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Original Research Article

Prognostic value of rise in neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in predicting the mortality in paediatric intensive care

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ABSTRACT

Background: When the body is stressed in diverse pathological conditions, it responds by mounting an inflammatory response. Predictive biomarkers reflecting the response may serve as guide to management. Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio has been frequently used in adult patients as an indicator for mortality. However, no study has looked into their use within pediatric population. The objective of the study is to assess the prognostic value of rise in NLR and PLR in pediatric intensive care as markers of mortality.
Methods: A retrospective study based on 3 year data from HIMS and G-HEALTH data systems of AJ Institute of Medical Science, of all patients admitted to PICU after excluding those in whom all the study parameters were not retrievable, were postoperative patients and/or stay was less than 5 days. NLR and PLR ratios were determined and compared to PELOD 2 using SPSS version 17.0.
Results: The demographic data was matched. PELOD 2 (>20) predicted mortality in 72.2% of the patients, while NLR increase predicted in 61.1% and PLR increase in 77.8%. A decreasing trend in NLR and PLR were both closely related to better survival. Among the 3, Rise in PLR had higher sensitivity, specificity, PPV, NPV, and overall accuracy of 72.73% ($p < 0.001$) to predict mortality.
Conclusions: The study gives an insight into the fact that simple and inexpensive markers such as rise in NLR and PLR helps in predicting the mortality in the pediatric intensive care which is comparable to PELOD 2 score.

Keywords: Mortality indicator, NLR, NLR rise, Pediatric intensive care, PLR, PLR rise, Prognostic indicator

INTRODUCTION

A variety of ingenious scores have been designed over time to augment the clinical acumen of the treating physician which serve as an objective basis for the decisions to ascertain, which includes the severity of the disease and predict mortality in the patient, thus streamlining the care in a more effective manner. The scores that are in use require multiple parameters to fulfill its criteria to predict mortality.[1] And most of these parameters require additional laboratory values thus adding in to the financial constraints of the patients.[1] A large number of such biomarkers have been studied; however none have been validated as a standalone marker to predict mortality, especially in the critically ill patients.[2]

When the body is stressed in diverse pathological conditions, it responds by mounting inflammatory responses to counter the attack on its self through its key

cellular components, neutrophils and lymphocytes, along with its various components.[3,4] Similarly platelets release the thromboxanes and other mediators, and consequently, in patients with higher platelets may cause increased inflammation of patients.[5]

Neutrophil lymphocyte ratio (NLR) has been proposed as a surrogate marker for endothelial dysfunction and inflammation in distinct populations and has prognostic and predictive values.[6-9] Elevated platelet lymphocyte ratio (PLR) is also a predictor of long-term mortality rather than just a marker of an acute medical condition.[10] These values will subsequently normalize when the patient becomes well. NLR and PLR though frequently used in adult patients as an indicator for mortality have not yet been much studied within pediatric populations.[2,11] No study till date has studied whether rising or falling trend of NLR and PLR over the course of a child's hospital stay can be used as an independent marker of outcome in comparison to standard scores for predicting mortality.

The aim of present study was to assess the prognostic value of rise in NLR and PLR in pediatric intensive care as markers of mortality. The outcomes measure is the trend of NLR and PLR in comparison to PELOD 2 score for children admitted to a tertiary care centre PICU.

METHODS

A retrospective cohort study was conducted in AJ Institute of Medical Science, Mangalore after obtaining permission from the Institutional Ethical Committee, from January 2015 to December 2017.

Inclusion criteria

- All patients admitted to PICU between the age of 1 month and 18 years were considered for the study.

Exclusion criteria

- Patients were excluded from the study if all the study parameters were not retrievable for them, if their duration of stay was less than 5 days or if patient was admitted for postoperative care.

Individual patient consent was not taken as all the study parameters were acquired retrospectively from the institutional database (Hospital Information Management System [HIMS] and G-HEALTH [Gestalt Technologies Pvt. Limited Bangalore] data systems) without any further blood sampling.

Once the patients were identified, information regarding demographic parameters like age, gender and relevant clinical history were collected. Blood parameters of day 1 and day 5 which included the total white blood cell count, neutrophil count, lymphocyte count, and platelets were retrieved for the calculation of NLR and PLR.

The data was then analyzed to determine NLR and PLR for on the day of admission, and also on day 5. The values were determined as per the formula given below:

Neutrophil lymphocyte ratio=
Neutrophil%/Lymphocyte% x 100

Platelet lymphocyte ratio =
Platelet count/Lymphocyte% x 100

Information retrieved also included vital parameters, CNS parameters, respiratory parameters and need of Invasive ventilation. PELOD 2 score for on the day of admission was calculated based on the study put forward by Leteurte et al.[1] The parameters included in the calculation of the score are based on the organ dysfunction and its associated variables:

- Neurologic (Glasgow coma scale, pupillary reaction)
- Cardiovascular (serum lactate, mean arterial pressure)
- Renal (serum creatinine)
- Respiratory (PaO_2, $PaCO_2$, need for invasive ventilation)
- Hematologic (total count and platelet count).

The change in NLR and PLR was the compared to the mortality stratification as on Day 1 PELOD 2. The stratification was done as <10, 10-20 and >20 of the score, where higher the band was associated with higher mortality. On admission and day 5 NLR and PLR were compared to PELOD 2 at admission.

Statistical analysis

Collected data was summarized by frequency, percentage, mean, standard deviation and median.

Sensitivity, specificity, PPV, NPV and overall accuracy were calculated between NLR rise, PLR rise and PELOD 2 score with mortality. Comparison of various parameters between with expired and surviving was done using Mann-Whitney Test. Karl-Pearson's coefficient was calculated to find the relationship between variables. ROC analysis was performed to identify a cut-off of PELOD 2 score and Rise in NLR and PLR. Analysis was performed using SPSS 17 software.

RESULTS

Of the 7487 patients, 1456 postoperative cases and 2465 cases with duration of stay <5 days were excluded. All parameters required for the study was not retrievable in 3511 cases. The demographic data was matched for those included in the study.

Table 1: Comparison between survivors and non-survivors.

Group		Mortality						p value
		Yes			No			
		Count	Mortality among the group	Mortality	Count	Survival among the group	Survival	
Age in years	<1	8	33.3%	44.4%	16	66.7%	43.2%	0.364
	1-5	6	33.3%	33.3%	12	66.7%	32.4%	
	6-10	1	12.5%	5.6%	7	87.5%	18.9%	
	>10	3	60.0%	16.7%	2	40.0%	5.4%	
	Total	18	32.7%	100.0%	37	67.3%	100.0%	
Sex	F	8	50.0%	44.4%	8	50.0%	21.6%	0.080
	M	10	25.6%	55.6%	29	74.4%	78.4%	
	Total	18	32.7%	100.0%	37	67.3%	100.0%	
Ventilator	Yes	18	62.1%	100.0%	11	37.9%	29.7%	0.001
	No	0	0%	0%	26	100.0%	70.3%	
	Total	18	32.7%	100.0%	37	67.3%	100.0%	
PELOD >20	Yes	13	46.4%	72.2%	15	53.6%	40.5%	0.027
	No	5	18.5%	27.8%	22	81.5%	59.5%	
	Total	18	32.7%	100.0%	37	67.3%	100.0%	
PELOD >10	Yes	18	39.1%	100.0%	28	60.9%	75.7%	0.022
	No	0	0%	0%	9	100.0%	24.3%	
	Total	18	32.7%	100.0%	37	67.3%	100.0%	
NLR rise	Yes	11	50.0%	61.1%	11	50.0%	29.7%	0.026
	No	7	21.2%	38.9%	26	78.8%	70.3%	
	Total	18	32.7%	100.0%	37	67.3%	100.0%	
PLR rise	Yes	14	56.0%	77.8%	11	44.0%	29.7%	0.001
	No	4	13.3%	22.2%	26	86.7%	70.3%	
	Total	18	32.7%	100.0%	37	67.3%	100.0%	

Table 2: Comparison of mortality between NLR rise, PLR rise and PELOD 2.

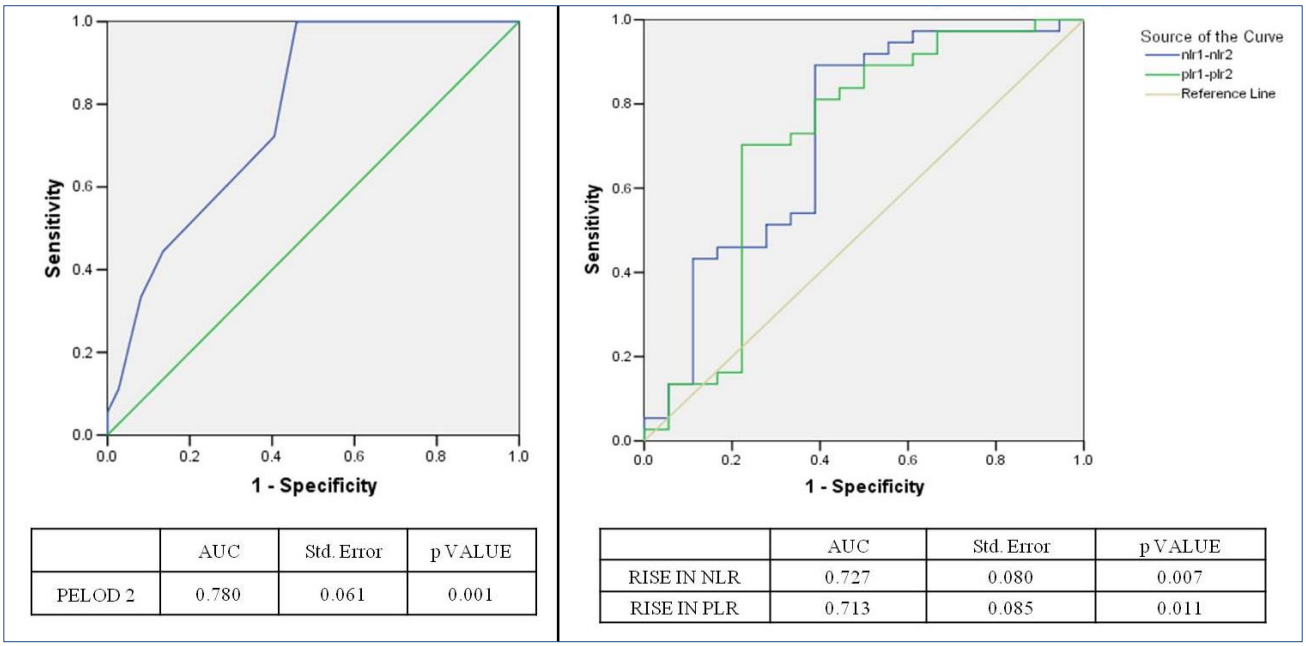
	Survivors	Mortality	Sensitivity	Specificity	PPV	NPV	Overall accuracy	p value
PELOD 2 >10	28 (60.9%)	18 (39.1%)	100	24.32	39.13	100	49.09	0.020 Sig
PELOD 2 >20	15 (53.6%)	13 (46.4%)	72.22	59.46	46.43	81.48	63.64	0.027 Sig
Rise in NLR	11 (50%)	11 (50%)	61.11	70.27	50	78.79	67.27	0.026 Sig
Rise in PLR	11 (44%)	14 (56%)	77.78	70.27	56	86.67	72.73	0.001 Hs

Higher incidence of mortality was noted among the study group in those with age less than 5 years, male gender, need for ventilator support and PELOD 2 score >10 (Table 1).

PELOD 2 (>20) predicted mortality in 72.2%% of the patients, while NLR increase predicted in 61.1% and PLR increase in 77.8% (Table 2). A decreasing trend in NLR and PLR were both closely related to better survival. Rising NLR and PLR followed the inverse relationship with length of stay similar to incidence of mortality, that is Mean of 8.23 days (STD 7.16, median 5.50) ,8.08 days (STD 6.82, median 6) and 6 days (STD 5.43, median 4) respectively. According to present study, the Positive Predictive Value (PPV) in predicting mortality of PELOD 2 > 20, Rise in NLR and PLR were 46.43, 50 and 56 while the Negative Predicting Value (NPV) of the same are 81.48, 78.79 and 86.67 respectively (Table 2). Among the 3 to predict mortality, Rise in PLR had higher sensitivity and specificity with higher PPV and NPV, thus having an overall accuracy of 72.73% (p <0.001).

Rise in NLR followed a near similar trend as PELOD 2 score in predicting mortality, with a slightly lower sensitivity and higher specificity but comparable PPV, NPV and overall accuracy.

Based on the receiver operating characteristic (ROC) curve PELOD 2 score >16 (Figure 1a) predicted mortality with a sensitivity 100% and specificity 54.1%. With rise in PLR >14 (Figure 1b) mortality was predictable with sensitivity of 81.1% and specificity 61.1%, and with rise in NLR >0.2 mortality was predictable with sensitivity of 89.2% and specificity 61.1%.



	AUC	Std. Error	p VALUE
PELOD 2	0.780	0.061	0.001

	AUC	Std. Error	p VALUE
RISE IN NLR	0.727	0.080	0.007
RISE IN PLR	0.713	0.085	0.011

Figure 1: ROC curve; 1a: PELOD 2 score in predicting mortality; 1b: NLR rise and PLR rise in predicting mortality.

DISCUSSION

The present study is perhaps the first to investigate the trend in NLR and PLR independently to predict mortality in pediatric patients. Early diagnosis of sepsis does improve the outcome of the patients especially those admitted to PICU. Hence, specific markers and molecular diagnostic assays are much needed to tailor the clinical management of the patient.

Many studies including those by Iskandar H et al, and El-Nawawy A et al, prove the usefulness of PELOD 2 score in predicting mortality.[12,13] Present study testifies to a similar trend that a higher PELOD 2 score is associated with a graver prognosis and higher mortality. However, the calculation of the score is cumbersome and involves many parameters requiring elaborate blood sampling.[14] The baseline demographic data was matched in present study and was comparable to previous studies that have compared PELOD 2 score to mortality.[15-17]

The mortality rate in present PICU during the study period was noted to be 3.3% which stands in line with the PICUs worldwide, which reports rates varying in between 2.9% and 5.6%.[18-22]

Dursun A et al suggested the use of biomarkers for monitoring the antimicrobial treatment and progression of illness and that they play a role in follow-up of septic pediatric patients.[23]

It is hypothesized that in response to systemic inflammation or stress there is an increase in neutrophils production and driven apoptosis of lymphocytes, thus the resulting neutrophilia and lymphopenia cause an increase in the NLR.[24,25] Zahorec is credited for describing the use of NLR as an inflammatory marker.[26] A higher NLR indicates a higher level of inflammation.[27] Therefore, NLR can be used to predict the severity of inflammation and also its prognosis.[28,29] Duffy BK et al, has reported higher rates of mortality among patients admitted to PICU with high NLR values.[29,30] Yegit et al, 2017 had studied the role of NLR and RDW in the classification of febrile seizures among 142 children and they reported that among the 142 patients under study, there was a statistical difference in the NLR values in the complex seizure group to simple seizures.[31] Yilmaz and Acar et al, 2017 had studied the diagnostic value of NLR in pediatric appendicitis among 658 patients and found the NLR to be raised in patients with appendicitis with statistical significance ($p<0.05$).[32]

Various studies have used different normal range for NLR, values such as 2.8 (1.2-4.4), 1.76 (0.83-3.92), 0.78 to 3.53 and 1.65 (±0.79) while for PLR 137 (75-199) and 132.40 (±43.68).[33-35]

Cutoff values to predict mortality as determined by many previous studies for NLR are >6.24 (sensitivity 81.08 specificity 69.17), >5.1 (sensitivity 75 specificity 62) and >3.28 (sensitivity 62.5 specificity 66.7) and in case of PLR >182.68 (sensitivity 64.86 specificity 58.27), >590.44 (sensitivity 62.5 specificity 66.7) and >176.[36-39]

Cytokines, released during inflammation or infection, cause an increase in platelets.[40,41] Thus, PLR can also

serve as a simple indicator of the severity of the inflammation as well as prognosis.[42] Furuncuoglu Y et al, had shown PLR and mortality were correlated such that high PLR ratios were associated with high mortality rates.[18,43]

The present study has shown the NLR and PLR follows a rising trend with worsening in the clinical condition and increase in the mortality in the subjects. PLR and NLR are inexpensive and quick to obtain and help in determining high risk patients and also to follow up closely the clinical improvement objectively as well as to predict the mortality in the patients. Pedrazzani et al, had assessed the NLR, PLR and platelet counts for predicting long term outcomes in colorectal cancer following R0 resection in 630 patients and compared to 5270 healthy blood donors and concluded that survival was worse in those with a higher NLR values.[44] Durmus et al, reported from their study that NLR and PLR were higher in the 56 heart failure patients than in 40 of their matched controls for age and sex, and the possibility of using NLR as a predictor of mortality in patients especially on follow up was suggested as an inverse relationship between NLR and left ventricular ejection fraction was noted.[37] They also came up with a cut-off value of NLR to predict HF of 3.0 and PLR of 137.3

Seo et al, had studied in retrospection NLR and PLR as novel markers in the diagnosis and prognostication of 348 patients with idiopathic sudden SNHL, and found that the mean values of the markers were significantly higher in the unrecovered group to the recovered group with high statistical significance ($p<0.001$).[45] So the NLR and PLR are simple yet useful indicators of the ongoing inflammatory process that have developed shortly before the presentation of the patient to the medical care.

This study is limited by being single centre retrospective study and requires further randomized control studies to establish the range of values for NLR and PLR, in helping to further stratify patients into risk of mortality, and thereby tailoring care to individual case based level. By comparing NLR and PLR to other known mortality predictors may improve the study.

CONCLUSION

All studies aim at point NLR or PLR, this study gives a cross-sectional view at the trend of NLR and PLR thus predicting the outcome toward mortality. The study shows a similar tendency of NLR and PLR consistent with the predicted trend as per previous studies in adults. Thus, by tracking these surging biomarkers at the time of stress could serve us to better understand the ongoing process and thereby determine the course of action thus aiding in the natural defenses and getting a more favorable outcome in the patients.

The study gives an insight into the fact that simple and inexpensive markers such as rise in Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) helps in predicting the mortality in the Pediatric Intensive Care which is comparable to PELOD 2 scoring.

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