Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio as Predictors of Disease Severity and Mortality in Critically Ill Children: A Retrospective Cohort Study

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Abstract

The aim of this study was to determine the ability of neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) to predict the severity of illness as assessed by two scoring systems, namely, Pediatric Logistic Organ Dysfunction-2 (PELOD-2) and Pediatric Risk of Mortality-III (PRISM-III) and outcome. This was a retrospective cohort study wherein all critically ill children aged 1 month to 18 years admitted in the pediatric intensive care unit from January 2021 to October 2022 were included. Children with chronic systemic diseases and hematological illness were excluded from the study. Demographic details, diagnosis, PRISM-III-24 and PELOD-2 scores at admission, and outcome were retrieved from the hospital case records. NLR and PLR values were compared among high and normal PRISM-III and PELOD-2 groups as well as among survivors and nonsurvivors. A total of 325 patients with critical illness were included with a mean (standard deviation) age of 7(5) years and a male: female ratio of 3:2. The values of NLR were significantly higher among the patients with high PRISM-III (2.2 vs. 1.3, p-value = 0.006) and PELOD-2 (2 vs. 1.4, p-value = 0.015) groups compared with normal. The NLR and PLR were significantly higher among the nonsurvivors compared with the survivors (2.3 vs. 1.4, p-value = 0.013, and 59.4 vs. 27.3, p-value = 0.016 for NLR and PLR, respectively). The area under the receiver operating characteristics curve for NLR and PLR was 0.617 and 0.609, respectively. A high PLR, PRISM-III, and PELOD-2 were the factors found to be independently associated with mortality on multiple logistic regression analysis. Patients with high NLR are associated with more severe illness at admission. NLR and PLR are useful parameters to predict mortality.

Keywords

- neutrophil lymphocyte ratio
- platelet lymphocyte ratio
- PRISM-III
- PELOD-2
- critical illness
- pediatric intensive care

Introduction

As the mortality and morbidity of critically ill children admitted to the pediatric intensive care unit (PICU) is high, there is a constant need for markers at admission to help in the assessment of disease severity and to predict the outcome. Identifying disease severity among children with critical illness helps in the judicious use of resources. Various scoring systems are being used to help in prognostication and determination of disease severity. Inflammatory markers like platelet indices[1] and red cell distribution width[2] are also being increasingly used for the prediction of outcomes.

Complete blood counts with differential counts are commonly sent, inexpensive investigations in the evaluation of

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critically ill children. Inflammation causes a rise in the neutrophils because of delay in apoptosis, demargination of neutrophils, and stimulation of stem cells by growth factors.[3] It also causes a shift in the differential count of the leucocytes (neutrophilia and lymphopenia).[4] Hemogram-derived parameters like neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) have been studied in inflammatory conditions and critical illness.[5] Similarly, these parameters have also been used to study sepsis-related mortality among children.[6] A retrospective study[7] found that high and low NLR were associated with mortality and also the inclusion of NLR improved the predictive power of Simplified Acute Physiology Score-II.

Pediatric Logistic Organ Dysfunction (PELOD-2) and Pediatric Risk of Mortality (PRISM-III) are scoring systems commonly used in the PICU. While the former is a descriptive scoring system which describes the course of illness in the PICU, the latter is a predictive score. These scores are calculated by taking the worst physiological and laboratory parameters in the first 24 hours after admission. The PELOD-2 and PRISM -III were found to have excellent discrimination and good calibration among children admitted to our PICU.[8]

In low-resource settings, where multiple laboratory tests required for PRISM-III and PELOD-2 are not available, ratios like NLR and PLR might help in the prognostication of the disease. Although many studies have assessed the role of NLR and PLR in the outcome, there are few studies[9,10] which have evaluated the role of these parameters in assessing disease severity. The aim of this study was to assess the predictive efficacy of NLR and PLR in determining the severity of disease in critically ill children as measured by PELOD-2 and PRISM-III and also in determining the mortality of critically ill children.

Materials and Methods

A retrospective cohort study was conducted in the PICU of a tertiary referral hospital with facilities for dialysis, transplant, and extracorporeal membrane oxygenation. The PICU has 13 beds and is managed by a pediatric intensivist with residents posted on rotation. The PICU receives sick children referred from other hospitals, transfer-ins from the pediatric wards, surgical patients requiring pre- and postoperative care, and patients requiring infusions of high-risk medications. All critically ill children aged 1 month to 18 years admitted in the PICU from January 2021 to October 2022 were included in the study. Children with chronic systemic diseases and hematological illnesses, and those in whom the ratios were not available were excluded from the study. Data regarding demographic details, diagnosis, PRISM-III and PELOD-2 score at admission, laboratory investigations (total count, differential count, and platelet count), need for ventilation, and outcome were retrieved from hospital records and entered in a predesigned proforma. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR was calculated by dividing the platelet count by the absolute lymphocyte count. The first hemogram indices at admission to PICU were taken to calculate the ratios.

PELOD-2 and PRISM-III[11,12] scores are validated scores which are used in our PICU. PELOD-2 has 10 variables including Glasgow coma score, pupillary reaction, lactatemia, mean arterial pressure, creatinine, PaO2 /FiO2, PaCO2, invasive ventilation, WBC count, and platelet count. PRISM-III has a total of 17 variables including systolic blood pressure, heart rate, temperature, mental status, pupillary response, acidosis, pH, $PaCO_2$, total CO2, PaO2, glucose, potassium, creatinine, BUN, white blood cell count, platelet count, and prothrombin or partial thromboplastin time. Both are scored taking the most abnormal parameter in the first 24 hours. PELOD-2 and PRISM-III were considered to be elevated if the values were more than 7.5 and 9.5, respectively, which were the cutoffs derived from a previous study.[13]

Sample Size after Proper Justification

From literature review in a study by Karagoz et al,[5] it was observed that the sensitivity of predicting mortality by NLR was 84%. In the present study expecting similar results and to get a precision of 95% confidence levels and 4% margin of error, the study required a minimum of 323 subjects.

Statistical Methods

Continuous variables like age, length of PICU stay, total leucocyte count, NLR, and PLR are expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]). Categorical values like gender are described in percentages. Nonparametric test was used to compare the NLR, PLR, PELOD-2, and PRISM-III between the survivors and the nonsurvivors and also among children who required ventilation as against those who did not. Receiver operating curve with 95% confidence interval (CI) was used to assess the ability of the ratios to differentiate between the survivors and the nonsurvivors. The Youden index was used to determine the cutoff value for each of the two ratios. For the purpose of analysis, the NLR, PLR, PRISM, and PELOD values were categorized into high and low values based on the cutoff values thus derived. Chi-square test was then used for univariate analysis to check the association of categorical variables (age, gender, NLR, PLR, PRISM, and PELOD) with mortality. The factors which were found to be significant on univariate analysis were analyzed by logistic regression analysis to find the independent predictors of mortality. Analysis was done using the SPSS. Inc. released 2009. PASW statistics for windows version 18.0. Chicago. p-Value of <0.05 was taken as significant.

Results

There were a total of 402 critically ill patients admitted to the PICU during the study period. After excluding children with chronic disease ($n = 56$) and hematological illness like malignancy and immune thrombocytopenia ($n = 21$), we had a total of 325 patients with a mean (SD) age of 7 (5) years and a male: female ratio of 3:2. The median (IQR) length of stay was 4(3, 6) days. The mortality rate was 14.7% ($n = 48$). Twenty-five percent ($n = 81$) patients were ventilated. The most common reason

Table 1 Comparison of patient characteristics between high and low PELOD-2 and PRISM-3 groups

Variables	High PELOD	Low PELOD	*p*-Value	High PRISM	Low PRISM	*p*-Value
Age (y)[a]	3 (0.5, 8.7)	7(3,11.5)	<0.001	3 (1,9.7)	7 (3,12)	0.003
Gender *n* (%)						
Male	29 (55.8)	164 (60.1)	0.563	34 (53.1)	159 (60.9)	0.256
Female	23 (44.2)	109(39.9)		30 (46.9)	102 (39.1)	
Length of PICU stay[a]	4 (1,7)	4 (3,6)	0.022	4 (2,7)	4 (3,6)	0.152
Total leucocyte count[a] (10^9/L)	12.4 (8.1,16.5)	7.8 (5.5, 13.2)	0.001	12.2 (7.2, 16.4)	8 (5.4, 13)	0.002
Platelet count[a] (10^9/L)	141 (41.5, 365)	50 (28, 249)	0.23	100 (40, 273)	50 (28, 257)	0.063
NLR[a]	2 (0.9,4.8)	1.4(0.8,2.9)	0.015	2.2 (1,5.2)	1.3 (0.8,2.8)	0.006
PLR[a]	55(15.1,105.6)	27.8(10.6,88.2)	0.068	45.6 (14.7,110.8)	29.2 (10.3, 88.5)	0.099

Abbreviations: NLR, neutrophil lymphocyte ratio; PELOD, Pediatric Logistic Organ Dysfunction-2; PRISM-III, Pediatric Risk of Mortality-III; PICU, pediatric intensive care unit; PLR, platelet lymphocyte ratio.
[a]Median (IQR).

for admission to PICU was infections (including viral hemorrhagic fever, sepsis) accounting for 60.6% of the total cases. This was followed by respiratory diseases in 12.6%, neurological diseases in 10.5%, metabolic in 8.6%, gastrointestinal in 3.7%, and miscellaneous causes in 4%.

The patient characteristics and laboratory parameters were compared between the high- and low-severity groups (►**Table 1**). The NLR values were significantly higher in the high PELOD-2 and PRISM-III groups. The PLR values were also higher in the high-severity groups but were not statistically significant. There was a positive correlation of NLR with PELOD-2 ($r = 0.08$, p-value $= 0.151$) and with PRISM-III ($r = 0.116$, p-value $= 0.037$) and of PLR with PELOD-2 ($r = 0.084$, p-value $= 0.13$) and with PRISM-3 ($r = 0.018$, p-value $= 0.75$). This was, however, not statistically significant except for the correlation between NLR and PRISM-III.

The NLR, PLR, PELOD-2, and PRISM III values were significantly higher in the nonsurvivor group compared with the survivors. (►**Table 2**) The AUC (area under the curve) for NLR and PLR in predicting mortality was 0.617 (95% CI: 0.535–0.7) and 0.609 (95% CI: 0.521–0.696), respectively (►**Table 3**; ►**Fig. 1**). The cutoff value of NLR in predicting mortality was 2.18 with a sensitivity of 54% and specificity of 67%. A high NLR score had a 2.2 times higher risk of mortality (95% CI: 1.3–3.6, $p = 0.003$). The cutoff point for PLR was 34.1 with a sensitivity of 68% and specificity of 55%. A high PLR

Table 2 Demographic characteristics of the survivors and nonsurvivors

Variable	Total ($n = 325$)	Survivors ($n = 277$)	Nonsurvivors ($n = 48$)	*p*-Value
Age (y) n (%)				
<1	56 (17.2)	37 (13.4)	19 (39.6)	<0.001
1–5	86 (26.5)	72 (26)	14 (29.2)	
6–10	91 (28)	85 (30.7)	6 (12.5)	
10–16	92 (28.3)	83 (30)	9 (18.8)	
Gender *n* (%)				
Male	193 (59.4)	163 (58.8)	30 (62.5)	0.628
Female	132 (40.6)	114 (41.2)	18 (37.5)	
Length of stay[a]	4(3,6)	4(3,6)	2 (1,4)	<0.001
Total leucocyte count[a] (10^9/L)	8.6 (5.6, 14.2)	7.9(5.4,13)	13.4(8,18)	<0.001
Platelet count[a] (10^9/L)	59 (29,266)	49(28,246)	215(49,367)	0.003
NLR[a]	1.29(0.83,2.48)	1.4 (0.8, 3.0)	2.3(1.2, 4.4)	0.013
PLR[a]	1.82(0.69,10.25)	27.3(10.6,85.8)	59.4(23,120.2)	0.016
PELOD-2[a]	2 (2,5)	2(2,4)	11 (9, 14.75)	<0.001
PRISM–III[a]	5 (5,9)	5 (4,8)	15(10,21)	<0.001

Abbreviations: NLR, neutrophil lymphocyte ratio; PELOD, Pediatric Logistic Organ Dysfunction-2; PRISM-III, Pediatric Risk of Mortality-III; PICU, pediatric intensive care unit; PLR, platelet lymphocyte ratio.
[a]Median (IQR).

Table 3 Performance of NLR and PLR in predicting mortality

	AUC	95% CI	*p*-Value	Best cutoff values	Sensitivity (%)	Specificity (%)
NLR	0.617	0.535–0.7	0.009	2.18	54	67
PLR	0.609	0.521–0.696	0.016	34.1	68	55

Abbreviations: AUC, area under the curve; CI, confidence interval; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ration.

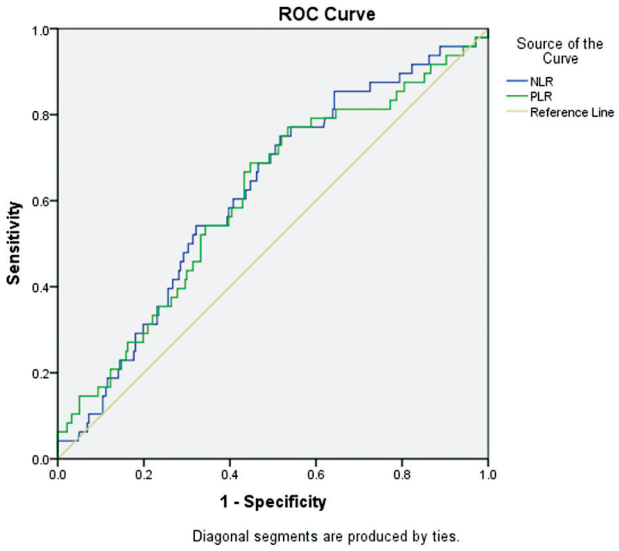

Fig. 1 Receiver operating characteristic curve of NLR and PLR.

had a 2.4 times higher risk of mortality which was statistically significant (95% CI: 1.3–4.2, $p = 0.002$).

The median (IQR) value of NLR among patients who were ventilated was significantly higher than among those who were not ventilated (2.5 [1.2, 7.0] and 1.2 [0.8, 2.4] *p*-value <0.001). The PLR was also significantly higher among patients who required mechanical ventilation with the median (IQR) values being 80 (34,175) and 21.2 (9.5,66.9) *p*-value < 0.001, respectively (►**Table 4**)

The NLR and PLR were analyzed with respect to disease categories. The NLR and PLR were highest in patients with neurological diseases and trauma with the mean NLR being 6.1 and 8.2 and the mean PLR being 144.6 and 165.1 among patients with neurological diseases and trauma,, whereas the lowest mean NLR and PLR of 1.4 and 20.3, respectively, were observed among patients with viral hemorrhagic fever.

On univariate analysis, age, high NLR, high PLR, high PELOD-2, and high PRISM-III were associated with mortality. However, on multiple logistic regression analysis, high PLR, PRISM-III, and PELOD-2 were the factors found to be independently associated with mortality (►**Table 5**).

Discussion

Various scoring systems take into account a combination of physiological variables and laboratory parameters and have been studied for discriminatory power and calibration with respect to outcome. These scoring systems are time-consuming with multiple variables. So there is a need to have a single, inexpensive, readily available parameter which could predict the outcome and also determine the severity of the disease. Hemogram is one of the commonly performed investigations which is rapid and inexpensive. Although it has been studied with respect to outcomes in many diseases, its correlation with disease severity as indicated by various scoring systems has not been studied in children. This study was conducted with the aim to evaluate the two ratios derived from easily available laboratory parameters as predictors of disease severity and outcome in the PICU.

Table 4 The PLR and NLR among patients requiring mechanical ventilation

	Mechanical ventilated	Not mechanically ventilated	*p*-Value
NLR median (IQR)	2.5 (1.2, 7.0)	1.2 (0.8, 2.4)	<0.001
PLR median (IQR)	80 (34,175)	21.2 (9.5,66.9)	<0.001

Abbreviations: IQR, interquartile range; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ration.

Table 5 Multivariate analysis of factors predicting mortality

Variable	Multivariate analysis OR	95% CI	*p*-Value
High NLR	2.2	0.7–6.7	0.157
High PLR	3.35	1.05–10.7	0.041
High PRISM-III	5.03	1.4–17.7	0.012
High PELOD-2	70.3	19.9–248.9	<0.001

Abbreviations: CI, confidence interval; NLR, neutrophil lymphocyte ratio; OR, odds ratio; PELOD, Pediatric Logistic Organ Dysfunction-2; PRISM-III, Pediatric Risk of Mortality-III; PICU, pediatric intensive care unit; PLR, platelet lymphocyte ratio.

Patients with high scores on PRISM-III and PELOD-2 had higher NLR values compared with those with normal scores which was statistically significant. The PLR values were also higher among those with high scores on the 2 scoring systems. However, it was not statistically significant. This implies that a high NLR can indicate the severity of illness. Both PRISM-III and PELOD-2 have leucopenia and thrombocytopenia as hematological parameters but none use the differential count in scoring.

The NLR and PLR have been compared in children in PICU[8] as well as in diseases like severe pneumonia[14] and sepsis.[6] In the sepsis study,[6] NLR was found to be significantly higher in the group with sepsis and also among the deceased septic children. The AUC for NLR in sepsis was 0.72. A high NLR had a 4.2 times higher risk of mortality. Another study[14] done in children with severe pneumonia also had similar results with a high NLR in the deceased group with AUC of 0.798 with the sensitivity of 56.25% and specificity of 89.83%. A study[7] which compared different inflammatory markers found NLR to have the best predictive ability in mortality among adult patients in an intensive care unit (AUC: 0.609 p-value < 0.001). They found that a very low and high NLR were associated with higher mortality rates compared with medium NLR. Our study also showed a statistically significant difference in the NLR among the survivors and nonsurvivors in critical illness with AUC of 0.617. However, our cutoff values for NLR were lower than those of other studies.[6,14] This implies that although NLR is higher among nonsurvivors, the cutoff value may need to be defined by multicentric studies for each population. The catecholamine[15] and cortisol[16] released during stress cause an increase in the neutrophils and a simultaneous decrease in lymphocytes. This change in the differential count occurs much faster than leukocytosis and bandemia which take longer to occur.[17] This makes the NLR a useful tool as an early marker of critical illness.

The PLR was found to be higher among nonsurvivors in patients admitted to PICU with AUC of 0.75 for mortality.[8] It was also higher in deceased patients with severe pneumonia[14] with AUC of 0.781 with the sensitivity of 90.63% and the specificity of 55.93%. However, there was no significant difference in PLR among children with and without sepsis.[6] We also found similar results with PLR being higher among nonsurvivors compared with survivors. However, the PLR cutoff in our study was lower than in other studies probably due to a predominance of viral hemorrhagic fever cases which had thrombocytopenia. Platelets have been found to play an important role in immunomodulatory and inflammatory processes.[18] This is mediated by the release of inflammatory cytokines and its interaction with bacteria as well as with neutrophils, NK cells, macrophages, and T lymphocytes.[19,20]

The predictive power of both ratios was not very high in our study. However, when the ratios were converted into categorical variables and analyzed as risk factors for mortality, we found PLR, PRISM-III, and PELOD-2 to be independent predictors of prognosis among critically ill children. Multivariate logistic regression analysis in another study in severe pneumonia[14] showed NLR, PLR, APACHE II score, and lactate to be independent risk factors for poor prognosis. In our study NLR was not found to have a good correlation with disease severity, and the odd's ratio of PLR was much less than that of PRISM-III and PELOD-2 inferring that PRISM-III and PELOD-2 are better indicators of disease severity. However, in settings where getting the biochemistry tests and blood gases required to score PRISM-III and PELOD-2 is difficult, the NLR and PLR may be used to assess disease severity.

The strength of the study is the large sample size. There are few limitations in our study. First, it is a single centric retrospective study. Second, noninfective conditions were not excluded in our analysis which could act as confounding factors. Also, prior medications received at referring hospitals might have influenced the ratios at admission. Further prospective multicentric studies with serial NLR and PLR monitoring would give a better understanding of its utility in pediatric critical illness. Also, a study on the ability of these ratios in the precritical phase in predicting patients who might need intensive care can provide useful information in guiding physicians/pediatricians in primary care centers on the need for referral to higher centers.

Conclusions

The NLR may be used to indicate the severity of illness, especially in settings where access to laboratory investigations required to score PRISM-III and PELOD-2 is limited . NLR and PLR can be used to predict the risk of mortality in critically ill children.

Conflict of Interest

None declared.

References

1 Aktas G, Sit M, Tekce H, et al. Mean platelet volume in nasal polyps. West Indian Med J 2013;62(06):515–518
2 Aktas G, Sit M, Dikbas O, et al. Could red cell distribution width be a marker in Hashimoto's thyroiditis? Exp Clin Endocrinol Diabetes 2014;122(10):572–574
3 Aydın İ, Ağıllı M, Aydın FN, et al. The reference ranges of neutrophil-lymphocyte ratio in different age groups. Gülhane Tip Derg 2015;57(04):414
4 Zahorec R. Ratio of neutrophil to lymphocyte counts–rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102(01):5–14
5 Karagoz I, Yoldas H. Platelet to lymphocyte and neutrophil to lymphocyte ratios as strong predictors of mortality in intensive care population. Rev Assoc Med Bras 2019;65(05):633–636
6 Pasaribu FM, Setyaningtyas A, Andarsini MR. Neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume as a predictor of sepsis mortality in children at Dr. Soetomo General Hospital. Crit Care Shock 2021; 24(02):65–71
7 Wu X, Luo Q, Su Z, et al. Neutrophil-to-lymphocyte ratio as a predictor of mortality in intensive care unit patients: a retrospective analysis of the Medical Information Mart for Intensive Care III Database. BMJ Open 2021;11(11):e053548
8 Mısırlıoğlu M, Bekdaş M, Kabakuş N Platelet-lymphocyte ratio in predicting mortality of patients in pediatric intensive care unit. J Clin Anal Med 2018;9(06):488–492

9 Zhong X, Ma A, Zhang Z, Liu Y, Liang G. Neutrophil-to-lymphocyte ratio as a predictive marker for severe pediatric sepsis. Transl Pediatr 2021;10(03):657–665
10 Mathews S, Rajan A, Soans ST. Prognostic value of rise in neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in predicting the mortality in pediatric intensive care. Int J Contemp Pediatrics 2019;6(03):1052–1058
11 Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc FGroupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP) PELOD-2: an update of the PEdiatric logistic organ dysfunction score. Crit Care Med 2013;41(07):1761–1773
12 Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated pediatric risk of mortality score. Crit Care Med 1996;24(05): 743–752
13 Shenoy S, Patil S, Karunakar P, Mangalgi S, Samaga V. Comparison between paediatric risk of mortality III and paediatric logistic organ dysfunction-2 as mortality predictor in paediatric intensive care. Sri Lanka J Child Health 2023;52(01):45–51
14 Qi X, Dong Y, Lin X, Xin W. Value of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and red blood cell distribution width in evaluating the prognosis of children with severe pneumonia. Evid Based Complement Alternat Med 2021;2021:1818469
15 Onsrud M, Thorsby E. Influence of in vivo hydrocortisone on some human blood lymphocyte subpopulations. I. Effect on natural killer cell activity. Scand J Immunol 1981;13(06):573–579
16 Benschop RJ, Rodriguez-Feuerhahn M, Schedlowski M. Catecholamine-induced leukocytosis: early observations, current research, and future directions. Brain Behav Immun 1996;10(02):77–91
17 Honda T, Uehara T, Matsumoto G, Arai S, Sugano M. Neutrophil left shift and white blood cell count as markers of bacterial infection. Clin Chim Acta 2016;457:46–53
18 Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis 2012; 34(03):326–334
19 Nording HM, Seizer P, Langer HF. Platelets in inflammation and atherogenesis. Front Immunol 2015;6:98
20 Kim CH, Kim SJ, Lee MJ, et al. An increase in mean platelet volume from baseline is associated with mortality in patients with severe sepsis or septic shock. PLoS One 2015;10(03):e0119437

