ORIGINAL ARTICLE

Platelet Indices as Predictive Markers of Prognosis in Critically Ill Patients: A Prospective Study

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Abstract

Introduction: Platelets (PLTs) are dynamic blood molecules which perform multiple physiological functions. Platelet derangements are commonly encountered in intensive care units (ICUs). The relationship of PLT indices with all-cause mortality, acute physiology and chronic health evaluation IV (APACHE IV), diabetes mellitus (DM), and length of stay in ICU is debatable and hence this study was undertaken to bridge this gap of knowledge.

Materials and methods: Prospective data were collected for 20 months in the ICU of our hospital. Platelet indices were analyzed among survivors and non-survivors. Acute physiology and chronic health evaluation IV scores were used to study the relationship between PLT indices and illness severity. Receiver operating characteristic curves were constructed to compare the performances of PLT indices in predicting mortality, while the effect of DM on PLT indices was evaluated using regression analysis.

Results: A total of 170 out of 345 patients (119 survivors, 51 non-survivors) met the study criteria. Patients with decreased PLT count and plateletcrit (PCT) ($p < 0.001$ and 0.001, respectively), increased mean platelet volume (MPV) and platelet distribution width (PDW) ($p = 0.014$ and 0.004, respectively) had a significant correlation with increased risk of mortality than those with normal PLT indices. These patients also had a higher APACHE IV and acute physiology score ($p < 0.001$). No significant relationship was found between the PLT indices and the length of ICU stay. The influence of each PLT index adjusted to DM was significant in univariate regression analysis, whereas in multivariate only PDW had a significant influence.

Conclusion: Patients with low PLT, PCT and high MPV, PDW were associated with more severe illness, poor prognosis, and a higher risk of mortality. Platelet distribution width is the preferred PLT index in a diabetic patient to predict clinical status.

Clinical significance: Platelet indices which are routinely available can be effectively used as a morbidity and mortality indicator in critically ill patients.

Keywords: Acute physiology and chronic health evaluation IV, Mean platelet volume, Platelet count, Platelet distribution width, Platelet indices, Plateletcrit.

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Introduction

Platelets (PLTs) are dynamic blood molecules which perform multiple physiological functions, such as thrombosis, coagulation, enhance host defense against microbes, inflammation and along with coagulation factors initiate hemostasis and therefore prevent excess bleeding.[1] Platelet indices are biomarkers of PLT activation and are reliable predictors of the PLT size, morphology, and proliferation kinetics and assist in assessment of its derangements.[2] The routinely utilized PLT indices include PLT count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT). The MPV is defined as the ratio of PCT to PLT count and is the index which measures the volume of the average circulating PLT. The PDW is a PLT index which measures the volume of PLT dispersion.[3] Platelet distribution width is defined numerically as the coefficient of PLT volume variation.[4] Platelet is defined as the arithmetic product of PLT volume and PLT count.

Platelet indices have been applied in diagnosing hematological disorders but recent studies have found a relationship between the changes in PLT indices and the activation of the coagulation system, severe infection, trauma, systemic inflammatory reaction syndrome, and thrombotic diseases.[5] Platelet indices provide a more comprehensive picture of the etiology of the illness and its severity. Studies have shown that low PLT count is an independent risk factor for mortality in patients in intensive care units (ICUs) and the rising or declining trend of PLTs has an impact on the overall survival of the patient.[6] In mortality scoring system, such as acute physiology and chronic health evaluation IV (APACHE IV), includes thrombocytopenia as an independent risk factor for mortality. In a recent research, it was reported that abnormally low PLT, high MPV value, and high PDW value are associated with more severe illness in ICU patients.[6] In addition, MPV, PDW, and PLT large cell ratio are strong, independent prognostic factors in acute myocardial infarction (MI).[7] In addition, increase in MPV, PDW in patients with cirrhosis and ascites were accurate diagnostic predictors for ascitic fluid infection.[8] There is a paucity of Indian studies which investigate whether PLT indices are related with all-cause mortality and the relation of these indices

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with ICU scoring systems for morbidity like APACHE IV in patients in intensive care. Thus, we conducted a prospective study, among patients admitted to our ICU from September 2017 to April 2019, to study whether PLT indices (PLT, MPV, PDW, and PCT) are related with all-cause mortality, APACHE IV, diabetes mellitus (DM), and length of stay in critically ill patients in ICU.

Materials and Methods

It is a prospective observational study conducted in ICU of our hospital from September 2017 to April 2019 after permission from the institutional ethical committee and conducted in accordance with the Declaration of Helsinki. The primary objectives were to compare PLT indices with the clinical condition of the patient using APACHE IV and to compare mortality rate in patients with normal and abnormal PLT indices. The secondary objectives were to study the effect of DM on PLT indices in ICU patients and to correlate PLT indices with duration of stay in the ICU.

Patients aged above 18 years with length of ICU stay >24 hours were included whereas pregnant and lactating women; patients with active hemorrhage; hematological and rheumatological diseases, diagnosed chronic liver disease were excluded. Also patients who were infused with PLT concentrate up to 48 hours prior to their admission and have used drugs known to cause thrombocytopenia or have received radiotherapy or chemotherapy or bone marrow transplantation 1 month prior to admission were excluded from the study.

All patients admitted to the ICU who satisfied the inclusion and exclusion criteria were recruited for the study and after informed consent, basic information was collected from medical records, and blood was sent for investigations and APACHE IV was calculated within first 24 hours of ICU admission and the patient were followed up during their ICU stay.

Platelet indices were analyzed using Beckham Coulter Unicel DXH 800 analyzer. The normal range for PLT count was 150,000–450,000, for MPV was 7–11 fL, while for PDW –17 and PCT is 0.108–0.282%. The data collected were analyzed using IBM SPSS Statistics 25. Categorical variables was presented as numerical data and percentages and statistical comparisons was performed using chi-square (χ^2) test. Comparisons between groups were performed using Student's *t* test. Sensitivity and specificity of each PLT index in predicting mortality were calculated using receiver operating characteristic (ROC) and the area under the curves (AUC) was compared. Kaplan–Meier method was used to construct ICU survival curve. Regression analysis was performed to study the effect of DM on PLT indices and APACHE. The *p* value <0.05 was considered to indicate statistical significance.

Results

During the study period from September 2017 to April 2019, there were 345 hospitalizations in the multispecialty ICU among which 170 subjects satisfied the study criteria. The clinical characteristics of the survival group and the non-survivor group were summarized in Table 1.

Among the 170 patients admitted in ICU, majority were males 96 patients and females 74 patients, and their mortality rates were 33.3 and 25.6%, respectively. Around 62 patients were hospitalized in the ICU because of sepsis, whereas 38 and 33 patients were admitted, respectively, because of respiratory and neurological etiologies. The other indications for hospitalization included surgical and miscellaneous (9 each), metabolic (8), gastroenterology (5), genitourinary (3), cardiovascular (2), and trauma (1).

Table 1: Comparison of baseline characteristics, acute physiology and chronic health evaluation IV, platelet indices among survivors and non-survivors

Variables	*Survivors (n = 119)*	*Non-survivors (n = 51)*	*p value*
Male, *n* (%)	64 (53.8)	32 (62.7)	0.280
Female, *n* (%)	55 (46.2)	19 (37.3)	
Age, years, mean ± SD	53.79 ± 17.61	53.69 ± 17.93	0.723
DM	37	13	0.463
Days of ICU stay, mean ± SD	8.92 ± 7.28	7.02 ± 6.51	0.008
APACHE IV, mean ± SD	63.58 ± 21.48	96.71 ± 22.40	<0.001
APS, mean ± SD	52.50 ± 19.58	85.80 ± 22.54	<0.001
Platelet indices, mean ± SD			
PLT, $\times 10^9$/L	255.1 ± 140.9	173.4 ± 130.2	<0.001
MPV, fL	8.52 ± 1.03	8.96 ± 1.22	0.014
PDW, %	17.07 ± 1.25	17.69 ± 1.13	0.004
PCT	0.21 ± 0.12	0.15 ± 0.1	0.001

DM, diabetes mellitus; APACHE IV, acute physiology and chronic health evaluation IV; APS, acute physiology score; SD, standard deviation; PLT, platelet; MPV, mean platelet volume; PDW, platelet distribution width percentage; PCT, plateletcrit

In our study, non-survivors had higher APACHE IV and acute physiology scores ($p < 0.001$) than survivors. Among the PLT indices, PLT and PCT were found to be significantly lower in non-survivors ($p < 0.001$ and $p = 0.001$, respectively) while MPV and PDW were higher in the non-survivors ($p = 0.014$ and $p = 0.004$, respectively) (Table 1).

Correlation of PLT Indices with APACHE IV and Acute Physiology Score

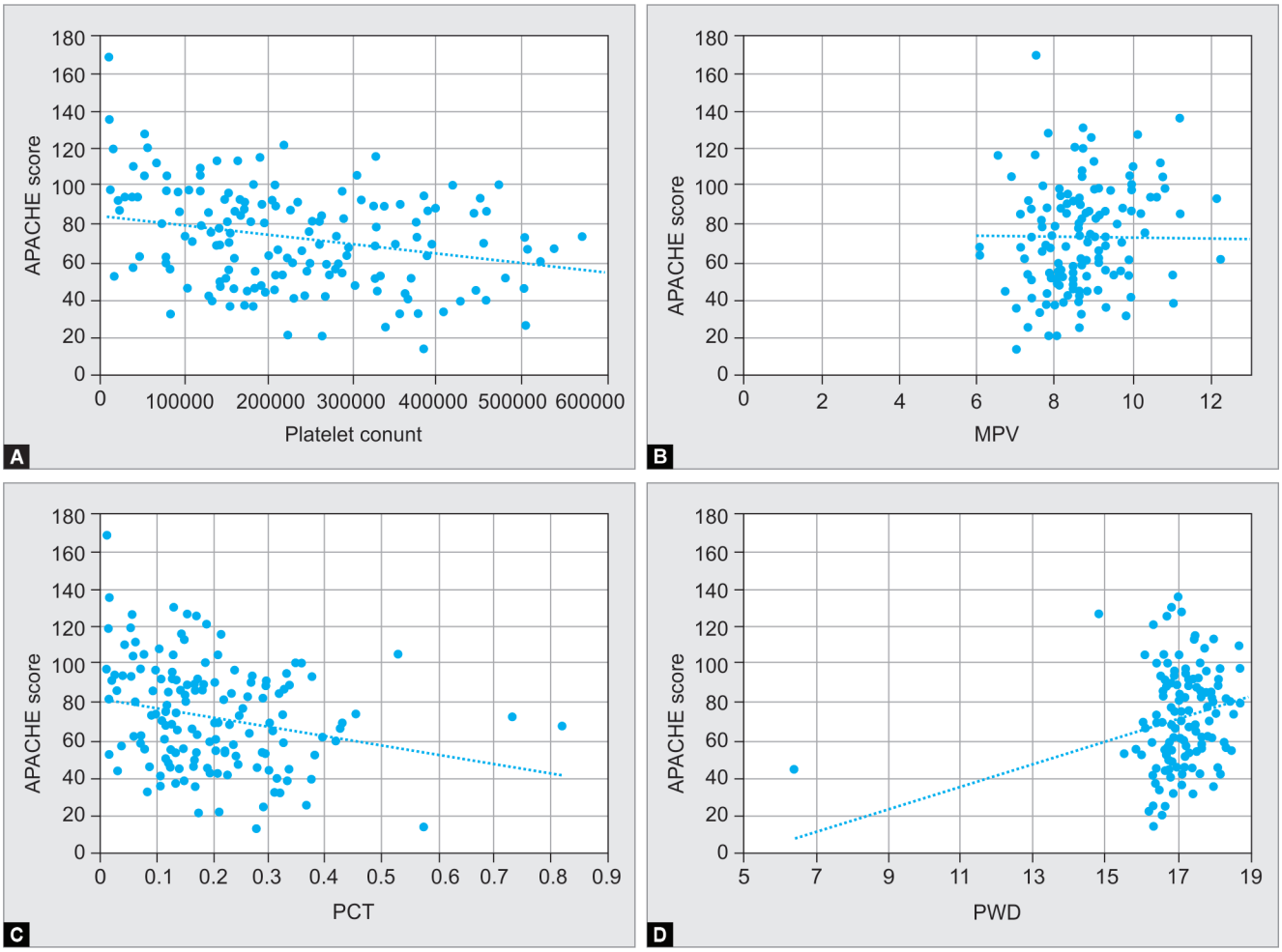
A negative correlation ($r = -0.265$) was observed between PLT count and APACHE IV score. This meant that lower the PLT count, higher is the APACHE IV score. *p* value of <0.001 being highly significant. A positive correlation ($r = 0.167$) was observed between MPV and APACHE IV score. This meant that higher the MPV, higher is the APACHE IV score. *p* value of 0.03 being significant. A negative correlation ($r = -0.224$) was observed between PCT and APACHE IV score. This meant that lower the PCT, higher is the APACHE IV score. *p* value of 0.003 being highly significant. A positive correlation ($r = 0.252$) was observed between PDW and APACHE IV score. This meant that higher the PDW, higher is the APACHE IV score. *p* value of 0.001 being highly significant (Fig. 1). The results were comparable when acute physiology score was correlated with the PLT indices (Table 2).

Days of ICU Stay and PLT Indices

A statistically nonsignificant ($p = 0.059$) and negative correlation was observed between days of ICU stay with PLT count, MPV, and PCT, whereas a statistically nonsignificant and positive correlation was observed between days of ICU stay with PDW.

Diagnostic Power of Platelet Indices for Predicting Mortality

In our study, ROCs were constructed to study the sensitivity and specificity of PLT indices as a predictor of mortality. Platelet and PCT



Figs 1A to D: Correlation of acute physiology and chronic health evaluation (APACHE) IV with each of the platelet index. PLT, platelet; MPV, mean platelet volume; PDW, platelet distribution width percentage; PCT, plateletcrit

Table 2: Correlation of platelet indices with acute physiology and chronic health evaluation IV and acute physiology score

Platelet indices	*Correlation with APACHE IV*	*p value*	*Correlation with APS*	*p value*
PLT	−0.265**	<0.001	−0.293**	<0.001
MPV	0.167*	0.030	0.179*	0.020
PDW	0.252**	0.001	0.263**	0.001
PCT	−0.224**	0.003	−0.236**	0.002

*Correlation is significant at the 0.05 level (two-tailed); **Correlation is significant at the 0.01 level (two-tailed); APACHE IV, acute physiology and chronic health evaluation IV; APS, acute physiology score; PLT, platelet; MPV, mean platelet volume; PDW, platelet distribution width percentage; PCT, plateletcrit

obtained the largest areas under ROCs of 0.68 and 0.66, respectively. Mean platelet volume and PDW obtained less areas under ROCs of 0.61 and 0.63, respectively. The sensitivity and specificity for PLT were 70 and 57%, both of which were similar to that of PCT (72 and 52%) (Table 3 and Fig. 2).

Kaplan–Meier Curve for Survival

It was observed that the mean ICU survival was 24.8 days with a confidence interval of 18.878–30.822, while the median days of ICU survival was 30 with confidence interval of 7.288–52.712 (Fig. 3).

Regression Analysis of DM with PLT Indices and APACHE

During univariate regression analysis of each of the PLT index with APACHE, it was found that individually each of the PLT index, i.e., PLT count, MPV, PDW, and PCT has a significant effect on APACHE. During multivariate analysis, it was observed that only the influence of PDW on APACHE adjusted to DM was significant, whereas PLT count, MPV, and PCT did not have an effect on APACHE in the presence of DM.

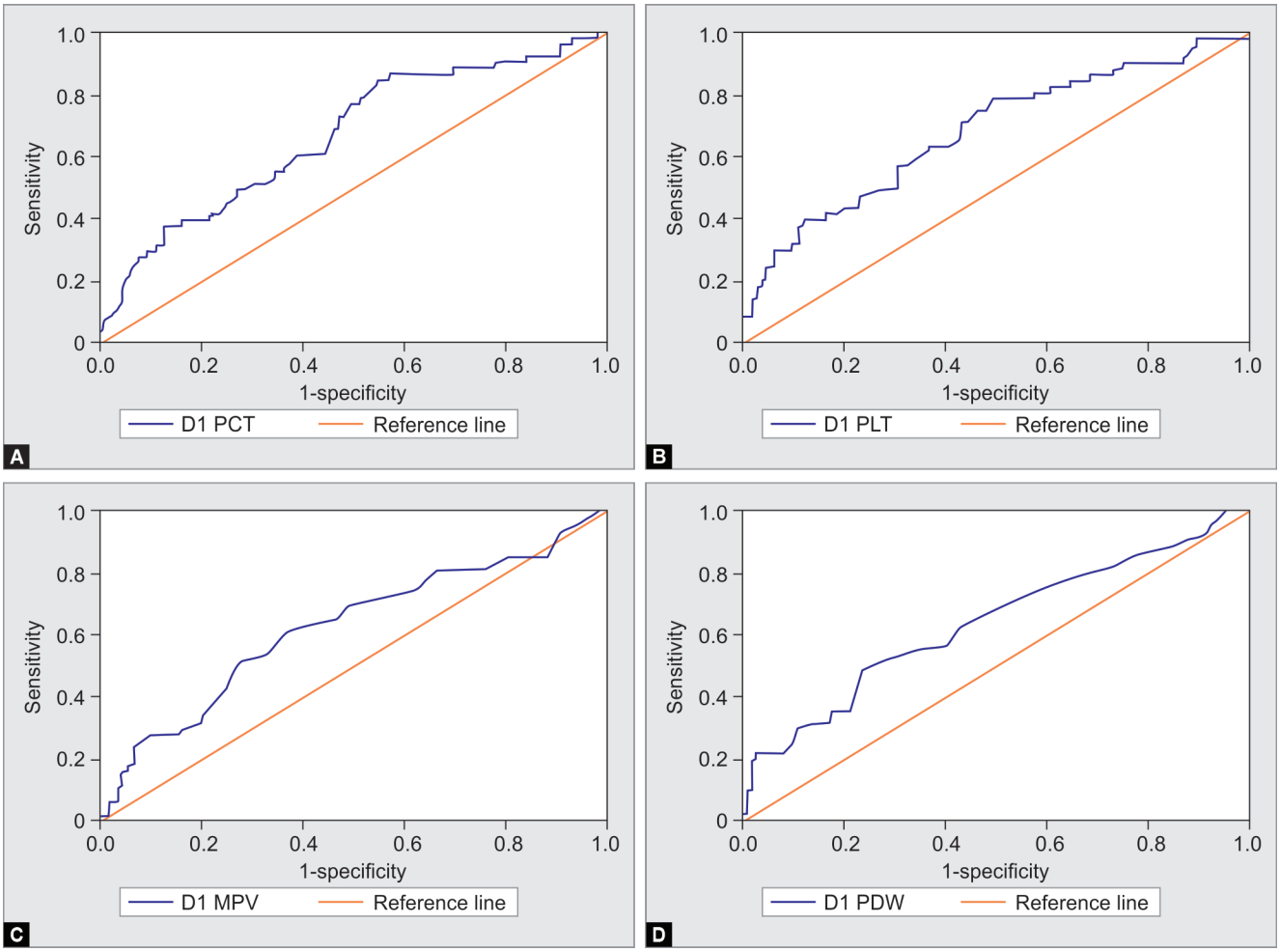
Discussion

In our study, it was observed that a patient in ICU who had a low PLT and PCT and a high MPV and PDW had a higher APACHE IV score and a comparatively poor prognosis including higher risk of mortality. Additionally, PDW is the only PLT index which has a statistically significant effect on APACHE when adjusted to DM. Platelet indices are easily accessible parameters which are being increasingly recognized as markers of inflammation and thrombosis. In pathological processes like sepsis, disseminated intravascular coagulation which is commonly encountered in ICUs, there is an excessive consumption of PLTs with increased PLT destruction which is reflected as a simultaneous reduction of both PLT and PCT. The bone marrow compensates for this by producing excess new PLTs

Table 3: Diagnostic parameters of receiver operating characteristics (ROCs) by platelet indices on predicting mortality

			Confidence interval			
Platelet indices	*AUC*	*p value*	*Lower bound*	*Upper bound*	*Sensitivity (%)*	*Specificity (%)*
PLT	0.681	<0.001	0.591	0.771	70	57
MPV	0.619	0.014	0.522	0.715	68	52
PCT	0.666	0.001	0.576	0.755	72	52
PDW	0.638	0.004	0.543	0.732	66	52

AUC, area under the ROC curve; PLT, platelet; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width



Figs 2A to D: Receiver operating characteristics for platelet indices in predicting mortality. PLT, platelet; MPV, mean platelet volume; PDW, platelet distribution width percentage; PCT, plateletcrit

which change from biconcave to spherical shape with an increase in formation of pseudopods which lead to PLTs which are large in size and volume.[9] This change is reflected as an increase in both MPV and PDW. There have been studies of thrombocytopenia in ICU but there is a paucity of studies involving the other PLT indices in the ICU and to the best of our knowledge ours is the first study in the Indian Subcontinent to explore the relationship of these indices with APACHE IV, mortality, length of ICU stay, and DM.

The relationship of PLT indices to APACHE which is used for assessing the clinical condition of ICU patients yielded similar results in a recent study which showed an elevation in APACHE II was related with PLT and PCT in the low tertile and MPV and PDW in the high tertile.[6] It was also seen that APACHE had a statistically significant negative correlation with PLT count and PCT and a statistically significant positive relation with MPV and PDW. To the best of our knowledge, ours is the only study to use APACHE IV to assess PLT indices in ICU.

In our study, it was observed that among the 170 patients, 51 patients did not survive among whom 86% of the patients did not survive beyond first 10 days of ICU stay. Among the 51 patients, around 47.1% had thrombocytopenia which was statistically significant ($p = 0.004$). Similarly, a statistically significant low PCT

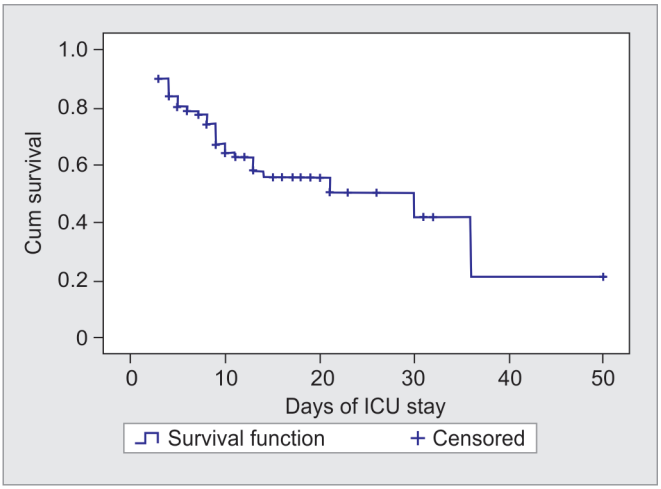


Fig. 3: Kaplan–Meier curve for days of intensive care unit (ICU) survival

was found in 31.3% patients who did not survive. A statistically significant association was not obtained between abnormal PLT indices and mortality. It may be because of the following reasons, majority of our patients both in the survivor and non-survivor group had values in the normal ranges and hence a statistically significant relationship could not be obtained because of low sample size and previous studies have shown that the positive and negative association of MPV varies depending on the underlying pathological process.[7]

In our study, thrombocytopenia, low PCT, high MPV and high PDW was significantly observed in non-survivors. This is similar to a recent study in 1,556 patients in ICU where it was observed that MPV and PDW were significantly elevated in non-survivors and PDW >17% and MPV >11.3 fL were independent risk factors for mortality.[3] A lower PCT was also associated with increased risk of mortality in these patients.

In our study, no significant association was obtained between the length of ICU stay and the PLT indices and neither was this parameter studied in previous studies. Thrombocytopenia when associated with other critical illness might prolong the ICU stay.

Diabetes mellitus was considered as a confounding factor as it is known to have an impact on the PLT indices and also has an effect on the scoring system in APACHE and hence might lead to an altered value of these indices. Hyperglycemia and insulin resistance are known to produce hyper-reactivity of PLTs which in turn also cause an increase in coagulation with impairment in endothelial function and fibrinolysis which has been implicated in the pathophysiology of development of complications in diabetics. This PLT hyper-reactivity can be observed as changes in PLT parameters.

In our study, in univariate regression analysis, it was observed that all the four PLT indices individually adjusted to DM had a significant effect on APACHE but in multivariate analysis only PDW had a statistically significant effect on APACHE when adjusted to DM as was seen in the above study. In a recent study, it was observed that only MPV, PDW, and PLT–large cell ratio were significantly higher in diabetic individuals with high HbA1c and also microvascular complications when compared with diabetics without complications.[10]

Our study included patients with a wide variety of etiologies for ICU admission irrespective of their PLT count and at the same time tried to avoid any possible exogenous factor which might cause an alteration in the PLT morphology by a strict exclusion criteria to ensure that the PLT indices were accurately calculated across both genders and in all adults who were admitted in our ICU, so that these indices could be used to assess their clinical condition, mortality, and length of ICU stay.

The limitations of our study include that majority of the cases included in our study were patients who were admitted in the ICU due to sepsis and very few surgical patients were included in the study. All the etiologies of ICU admission were considered together and their influence on PLT indices were studied. Each pathological process has its own varying degree of inflammation and eventual one marrow stimulation and the individual effect of different processes could not be studied.

Further studies can be performed to study the causal relationship between PLT indices and different pathological processes and to estimate probable cutoffs for the same and in surgical patients not in sepsis to identify whether PLT indices can be used for prognosis in them too.

Conclusion

In our study, it was observed that a patient in ICU who had a low PLT count and PCT and a high MPV and PDW had a higher APACHE IV score and a comparatively poor prognosis. Also, ICU patients who had a low PLT count and PCT and a high MPV and PDW had a higher risk of mortality. No relation was observed between days of ICU stay and the PLT indices. Platelet distribution width is the only PLT index which has a statistically significant effect on APACHE when adjusted to DM.

Clinical Significance

Platelet indices which are routinely available can be effectively used as a morbidity and mortality indicators in critically ill patients.

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