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A study of platelet indices as a prognostic marker in sepsis

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Abstract

Background: Sepsis is associated with thrombocytopenia and platelet indices reflect the platelet function better than the platelet count itself. Studies have proved the role of platelet indices in severe sepsis and prognosis of clinical outcome.

Objectives

1. To compare platelet indices between survivors and non survivors in sepsis patients.
2. To study if platelet indices have an impact on the prognosis of sepsis.

Materials And Methods : A prospective observational study for a period of 12 months was carried out and 77 patients were included in the study. Bedside qSOFA scoring was used to identify infected patients outside the ICU who are likely to be septic. Patients presented to our ED were evaluated at admission and platelet indices were compared between survivors and non survivors in sepsis patients.

Results: Mean MPV,PDW,PLCR were noted to be increasing trend first three days among survivors and non survivors except mean PLCR was noted to decrease on day three among survivors. The mean change in MPV was found to be high among non survivors 0.42 compared to survivors 0.29 but was not statistically significant. ROC of platelet count ,plateletcrit ,MPV,PDW,PLCR and Procalcitonin were compared at 72 hours after admission Procalcitonin showed maximum AUC with 0.59, followed by Platelet count and Plateletcrit with 0.50 and PDW and PLCR of 0.48, but was not statistically significant. MPV at baseline were compared to change in MPV AUC was noted to be 0.50 for both and was not statistically significant.

Conclusion: In our study, there was no significant difference between the platelet indices of those who died compared to survivors. Considering all the AUC values none of the Platelet indices were strong predictors of mortality.

Keywords: qSOFA: quick Sequential (Sepsis-related) Organ Failure Assessment, MPV- Mean platelet volume**,** PDW-Platelet distribution width**,** PLCR-Platelet large cell ratio**,** AUC area under curve

Introduction

Sepsis is the most common cause of death in critically ill patients [1]. Sepsis is a life-threatening condition, following the body's immune response to an infection. Immune by the body is triggered by an infection which can lead to injury to its own tissues and organs [2]. Sepsis develops when the chemicals of the immune system releases into the bloodstream to fight an infection cause inflammation throughout the entire body instead. Severe cases of sepsis can lead to septic shock. Most common infection is bacterial, but it may also be from fungi, viruses, or parasites. Most often the primary source of is from lungs, brain, urinary tract, skin, and abdominal organs. Risk factors include old age, cancer, diabetes, major trauma, or burns. The Third International Sepsis Consensus Definitions Task Force sought to differentiate sepsis from uncomplicated infection, and to update definitions of sepsis and septic shock. They defined sepsis as "as life-threatening organ dysfunction due to a dysregulated host response to infection [3].

Studies have shown the association of severe sepsis with thrombocytopenia. Sepsis decreases circulating platelets haemostatic function, maintains adhesion molecule expression and secretion capability, and modulates growth factor production [4]. It is very essential to diagnose such patients to start early goal directed therapy in order to prevent the complications and reduce mortality [5].Therefore it is essential to start antibiotic therapy as early as possible as inappropriate therapy can lead to increased morbidity and mortality [6].

Several clinical scoring systems have been found to have to access to the severity of illness and prognosis in patient with sepsis. Scoring systems for severity of illness and organ dysfunction have been validated and used as tools to predict the risk of death in intensive care unit (ICU) patients. APACHE II, SOFA, MEDS, and REMS and many other scoring system are being used commonly [7,8]. The predominant score in current use is the Sequential Organ Failure Assessment (SOFA) (Sepsis-related Organ Failure Assessment). The score is based on six different scores, cardiovascular, hepatic, coagulation, renal and respiratory, neurological systems. It is used to track a person's status during the stay in an intensive care unit (ICU) prognosis [9]. The minimum score is zero in a patient without any preexisting organ dysfunction. ASOFA score ≥2 points consequent to the infection is significant and reflects 10% mortality in population with suspected infection. Thus scoring system emphasizes the seriousness of the condition and the need for prompt and appropriate intervention.

2016 a new consensus was reached to replace screening by systemic inflammatory response syndrome (SIRS) with qSOFA [10]. Third International Consensus Definitions for Sepsis recommends qSOFA as a simple prompt to identify infected patients outside the ICU who are likely to be septic and who are at greater risk for a poor outcome outside the intensive care unit (ICU) [11]. The score ranges from 0 to 3 points. A qSOFA score of >2 are associated with a greater risk mortality or prolonged intensive care unit stay. These

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are outcomes that are more common in infected patients who may be septic than those with uncomplicated infection.

More than 200 biomarkers have already been published as markers of sepsis, CRP, LDH, Procalcitonin are the common markers used to access the severity and prognosis in a patient with sepsis. Besides serum parameters, the urinary levels of these markers are also elaborated, since urinary biomarkers of sepsis provide new diagnostic implications and are helpful for monitoring both the kidney function and the septic process [12]. Sepsis leads to altered coagulopathy [13]. The drop in platelet count is correlated to the prognosis, and when the patient recovers platelet count raises towards normal values [14,15]. Platelet indices are readily available blood tests, and their prognostic value in patients with septic shock has been reported in several studies [16]. Various parameters studied under platelet indices are Platelet volume distribution width (PDW), Plateletcrit (PCT), and platelet large cell ratio (PLCR).These indices are related to morphology and proliferation kinetics of platelets and hence have a definite clinical utility in patients with sepsis. The other indices include mean platelet component, mean platelet mass, platelet component distribution width, platelet large cell ratio (P-LCR) and immature platelet fraction (IPF), these latter indices are studied very rarely.

In sepsis, there is excess destruction of platelets leading to increase production and release of young platelets into the peripheral blood which are larger hence MPV levels increase. Increased platelet volume and size reflects the existence of a thrombotic and inflammatory milieu; thus, MPV is suggested as a possible marker of platelet function and activation [17,18,19]. Therefore, increased MPV is useful clinically as a marker of production rate and platelet activation. The MPV refers to the ratio of PCT to PLT count. PDW is numerically equal to the coefficient of PLT volume variation which is used to describe the dispersion of PLTs volume [20]. Acute Physiology and Chronic Health Evaluation II (APACHE II) System also includes thrombocytopenia as an independent risk factor for mortality [21]. MPV changes has been already observed in various conditions like acute appendicitis, pancreatitis, infective endocarditis, and malaria [22,23]. Van der Lelie et al found that half of patients diagnosed with sepsis had an increased MPV and suggested that an increased MPV could be associated with invasive infections [24]. On the other hand, Bessman et al found MPV decreases in sepsis [25].

The PDW increases during platelet depletion, and shares similar behavior to MPV during acute severe infections. PLCR is another surrogate marker for the platelet volume, which identifies the largest-sized fraction of platelets. An increase in PLCR usually signifies that there is an increase in new platelets (which are larger in size). PCT is the Plateletcrit and is influenced by the number and the size of platelets therefore it is in positive relationship with the platelet count. Only a few studies have revealed the relationship between MPV and prognosis in infectious diseases [26,27]. An increase in MPV during the first 72 hours of hospitalization has been found to be an independent risk factor for adverse clinical outcomes [28]. Among the traditional prognostic markers of sepsis MPV was found to be more closely correlated with Mortality[29]. This study aims to explore the trend of platelet indices in septic shock and their clinical prognostic value.

Methodology

A prospective study entitled “A study of platelet indices as a prognostic marker in sepsis” was undertaken at a tertiary care hospital after the approval from Ethics

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Committee. The study was carried out for a period of 12months, and 77 patients who fulfilled inclusion criteria were included in the study from the ED patients, conditions were defined according the The Third International Consensus Definitions Task Force.

Each patient presenting to our ED were evaluated at the time of admission and detailed history and physical examination were documented. The data collected includes demographic profile, co-morbidities and quick SOFA score.Venous blood samples were collected from the patients at the time of presentation in tubes containing Ethylenediamine tetra-acetic acid (EDTA) and analyzed with Sysmex XT1800i within 30 minutes of sample collection. Platelet indices such as platelet count, plateletcrit (PCT), *platelet* large cell ratio (*P-LCR*), platelet distribution width (PDW) and mean platelet volume (MPV) were measured at the time of admission and three consecutive days after admission.

All the patients of sepsis admitted to ICU/ emergency ward were compared between two groups; survivor group (which include the patients who are successfully discharged after recovery) and non-survivor group (the patients who expired).

Inclusion criteria

1. All patients above 18 years of age fulfilling the quickSOFA score criteria.

It uses three criteria, assigning one point for each, The score ranges from 0 to 3 points.

- Low blood pressure (SBP≤100 mmHg)
- High respiratory rate (≥22 breaths per min)
- Altered mentation (Glasgow coma scale<15)

Exclusion criteria

- Patients with sepsis of non-infectious aetiology like burns, pancreatitis
- Patients who have haematological diseases, reactive thrombocytosis hematological malignancies, autoimmune thrombocytopenic purpura, and hypersplenism.

Method of Statistical Analysis

Continuous variables were expressed as means with standard deviations and categorical variables as numbers with percentages. Chi Square Test was used to compare the categorical distribution of the clinical signs and symptoms, co-morbidities, physiological and laboratory parameters, source of infections, etiological diagnosis between non-survivors and survivors. Mann Whitney U test was used to compare the mean age, physiological and laboratory parameters with continuous data between non-survivors and survivor.

ROC curve analysis was done for platelet indices, Procalcitonin levels and MPV change for predicting the mortality among the study patients. In the entire above test the “p” value of less than 0.05 was accepted as indicating statistical significance. Statistical Package for Social Sciences [SPSS] for Windows, Version 22.0. Released 2013. Armonk, NY: IBM Corp., was used to perform statistical analyses.

Results

The study was carried out during the period of 12 months and 77 patients presented to the Emergency Medicine Department who fulfilled inclusion criteria were included in the study. [Table 1] shows the distribution of demographic and other study variables between Survivors and Non-Survivors. 77 subjects were included in this study. Out of these, 46 patients (59.7%) survived and 31 patients (40.2%) did not survive. Out of 77patients, 46 patients (59.7%) were males, 31 patients (40.3%) were females. The mean age among non survivors and survivors were 58.1 [SD 13.4] and 59.7 [SD 15.7] respectively. The age was ranging from 22 to 92 years among the study population.

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[Figure 1] shows, Out of 77 patients, (16.8%) had both Diabetes and Hypertension each and (15.5%) patients had only Diabetes and (15.5%) patients only had Hypertension, followed by (12.9%) patients had IHD. Co morbidities like DM (38.7%) ,CVA (12.9%), Others (9.7%),Tuberculosis (6.5%) were more among non survivors than survivors, but was not statistically significant. CKD patients were found to be more among survivors (13%) and were statistically significant with p value of 0.04.

All the cultures were negative found to be negative among survivors than non survivors but was not statistically significant. [Figure 2] shows the most common organism found in urine culture, was Ecoli (9.1%) followed by Klebsiella (3.9%) .Organisms isolated from sputum culture were Klebsiella (14.3%), followed by Acinetobcater (13.0 %), Pseudomonas (5.2%) . Acinetobactor (3.9%) and Salmonella (3.9%) were the two common organisms predominant in blood culture. Among the organism isolated from urine culture in non survivors Ecoli (12.9%), Klebsiella (9.7%) were more than survivors. Klebsiella (22.6%) and Staphylococcus aureus (3.2%) were the other organisms isolated from sputum in non survivors and was found to be more than survivors, but was not statistically significant. None of the cases included in this study had fungal infection on presentation

The mean total count and procalcitonin 19.58× 103/mm3 , 32.00 respectively were high among non survivors compared to survivors but was not statistically significant p value was 0.07 as shown in [table 2]. A qSOFA of >2 even though was high among non survivors and predicts mortality but was not statistically significant since the p value was 0.13, and patients with qSOFA of <2 were among of survivors.

[Table 3] shows the mean platelet count and plateletcrit were found to be in decreasing trend first three days in non survivors and survivors except, mild increase in mean platelet count was noticed on day three among survivors . Median platelet count and plateletcrit of cases who expired was higher as compared with the platelet counts of those who survived as shown in [figure 3and 4]. Mean MPV,PDW,PLCR were noted to be increasing trend first three days among survivors and non survivors except mean PLCR was noted to decrease on day three among survivors. [Figures 5,6,7] shows the mean MPV,PDW,PLCR was found to be high among non survivors compared to survivors but was not statistically significant .

[Figure 8] shows ROC of procalcitonin studied on 72 hours after admission showed a cutoff value of 10.36 with sensitivity of 61%and specificity of 61% with AUC of .59 [95% CI .46 to .72] but was not statistically significant. The cut of values for the rest of the parameters Platelet count, Plateletcrit, MPV, PDW, PLCR were1.18, 0.12, 10.85, 13.85 respectively in [table 4]. Receiver operating characteristic curve analysis for predicting mortality revealed Platelet count and Plateletcrit with 0.50 both and PDW and PLCR of 0.48 for both, but was not statistically significant.

Figure 1

Distribution of Co-morbidities among Survivors and Non-Survivors

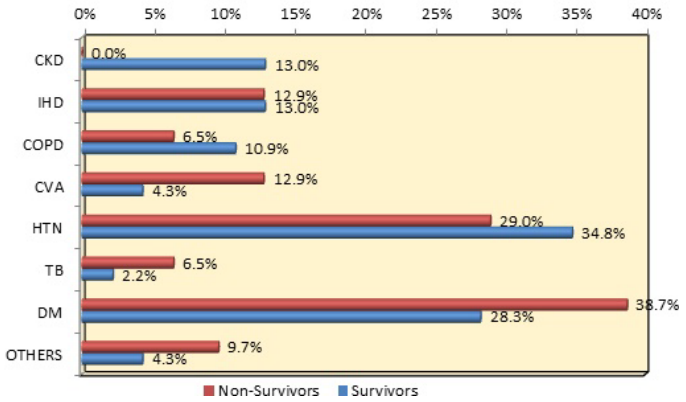

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Figure 2
Distribution culture organisms between Survivors and Non-Survivors

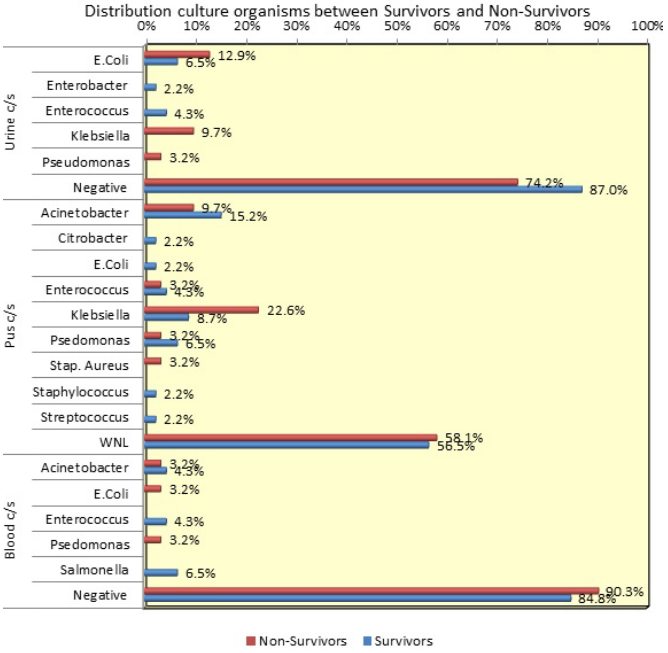

Figure 3
Mean Platelet count among Non-survivors and Survivors

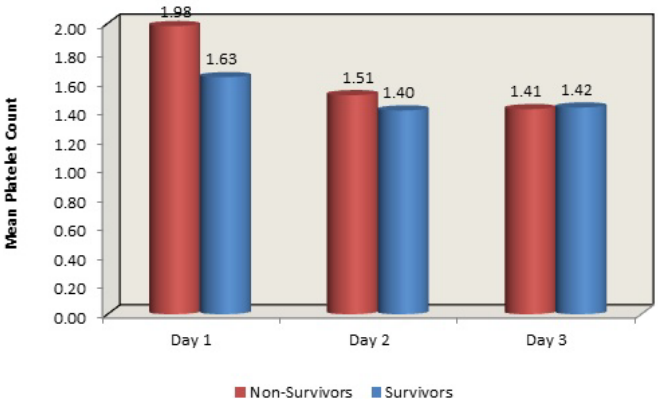

Figure 4
Mean Plateletcrit values among Non-survivors and Survivors

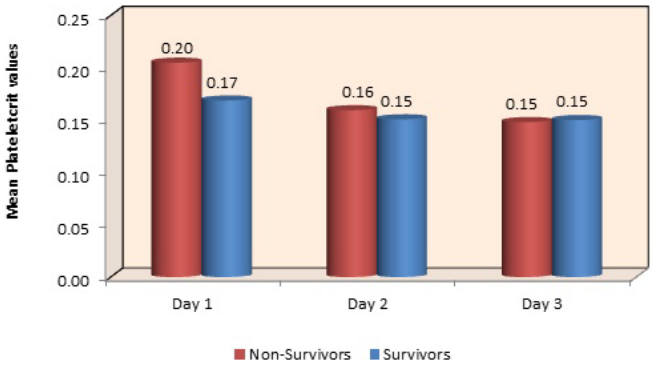

Figure 5
Mean Platelet volume among Non-survivors and Survivors

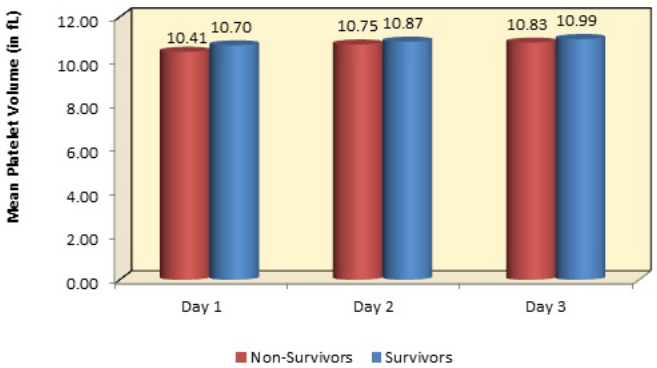

Figure 6
Mean Platelet distribution width among Non-survivors and Survivors

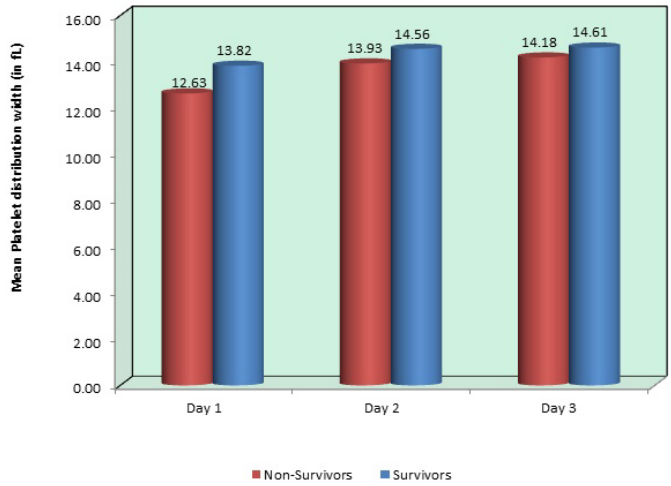

Figure 7
Mean Platelet Large Cell Ratio among Non-survivors and Survivors

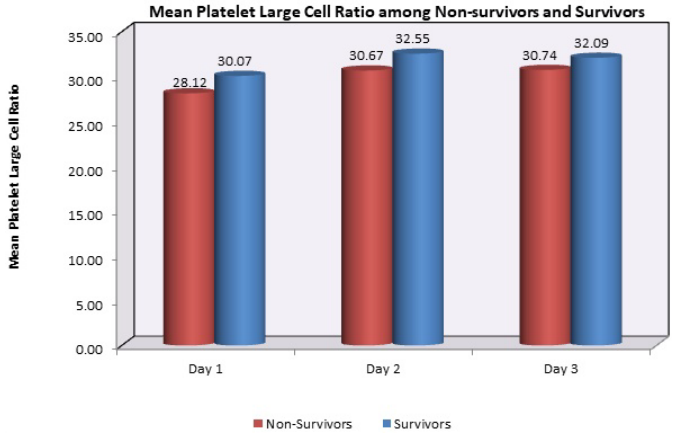

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Figure 8

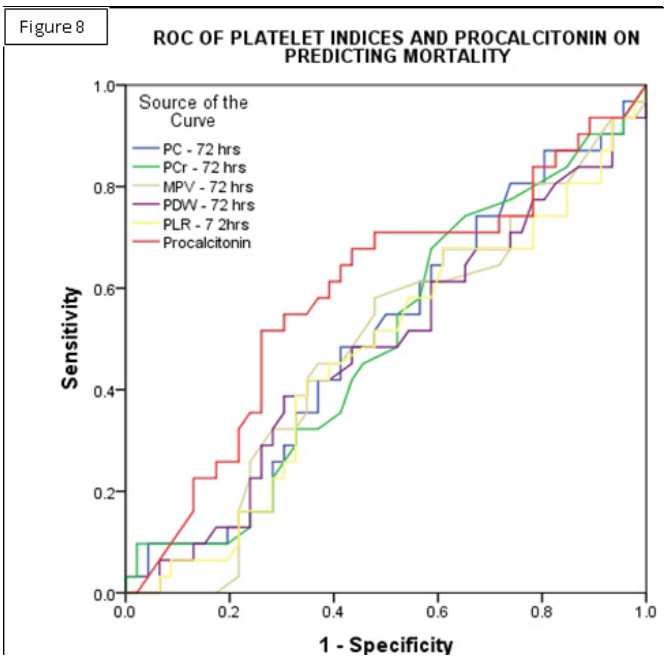

Table 1 Distribution of demographic and other study variables between Survivors and Non-Survivors								
		Non-survivors [n=31]		Survivors [n=46]		Total [N=77]		
Variables	Category	Mean	SD	Mean	SD	Mean	SD	P-Value
Age	Mean & SD	58.1	13.4	59.7	15.7	59.0	14.7	0.45[a]
	Range	23 – 90		22 – 92		22 – 92		
		N	%	N	%	N	%	
Sex	Males	15	48.4%	31	67.4%	46	59.7%	0.10
	Females	16	51.6%	15	32.6%	31	40.3%	

Table 2 Laboratory parameters between Survivors and Non-Survivors								
		Non-survivors [n=31]		Survivors [n=46]		Total [N=77]		
Variables	Expression	Mean	SD	Mean	SD	Mean	SD	P-Value
Procalcitonin	ng / ml	32.00	35.45	25.17	44.28	27.92	40.85	0.19
	Categories	N	%	N	%	n	%	
qSOFA	≤ 2	21	67.7%	38	82.6%	59	76.6%	0.13
	> 2	10	32.3%	8	17.4%	18	23.4%	

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Table 3 Comparison of platelet related parameters and Hospital stay between Survivors and Non-Survivors

Parameters	Time	Non-survivors [n=31]		Survivors [n=46]		Total [N=77]		P-Value
		Mean	SD	Mean	SD	Mean	SD	
Platelet Count	Day 1	1.98	1.09	1.63	0.98	1.77	1.03	0.16
	Day 2	1.51	0.78	1.40	0.89	1.44	0.84	0.36
	Day 3	1.41	0.92	1.42	0.93	1.42	0.92	0.96
Plateletcrit	Day 1	0.20	0.11	0.17	0.09	0.18	0.10	0.15
	Day 2	0.16	0.09	0.15	0.08	0.15	0.08	0.56
	Day 3	0.15	0.10	0.15	0.10	0.15	0.10	0.94
Mean Platelet volume	Day 1	10.41	0.98	10.70	1.18	10.59	1.10	0.32
	Day 2	10.75	1.07	10.87	1.85	10.82	1.58	0.50
	Day 3	10.83	1.04	10.99	1.21	10.93	1.14	0.81
Platelet Distribution Width	Day 1	12.63	2.05	13.82	3.16	13.34	2.81	0.14
	Day 2	13.93	2.83	14.56	3.32	14.30	3.13	0.59
	Day 3	14.18	2.98	14.61	3.26	14.44	3.14	0.78
Platelet Large Cell Ratio	Day 1	28.12	6.93	30.07	7.97	29.28	7.58	0.36
	Day 2	30.67	7.55	32.55	7.85	31.79	7.74	0.55
	Day 3	30.74	6.92	32.09	7.25	31.54	7.10	0.66

Table 4 Area Under the Curve for Platelet Indices at 72 hrs and Procalcitonin

Variables	Cut-off Value	Sn & Sp		AUC	Std. Error	95% Conf. Interval		P-Value
		Sn	Sp			Lower	Upper	
PC at 72 hrs	1.18	55.0%	50.0%	0.50	0.07	0.37	0.64	0.96
PCr at 72 hrs	0.12	55.0%	48.0%	0.50	0.07	0.36	0.63	0.94
MPV at 72 hrs	10.85	55.0%	42.0%	0.48	0.07	0.35	0.62	0.81
PDW at 72 hrs	13.85	48.0%	48.0%	0.48	0.07	0.35	0.61	0.78
PLR at 72 hrs	31.25	48.0%	44.0%	0.47	0.07	0.34	0.60	0.66
Procalcitonin	10.36	61.0%	61.0%	0.59	0.07	0.46	0.72	0.19

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Table 5	Survivours						Nonsurvivours				
STUDY	YEAR	Platelet count	Plateletcrit	MPV	PDW	PLCR	Platelet count	Plateletcrit	MPV	PDW	PLCR
OUR	2018	163	.17	10.8	13.8	30.07	198	.20	10.4	12.6	28.1
Sergi etal	2015			9.1					8.8		
Guclu at al	2013	201		8.0			242		7.0		
Kuchukardali et al	2010			8.2					8.4		
Sadaka et al	2014	314		10.5			170		10.6		
Kavya et al	2017	210	.14	6.5	17.8	29.3	191	.12	6.7	18.2	29.9
Gao et al	2014	164	.18	10.3 *	11.7	26.8	105	.12	11.2	13.7	33.65
Kim et al	2015	214.5*		8.54*			160.7*		9.54*		
Golwala et al	2016	312.7*	.26*	8.7	16.4		217.4*	.18*	8.7	16.4	
Zhang	2014	196.5*	.26*	12.8*	14.5*		141.1*	.17*	15.8*	17*	

Discussion

Sepsis is a major cause of morbidity and mortality. However, assessing the prognosis of sepsis remains difficult. Several parameters like procalcitonin, CRP, TLC, Lactate, qSOFA has been attempted for both diagnosis and prognosis in septic patients. Thrombocytopenia is often seen in critically ill patients, and is associated with increased mortality [30]. Out of 77 subjects studied, (59.7%) were males, (40.3%) were females [31]. The age was ranging from 22 to 92 years among the study population. Mortality in our study was (40.2%) and was found to be comparable to the German study (48.4%)[32]. However, some Indian studies have shown mortality associated with sepsis above (60%) [33,34].

In our study (16.8%) had both Diabetes and Hypertension and was lower compared to another study which showed 20%, 34% respectively [35]. Most common cause of sepsis was pneumonia (41.6%),it was comparable to the study by DASH, Laxmikanta et al which showed the respiratory tract (37.2%) [36]. Most common organism isolated from either respiratory secretions, blood, urine, were Klebsiella, Acinetobactor, Ecoli respectively similar study to study done by Mohammed AK et al [37]. Manzoni et al. showed that there was no significant difference in the incidence of thrombocytopenia among cases of fungal, gram negative, and gram positive sepsis [38]. A qSOFA of >2 even though was high among non survivors and predicts mortality but was not statistically significant. However other studies show, a positive qSOFA had a sensitivity of 61% (57–65) and a specificity of 80% (79–81). The positive likelihood ratio of a positive qSOFA for in-hospital mortality was 3.09 (2.86–3.35) [39].

[Table 5] shows comparison of our study results with various other studies among survivours and non survivours. MPV values were found to be high in patients with sepsis and severe sepsis [40]. Our study results was similar to other studies done by Sergi et al ,Guclu et al where the mean platelet count, plateletcrit were high among non survivours and the mean MPV was low compared to survivours which was not statistically significant [41,42].

Studies by Kuchukardali et al and Sadaka et and Kavya et al had high MPV among non survivours compared

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to survivours but was not statistically significant [42,43,44]. However study results of Kim et al , Zhang et al had low plateletcount ,plateletcrit and high MPV among non survivours compared to survivours which was statistically significant [45,46].

No significant difference between the groups were noted among the platelet indices in our study, similarly in the study by Kucukardali et al [42]. Our results oppose the results of Eberhardt et al's study of patients with sepsis. Eberhardt et al. showed patients with sepsis who died had a higher MPV than survivors [47].

In our study we found that the platelet count was high in patients who died than those who survived. Our results are oppose the results of Vanderschueren et al who have shown that in adults admitted in the ICU, patients who died had a lower platelet count than survivors [48].In our study there was no significant difference between MPV and PDW of the cases who died and the cases who survived. Study by Patrick et al showed PDW association in neonates with late onset sepsis, He found that PDW increased with sepsis [49].Although there was no statistically significant difference in MPV and PDW between those who survived and those who died, ratio of MPV / PCT was more meaningful as an indicator of survival than either of the parameters taken alone. The study by Golwala ZM et al showed MPV/PCT, PDW/Platelet count and MPV/Platelet count, in a case control study were predictors of mortality and could predict 65% to 67% of deaths accurately [50].

MPV/PC has a role for activation of platelets with considering PC in the diagnosis of systemic inflammation. MPV/PC ratio has already been used as a new parameter for the prediction of long-term mortality in patients with myocardial infarction [51].Djordjevic D demonstrated statistically significant differences in MPV/PC, MLR, and PLR values regarding nature of bacteremia [52].

Conclusion

In our study, there was no significant difference between the platelet indices of those who died compared to survivors. Considering all the AUC values very close to the null value of 0.5-0.6, none of the Platelet indices as well as Procalcitonin levels were strong predictors of mortality. Therefore Platelet indices might not be useful as a prognostic marker of mortality in critically ill patients. An inverse trend was noted among Platelet indices in sepsis patients among survivors and non survivors that is , when platelet count and plateletcrit dropped, MPV,PDW,PLCR increased. Newer platelet parameters, Immature platelet fraction(IPF), Mean platelet component(MPC), Platelet component distribution width (PCDW) and Mean platelet mass (MPM),to determine the changes in the status of platelet activation would be of much help in assessing the severity of inflammation, in near future.

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