

MEAN PLATELET VOLUME TO PLATELET COUNT RATIO AS A PREDICTOR OF EARLY MORTALITY IN SEPSIS

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Abstract

Background: Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis frequently results in dysfunction of the hemostatic system. A humble attempt has been made to see the relation of mean platelet volume to platelet count ratio in predicting immediate outcome in sepsis in this study.

Methods: This study was conducted in Silchar Medical College and Hospital. It is a hospital-based prospective observational study. 50 cases diagnosed according to "Sepsis 3" clinical criteria were included in the study. Complete blood count and Blood culture was done for all patients. The clinical outcome was 28-day mortality.

Results: According to Chi-square Test (along with Fisher's Exact Test), there was no statistically significant association between MPV/Platelet Ratio and survival of the patients ($\chi^2 = 1.247$ at $df = 1$, $p = 0.264$), which means survival of patients was almost similar in low as well as high MPV/Platelet Ratio values. According to Kaplan-Meier Survival Curve, low MPV/Platelet ratio has comparatively more benefit in survival of the patients than that of high MPV/Platelet ratio. However, according to the Log Rank Test the low MPV/Platelet ratio does not have any statistically significant difference on patient survival than that of high MPV/Platelet ratio ($\chi^2 = 0.817$ at $df = 1$, $p = 0.366$). Hence even if Kaplan-Meier Curve showed some difference in both the lines, it is not statistically significant hence it can be concluded that both low as well as high MPV/Platelet ratio have somewhat similar effect on survival of the patients.

Conclusion: The present study could not yield similar results on logistic regression showing that MPV alone as well as MPV/Platelet ratio did not have any significant effect on survival of the sepsis patients.

Keywords: Mean platelet volume, Mortality predictor, Sepsis

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.¹

The "Sepsis 3" clinical criteria² for sepsis includes:

1. Suspected infection; and
2. Acute organ dysfunction, which is indicated by an increase of at least two points from baseline in the sequential (or sepsis-related) organ failure assessment (SOFA) score.

Six organ systems—renal, cardiovascular, pulmonary, hepatic, neurologic, and hematologic—are considered in the SOFA score, a 24-point evaluation of organ dysfunction.²

Septic shock results in circulatory and cellular/metabolic abnormalities that are severe enough to raise the risk of fatality. Criteria² for septic shock includes:

1. Possible infection
2. Serum lactate concentration of more than 2 mmol/L after appropriate fluid resuscitation
3. The need for a vasopressor to raise mean arterial pressure to greater than or equal to 65 mmHg

The function of platelets in several physiological and pathological processes, include hemostasis, coagulation, thrombosis, inflammation, microbial host defense, angiogenesis, and remodeling.³

Sepsis frequently results in dysfunction of the hemostatic system. Sepsis results in the depletion of coagulation factors, thrombocytopenia, and DIC because the coagulation system and platelets are severely active.⁴

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The factors contributing to thrombocytopenia in septic patients include peripheral nonimmune destruction, hemophagocytic histiocytosis, and marrow suppression⁵. The overall number of platelets, their shape, and their rate of proliferation are all measured using a set of criteria called platelet indices. The most often used platelet indices are platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT).⁶

In healthy patients, mean platelet volume (MPV) and platelet counts are inversely correlated; however, the clinical significance of these relationships in severe sepsis has not been studied.⁷ Platelet size can be accurately determined by MPV, which also indicates platelet reactivity.^(8,9) Platelets with increased MPV are more prothrombotic, active, and big, which promotes platelet adhesion and aggregation.^(8, 9) A larger MPV typically indicates compensatory bone marrow production following stress-induced platelet loss which takes place during sepsis.^(10, 11) Infection, sepsis, coronary artery disease, cerebrovascular illness, arterial and venous thrombosis, and chronic inflammatory disorders have all been linked to alterations in MPV, according to several studies.^(8, 12-16)

The MPV/platelet ratio has been shown to be more accurate than MPV alone in predicting long-term mortality in individuals with non-ST-elevation myocardial infarction.¹²

All of these indicators can be assessed by a routine blood count, which is affordable and widely available, although their use as sepsis predictors is still uncertain¹⁷. A humble attempt has been made to see the relation of mean platelet volume to platelet count ratio in immediate outcome in sepsis in this study.

PATIENTS AND METHODS

The current study was a hospital-based prospective observational study that was carried out from June 2023 to November 2023 on 50 sepsis patients who had been admitted to the department of general medicine at Silchar Medical College and Hospital. The study was approved by the Silchar Medical College institutional ethical committee, and the ethical clearance number was SMC/20919. Informed written consent was obtained from the patient in their own language prior to data collection. The inclusion criteria were:

- Age >18 years
- Suspected infection
- Acute organ dysfunction defined as increase by 2 or more SOFA points

The exclusion criteria were:

- Age <18 years
- Pregnancy
- Patients with clinical suspicion of thrombocytopenia due to drugs such as heparin or quinine
- Diagnosed or suspected cases of hematological disorders such as leukemia, thrombotic thrombocytopenic purpura and immune thrombocytopenic purpura
- Patients who have undergone chemotherapy or radiotherapy in last 30 days
- Alcohol abuse
- Pre-existing chronic renal failure with eGFR <60ml/min per 1.73 m², Albuminuria with structural abnormalities on ultrasonography
- Pre-existing Cirrhosis of liver on ultrasonography
- Active gastrointestinal bleed
- Cerebrovascular Accident
- Acute Coronary Syndrome

Using blood that was obtained right after admission, serum MPV and platelets were assessed. We performed additional laboratory tests including white blood cell count, haemoglobin, random blood sugar, bilirubin fractions, creatinine level and sodium and potassium level. As the definitive diagnosis, we established the probable cause of suspected sepsis and provided microorganism results based on blood culture data.

Patients' blood samples were taken from the antecubital vein with a 5 ml syringe and immediately mixed in EDTA vacutainers. The sample was run within two hours after venipuncture using an automatic haematology analyzer (Sysmex XN 550). The Sysmex analyzer works on the principles of the RF/DC detection method,

hydrodynamic focusing (DC detection), flow cytometry method (using the semiconductor laser), and SLS-haemoglobin method to perform the complete blood count.

At predefined intervals following admission, we calculated the MPV/platelet ratio using the formula:

$$\left\{ \frac{\text{MPV value}}{\left(\frac{\text{Platelet count}}{1000} \right)} \times 100 \right\}$$

The clinical outcome was mortality at 28 days.

Statistical analysis

A predetermined proforma was used for collecting the data. Calculations and analysis were done using the Social Statistics Website, Tables and graphs were made using Microsoft Word Plus and Microsoft Excel Professional Plus.

Association analysis was done using Chi-square Test (along with Fisher's Exact Test) to look for association between MPV/Platelet Ratio and survival of the patients.

Kaplan-Meier Survival Curve and Log Rank Test was used to look for any statistically significant difference on patient survival based on MPV/Platelet ratio.

Lastly, Cox regression survival analysis was also used to infer whether MPV/platelet ratio had any significant effect on survival of the patients.

A p-value of less than 0.05 was considered significant. Results

A) Patient characteristics:

A total of 50 patients were recruited for the present study out of which 29 (58%) were females and 21 (42%) were males. Mean age of all patients were found to be 50.24 years (SD: ± 18.07) with median 50.5 years. Mean MPV/Platelet ratio was 0.0937 (SD: ± 0.09821). A total of 31 (62%) patients (15 females, 16 males) had high MPV/Platelet ratio (> 0.0575). Remaining 19 (38%) patients had MPV/Platelet ratio ≤ 0.0575 . The suggested cut off value of 0.0575 was tested with ROC curve analysis which yielded significant results with area under curve to be 1.00 and $p < 0.001$. Hence we further analysed the data with the same cut off value. Twenty-three (46%) patients had pneumonia due to which they got admitted in the hospital with consolidation on chest x-ray. Out of 50, 19 (38%) patients had either DM or HTN or both. Twenty-six (52%) patients were given vasopressors and 17 (34%) patients needed mechanical ventilation. Three (6%) patients were on haemodialysis. At the end only 32 patients (64%) could survive their disease and complications. Detailed descriptive analysis of all baseline parameters is given in Table 1.

Table 1:

Sr. No.	Variable	Mean	95% CI		SD	Shapiro-Wilk Test p value	Distribution
			Lower	Upper			
01	Age	50.24	44.10	55.38	18.07	0.191	Normal
02	Total WBC	17580.14	15022.05	20138.23	9001.11	0.272	Normal
03	Hb	9.63	8.82	10.44	2.85	0.900	Normal
04	Platelets	190.80	161.19	219.61	102.80	0.016	Non-normal

05	MPV	11.20	10.84	11.57	1.29	0.078	Normal
06	MPV/Platelets	0.09377	0.06586	0.12168	0.09822	< 0.001	Non-normal
07	RBS	167.80	133.27	202.33	121.49	< 0.001	Non-normal
08	T. Bilirubin	1.21	0.48	1.94	2.57	< 0.001	Non-normal
09	S. Creatinine	2.17	1.58	2.77	2.10	< 0.001	Non-normal
10	Na ⁺	134.82	132.43	137.20	8.40	0.915	Normal
11	K ⁺	4.07	3.83	4.31	0.84	0.737	Normal
12	NT proBNP	10621.54	7291.62	13951.46	11716.94	< 0.001	Non-normal

B) Association analysis:

According to Chi-square Test (along with Fisher's Exact Test), there was no statistically significant association between MPV/Platelet Ratio and survival of the patients ($\chi^2 = 1.247$ at $df = 1$, $p = 0.264$), which means survival of patients was almost similar in low as well as high MPV/Platelet Ratio values. Additionally, except absolute Platelet count ($10^9/L$), all other variables mentioned in Table 2, don't have statistically significant association with MPV/Platelet Ratio. Absolute Platelet count is significantly associated with MPV/Platelet Ratio ($\chi^2 = 13.134$ at $df = 1$, $p < 0.001$).

Table 2: Association between MPV/Platelet Ratio and other variables of the patients.

Sr. No.	Variable	Category	MPV/Platelet Ratio		Chi Square Statistics (χ^2)	p value
			Low (≤ 0.0575)	High (> 0.0575)		
01	Age (years)	< 60	14 (38.9%)	22 (61.1%)	0.043	0.836
		> 60	5 (35.7%)	9 (64.3%)		
02	Sex	Female	14 (48.3%)	15 (51.7%)	3.095	0.079
		Male	5 (23.8%)	16 (76.2%)		
03	Total WBC Count	Low	1 (33.3%)	2 (66.7%)	0.052	0.974*
		Normal	4 (36.4%)	7 (63.6%)		
		High	14 (38.9%)	22 (61.1%)		
04	Haemoglobin	Low	14 (34.1%)	27 (65.9%)	1.436	0.273*
		Normal	5 (55.6%)	4 (44.4%)		
05	Platelets	Low	0 (0%)	15 (100%)	13.134	< 0.001

		Normal	19 (54.3%)	16 (45.7%)		
06	MPV	Low	16 (41.0%)	23 (59.0%)	0.689	0.498*
		Normal	3 (27.3%)	8 (72.7%)		
07	DM	No	11 (34.4%)	21 (65.6%)	0.496	0.552
		Yes	8 (44.4%)	10 (55.6%)		
08	HTN	No	17 (38.6%)	27 (61.4%)	0.063	1.000*
		Yes	2 (33.3%)	4 (66.7%)		
09	DM and HTN	No	17 (37.8%)	28 (62.2%)	0.009	1.000*
		Yes	2 (40.0%)	3 (60.0%)		
10	RBS	Normal	11 (34.4%)	21 (65.6%)	0.496	0.552
		High	8 (44.4%)	10 (55.6%)		
11	Total Bilirubin	Normal	16 (41.0%)	23 (59.0%)	0.689	0.498*
		High	3 (27.3%)	8 (72.7%)		
12	Serum Creatinine	Normal	7 (35.0%)	13 (65.0%)	0.127	0.774
		High	12 (40.0%)	18 (60.0%)		
13	Na ⁺	Low	9 (34.6%)	17 (65.4%)	0.499	0.778*
		Normal	7 (38.9%)	11 (61.1%)		
		High	3 (50.0%)	3 (50.0%)		
14	K ⁺	Low	5 (41.7%)	7 (58.3%)	0.114	0.907*
		Normal	12 (36.4%)	21 (63.6%)		
		High	2 (40.0%)	3 (60.0%)		
15	Vasopressor	No	10 (41.7%)	14 (58.3%)	0.263	0.772
		Yes	9 (34.6%)	17 (65.4%)		
16	Mechanical Ventilation	No	13 (39.4%)	20 (60.6%)	0.080	1.000
		Yes	6 (35.3%)	11 (64.7%)		
17	Haemodialysis (HD)	No	17 (36.2%)	30 (63.8%)	1.113	0.549*
		Yes	2 (66.7%)	1 (33.3%)		
18	Survival	Dead	5 (27.8%)	13 (72.2%)	1.247	0.264

	Alive	14 (43.8%)	18 (56.3%)		
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WBC, White Blood Cells; MPV, Mean Platelet Volume; DM, Diabetes Mellitus, HTN, Hypertension; RBS, Random Blood Sugar; Na⁺, Sodium, K⁺, Potassium.

*p value as per Fisher's Exact Test.

According to Chi-square Test (along with Fisher's Exact Test), survival of the patients was found to be statistically significantly associated with sex of the patients ($\chi^2 = 10.546$ at $df = 1$, $p = 0.001$), total WBC count ($\chi^2 = 5.183$ at $df = 1$, $p = 0.049$), vasopressor treatment ($\chi^2 = 20.300$ at $df = 1$, $p < 0.001$) and mechanical ventilation ($\chi^2 = 30.504$ at $df = 1$, $p < 0.001$). More females, patients with normal WBC count, patients who did not receive vasopressor and mechanical ventilation were found to be survived as compared. Detailed counts are given in Table 3.

Table 3: Association between survival and other variables of the patients.

Sr. No.	Variable	Category	Survival of the patients		Chi Square Statistics (χ^2)	p value
			Dead	Alive		
01	Age (years)	< 60	12 (33.3%)	24 (66.7%)	0.397	0.529
		> 60	6 (42.9%)	8 (57.1%)		
02	Sex	Female	5 (17.2%)	24 (82.8%)	10.546	0.001
		Male	13 (61.9%)	8 (38.1%)		
03	Total WBC Count	Low	2 (66.7%)	1 (33.3%)	5.183	0.049*
		Normal	1 (9.1%)	10 (90.9%)		
		High	15 (41.7%)	21 (58.3%)		
04	Haemoglobin	Low	15 (36.6%)	26 (63.4%)	0.034	1.000*
		Normal	3 (33.3%)	6 (66.7%)		
05	Platelets	Low	6 (40.0%)	9 (60.0%)	0.149	0.700
		Normal	12 (34.3%)	23 (65.7%)		
06	MPV	Low	13 (33.3%)	26 (66.7%)	0.547	0.494*
		Normal	5 (45.5%)	6 (54.5%)		
07	DM	No	13 (40.6%)	19 (59.4%)	0.825	0.364
		Yes	5 (27.8%)	13 (72.2%)		
08	HTN	No	16 (36.4%)	28 (63.6%)	0.021	1.000*
		Yes	2 (33.3%)	4 (66.7%)		

09	DM and HTN	No	17 (37.8%)	28 (62.2%)	0.617	0.642*
		Yes	1 (20.0%)	4 (80.0%)		
10	RBS	Normal	13 (40.6%)	19 (59.4%)	0.825	0.364
		High	5 (27.8%)	13 (72.2%)		
11	Total Bilirubin	Normal	12 (30.8%)	27 (69.2%)	2.105	0.172*
		High	6 (54.5%)	5 (45.5%)		
12	Serum Creatinine	Normal	6 (30.0%)	14 (70.0%)	0.521	0.470
		High	12 (40.0%)	18 (60.0%)		
13	Na ⁺	Low	7 (26.9%)	19 (73.1%)	1.997	0.405*
		Normal	8 (44.4%)	10 (55.6%)		
		High	3 (50.0%)	3 (50.0%)		
14	K ⁺	Low	6 (50%)	6 (50%)	1.520	0.439*
		Normal	10 (30.3%)	23 (69.7%)		
		High	2 (40.0%)	3 (60.0%)		
15	Vasopressor	No	1 (4.2%)	23 (95.8%)	20.300	< 0.001
		Yes	17 (65.4%)	9 (34.6%)		
16	Mechanical Ventilation	No	3 (9.1%)	30 (90.9%)	30.504	< 0.001
		Yes	15 (88.2%)	2 (11.8%)		
17	Haemodialysis (HD)	No	16 (34.0%)	31 (66.0%)	1.303	0.254*
		Yes	2 (66.7%)	1 (33.3%)		

WBC, White Blood Cells; MPV, Mean Platelet Volume; DM, Diabetes Mellitus, HTN, Hypertension; RBS, Random Blood Sugar; Na⁺, Sodium, K⁺, Potassium.

*p value as per Fisher's Exact Test.

C) Kaplan Meier Survival Analysis:

According to Kaplan-Meier Survival Curve, low MPV/Platelet ratio (blue line) has comparatively more benefit in survival of the patients than that of high MPV/Platelet ratio (green line) (Figure 1). However, according to the Log Rank Test the low MPV/Platelet ratio does not have any statistically significant difference on patient survival than that of high MPV/Platelet ratio ($\chi^2 = 0.817$ at $df = 1$, $p = 0.366$) (Table 4). Hence even if Kaplan-Meier Curve showed some difference in both the lines, it is not statistically significant hence it can be concluded that both low as well as high MPV/Platelet ratio have somewhat similar effect on survival of the patients.

Figure 1: Kaplan Meier survival curve

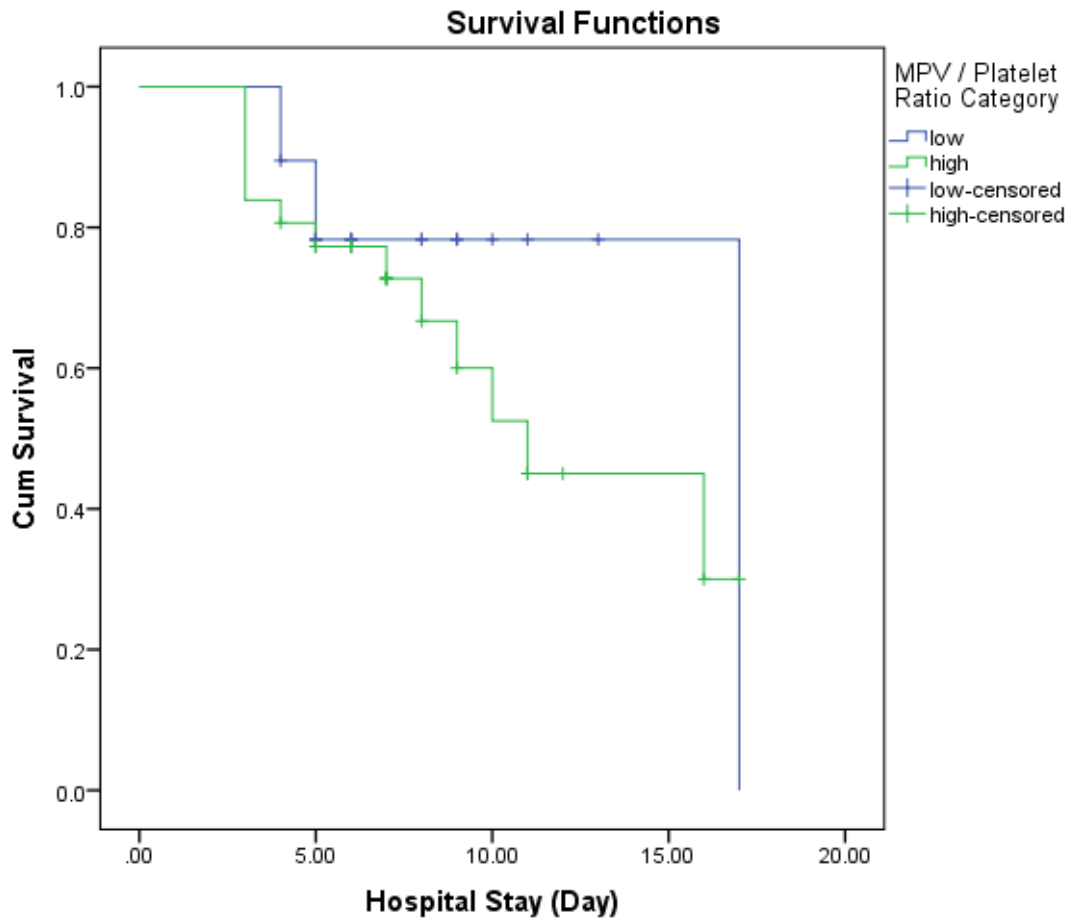


Table 4: Log rank test for survival analysis of participants with high and low MPV:Platelet ratio.

Overall Comparisons			
	Chi-Square	df	p value
Log Rank (Mantel-Cox)	0.817	1	0.366

D) Cox regression survival analysis:

After conducting multivariate cox regression, it can be inferred that MPV/platelet ratio ($p = 0.196$, $HR = 1.762$) has no significant effect on survival of the patients whereas mechanical ventilation individually had higher hazard ratio and had statistically significant effect on survival ($p = 0.038$, $HR = 5.383$) (Table 5).

Table 5: Multivariate Cox regression analysis of progression free survival.

Variable	Hazard ratio	95% CI	p value
MPV/platelet ratio	1.762	0.747 - 4.156	0.196
MPV	1.633	0.648 - 4.115	0.299
Platelet count	1.459	0.572 - 3.718	0.429
Vasopressor	1.695	0.545 - 5.267	0.362
Mechanical ventilation	5.383	1.093 - 26.507	0.038

DISCUSSION

This study was conducted to determine the significance of MPV/Platelet ratio as a prognostic marker for early mortality in critically ill patients with suspected sepsis receiving early goal directed therapy. A total of 50 patients of which 29 (58%) were females and 21 (42%) were males and mean age of 50.24 years (SD: ± 18.07) with median 50.5 years was included in our study. Manglesh et al. (2021), Gao et al. (2014) and Wach et al. (2021) are similar studies conducted in 97 (39 females, 58 males) patients with sepsis, 124 (74 females, 50 males) with septic shock and 191 (119 females, 72 males) with glioblastoma.^[18,26,27] There were 32 (64%) survivors and 18 (36%) non-survivors in our study as compared to 64 (66%) survivors and 33 (34%) non-survivors in Manglesh et al. (2021); 36 (29%) survivors and 88 (71%) in Gao et al. (2014).^[26,27]

Various biomarkers like platelet, mean platelet volume, complete blood count, random blood sugar level, serum creatinine, serum sodium, serum potassium levels and comorbidities like diabetes, hypertension were also studied. In addition to these, Mangesh et al. (2021) and Gao et al. (2014) studied other clotting indices, microbiological studies of the infection and origin and location of the infection in their respective study subjects, whereas Wach et al. (2021) has studied the body mass index (BMI), preoperative KPS, presence of another extracranial neoplasia dexamethasone intake, tumor area, maximum diameter of peritumoral edema, Molecular Immunology Borstel (MIB) - I index values, rate of tumors located in the eloquent area, IDH1 mutation, and MGMT promoter hypermethylation status in the participants. Total WBC count and sex of the participants was statistically significantly associated with the survival outcome of the patients while lactate and procalcitonin was significant in Mangesh et al. (2021). The prognosis of the patient was studied using APACHE II score in Gao et al. (2014) and was also found to be statistically significant with survival outcome of the patients.^[27]

Recently, MPV/Platelet ratio is getting more attention as a potential biomarker for predicting outcome of patients.^[18] MPV is known as an early activator of platelets and both having high values potentially aggravate inflammation by releasing more prothrombotic factors. ^[18,19] Elevated MPV/Platelet ratio can be observed in many malignancies such as oesophageal cancer, pancreatic cancer, hepatobiliary cancer, papillary thyroid cancer etc.^[20-23] Some studies suggested that elevated MPV alone is an important biomarker for poor survival, whereas a few studies observed that MPV/Platelet ratio is superior index to MPV alone for estimating survival in some diseases.^[22,24,25] Additionally, the ratio can serve as a good biomarker for survival of sepsis patients with notably high MPV in non-survivors at the time of admission and through their clinical course. ^[26] Elevated MPV is an indicator of increased platelet turnover by the bone marrow in response to stress in sepsis patients. ^[26] A few studies showed that high levels of MPV in sepsis patients returned to normal after effective antibiotic therapy, which may suggest that high MPV is a response to active and invasive infection.^[26-29] Oh et al. (2017) found that MPV/platelet ratio is a promising prognostic marker for 28-day mortality in patients with severe sepsis. The present study agrees with these findings, i.e relatively more deaths in patients with high MPV/Platelet ratio, but there was no statistically significant association between survival and elevated ratio. Similarly elevated MPV value could not yield statistically significant association with survival of the patients. However, high total WBC count, administration of vasopressors and mechanical ventilation were found to have significant association with mortality in sepsis patients. Oh et al. (2017) did not find any significant association between WBC counts and survival.^[30]

Kaplan-Meier Survival Analysis showed no statistically significant difference between survival of low MPV/Platelet ratio and survival of high MPV/Platelet ratio in the current study. Wach et al. 2021 did KM survival analysis and found that low MPV/Platelet ratio had significant difference in survival as compared to those with high MPV/Platelet ratio. ^[18] Mangalesh et al. 2021 did not present a survival curve but they provided logistic regression values between MPV alone and survival which was statistically significant.

LIMITATIONS OF THE STUDY

The current study involves only single observation of all parameters including Platelets, MPV and MPV/Platelet ratio. Additionally it does not record timely values (e.g. at admission, after 12 hours, after 24 hours, after 1 week etc.) which can be a potential reason for MPV/Platelet ratio being non-significant with survival. Though according to Kaplan-Meier Survival Curve (Figure 1), low MPV/Platelet ratio has some benefit on survival, the association can be determined with timely follow up values in all the patients.

CONCLUSION

The present study could not yield similar results on logistic regression showing that MPV alone as well as MPV/Platelet ratio did not have any significant effect on survival of the sepsis patients. It was observed that patients requiring vasopressors and mechanical

ventilation had significantly increased patient mortality. The exact indication and time of administration of these therapeutic ailments may play a crucial role in the current scenario. This can be reduced by strict revision and adherence to treatment protocols while managing sepsis patients.

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