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UTILITY OF PLATELET INDICES IN ASSESSING RISK OF MORTALITY IN INTENSIVE CARE PATIENTS ADMITTED AT A TERTIARY HOSPITAL.

Pathology

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ABSTRACT

Background - Platelet volume indices are routine parameters provided by any automated hematology analyser. Increased platelet activity can be diagnosed by raised platelet volume suggesting increases prothrombotic state which is associated with adverse outcomes in intensive care patients. Advancements in health care facilities are now focusing on identifying new predictors of clinical outcome of patients with critical illness. Newer indices such as presepsin and soluble CD 14 subtype can be used but are expensive. Platelet volume indices are and hence be used for routine monitoring and assessing the risk of mortality in intensive care patients.

Objective -The objective was to to study the correlation between platelet volume indices and mortality in intensive care unit patients.

Methods -This was to retrospective case control study conducted in a tertiary 14 bed Intensive care unit(ICU) with a sample size of 65 non survivors(cases) and 130 survivors(controls).

Results - Multivariate logistic regression analysis was done and only hemoglobin at admission was the only predicting factor with low haemoglobin level associated with increased mortality with Odds ratio: 0.793 and p value 0.002. Pearson's Correlation was calculated between MPV and other parameters and a moderate positive correlation was found between MPV and Plateletcrit with Pearsons's correlation coefficient: 0.262 and PLCR. In conclusion there was no correlation between platelet count and other platelet indices on admission to ICU with mortality. Hemoglobin was found to be the only significant indicator in assessing mortality in ICU patients. However prospective studies need to be done on not only platelet indices at admission but serial platelet indices before ruling out use of platelet indices in assessing mortality in ICU patients.

KEYWORDS

Introduction

Platelet volume indices comprising of platelet count, mean platelet volume, plateletcrit and platelet distribution width are routine parameters provided by any automated hematology analyser. Mean platelet volume is calculated using plateletcrit and platelet count. Platelet distribution width denotes the degree of anisocytosis in platelets.[1]

Majority of the patients admitted to intensive care unit(ICU) die of sepsis and sepsis is due to release of pro inflammatory cytokines and activation of coagulation cascade which usually leads to disseminated intravascular coagulation with platelet activation, thrombus formation and activation of fibrinolytic sytem.[2] Numerous complete blood count parameters have already been used to detect the prognosis of critically ill patients and parameters such as packed cell volume, total leucocyte count and platelet count are being used in scoring system of intensive care patients such as sequential organ failure assessment (SOFA) score, multiple organ dysfunction score (MODS), and logistic organ dysfunction score (LODS).[3-5] Since the advent of newer hematology analysers research has been going on to identify the utility of all the indices including platelet indices in assessing risk and predicting prognosis in critically ill patients. Majority of the patients with sepsis have platelet counts less than 80,000/cumm and low platelet counts have been associated with severe sepsis and predict poor outcome of the patient. [6-7] Lately studies have been done suggesting association between these indices and platelet activation which is an independent risk factor in systemic inflammatory response, sepsis, myocardial infarction, diabetes mellitus and hemodialysis patients.[8-15] Increased platelet activity can be diagnosed by raised platelet volume suggesting increases prothrombotic state which is associated with adverse outcomes in intensive care patients.[16] Large platelets have increased platelet activity as they produce large amounts of thrombaxane A2.[17] Platelet activation is an earlier phenomenon in thrombosis and platelet volume indices can be used as biomarkers in platelet activation.18 Platelet volume indices such as platelet count, Mean Platelet Volume(MPV), Platelet Crit (PCT), Platelet Distribution Width (PDW) and Platelet Large Cell Ratio(PLCR) are being routinely obtained from analyser reports may be useful and inexpensive alternative to all patients with critical illness in assessing risk of mortality which may aid in choosing a more aggressive approach in patients with adverse outcome.

A relationship between sepsis severity and thrombocytopenia has already been proven in many studies.[19,20] Studies have also shown a correlation of the MPV with mortality in diseases such as myocardial infarction[12,21], acute ischemic cerebrovascular events[8,22], diabetes[23] and congestive heart failure.[24]

Advancements in health care facilities are now focusing on identifying new predictors of clinical outcome of patients with critical illness. Newer indices such as presepsin and soluble CD 14 subtype have been used which are very expensive.[25-26] Platelet volume indices can be inexpensive as is available in all hemogram reports and hence be used for routine monitoring and assessing the risk of mortality in intensive care patients. Hence this study was done to see if platelet indices can be cheap and inexpensive alternate predictive markers of mortality in patients admitted to ICUs.

Review of literature

In the 1960s, John Wright identified megakaryocytes give rise to platelets. Later Behnke O described the electron microscope structure of platelet membranewhich was followed by others who showed that thrombopoiesis is regulated by humoral mechanisms megakaryocytes respond by an increase in number, size, ploidy and increase in the rate of maturation whenever there is a decrease in the platelet count either due to immune destruction on increased removal.[27-29] Platelet counts normally range between 1.5 lakhs to 4.5 lakhs per microlitre and a count below 1.5 lakh is generally considered to constitute thrombocytopenia.[30]

Thrombocytopenia may be due to reduced platelet production, increased platelet destruction, artifactual thrombocytopenia or abnormal distribution or pooling of platelets within the body. Thrombocytopenia should be confirmed by the second platelet count after the first platelet count is lower than the normal count. Though bleeding tendency increases with increasingly low platelet count necessitating platelet transfusion. Not all thrombocytopenic patients with platelet count less than 20,000/cumm bleed.[31]

According to one study, Platelet size distribution width and mean platelet volume have sufficient sensitivity and specificity in the diagnosis of immune thrombocytopenia they concluded that though there are many causes of thrombocytopenia, aetiology may vary in given clinical setting. However, viral infections, drugs are responsible for the majority of cases.[32]

Modern haematology analysers, electronically generate data on the platelet indices like MPV, PDW and Platelet crit which may give

information on the functional aspects of the platelets. Larger platelets with high MPV have higher platelet membrane contents and greater extent of secretions, membrane protein activation and platelet aggregation. There are studies that suggest that though thrombo cytopenia is associated with bleeding but there is no clear association between platelet count and bleeding.[32]

Platelet distribution Width (PDW) tells us about the variation of the platelet size.[33] Platelet crit (PCT) is the ratio of total blood platelets in the blood. Platelet count decline is an early prognostic marker in critically ill patients with prolonged ICU stay.[34]

PLCR - Platelet Large Cell ratio is calculate by ratio of Large platelets and total platelets with large platelets being the ones with MPV > 12fl and increase in PLCR is diagnostic of auto immune thrombocytopenia purpura but increase is seen in conditions with activated platelets.

Both increase and decrease in platelet indices are significant. Decreased platelet indices seen in Alzheimer's disease, vascular dementia, pulmonary arterial hypertension, osteoporosis. Increased platelet indices are seen in myocardial infarction, unstable angina and vascular complications of diabetes.[34]

Once the platelets gets activated, shape of the platelets changes from discoid to spherical and acquires more surface area and leads to pseudopodia formation. PDW varies with the increased number and size of pseudopodia. On platelet activation, both MPV and PDW increases, PDW being more specific indicator of platelet activation but no change in platelet count.[35]

Immature platelets being larger than normal platelets. Increase in immature platelets indicates increased platelet production due to overconsumption induced by inflammation. Large platelets are functionally, metabolically and enzymatically more active than normal ones.

Several studies have shown that raised MPV is associated with increased risk and adverse outcome in cardiovascular and cerebrovascular diseases.[36-39] MPV has also been used to indicate inflammation, disease activity and efficacy of treatment in inflammatory bowel disease, rheumatoid arthritis and ankylosing spondyloarthritis.40-44

However only few studies have been done on correlation between platelet indices at admission and mortality in ICU patients

Aims and Objectives

The aim of this study was to investigate predictive value of platelet indices at admission to estimate the severity of illness in ICU patients with end result being mortality.

Platelet volume indices can be inexpensive as is available in all hemogram reports and hence be used for routine monitoring and assessing the risk of mortality in intensive care patients.

Our objective was to study the correlation between platelet volume indices and mortality in intensive care unit patients.

Material and Methods

A retrospective case control study was conducted in Intensive care unit(ICU) of our tertiary hospital with the study period of six months between October 2015 to March 2016. Sample Size was estimated by using the Mean MPV values between survivors and Non survivors from the study by Zhongheng Zhang et. al.,[45] using this values at 95% Confidence Interval and 80% power, a sample size of 65 non survivors(cases) and 130 survivors(controls) at 1:2 ratio was obtained. The ICU has a mixed population of patients admitted under various specialities.

Exclusion Criteria :

a) Patients in the ICU for less than 24 hours
b) Platelet volume indices couldn't be obtained
c) Patients were transferred to another hospital for further management or were discharged against medical advice
d) Pregnancy or patients with active hemorrhage
e) Patients on chemotherapy / radiotherapy / platelet transfusion.

Data was collected through medical records section for patients included in the study. Data includes demographics of the patient, date of admission, diagnosis and laboratory hematology parameters at admission.

Laboratory parameters includes Platelet Indices such as platelet count, plateletcrit, mean platelet volume, platelet distribution width, Platelet Large cell Ratio. RBC parameters such as Hemoglobin(Hb), Mean Corpuscular Volume(MCV), Mean Corpuscular Hemoglobin(MCH), Mean Corpuscular Hemoglobin Concentration(MCHC) and WBC parameters obtained from a Alere 360 , an automated hematology analyser from EDTA anticoagulated venous blood at admission

Statistical analysis:

Data was entered into Microsoft excel data sheet and analyzed using SPSS 22 version software. Categorical data is represented in the form of Frequencies and proportions. Continuous data will be represented as mean and standard deviation. Independent t test is the test of significance to identify the mean difference between two groups. p value <0.05 is considered as statistically significant.

Institution ethics committee approval was taken before start of the study

Observations and Results

Parameters	Survivors	Non Survivors	p value
Number of cases	130	65	
Age	49.52 ± 20.98	50.85 ± 19.21	0.668
Hemoglobin	12.57 ± 2.67	11.07 ± 2.66	**0.0001**
MCV	84.20 ± 9.26	81.66 ± 8.39	0.065
MCH	28.05 ± 3.79	27.47 ± 3.67	0.318
MCHC	33.12 ± 1.46	33.75 ± 2.09	**0.016**
TLC	13.66 ± 5.62	14.70 ± 6.19	0.246
Platelet count	218 ± 117	191 ± 126	0.139
PCT	0.146 ± 0.08	0.126 ± 0.08	0.124
PDW	17.81 ± 3.46	18.29 ± 4.46	0.405
MPV	6.52 ± 1.50	6.72 ± 1.81	0.421
PLCR	29.35 ± 9.20	29.98 ± 14.32	0.709

Table 1 - Comparison of demographic and clinical variables between survivors and non survivors

A total of 195 subjects were included in our study with 65 patients who did not survive and 130 patients who survived after admission in ICU. The mean ages of patients were 49.5 ± 20.9 years and 50.8 ± 19.2 years in survivor and non-survivor groups respectively. Majority of patients admitted to ICU in both the survivors and non-survivors group were admitted for respiratory ailments. We found significant differences in haemoglobin and MCHC between two groups (z<0.05). There waslower Platelet count, Plateletcrit and increased PDW, MPV and PLCR in survivors when compared to non survivors. However though there was a difference in mean values of platelet count, PDW and MPV in non survivors and survivors there was no significance on calculation of p value. (Table 1)

Sex					
	Frequency	Percent	Valid Percent	Cumulative Percent	
Non Survivor	FEMALE	48	36.9	36.9	36.9
	MALE	82	63.1	63.1	100.0
	Total	130	100.0	100.0	
Survivor	FEMALE	28	43.1	43.1	43.1
	MALE	37	56.9	56.9	100.0
	Total	65	100.0	100.0	

Table 2 - Sex distribution of survivors and non survivors

Majority of the patients in both survivor and non survivor groups were males. (Table 2)

Parameters	p value	Odds ratio	95% Confidence Interval	
			Lower	Upper
Age	0.885	1.001	0.985	1.018
Platelet	0.810	1.000	1.000	1.000
PCT	0.255	0.007	0.0001	34.737
PDW	0.144	1.072	0.977	1.176
MPV	0.180	1.201	0.919	1.572

HB	**0.002**	0.793	0.685	0.918
MCV	0.633	0.990	0.951	1.031

Table 3 - Multivariate logistic regression analysis for independent predictors of mortality

Multivariate logistic regression analysis was done and only hemoglobin at admission was the only predicting factor with low haemoglobin level associated with increased mortality with Odds ratio: 0.793 and p value 0.002. Platelet indices did not show any significance and couldn't predict mortality on logistic regression analysis. (Table 3)

	All Patients		Survivors		Non Survivor	
	R	p value	R	p value	R	p value
Hemoglobin	0.019	0.794	0.011	0.901	0.075	0.552
MCV	0.083	0.249	0.020	0.822	0.226	0.070
MCH	0.077	0.283	0.043	0.630	0.151	0.231
MCHC	0.119	0.098	0.058	0.515	0.173	0.167
TLC	-0.026	0.723	-0.025	0.777	-0.039	0.758
Platelet count	-0.139	0.052	-0.107	0.224	-0.176	0.161
PCT	0.272	0.0001	0.262	0.0003	0.319	**0.010**
PDW	-0.058	0.418	-0.027	0.757	-0.107	0.397
PLCR	0.015	0.835	0.260	0.003	-0.251	**0.044**

Table 4 - Correlation between MPV and other parameters ® –Pearsons's Correlation co-efficient)

Pearson's Correlation was calculated between MPV and other parameters and a moderate positive correlation was found between MPV and Plateletcrit with Pearsons's correlation coefficient: 0.262 and PLCR. No correlation was found between MPV and MCH, MCHC,TLC,Platelet count and PDW. (Table 4)

Discussion

Platelet indices have been available since the early 1980s and many studies have tried to correlate their use in predicting severity of critical diseases. However very few studies have proved the use of platelet indices at admission to mortality. In our study we found no significant correlation with platelet count and indices at admission and mortality.

Studies	Year	Setting	Non Survivors			Survivors		
			Number	Age(yrs)	MPV(fl)	Number	Age(yrs)	MPV(fl)
Present Study	2016	All	65	50.8± 19.2	6.7 +/- 1.8	130	49.52 ± 20.9	6.5 ± 1.5
Kucukardali et al [46]	2010	All	62	76.5 ± 11.1	8.5 ± 1.5	68	65.7 ± 21.6	8.3 ± 1.2
Guclu et al[47]	2013	Sepsis	94	60.7 ± 18.5	7.0	51	66.5 ± 18.5	8.0
Kitazawa et al[48]	2013	Sepsis	25	72.3 ± 11.3	7.5 ± 1.1	325	66.8 ± 15.7	7.6 ± 1.0
Sadaka et al [49]	2014	Sepsis	170	70 ± 14	10.6 ± 0.9	314	66 ± 15	10.5 ± 1.5
Gao et al [50]	2014	Sepsis	88	61.7 ± 17.9	11.2	61.2 +/- 20.6	61.2 ± 20.6	10.3
Sergi et al [51]	2015	All	95	69 ± 14.3	8.8 ± 2.3	80	62.4 ± 15.2	9.1 ± 2.4
Zhang et al[40]	2014	All	443	63.1 ± 20	11.1 ± 1.4	1113	60.7 ± 19	10.5 ± 1.4
Kim et al [52]	2015	Sepsis	35	68.9 ± 13	9.5 ± 1.7	310	63.7 ± 15.9	8.5 ± 1.1

Table 5 Comparison of present study with other studies

Similar to our study age at admission was slightly higher in non survivors than survivors in a few studies with even significant p value.[40,46, 48,49,50,51] However our study did not show significance with p value > 0.05. One study showed higher age in survivors. [47]

Like our study, few studies done have show raised MPV in non survivors compared to survivors with significant p value. [40,46, 49,50,52] However p value wasn't significant in our study. MPV reflects platelet size and raised MPV suggests and increased platelet production and activation suggestive of prothrombotic activity and associated with adverse cardiovascular and cerebrovascular outcomes. Few studies showed lower MPV in non survivors than survivors. [47,48]

However the limitations of the study such as retrospective nature, small number of cases, variation in baseline level of platelet indices, bias due to loss of cases due to transfer to other hospitals/ admission in ICU for less than 24 hrs and different etiology of patients admitted to ICU. Many factors that may cause elevated platelet indices such as smoking, anticoagulant history, liver diseases, malignancies may have influenced the study which can be excluded in further studies to evaluate the use of platelet indices in ICU patient mortality.

Conclusion

In our study there was no relation between platelet count and other platelet indices on admission to ICU with mortality. Hemoglobin was found to be the only significant indicator in assessing mortality in ICU patients. However prospective studies need to be done on not only platelet indices at admission but serial platelet indices before ruling out use of platelet indices in assessing mortality in ICU patients.

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