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Original article

Platelet-Lymphocyte Ratio in Predicting Mortality of Patients in Pediatric Intensive Care Unit

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Abstract:

Background: Pediatric intensive care units (PICU) have special equipment for treatment of children with life-threatening conditions. Platelet-lymphocyte ratio (PLR) is a novel inflammatory marker. It has been shown that PLR can be used as a useful marker for early diagnosis and treatment of some diseases. This study aimed to research whether PLR is a predictive factor of mortality risk in PICU patients. **Methods:** This retrospective and prospective observational cohort study was conducted on 100 children hospitalized in the PICU in Benha University Hospitals. Patients were evaluated by different disease severity scores using sequential organ failure assessment (SOFA), pediatric index of mortality 2 score (PIM2), preserved ratio impaired spirometry (PRISM III) and pediatric logistic organ dysfunction (PELOD). **Results:** PLR, and NLR were significantly lower in non- survivors compared to survivors ($P<0.05$). PLR with AUC 0.975 can significantly predict survivors ($P<0.001$), at cutoff value of ≤4.97, with 93.55 % sensitivity, 91.30% specificity, 82.9% PPV and 96.9% NPV. NLR with AUC 0.821 can significantly predict survivors ($P<0.001$), at cutoff value of ≤0.20 with 77.42% sensitivity, 68.12% specificity, 52.2% PPV and 87.0% NPV. **Conclusion:** Hematological parameters and scores were used for predicting PICU mortality PLR and NLR are simple hematological biomarkers, easy to calculate, and cost-effective, and ratios are better than individual parameters.

Keywords: Platelet-Lymphocyte Ratio, Mortality, PICU.

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Introduction

Pediatric intensive care units (PICU) have special equipment for treatment of children with life-threatening conditions [1]. These patients' conditions may be due to a severe illness, poisoning, trauma, or unpredictable complications arising from surgery [2]. The main purpose of therapies in a PICU is supporting patients until the dysfunction heals by natural means or the toxic material or the infection is eliminated [3]. Morbidity and mortality rates in patients admitted to the PICU are higher than in other pediatric patients, because of the worse clinical picture [4, 5]. In PICU patients with a severe clinical course, there are several markers that can reveal the severity of inflammation, but they are expensive and difficult to work with [6].

Lymphocytes are immune cells, which play an important role in immune response. Platelets are a key factor affecting coagulation function and inflammatory response [7, 8]. Actually, platelet-to-lymphocyte ratio (PLR) is considered a simple, inexpensive, widely available inflammatory indicator, independent risk factor and prognostic predictor for many critical cases [9]. PLR is a novel inflammatory marker. It has been shown that PLR can be used as a useful marker for early diagnosis and treatment of some diseases [10]. Also, it has been shown that PLR is a useful marker in predicting the prognosis of some diseases in adults [11].

In recent years, studies have reported that platelets and lymphocytes play critical roles in the inflammatory process [12]. Therefore, the PLR has received research attention recently, as it may act as an indicator of inflammation in a wide spectrum of diseases, such as myocardial infarction, acute kidney injury (AKI), hepatocellular carcinoma and non-small cell lung cancer [13, 14].

Based on the findings of previous studies, it is reasonable to speculate the presence of a potential relationship between PLR and mortality of patients in pediatric intensive care unit. However, there is a lack in investigations that had been conducted. Therefore, this study aims to research whether PLR is a predictive factor of mortality risk in PICU patients.

The purpose of this study was to research whether PLR is a predictive factor of mortality risk in PICU patients.

Patients and methods

This retrospective and prospective observational cohort study was conducted on 100 children hospitalized in the PICU in Benha University Hospitals in the duration from July 2023 to July 2024

An informed written consent was obtained from the parents or guardian, they received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University (MS 22-3-2023).

Inclusion criteria were children aged between 1 month to 18 years, both sexes, and children who were hospitalized in the PICU with any disease except oncological conditions

Exclusion criteria were patients with incomplete intervention or medical records, and conditions that may affect the hematological parameters of patients (chemotherapy, immunosuppressive therapy and conditions, hematological malignancy, immunodeficiency).

Patients admitted to PICU with multi system affection were retrospectively registered in terms of: Demographical features: [name, age, sex, body mass index (BMI), cause of admission]. Complete history included: diagnosis, length of stay, the sequential organ failure assessment score (SOFA score), and platelet]. Complete examination for detection of any abnormalities: [Respiratory, circulatory, gastrointestinal and neurological dysfunction).

Blood sampling

A total of 2 mL of venous blood was collected from the peripheral accessible veins in an ethylenediamine tetra acetic acid (EDTA) vial within one hour of admission to the PICU. Complete blood indices were assessed by an automated hematology analyzer and ratios (PLR, PLT/MPV, and NLR) were subsequently calculated from the values obtained from the analyzer.

RBCs indices including RDW, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) and platelet indices including platelet count, platletcrit, mean platelet volume (MPV), platelet differential width (PDW) and large platelet cell ratio (L-PCR) were measured by automated hematology analyzer "Sysmex XS-800i (SN: 63387)" as one part of a complete blood cell count. Normal red cell distribution width coefficient variant (RDWCV) was defined as 11.5%-14.5% in the laboratory of our hospital while the normal range of PLT, MPV, PDW, PLCR, and PCT were 140 – 440 x 109 /L, 8–15 fl, 10– 17%, 13–43%, and 0.11–0.28% respectively. Serum CRP levels were examined with Quick Read CRP test kit (Orion Corporation, Orion Diagnostica, Espoo, Finland).

All patients had neutrophil, lymphocyte, and platelet counts results within the first hour of intensive care unit admission and within 24 hours before discharge. Both on the first day and on the day of discharge, PLR1 and PLR2 were calculated by the division of platelet count to the lymphocyte count. The complete blood parameters were examined at our university hospital biochemistry laboratory. Leucocyte, lymphocyte, neutrophil and platelet counts, and NLR, PLR values in complete blood count during intensive care unit stay and on the day of discharge.

All patients were evaluated by different disease severity scores using SOFA score: SOFA [(15)], pediatric index of mortality 2 score (PIM2), PRISM III [(16)] and pediatric logistic organ dysfunction (PELOD)[(17)].

Outcomes

Length of stay (LOS): referred to the duration of stay in days from the date of admission to the date of discharge, at the end of the PICU stay regarding survival.

Statistical analysis

Statistical analysis was done by SPSS v28 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant. Evaluation of diagnostic performance was performed and presented as diagnostic sensitivity, specificity, positive predictive value (PPV) and negative Predictive value (NPV). Receiver operating characteristic curve (ROC-curve) analysis: The overall diagnostic performance of each test was assessed by ROC curve analysis. The area under the curve (AUC) evaluates the overall test performance (where the area under the curve >50% denotes acceptable performance and area about 100% is the best performance for the test)

Results

Our study included 100 patients; of them 69 (68%) were survivors and 31 (31%) were non-survivors. There was no significant difference between both groups regarding age, sex and residence, causes of admission including and vital signs. Table 1

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Table 1: Demographic data, causes of admission and vital signs of the studied groups

		Total (n=100)	Survivors (n=69)	Non survivors (n=31)	P value
Age (years)	**Mean± SD**	8.1 ± 5	8.3 ± 5.08	7.7 ± 4.86	0.583
	Range	0.08 - 18	0.42 - 18	0.08 - 17	
Sex	**Male**	52 (52%)	33 (47.83%)	19 (61.29%)	0.130
	Female	48 (48%)	36 (52.17%)	12 (38.71%)	
Residence	**Urban**	48 (48%)	33 (47.83%)	15 (48.39%)	0.956
	Rural	52 (52%)	36 (52.17%)	16 (51.61%)	
Congestive heart failure		29 (29%)	17 (24.64%)	12 (38.71%)	0.222
Multi-organ failure		3 (3%)	1 (1.45%)	2 (6.45%)	
Pneumonia		40 (40%)	30 (43.48%)	10 (32.26%)	
Sepsis		28 (28%)	21 (30.43%)	7 (22.58%)	
Pulse rate (bpm)	**Mean± SD**	137.7 ± 11.72	138.8 ± 11.52	135.3 ± 11.99	0.162
	Range	120 - 170	120 - 168	120 - 170	
RR (breath/min)	**Mean± SD**	32.6 ± 7.72	33.1 ± 7.92	31.5 ± 7.24	0.349
	Range	20 - 45	20 - 45	20 - 45	
SBP (mmHg)	**Mean± SD**	129.9 ± 11.68	130.06±11.67	129.42±11.9	0.802
	Range	110 - 150	110-150	111-149	
DBP (mmHg)	**Mean± SD**	85.4 ± 8.09	85.14±8.43	86.1±7.37	0.589
	Range	70 - 100	70-100	72-98	

RR: respiratory rate, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Hb concentration, PLT count, PLR, NLR, phosphorus and Na and albumin were significantly lower in non- survivors compared to survivors (P<0.05). Lymphocytes, Monocytes, neutrophil, liver enzymes (ALT and AST), CRP and lactate were significantly higher in non-survivors compared to survivors (P<0.05), with no significant difference between both groups regrading WBCs count, K and Ca, Non-survivors had significantly lower pH and bicarbonate levels compared to survivors (P<0.001, <0.001). Table 2

SOFA score, PIM2 score, PRISM, PELOD were significantly higher in non survivors compared to survivors (P<0.05). The length of hospital stay was significantly prolonged in non survivors compared to survivors (P<0.001). Table 3

PLR with AUC 0.975 can significantly predict survivors (P<0.001), at cutoff value of ≤4.97, with 93.55 % sensitivity, 91.30% specificity, 82.9% PPV and 96.9% NPV. NLR with AUC 0.821 can significantly predict survivors (P<0.001), at cutoff value of ≤0.20 with 77.42% sensitivity, 68.12% specificity, 52.2% PPV and 87.0% NPV. SOFA score with AUC 0.987 can significantly predict survivors (P<0.001), at cutoff value of >6 with 100% sensitivity, 94.20% specificity, 88.6% PPV and 100% NPV. PIM2 score with AUC 0.850 can significantly predict survivors (P<0.001), at cutoff value of >5.3 with 87.10% sensitivity, 71.01% specificity, 57.4% PPV and 92.5% NPV. PRISM with AUC 0.889 can significantly predict survivors (P<0.001), at cutoff value of >6 with 80.65% sensitivity, 63.77% specificity, 51.9% PPV and 91.7% NPV. PELOD with AUC 0.987 can significantly predict survivors (P<0.001), at cutoff value of >5.3 with 100% sensitivity, 94.20% specificity, 88.6% PPV and 100% NPV. Figure 1

Table 2: Laboratory investigations and arterial blood gas (ABG) of the studied groups

		Total (n=100)	Survivors (n=69)	Non survivors (n=31)	P value
Hb (g/dL)	**Mean± SD**	12.4 ± 0.89	12.54±0.89	12.02±0.81	**0.006***
	Range	11 - 14	11-14	11-13.8	
WBCs	**Mean± SD**	8.1 ± 1.4	8.24±1.37	7.85±1.45	0.200
($*10^9$/L)	**Range**	5.5 - 10.5	5.5-10.4	5.6-10.5	
PLT ($*10^9$/L)	**Mean± SD**	198.9 ± 48.57	215.32 ± 42.27	162.26±41.57	<**0.001***
	Range	100 - 298	154-298	100-230	
Lymphocytes (%)	**Mean± SD**	38.1 ± 13.38	30.74±5.59	54.35±11.05	<**0.001***
	Range	21 - 67	21-42	33-67	
Monocytes (%)	**Mean± SD**	7.3 ± 1.68	7.04±1.53	7.86±1.88	**0.024***
	Range	4 - 11	4-9.2	4.2-11	
Neutrophil (%)	**Mean± SD**	7.8 ± 1.3	7.2±0.88	9.25±0.91	<**0.001***
	Range	5.6 - 10.8	5.6-8.6	7.9-10.8	
PLR	**Mean± SD**	5.96 ± 2.58	7.23±1.96	3.12±1.12	<**0.001***
	Range	1.61 - 13.41	3.93-13.41	1.61-6.76	
NLR	**Mean± SD**	0.22 ± 0.06	0.24±0.05	0.18±0.05	**0.025***
	Range	0.12 - 0.38	0.16-0.38	0.12-0.32	
Phosphorus (mg/dl)	**Mean± SD**	4.1 ± 1.02	4.62±0.74	2.96±0.46	<**0.001***
	Range	2.1 - 5.8	3.5-5.8	2.1-3.7	
Na^+ (mEq/L)	**Mean± SD**	136.8 ± 3.13	138.68 ± 1.14	132.65±1.82	<**0.001***
	Range	130 - 140	137_140	130-135	
K^+ (mEq/L)	**Mean± SD**	4.3 ± 0.45	4.34±0.45	4.3±0.47	0.714
	Range	3.5 - 5.1	3.5_5.1	3.5-5	
Ca^{+2} (mg/dL)	**Mean± SD**	9 ± 0.89	9±0.92	8.97±0.83	0.888
	Range	7.5 - 10.5	7.5-10.5	7.7-10.2	
ALT (IU/L)	**Mean± SD**	57.1 ± 41.02	30.84±7.89	115.42±17.61	<**0.001***
	Range	18 - 140	18-60	83-140	
AST (IU/L)	**Mean± SD**	51.8 ± 40.77	31.25±6.77	97.55±47.4	<**0.001***
	Range	20 - 230	20-50	42-230	
Albumin (g/dl)	**Mean± SD**	3.7 ± 0.34	3.84±0.27	3.5±0.36	<**0.001***
	Range	3 - 4.5	3.4-4.5	3-4	
CRP (mg/dl)	**Mean± SD**	88.8± 51.04	61.73±18.57	148.98±48.86	<**0.001***
	Range	31.2 - 235.8	31.2-100.2	57.8-235.8	
Lactate	**Mean± SD**	2.1 ± 0.73	1.64±0.25	2.97±0.59	<**0.001***
(mmol/L)	**Range**	1.3 - 4.1	1.3-2	2.2-4.1	
PH	**Mean± SD**	7.3 ± 0.09	7.37±0.01	7.18±0.05	<**0.001***
	Range	7.1 - 7.39	7.35-7.39	7.1-7.25	
Bicarbonate	**Mean± SD**	22.1 ± 3.16	23.57±2.36	18.87±2.14	<**0.001***
(mEq/L)	**Range**	15 - 27	20-27	15-22	

Hb: haemoglobin, PLT: platelet count, WBCs: white blood cells, *: statistically significant as p value <0.05, PLR: platelet-lymphocyte ratio, NLR: Neutrophil-lymphocyte ratio,

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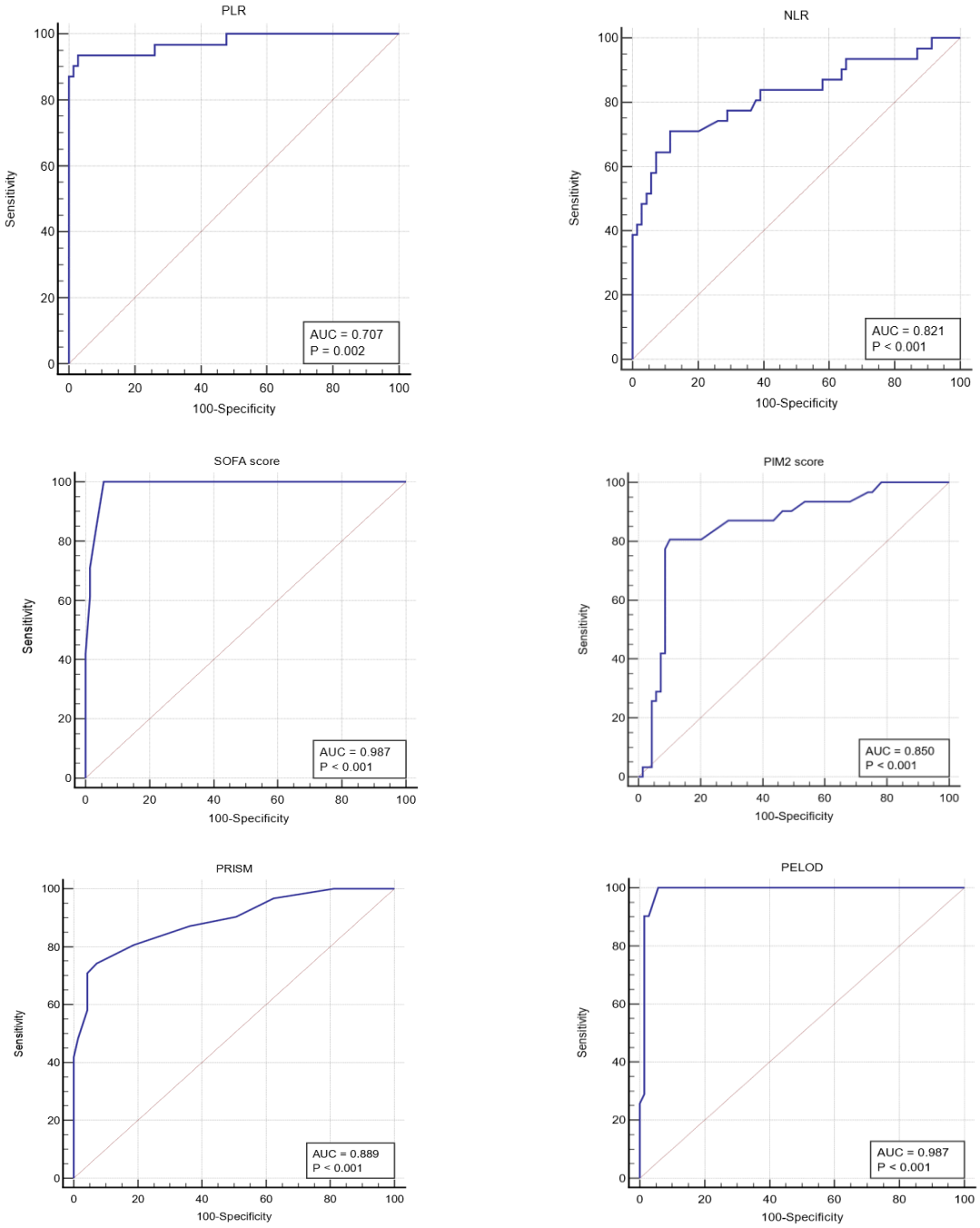

Figure 1: ROC curve analysis for prediction of survivor

Table 3: Clinical scores and length of hospital stay of the studied groups

		Total (n=100)	Survivors (n=69)	Non survivors (n=31)	P value
SOFA score	**Mean± SD**	5.3 ± 3.41	3.26±1.58	9.71±1.77	<**0.001***
	Range	1 - 12	1-10	7-12	
PIM2 score	**Mean± SD**	10.9 ± 12.21	6.71±9.55	20.3±12.39	<**0.001***
	Range	3.5 - 68	3.5_68	4.1_45.8	
	Median (IQR)	5.15 (4.375 - 11.05)	4.7 (4.2 - 5.4)	20.9 (9.65 - 31.8)	
PRISM	**Mean± SD**	7.6 ± 4.15	5.7±2.4	11.94±4.01	<**0.001***
	Range	1 - 17	1_13	4_17	
PELOD Score	**Mean± SD**	4.8 ± 1.65	3.93±0.97	6.84±0.89	<**0.001***
	Range	2.1 - 8.3	2.1-7.4	5.4-8.3	
Length of hospital stay (days)	**Mean± SD**	7.8 ± 4.4	5.86±2.6	12.13±4.53	<**0.001***
	Range	1 - 20	1-13	4-20	

SOFA: sequential organ failure assessment, PIM2: paediatric index of mortality 2, PELOD: pediatric logistic organ dysfunction, PRISM: Preserved Ratio Impaired Spirometry *: statistically significant as p value <0.05,

Discussion

In our study, 69 (69%) children were survivors, and 31 (31%) children were non-survivors. There was no significant difference between both groups regarding age, sex, and residence.

In agreement with our findings, Mahalingam et al. [18] reported that 156 (56.7%) children were survivors and 119 (43.3%) children were non-survivors during the study period. There was no significant difference between both groups regarding age and sex (p=0.19 and p=0.55 respectively).

In disagreement with our results, Wu et al. [19] reported that there was a significant difference between both groups regarding age and sex (p<0.001 and p=0.004 respectively). This could be explained by larger sample size and different research design.

In the present study, there was an insignificant difference between both groups regarding vital signs (pulse rate, RR, SBP, and DBP).

In agreement with our findings, Mahalingam et al. [18] showed that there was no significant difference between survivors (n=156) and non-survivors (n=119) groups regarding pulse rate, RR, and SBP (p=0.08, p=0.86 and p=0.64 respectively).

In contrast with us, Misirlioglu [20] reported that sepsis was significantly higher in survivors compared to non-survivors (p<0.001). Shock, multi-organ failure, and renal failure were significantly lower in survivors compared to non-survivors (p<0.001).

According to our study, Hb concentration and PLT count were significantly lower in non-survivors compared to survivors (P=0.006, <0.001). Lymphocytes, monocytes, and neutrophils were significantly higher in non-survivors compared to survivors (P<0.001, 0.024, <0.001), with no significant difference between both groups regarding WBC count. Platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) were significantly lower in non-survivors compared to survivors (P<0.001, 0.025).

In alignment with our findings, Tekin et al [21] reported that the NLR, and PLR values were significantly lower in non-survivors (n=13) than in survivors (n=345) (NLR, 6.2±5.7 versus 2.6±2.5, P<0.001; PLR, 145.3±85.0 versus 46.2±25.2, P<0.001). Hb concentration was significantly lower in non-survivors compared to survivors (P<0.001). Lymphocytes, monocytes, and

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neutrophils were significantly higher in non-survivors compared to survivors (p<0.05).

This result came in disagreement with Wu et al. [19] showed that NLR and PLR were significantly lower in survivors (n=18673) compared to non-survivors (n=3149) (p<0.001)). Lymphocytes and neutrophils were significantly lower in non-survivors (n=18673) compared to survivors (n=3149) (p<0.001)). This could be explained by larger sample size and different research design.

In the current study, with regard to the serum electrolytes, phosphorus and Na were significantly lower in non-survivors compared to survivors (P<0.001, <0.001), whereas K and Ca were insignificantly different between both groups. Concerning the other laboratory investigation, liver enzymes (ALT and AST), CRP, and lactate were significantly higher in non-survivors compared to survivors (P<0.05). Albumin was significantly lower in non-survivors compared to survivors (P<0.001). The non-survivor's group had significantly lower pH and bicarbonate levels compared to the survivors (P<0.001, <0.001).

In alignment with our findings, Tekin et al [21] reported that the ALT, and AST values were significantly higher in non-survivors (n=13) than in survivors (n=345) (p<0.05).

Regarding the present study, SOFA score, PRISM, PELOD, and PIM2 score were significantly higher in non-survivors compared to survivors (P<0.001). The length of hospital stay was significantly prolonged in non-survivors compared to survivors (P<0.001).

These results were in agreement with Shenoy and Patil [22] who reported that PELOD-2 and PRISM III were significantly higher in non-survivors (n=48) compared to survivors (n=277) (P<0.001). However, the length of hospital stay was significantly prolonged in survivors compared to non-survivors (P<0.001).

In the current study, PLR with AUC 0.975 can significantly predict survivors (P<0.001), at a cutoff value of ≤4.97, with 93.55 % sensitivity, 91.30% specificity, 82.9% PPV, and 96.9% NPV. NLR with AUC 0.821 can significantly predict survivors (P<0.001), at a cutoff value of ≤0.20 with 77.42% sensitivity, 68.12% specificity, 52.2% PPV and 87.0% NPV.

In agreement with our findings, Mahalingam et al. [18] studied the sensitivity and specificity of PLR ≥ 3.9 and NLR ≥ 7 for the prediction of mortality in 275 children admitted to the PICU. They showed that PLR had a sensitivity of 85.71 %, specificity of 14.10%, PPV of 43.22%, and NPV of 56.41% for predicting mortality. NLR had a specificity of 92.31% and an NPV of 56.69% for predicting mortality.

In the present study, a SOFA score with AUC 0.987 can significantly predict survivors (P<0.001), at a cutoff value of >6 with 100% sensitivity, 94.20% specificity, 88.6% PPV, and 100% NPV. PIM2 score with AUC 0.850 can significantly predict survivors (P<0.001), at a cutoff value of >5.3 with 87.10% sensitivity, 71.01% specificity, 57.4% PPV and 92.5% NPV. PRISM with AUC 0.889 can significantly predict survivors (P<0.001), at a cutoff value of >6 with 80.65% sensitivity, 63.77% specificity, 51.9% PPV and 91.7% NPV. PELOD with AUC 0.987 can significantly predict survivors (P<0.001), at a cutoff value of >5.3 with 100% sensitivity, 94.20% specificity, 88.6% PPV and 100% NPV.

In agreement with us, Misirlioglu [20] studied the sensitivity and specificity of PELOD, PIM2, and PRISM in 670 PICU children. They reported that the PELOD cut-off value of ≥ 7 predicted increased mortality with a sensitivity of 100% and specificity of 96.1%. The PIM2 cut-off value of ≥ 90 predicted increased mortality with a sensitivity of 100% and specificity of 98.2%. The PRISM cut-off value of ≥ 12 predicted increased mortality with a

sensitivity of 96% and specificity of 94.8%.

Moreover, Shimoyama et al. [23] studied the SOFA score for predicting mortality in 32 patients with GIP treated in the ICU. They reported that SOFA score with a cut-off value of ≥ 6 predicted increased mortality with a sensitivity of 75%, specificity of 87.5%, PPV of 666.7%, and NPV of 91.3%.

Conclusion

Hematological parameters and scores were used for predicting PICU mortality PLR and NLR are simple hematological biomarkers, easy to calculate, and cost-effective, and ratios are better than individual parameters. Our study showed that the PLR with AUC 0.975 can significantly predict survivors, at a cutoff value of ≤4.97, with 93.55 % sensitivity, 91.30% specificity, 82.9% PPV, and 96.9% NPV.

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Author contribution

Authors contributed equally to the study.

Conflicts of interest

No conflicts of interest

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