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Usefulness of Platelet Count and Other Platelet Indices in Sepsis and Septic Shock Mortality Prediction

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Abstract:

Background: Platelet (PLT) count and other indices have been studied for their prognostic value in sepsis and septic shock, but their results are inconsistent. This study aimed to determine the usefulness of PLT count and other PLT indices in prediction of mortality in these patients. **Methods:** 108 patients with clear evidence of sepsis or septic shock were enrolled. PLT count, mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW) were measured on admission and daily for the 1st 5 days following admission. Patients were followed during their ICU and hospital stay, and then categorized as survivors and non survivors. All data were statistically analyzed. **Results:** PLT count and other PLT indices were significantly different between both non survivors and survivors groups. At the 5th day, ΔPLT count, PDW, MPV were significantly different in non survivors compared to survivors, -27.16 ± 11.19, 0.34 ± 0.3, 0.7 ± 0.23 vs 23.18 ± 3.5, -0.14 ± 0.07, -0.37 ± 0.19, p value: 0.014,0.027 and 0.002 respectively while ΔPCT shows no statistical significance. The cutoff values of PLT count, PCT, MPV, and PDW that predict mortality were 100,000 /ul, 0.10% 10.25fL, and 12%, with area under ROC (AUROC) were 0.94, 0.75, 0.97,0.96, and p value <0.001, 0.002 <0.001, and <0.001 respectively. **Conclusion:** PLT count and PCT were significantly decreased while MPV and PDW were significantly increased during the ICU stay in non survivor patients. MPV of 10.25 fL and PLT count of 100,000 /ul could be used as cutoff values in mortality prediction.

Keywords: Platelet indices; sepsis; septic shock; Platelet count

1. Introduction:

Sepsis and septic shock are serious conditions that affect millions of people worldwide each year. The pathophysiology is related to sequence of events due to inflammatory responses to components of micro-organisms. These inflammatory responses lead to activation of cytokines, endothelial injury, leukocyte induced damage, and peripheral vasodilatation with subsequent affection of almost all organs and systems including haemostatic system (1, 2).

In sepsis and septic shock, the pro-inflammatory cytokines increase expression of tissue factor that induce a procoagulant state with subsequent consumption coagulopathy. Several markers like prothrombin, thrombin, anti-thrombin activity, and fibrinogen have been used to define the former state (3, 4). Evidence of the important role of platelets (PLTs) in the process of inflammatory response and development of multiple organ damage was previously mentioned (3-5). Studies revealed the influence of PLT activation, through proteins released from activated PLT granules, in both vascular wall and immune cell function (5-8).

Value of PLT count and other PLT indices have been studied for their prognostic value in sepsis and septic shock, but their results are still inconsistent (9, 10). This study aimed to determine the usefulness of PLT count and other PLT indices in prediction of mortality in these patients.

2. Patients and methods:

This study was a prospective cohort study, that conducted on108 patients admitted to critical care department, of Cairo University with clear evidence of sepsis or septic shock during the period from January, 2019 till June, 2019. The study was approved by the critical care department, Cairo university research and ethical committee.

Inclusion criteria:

All patients with clear evidence of sepsis or septic shock were enrolled. Sepsis was diagnosed at the bedside with qSOFA; i.e. 2 or more of: Hypotension: SBP ≤ 100 mmHg, Altered mental status (any GCS < 15), Tachypnoea: RR ≥ 22 b/min. Septic shock was defined as persistent hypotension after adequate volume resuscitation that required use of vasopressors to maintain MAP ≥ 65 mm Hg, in addition to elevation of serum lactate level ≥ 2 mmol/L (11).

Exclusion criteria:

All patients with any of the following were excluded: pregnant females, age ≤ 18 years, acute cerebrovascular accident, malignant hematological disease, taking immunosuppressant.

On admission, all patients had routine labs including: complete blood picture, kidney and liver functions tests, coagulation profile, C-reactive protein (CRP), arterial blood gases, and serum lactate. All patients were managed according to the fourth edition of surviving sepsis campaign guidelines (2016) which were the latest at the time of the study (12).

PLT count and other PLT indices including: mean platelet volume (MPV) that indicates the average size of the platelets, plateletcrit (PCT) that indicates the volume that platelets occupy in the blood as a percentage, platelet distribution width (PDW) that reflects the variation in the PLT size were recorded on admission and daily for the 1st 5 days following admission. All patients were followed during their ICU stay, and then categorized as survivors and non survivors.

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) software package version 20.0**.** **(**Armonk, NY: IBM Corp**)** was used for analyzing our data. Normality of distribution was verified using the Kolmogorov-Smirnov test. Qualitative and quantitative data were described as number, percent, mean, and standard deviation. Comparison between the 2 groups was done using chi-square test, and student t-test for categorical and normally distributed quantitative variables, respectively. The obtained results were considered significant at the 5% level.

3. Results:

The total number of patients included in the study was 108 patients. The mean age was 58.98±11.21, of them 68 (73.44%) had died during ICU stay. The general characteristics of survivors and non survivors were illustrated in table (1).

At admission, PLT count and PCT were significantly lower and MPV and PDW were significantly higher in non survivors compared to survivors, 114.70 ± 39.09 x10^3/uL, 0.093 ± 0.0342 %, 11.45 ± 1.10 fL, and 14.64 ± 2.38 % vs 180.35 ± 42.59 x10^3/uL and 0.21 ± 0.024 %, 8.26 ± 1.55 fL, and 10.42 ± 1.63 %, p value: 0.002, 0.008, <0.001, and 0.038 respectively. Also, the time trends of PLT count and other PLT indices revealed significant difference between survivors and non survivors' cohort (Figure 1: A to D).

At the 5th day, the changes in PLT count, PDW, MPV were significantly different in non survivors compared to survivors, -27.16 ± 11.19 x10^3/uL, 0.34 ± 0.3 %, 0.7 ± 0.23 fL vs 23.18 ± 3.5 x10^3/uL, -0.14 ± 0.07 %, -0.37 ± 0.19 fL, p value: 0.014, 0.027 and 0.002 respectively while the change of PCT shows no statistical significance, -1.45 ± 0.87 % vs 0.21 ± 0.19 %, p value: 0.097 (Table 2).

Using receiver operating characteristic (ROC) curve, the cutoff values of PLT

count, PCT, MPV, and PDW that predict mortality in our cohort were 100,000 /ul, 0.10% 10.25fL, and 12%, with area under ROC (AUROC) were 0.94, 0.75, 0.97, and 0.96, and p value <0.001, 0.002 <0.001, and <0.001 respectively. The accuracy of these values in mortality prediction was 86.1%, 63%, 88.9%, and 84.6% respectively (Figures 2: A to D).

4. Discussion:

Thrombocytopenia is a common finding in septic patients. This finding is multi-factorial; and included increased platelet sequestration in micro-vessels with formation of micro-thrombi secondary to cytokine activation, decreased platelet production, immune mediated platelet destruction, and hemo-dilution following fluid resuscitation (13). In sepsis, the relation between low PLT count and mortality was previously mentioned (9, 14). Our results are in keeping with this previously mentioned data. The PLT count was lower in non survivor group both at admission and during the 5 days follow up period. Also, Δ $PLTS_{5ds}$ was significantly decreased in non-survivors compared to survivors. The same conclusion was previously observed by Raja Sekhar SVR, et al (15), who mentioned that the mean PLT count was significantly lower in his succumbed compared to his revived patients. Similarly, Sridhar Mangalesh, et al. (16) reported decreased PLT counts over time in his non-survivors' cohort. In fact, the value of developing thrombocytopenia rather than single initial PLT count is more valid in mortality prediction (17, 18).

Other PLT indices, like PCT, PDW, and MPV are also valuable in discrimination patients with higher mortality in our cohort. Despite, Δ PCT_{5ds} was not changed significantly between the 2 groups. PCT, at admission, was significantly lower in non survivors compared to survivors. In addition, MPV and PDW were observed to be higher in our non survivors. These findings may reflect the over production from compensated bone marrow following the stress-induced platelet destruction as a result of sepsis. Despite this compensation, the more is the MPV, the less is the PLT maturity and function (9). Value of studying kinetics of PLT indices in septic patients have been previously emphasized (15, 18, and 19). In concordance to our results, previous studies reported the elevation of MPV levels in sepsis non-survivors patients, compared to normal levels in survivors (9, 10). Despite the fact that a high MPV is probably a sign of active and invasive systemic, the value of MPV in sepsis is, however, disputed by the available data. In the study of Guclu E, et al. (1), a lower level of MPV was observed in non-survivors. Yet, this study failed to prove significant difference of this observation.

We constructed ROC curves to compare between PLT count and indices in their prediction of mortality. In our cohort, MPV followed by PLT count were the best in prediction of mortality, with accuracy of 88.9% and 86.1%, and AUROC of 0.97 and 0.94 respectively. The cutoff values were 10.25fL and 100,000 /ul for these values, respectively. Our MPV cutoff value was close to the cutoff values of previous results (1, 16, 18), that were 10.5, 10.25, and 8.0 fL. In the study of Samuel D, et al. (21), the highest AUROCs, 0.68 and 0.66, were acquired by PLT count and PCT, whereas 0.61 and 0.63 were produced by MPV and PDW, respectively. The PLT count had a sensitivity and specificity of 70 and 57%, which were comparable to PCT's (72 and 52%).

In conclusion, the PLT count and other PLT indices are important, easy accessible and cheap parameters that could be used in prediction of mortality in sepsis. A higher MPV, PDW, and lower PLT count and PCT was associated with mortality in this study. An MPV of 10.25 fL and PLT count of 100,000 /ul could be used as cutoff values that predict mortality at admission. PLT count and PCT were significantly decreased while MPV and PDW were significantly increased during the ICU stay in non survivor patients

Tables and Figures:

	Non survivors(N:68)	**Survivors(N:40)**	**P value**
Age, years	57±15.2	56±11.3	0.961
Sex , male	41 (60.3%)	28 (70%)	0.372
RBC (x10^6/uL)	3.61 ± 0.67	4.67 ± 0.73	0.583
Hb (g/dL)	10.74 ± 1.42	12.06 ± 1.48	0.007
TLC (x10^3/uL)	18.70 ± 3.04	16.76 ± 11.7	0.001
INR	2.53 ± 0.75	2.2 ± 0.80	0.632
Bilirubin,T (mg/dL)	2.90 ± 3.11	1.08 ± 0.62	0.486
ALT (U/L)	63.11 ± 20.62	43.5 ± 18.98	0.007
AST (U/L)	66.22 ± 37.94	43.32 ± 24.56	0.535
Albumin (g/dL)	2.55 ± 0.66	3.07 ± 0.90	0.333
pH	7.17 ± 0.13	7.34 ± 0.06	0.091
Bicarbonate (mEq/L)	17.57 ± 6.91	23.99 ± 6.86	0.166
PCO_2	49.18 ± 25.03	44.91 ± 12.72	0.003
PO_2	54.18 ± 8.71	102.37 ± 9.28	0.002
Urea (mg/dL)	138.25 ± 28.8	86.05 ± 29.18	0.031
Creatinine (mg/dL)	2.86 ± 1.01	2.18 ± 0.91	0.885
Procalcitonin (ng/mL)	4.42 ± 1.6	2.21 ± 0.25	<0.001
Gram –ve/+ve	33/35	18/22	0.210

Table (1): General characteristics and admission laboratory data in non survivors and survivors' cohort. Abbreviations: RBCs: red blood cells, Hb: hemoglobin, TLC: total leucocytic count, INR: international normalized ratio, ALT: alanine transaminase, AST: aspartate transaminase, pH: potential of hydrogen, PCO_2: partial pressure of carbon dioxide, PO_2: partial pressure of oxygen.

		Non survivors (n=68)	**Survivors (n=40)**	**P value**
Δ PLT, (x10^3/uL)	Range	-63 – -9	13 – 46	0.014
	Mean ± SD	-27.16 ± 11.19	23.18 ± 3.5	
Δ PCT,%	Range	-2.34 – -0.9	0.20 – 0.22	0.097
	Mean ± SD	-1.45 ± 0.87	0.21 ± 0.19	
Δ PDW,%	Range	0.19 – 0.39	-0.18 – -0.15	0.027
	Mean ± SD	0.34 ± 0.3	-0.14 ± 0.07	
ΔMPV,fL	Range	0.56 – 0.82	-0.21 – -0.45	0.002
	Mean ± SD	0.7 ± 0.23	-0.37 ± 0.19	

Table (2): Changes in PLT count, and other PLT indices in non survivors and survivors' cohort. Abbreviations: PLTs: platelet count, PCT: plateletcrit, MPV: mean platelet volume, PDW: platelet distribution width.

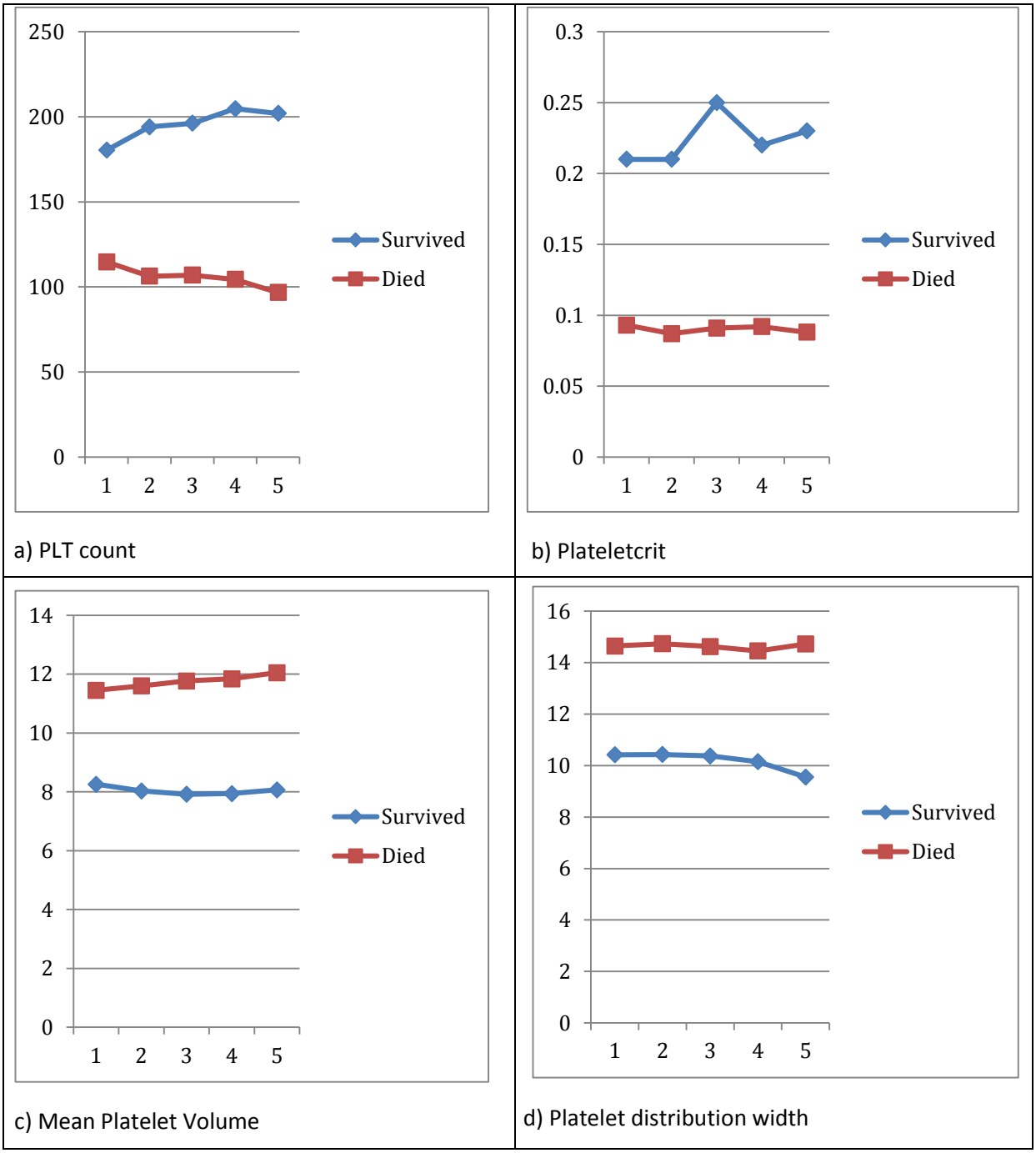
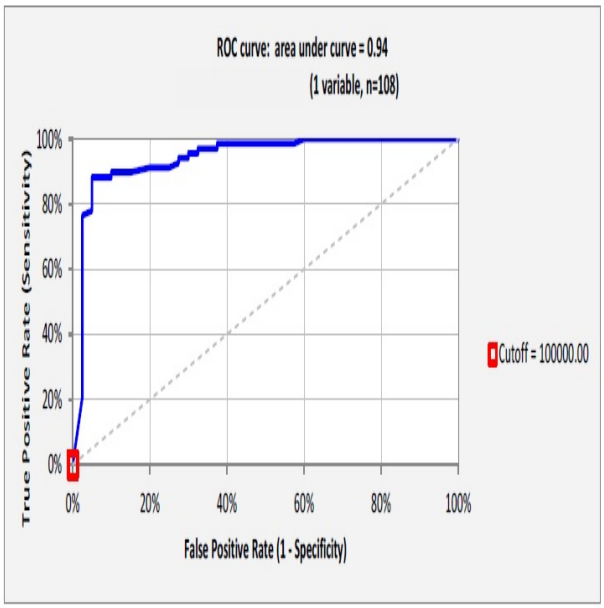
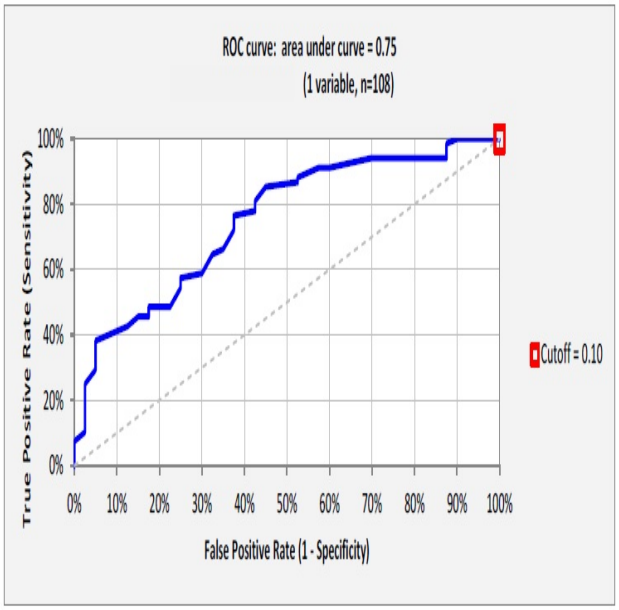


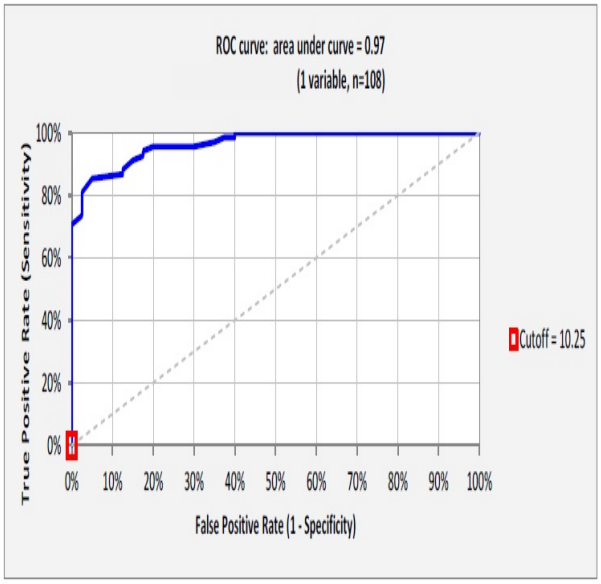
Figure 1 (a to d): The time trends of PLT count and other PLT indices in non survivors and survivors' cohort. a) PLT count, b) Plateletcrit, c) MPV, d) PDW



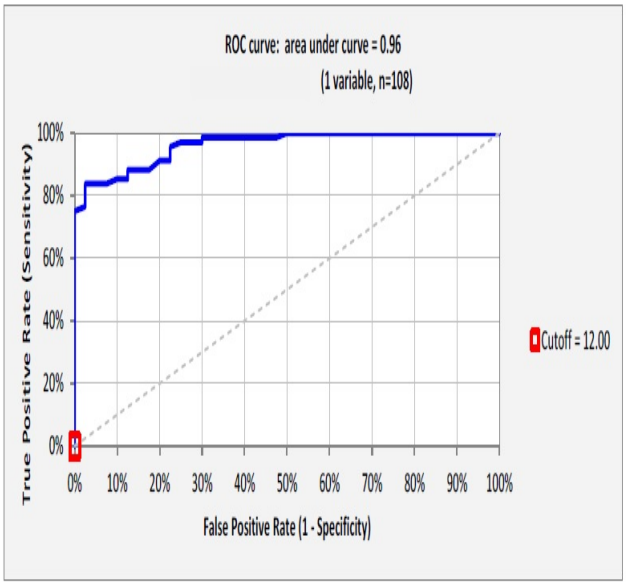
a) PLT count



b) Plateletcrit



c) Mean Platelet Volume



d) Platelet distribution width

Figure 2 (a to d): Receiving Operating Characteristic (ROC)curve for PLT count and other PLT indices to predict mortality: a) PLT count, b) Plateletcrit, c) Mean Platelet Volume, d) Platelet Distribution width.

5. References:

1. Guclu E, Durmaz Y, Karabay O. African Health Sciences 2013; 13(2): 333 – 338
2. Hotchkiss RS, Karl IE (2003) The pathophysiology and treatment of sepsis. N Engl J Med 348:138–150
3. Matsubara T, Yamakawa K, Umemura Y, Gando S, Ogura H, Shiraishi A et al (2019) Significance of plasma fibrinogen level and antithrombin activity in sepsis: a multicenter cohort study using a cubic spline model. Thromb Res 181:17–23
4. Mitra P, Guha D, Nag SS, Mondal BC, Dasgupta S (2017) Role of plasma fibrinogen in diagnosis and prediction of short termoutcome in neonatal sepsis. Indian J Hematol Blood Transfus 33:195–199
5. Golebiewska EM, Poole AW. Platelet secretion: from haemostasis to wound healing and beyond. Blood Rev. 2015;29:153–62
6. Margetic S. Inflammation and haemostasis. Biochem Med (Zagreb). 2012;22: 49–62.
7. Mariani E, Filardo G, Canella V, Berlingeri A, Bielli A, Cattini L, et al. Plateletrich plasma affects bacterial growth in vitro. Cytotherapy. 2014;16:1294–304
8. Frelinger AL 3rd, Torres AS, Caiafa A, Morton CA, Berny-Lang MA, Gerrits AJ, et al. Platelet-rich plasma stimulated by pulse electric fields: platelet activation, procoagulant markers, growth factor release and cell proliferation. Platelets. 2016;27(2):128–35.
9. Gao Y, Li Y, Yu X, Guo S, Ji X, Sun T et al (2014) The impact of various platelet indices as prognostic markers of septic shock. PLoS ONE 9:e103761
10. Zampieri FG, Ranzani OT, Sabatoski V, de Souza HP, Barbeiro H, da Neto LM et al (2014) An increase in mean platelet volume after admission is associated with higher mortality in critically ill patients. Ann Intensive Care 4:20
11. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.
12. Rhodes Andrew MB, Evans Laura E, Alhazzani Waleed , Levy Mitchell M , Antonelli Massimo, Ferrer Ricard, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Critical Care Medicine 45(3): p 486-552, March 2017.
13. Vardon-Bounes F, Ruiz S, Gratacap MP, Garcia C, Payrastre B, Minville V. Platelets Are Critical Key Players in Sepsis. Int J Mol Sci. 2019 Jul 16;20(14):3494.
14. Irmak K, Sen I, Co¨l R, Birdane FM, Gu¨zelbektes H, et al.(2006) The

evaluation of coagulation profiles in calves with suspected septic shock. Vet 30:497–503.

15. Raja Sekhar SVR, Naidu PJ, Giri Kumar E, Shamili M, Sanjeeva Rao E. Prognostic Role of Platelet Indices in Sepsis Patients. Saudi J Pathol Microbiol,. 2019; 4(12): 898-901.
16. Mangalesh S, Dudani S, Malik A. Platelet Indices and Their Kinetics Predict Mortality in Patients of Sepsis. Indian J Hematol Blood Transfus. 2021 Oct; 37(4):600-608.
17. Venkata C, Kashyap R, Farmer JC, Afessa B (2013) Thrombocytopeni in adult patients with sepsis: incidence, risk factors, and its association with clinical outcome. J Intensive Care 1:9
18. Vincent JL, Castro P, Hunt BJ, Jo¨rres A, Praga M, Rojas-Suarez J et al (2018) Thrombocytopenia in the ICU: disseminated intravascular coagulation and thrombotic microangiopathies-whatintensivists need to know. Crit Care 22:158.
19. Kim CH, Kim SJ, Lee MJ, Kwon YE, Kim YL, Park KS et al (2015) An increase in mean platelet volume from baseline is associated with mortality in patients with severe sepsis or septic shock. PLoS ONE 10:e0119437
20. Aydemir H, Piskin N, Akduman D, Kokturk F, Aktas E (2015)Platelet and mean platelet volume kinetics in adult patients withsepsis. Platelets 26:331–335.
21. Samuel D, Bhat AN, Prabhu VM. Platelet Indices as Predictive Markers of Prognosis in Critically Ill Patients: A Prospective Study. Indian J Crit Care Med. 2020 Sep; 24(9):817-822.