statistically significant (p=0.001).

DISCUSSION

Three hundred eleven patients were enrolled in this prospective observational study in which 244 (78.5%) had sepsis and 67 (21.5%) had "no sepsis." The mean MPV was significantly higher on day four compared to day one in non-survivors. The increase of MPV was higher in non-survivors compared with survivors. Persistent high levels of fibrinogen were in the non-survivor group.

In the present study, of 311 patients, 54 (17.4%), 35 (11.3%) and 155 (49.8%) had sepsis, severe sepsis and septic shock respectively. In a study conducted by Mavrommatis et al 45 (60.8%), 15 (20.27%) and 14 (18.9%) had sepsis, severe sepsis and septic shock respectively.[9] In our study, the mean APACHE II score was significantly higher in the group of patients with severe sepsis and septic shock. The mean APACHE II score was significantly higher in the expired group of patients (34.0±8.6) compared to the survived group of patients (31.0±7.0). Gao et al reported that the median APACHE II score was 30.0 in survivors and 35.0 in non-survivors.[10] Kim et al stated that the mean APACHE II score was 16.5±6.6 in survivors and 25.9±6.8 in non-survivors (p<0.001).[11] A study conducted by Lorente et al showed the APACHE II score was (20.2±2.9) in survivors and (23.3±2.3) in non-survivors.[12] These findings are similar to our study.

In the present study, the mean MPV on day one and day four did not differ significantly between the groups of patients with no sepsis, sepsis, severe sepsis and septic shock. Sadaka et al also reported that there was no significant change in MPV according to the severity of sepsis.[13] The incidence of mortality was significantly higher in the group of patients with septic shock because of multiple organ failures compared "no sepsis" group.

In our study, the mean MPV on day one was significantly lower in the expired group of patients compared to the survived group of patients. The mean MPV on day four was significantly higher in the expired group of patients compared to the survived group of patients. The possible explanation for the link between MPV and mortality is an inflammatory response which is significantly associated with the adverse clinical outcomes in ICU patients. Platelet volume indices are immediate indicators of platelet activation that are regulated by the inflammatory process.[14] The uncontrolled inflammatory response is thought to be associated with the activation of the coagulation system, consumption of platelet and adverse outcome. Higher MPV as strong predictors of mortality was also reported by Zhang et al.[15] In the present study, we found that ΔMPV (day four-day one) significantly increased in non-survivors than in survivors. A persistent rise or a further increase might indicate that the treatment response is inadequate, or the disease was too severe. This result is similar to the study conducted by Kim et al.[11]

Kim et al reported that non-survivors exhibited a significantly higher baseline MPV than survivors (9.54±1.66 vs. 8.54±1.10; p=0.001). MPV levels increased significantly during the first 72 hours in both non-survivors (p=0.001) and survivors (p<0.001).[11] Becchi et al examined the trends of MPV and platelet count during the course of sepsis in a small population and found that the average MPV gradually increased in non-survivors, whereas it decreased in survivors.[7] In a study conducted by Sadaka et al MPV was (10.5±0.9) for survivors and (10.6±0.9) for non-survivors on day one. They observed that single MPV was not a useful predictor of mortality in septic shock.[13] Kitazawa et al reported that an increase in the MPV levels was significantly lower in the non-survivors than in the survivors during the initial period but later in the course of the disease, an increase in the MPV levels was significantly higher in the non-survivors than in the survivors. The degree of elevation of the MPV levels at the onset was lower in the non-survivors than in the survivors; however, after the elevation of MPV, the MPV levels remained higher in the non-survivors than in the survivors.[16]

In the present study, mean fibrinogen on day one and day seven was significantly higher in the expired group of patients compared to the survived group of patients. With the severity of sepsis, more marked inflammation and stronger activation of coagulation lead to a more marked rise in fibrinogen level. [9] In contrast, in severe sepsis and mainly in septic shock, most of the coagulation factors are depleted; platelets are also decreased and global coagulation tests are prolonged, indicating exhaustion of haemostasis. In our study, mean fibrinogen on day one was 461.8±153.8, 441.5±100.6, 461.6±124.2, and 519.2±163.0 in no sepsis, sepsis, severe sepsis and septic

shock group respectively (p <0.05).This result is similar to the study conducted by Mavrommatis et al in which distribution of the mean fibrinogen on day one were 301.71±20.9, 429.53±22.2, 598.93±43.17, and 578.57±35.83 in no sepsis, sepsis, severe sepsis and septic shock group respectively (p<0.001). [9] Fibrinogen is an acute-phase reactant; so, plasma fibrinogen is elevated two to 20 fold, in "no sepsis" group (SIRS) and sepsis group initially but returned to baseline following resolution of the inflammatory stimulus and control of infection.[17-19] But with the severity of sepsis, more marked inflammation and stronger activation of coagulation lead to a more marked rise in fibrinogen level.

The profile described here in septic patients during one week indicates that most of the differences between survivors and non-survivor may not become evident until several days after the diagnosis was established or if only isolated parameter measurements of coagulation profile were performed. Many parameters should be measured to know about complete coagulation profile-changes such as anti-thrombin III, plasminogen/a2-antiplasmin ratio, protein C and plasminogen activator inhibitor-1 (PAI-1) levels because these more characteristically varied differently in the group of survivors as compared with the non-survivor.[12] It remains to be established whether a pharmacologic intervention to modify that profile, i.e. inhibiting PAI-1 secretion, administering activated protein C, or anti-tissue factor antibodies alters the outcome of these patients. In severe sepsis, and mainly in septic shock, the entire coagulation system seems to be exhausted, as suggested by a marked decrease in coagulation factors, prolongation of global coagulation tests and reduction of platelets but fibrinogen, an acute phase reactant, was elevated in all groups of septic patients its adequate production by the liver in response to inflammation was greater than increased consumption.[9]

Lorente et al reported that fibrinogen plasma levels were high in both the survived and non-survived group. Levels in the non-survivor group on day seven were significantly higher than in the survivors.[12] Azfar et al reported a significant correlation of APACHE II, platelet, prothrombin time, activated partial thromboplastin time, fibrinogen and D-dimer with mortality in patients with severe sepsis or septic shock. They further stated that the fibrinogen level at the admission was an independent predictor of mortality in patients with sepsis or septic shock.[20]

Potential limitations of the study merit consideration. Patients were enrolled from a single medical center. We included all critically ill patients suspected to be having sepsis for analysis, heterogeneity of the study population may arise. Multiple parameters should be measured in a study to know about complete coagulation profile-changes in antithrombin III, plasminogen/a2-antiplasmin ratio, protein C and PAI-1 levels. Higher mortality and prolonged hospital stay may be due to patients with multiple co-morbidities. A blood culture can miss many genuinely infected septic patients (falsely falls into the "no sepsis" group). Procalcitonin can be falsely positive in any intense inflammatory conditions like a circulatory shock.

CONCLUSION

Mean plasma fibrinogen on day one and day seven were significantly higher in patients who had septic shock and in expired patients. The mean MPV on day four was significantly higher in patients who expired compared to those who survived. The mean MPV on day four was significantly higher compared to the mean MPV on day one in patients who expired.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee- RECH/EC/2017-18/369

REFERENCES

1. Wang HE, Shapiro NI, Angus DC, Yealy DM. National estimates of severe sepsis in United States emergency departments. Crit Care Med. 2007;35:1928-36.
2. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med. 2007;35:1244-50.
3. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis. 2007;7:210-7.
4. De Stoppelaar SF, Veer VC, Van der Poll T. The role of platelets in sepsis. Throm Haemost. 2014;112:666-77.
5. Acikgoz S, Akduman D, Eskici Z, Can M, Mungan G, Guven B et al. Thrombocyte and erythrocyte indices in sepsis and disseminated intravascular coagulation. J Med Biochem. 2012;31:60-4.
6. Farias MG, Schunck EG, DalBó S, De Castro SM. Definition of reference ranges for the platelet distribution width (PDW): a local need. Clin Chem Lab Med. 2010;48:255-7.
7. Becchi C, Al MM, Fabbri LP, Marsili M, Boddi V, Boncinelli S. Mean platelet volume trend in sepsis: is it a useful parameter? Minerva Anestesiol. 2006;72:749-56.
8. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med. 2013;35(2):121.
9. Mavrommatis AC, Theodoridis T, Orfanidou A, Roussos C, Christopoulou-Kokkinou V, Zakynthinos S. Coagulation system and platelets are fully activated in uncomplicated sepsis. Crit Care Med. 2000;28:451-7.

10. Gao Y, Li Y, Yu X, Guo S, Ji X, Sun T et al. The impact of various platelet indices as prognostic markers of septic shock. PLoS One. 2014;9:e103761.
11. Kim CH, Kim SJ, Lee MJ, Kwon YE, Kim YL, Park KS et al. An increase in mean platelet volume from baseline is associated with mortality in patients with severe sepsis or septic shock. PLoS One. 2015;10:e0119437.
12. Lorente JA, García-Frade LJ, Landín L, De Pablo R, Torrado C, Renes E et al. Time course of hemostatic abnormalities in sepsis and its relation to outcome. Chest. 1993;103:1536-42.
13. Sadaka F, Donnelly PL, Griffin MT, O'Brien J, Lakshmanan R. Mean platelet volume is not a useful predictor of mortality in septic shock. J Blood Disorders Transf. 2014;5:194.
14. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia. 2010;14:28.
15. Zhang S, Cui YL, Diao MY, Chen DC, Lin ZF. Use of platelet indices for determining illness severity and predicting prognosis in critically ill patients. Chin Med J. 2015;128:2012.
16. Kitazawa T, Yoshino Y, Tatsuno K, Ota Y, Yotsuyanagi H. Changes in the mean platelet volume levels after bloodstream infection have prognostic value. Intern Med. 2013;52:1487-93.
17. Green F, Humphries S. Control of plasma fibrinogen levels. Baillieres Clin Haematol. 1989;2:945-59.
18. Woods A, Brull DJ, Humphries SE, Montgomery HE. Genetics of inflammation and risk of coronary artery disease: the central role of interleukin-6. Eur Heart J. 2000;21:1574-83.
19. Rosenson RS. Myocardial injury: the acute phase response and lipoprotein metabolism. J Am Coll Cardiol. 1993;22:933-40.
20. Azfar M, Khan M, Khurshid M. Fibrinogen at admission is an independent predictor of mortality in severe sepsis and septic shock. Crit Care. 2014;18:P209.

Cite this article as: Chalodiya K, Bahulikar A, Khadke V, Phalgune D. Correlation of plasma fibrinogen and mean platelet volume in patients of sepsis to the severity of sepsis and its outcome. Int J Adv Med 2020;7:1830-5.