Original Article

Addition of platelet-lymphocyte ratio to risk factors to improve the early prediction of acute kidney injury and mortality in critically ill neonates

Zhenjiang Chen[1,2]^, Xiaomei Dai[1], Yanhong Li[1,3]^

[1]Department of Nephrology and Immunology, Children's Hospital of Soochow University, Suzhou, China; [2]Department of Neonatology, Children's Hospital of Soochow University, Suzhou, China; [3]Institute of Pediatric Research, Children's Hospital of Soochow University, Suzhou, China

Contributions: (I) Conception and design: Y Li; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Yanhong Li. Department of Nephrology and Immunology, Institute of Pediatric Research, Children's Hospital of Soochow University, 92 Zhongnan Street, Suzhou 215025, China. Email: lyh072006@hotmail.com.

Background: To determine whether early neutrophil, lymphocyte, and platelet ratio (NLPR), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), calculated based on easily available parameters in complete blood count, are associated with the development of acute kidney injury (AKI) and mortality during neonatal intensive care unit (NICU) stay, and to evaluate whether these ratios could act as a predictor of AKI and mortality in neonates.

Methods: The pooled data of 442 critically ill neonates from our previously published prospective observational studies of urinary biomarkers were analyzed. Complete blood count (CBC) was measured on NICU admission. The clinical outcomes included AKI developed during the first 7 days after admission and NICU mortality.

Results: Of the neonates, 49 developed AKI and 35 died. The association of the PLR, but not NLPR and NLR, with AKI and mortality remained significant after adjustment for potential confounders including birth weight and illness severity as assessed by the score for neonatal acute physiology (SNAP). The area under the curve (AUC) of the PLR for predicting AKI and mortality was 0.62 (P=0.008) and 0.63 (P=0.010), respectively, with additional predictive value when combined with other perinatal risk factors. The combination of PLR with birth weight, SNAP, and serum creatinine (SCr) had an AUC of 0.78 (P<0.001) in predicting AKI, and its combination with birth weight and SNAP had an AUC of 0.79 (P<0.001) in predicting mortality.

Conclusions: Low PLR on admission is associated with increased risk for AKI and NICU mortality. Although the PLR alone is not predictive of AKI and mortally, it adds predictive value to other risk factors for AKI prediction in critically ill neonates.

Keywords: Acute kidney injury (AKI); complete blood count (CBC); critically ill neonates; mortality; platelet-lymphocyte ratio (PLR)

Submitted Sep 17, 2022. Accepted for publication Feb 14, 2023. Published online May 15, 2023.
doi: 10.21037/apm-22-1075
View this article at: https://dx.doi.org/10.21037/apm-22-1075

^ ORCID: Zhenjiang Chen, 0000-0002-7181-9633; Yanhong Li, 0000-0003-0882-6408.

Introduction

Acute kidney injury (AKI), which is highly prevalent among hospitalized neonates, especially those who are in critically ill, has a negative impact on neonatal prognosis, forcing up the risk of in-hospital mortality and morbidity (1-3). Therefore, early prediction and diagnosis are necessary to prevent AKI. The diagnosis of neonatal AKI depends upon serum creatinine (SCr) and urine output, although they are not early and sensitive AKI markers, especially in neonates (1). Previous researchers have developed biomarkers for predicting AKI in neonates (4,5). However, the accuracy of these biomarkers in the clinical diagnosis, especially in more heterogeneous populations such as neonatal intensive care unit (NICU) patients, has not been clearly defined. None of these biomarkers is currently routinely used in neonatal clinical practice.

Numerous studies have revealed that inflammatory processes mediated by the immune system are crucial in the pathophysiology of AKI (6,7). The inflammatory cells, such as neutrophils and lymphocytes, have been detected in kidneys with AKI in the early stage and are expected to have an important role in the pathogenesis of renal injury (6-8). Therefore, the use of easily available parameters found in a complete blood count (CBC) to provide an early diagnosis of AKI and to predict associated patient outcomes has been considered in multiple settings in adults (9). In addition, since the interactions of neutrophils, lymphocytes, and platelets appear to be a critical step in inflammation, the neutrophil, lymphocyte, and platelet ratio (NLPR), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) have been calculated and various attempts have been made to associate these ratios with the prediction of AKI and outcomes in adults and children (10-17). In addition to the fact that absolute neutrophil, lymphocyte, and platelet counts in newborns are different from those in children and adults, they also differ between preterm and full-term infants (18-20). The relationship between these ratios and AKI in neonates currently remains undefined. Therefore, evaluation of the association of these ratios with AKI and outcomes in a heterogeneous population of neonates with a wide range of gestational ages would be meaningful.

The aims of this study were to investigate the associations of the NLPR, NLR, and PLR on NICU admission with AKI and mortality and to determine whether these ratios could act as an early predictor in critically ill neonates. We present this article in accordance with the STARD reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1075/rc).

Highlight box

Key findings

- Low PLR on admission adds predictive value to other risk factors for the prediction of AKI and mortality in critically ill neonates.

What is known and what is new?

- LPR, NLR, and PLR were associated with AKI and outcomes in adults and children.
- PLR is associated with AKI and outcomes in critically ill neonates.

What is the implication, and what should change now?

- Low PLR may be useful in the prediction of AKI and outcome in critically ill neonates.

Methods

Participants

A summary patient-level analysis was performed using pooled data from our previously published prospective studies conducted in critically ill neonates (4,21-23). All previous studies, which were originally designed to examine the diagnostic accuracy of urinary biomarkers and enrolled neonates admitted to the NICU prospectively, had clearly defined enrolment and exclusion criteria (4,21-23). The priori exclusion criteria of these previous studies were as follows: parental refusal to participate, neonates with severe congenital malformations, and failure to collect urine samples before discharge from the NICU or death. The parents or guardians of all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Children's Hospital of Soochow University (No. 2015LW005).

Clinical data collection

Neonatal clinical information and maternal information were collected. Clinical laboratory results were obtained during the first 24 h after admission as part of routine care. The score for neonatal acute physiology (SNAP) was used to assess the illness severity (4,21-23).

AKI definition and clinical outcome

Diagnosis of AKI that developed during the first 7 days after NICU admission was consistent with our previous

studies (4,23), and was based on (I) the neonatal AKI Kidney Disease: Improving Global Outcome (KDIGO): SCr rise greater than or equal to 0.3 mg/dL (26.5 μmol/L) within 48 h; SCr rise greater than or equal to 1.5 times the reference SCr within 7 days; urine output less than or equal to 0.5 mL/kg/h for 6–12 h (4,23), or (II) SCr greater than 1.5 mg/dL (132.6 μmol/L) sustained for at least 48 h and the mother of the neonates had normal renal function (4,23). The SCr level was routinely measured, and all neonates underwent at least 2 SCr measurements during the first 7 days after admission.

CBC and calculation of the NLPR, NLR, and PLR

A sample of venous blood was routinely collected on admission for the measurement of the CBC using a Sysmex XN-1000 blood cell analyzer (Sysmex Corporation, Tokyo, Japan). In accordance with the previous study (9), the NLPR was defined as the neutrophil, lymphocyte, and platelet ratio and calculated as: (neutrophil count ×100)/(lymphocyte count × platelet count). The NLR was defined as the ratio of neutrophil count to lymphocyte count. The PLR was defined as the ratio of platelet count to lymphocyte count.

Statistical analysis

The data were analyzed using SPSS 16.0 software (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov and Levene's tests were performed to analyze normality and homogeneity of variance. Continuous variables were presented as the median [interquartile range (IQR)] and categorical variables as the total number (percentage). The Mann-Whitney U test and chi-square or Fisher's exact test were used to analyze the differences between groups. Multivariate linear regression analysis was performed to investigate factors independently associated with these ratios. Continuous variables with skewed distribution were $\log_{10}$ transformed for linear regression, and the multicollinearity was judged by variance inflation factor (VIF) and tolerance values. The VIF and tolerance values of less than 2 and greater than 0.5, respectively, indicated the absence of multicollinearity. To identify independent variables associated with AKI and outcome, univariate and multivariate (forward conditional) logistic regression analyses were performed. The odds ratio (OR), adjusted OR (AOR), and 95% confidence interval (CI) were calculated. Model fit was assessed by the Hosmer-Lemeshow goodness-of-fit test. The area under the curve (AUC) of the receiver-operating characteristic (ROC) curve was performed to assess discriminative ability of variables, and the sensitivity and specificity were calculated. The nonparametric method of Delong in SigmaPlot 10.0 software (Systat Software, Inc., San Jose, CA, USA) was used to compare differences between AUCs. All statistical analyses were 2-sided with an alpha level of 0.05.

Results

Patient characteristics

In total, 442 neonates were included in the study, and the study flow diagram is displayed in Figure S1. Of the neonates, 49 (11.1%) were identified as having AKI during the first 7 days after admission, including 22 with AKI stage 1, 17 with stage 2, and 10 with stage 3. The demographic and clinical characteristics, the first available laboratory results during the first 24 hours after admission, and the levels of NLPR, NLR, and PLR on admission were compared between neonates with and without AKI (*Table 1*).

In addition, of the neonates, 429 (97.1%) received antibiotics, including cephalosporin, penicillin, meropenem, and vancomycin. None of the neonates received aminoglycosides, indomethacin, or ibuprofen during their NICU stay. Of the 442 neonates, 2 were born from mothers with chronic kidney disease, and 25 were born from mothers who were diagnosed with diabetes mellitus during the pregnancy.

Correlation of the NLPR, NLR, and PLR with clinical variables

To investigate whether these ratios on admission were associated with gestational age, birth weight, sex, and illness severity as assessed by the SNAP, multivariate linear regression analyses were performed after checking the multicollinearity in *Table 2*. In addition, Spearman's correlation analysis was used to investigate the correlation of these ratios with clinical factors (Table S1).

Association of the NLPR, NLR, and PLR with AKI

To explore whether these ratios on admission could be used for early prediction of the development of AKI during the first 7 days after admission, the demographic and clinical variables, including gestational age, birth weight, sex, and SNAP, and the first available laboratory results with P less

Table 1 Demographic and clinical characteristics and laboratory results between critically ill neonates with and without AKI

Variables	Non-AKI, n=393	AKI, n=49	P value
Neonatal characteristics			
Gestational age, weeks	35.1 [32.7–38.1]	33.4 [30.3–37.2]	0.018
26–28	10 (2.5)	6 (12.2)	0.001
29–32	98 (24.9)	17 (34.7)	0.142
33–36	153 (38.9)	13 (26.5)	0.091
37–42	132 (33.6)	13 (26.5)	0.321
Birth weight, g	2,300.0 [1,785.0–3,092.5]	1,600.0 [1,315.0–2,875.0]	0.001
Male	238 (60.6)	37 (75.5)	0.042
SNAP score	7.0 [5.0–10.0]	10.0 [6.5–13.0]	<0.001
Apnea[a]	60 (15.3)	20 (40.8)	<0.001
Sepsis[a]	32 (8.1)	4 (8.2)	1.000
RDS[a]	50 (12.7)	17 (34.7)	<0.001
HIE[a]	21 (5.3)	5 (10.2)	0.173
CPAP[a]	119 (30.3)	29 (59.2)	<0.001
MV[a]	56 (14.2)	22 (44.9)	<0.001
Surfactant[a]	39 (9.9)	12 (24.5)	0.003
Inotrope[a]	55 (14.0)	13 (26.5)	0.022
Serum sodium[b], mmol/L	135.6 [133.0–138.1]	135.0 [132.0–137.3]	0.266
Serum potassium[b], mmol/L	4.6 [4.2–5.1]	4.6 [4.1–5.0]	0.773
Serum glucose[b], mmol/L	3.3 [2.5–4.3]	3.8 [2.6–4.9]	0.165
Serum bicarbonate[b], mmol/L	19.3 [17.5–21.2]	18.7 [16.3–20.9]	0.209
Serum creatinine[b], μmol/L	58.0 [48.9–68.0]	65.0 [47.0–105.1]	0.012
BUN[b], mmol/L	3.8 [3.1–4.8]	4.5 [3.2–6.2]	0.011
NLPR[c]	0.9 [0.5–1.6]	0.9 [0.4–1.7]	0.585
NLR[c]	2.1 [1.2–3.6]	1.8 [1.0–2.6]	0.036
PLR[c]	67.3 [50.1–94.6]	57.6 [33.8–74.2]	0.008
NICU mortality	25 (6.4)	10 (20.4)	0.001
Maternal characteristics			
Hypertension[d]	32 (8.1)	6 (12.2)	0.334
Diabetes[d]	23 (5.9)	2 (4.1)	0.610
Prenatal steroids	44 (11.2)	7 (14.3)	0.532

Values are median [interquartile range] or number (percentage). AKI was developed during the first 7 days after NICU admission. [a], developed during NICU stay; [b], the first available laboratory results during the first 24 h after NICU admission; [c], obtained on NICU admission; [d], diagnosed during the pregnancy. AKI, acute kidney injury; BUN, blood urea nitrogen; CPAP, continuous positive air way pressure; HIE, hypoxic ischemic encephalopathy; MV, mechanical ventilation; NICU, neonatal intensive care unit; NLPR, neutrophil, lymphocyte, and platelet ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; RDS, respiratory distress syndrome; SNAP, the score for neonatal acute physiology.

Table 2 Clinical factors potentially associated with these ratios in critically ill neonates in multivariate linear regression analysis

Variables	β	SE	P value	Tolerance	VIF
NLPR					
Gestational age, weeks	2.785	0.406	<0.001	0.95	1.05
Male	−0.037	0.037	0.323	0.98	1.02
SNAP, score	−0.007	0.005	0.080	0.93	1.07
NLR					
Birth weight, g	0.862	0.100	<0.001	0.95	1.06
Male	−0.006	0.033	0.851	0.97	1.03
SNAP, score	−0.015	0.004	<0.001	0.94	1.07
PLR					
Birth weight, g	−0.007	0.084	0.929	0.95	1.06
Male	−0.003	0.028	0.906	0.97	1.03
SNAP, score	−0.018	0.003	<0.001	0.94	1.07

Variables of gestational age, birth weight, sex and the SNAP were entered in multivariate linear regression analysis after checking multicollinearity. Continuous variables were log-transformed. β, coefficient; SE, standard error; NLPR, neutrophil, lymphocyte, and platelet ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SNAP, the score for neonatal acute physiology; VIF variance inflation factor.

than 0.05 in the comparison of *Table 1* were considered confounding factors and analyzed. As shown in *Table 3*, the final forward multivariate regression model identified birth weight, SNAP, SCr, and PLR as independent factors significantly associated with AKI.

The ability of the PLR to predict AKI is displayed in *Table 4*. The PLR on NICU admission provided an AUC of 0.62, which was similar to that of SCr (AUC =0.61), for discriminating AKI. When combining PLR and SCr, the performance improved significantly (AUC =0.68), as compared with SCr alone (AUC =0.68 *vs.* 0.61, P=0.010). The combination of the PLR with birth weight, SNAP, and SCr displayed the best performance (AUC =0.78), which was significantly better than PLR (AUC =0.78 *vs.* 0.62, P=0.002) or SCr (AUC =0.78 *vs.* 0.61, P<0.001) alone in the early prediction of AKI.

Association of the NLPR, NLR, and PLR with NICU mortality

Of the 442 neonates, a total of 35 died during NICU stay. The comparisons of the demographic and clinical characteristics, the first available laboratory results during the first 24 h after admission, and the levels of NLPR, NLR, and PLR on admission between survival and non-survival neonates are displayed in Table S2.

To explore whether these ratios on admission were suitable for early prediction of NICU mortality, the demographic and clinical variables, including gestational age, birth weight, sex, and SNAP, and the first available laboratory results with P less than 0.05 in the comparison displayed in *Table 1* were considered confounding factors and analyzed. The final forward multivariate regression model identified birth weight, SNAP, and PLR as independent factors significantly associated with mortality (*Table 5*).

The PLR provided an AUC of 0.63, which was not better than birth weight or SNAP, in predicting mortality (*Table 6*). The combination of the PLR with birth weight and SNAP displayed the best performance (AUC =0.79), which was significantly better than PLR (AUC =0.79 *vs.* 0.63, P=0.029) or SNAP (AUC =0.79 *vs.* 0.69, P=0.019) alone in the early prediction of NICU mortality.

Discussion

Our data demonstrate that the PLR on NICU admission, but not NLPR and NLR, is independently associated with AKI and mortality in critically ill neonates. The potential mechanism of low PLR might be related to decreased

Table 3 Logistic regression analysis of risk factors for acute kidney injury

Variables	Univariate regression			Multivariate regression (forward)		
	OR	95% CI	P value	AOR	95% CI	P value
Gestational age, weeks	0.895	0.822–0.974	0.010	Out		
Birth weight, 100 g	0.940[a]	0.903–0.978	0.002	0.937[a]	0.899–0.976	0.002
Male	0.498	0.252–0.985	0.045	Out		
SNAP, score	1.139	1.069–1.212	<0.001	1.093	1.018–1.175	0.015
SCr, μmol/L	1.031	1.017–1.046	<0.001	1.028	1.011–1.046	0.001
BUN, mmol/L	1.232	1.114–1.363	<0.001	1.102	0.989–1.228	0.080
NLR	0.813	0.672–0.984	0.033	Out		
PLR	0.988	0.979–0.997	0.009	0.989	0.979–0.999	0.032

The demographic and clinical variables, including gestational age, birth weight, sex and SNAP, and the first available laboratory results with P<0.05 in the comparison of *Table 1* were considered confounding factors and entered in the logistic regression analyses. [a], odds ratio represents the increase in risk per 100 g increase in birth weight. AOR, adjusted odds ratio; BUN, blood urea nitrogen; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; OR, odds ratio; PLR, platelet-lymphocyte ratio; SCr, serum creatinine; SNAP, the score for neonatal acute physiology.

Table 4 Predictive ability of risk factors for acute kidney injury

Variables	AUC	95% CI	P value	Cut-off value	Sensitivity, %	Specificity, %
Low birth weight, g	0.64	0.55–0.74	0.001	1,615.0	51.0	80.3
SNAP, score	0.66	0.58–0.74	<0.001	9.5	53.1	72.1
SCr, μmol/L	0.61	0.50–0.72	0.012	89.0	42.9	95.4
Low PLR	0.62	0.53–0.70	0.008	75.9	79.6	40.4
Combination[a]	0.71	0.63–0.78	<0.001	N/A		
Combination[b]	0.68	0.59–0.78	<0.001	N/A		
Combination[c]	0.78	0.71–0.85	<0.001	N/A		

[a], combination of PLR with birth weight and SNAP; [b], combination of PLR with SCr; [c], combination of PLR with birth weight, SNAP and SCr. AUC, area under the curve; CI, confidence interval; N/A, not applicable; PLR, platelet-lymphocyte ratio; SCr, serum creatinine; SNAP, the score for neonatal acute physiology.

platelet production or excessive platelet destruction caused by diseases, therapeutic interventions, inflammation, and hypoxia. To our knowledge, the study was the first to explore the relationship between the NLPR, NLR, and PLR and risk of AKI and mortality in critically ill neonates. The OR for the association of the PLR with AKI and mortality remained significant after adjustment for body weight and illness severity, as assessed by the SNAP, demonstrating that an association between the PLR exists, calculated from CBC obtained on admission, and AKI or NICU mortality in critically ill neonates.

Our observation of NLPR and NLR, which were not associated with AKI and mortality in critically ill neonates, is not in accordance with previous studies (11-13,24). Unlike the PLR, the results of NLPR and NLR were largely related to the absolute neutrophil count. The most likely explanation for this discrepancy between our data and previous data conducted in adults might be that we evaluated the association of the ratios in a general and heterogeneous NICU population. In a prospective cohort of critically ill patients, Han *et al.* demonstrated a U-shaped relationship between WBC count and risk of AKI and mortality, and proposed that the higher risk of AKI in leucocytosis could be related to neutrophilia, and the higher

Table 5 Logistic regression analysis of risk factors for NICU mortality

Variables	Univariate regression			Multivariate regression (forward)		
	OR	95% CI	P value	AOR	95%CI	P value
Gestational age, weeks	0.797	0.715–0.887	<0.001	Out		
Birth weight, 100 g	0.875[b]	0.826–0.928	<0.001	0.891[b]	0.842–0.943	<0.001
SNAP	1.148	1.071–1.231	<0.001	1.091	1.007–1.181	0.033
NLR	0.549	0.391–0.773	0.001	Out		
PLR[a]	0.209[c]	0.079–0.556	0.002	0.306[c]	0.100–0.935	0.038

The demographic and clinical variables, including gestational age, birth weight, sex and SNAP, and the first available laboratory results with P<0.05 in the comparison of *Table 1* were considered confounding factors and entered in the logistic regression analyses. [a], data were log-transformed in regression analyses to meet the Hosmer-Lemeshow goodness-of-fit test; [b], odds ratio represents the increase in risk per 100 g increase in birth weight; [c], odds ratio represents the increase in risk per log increase in PLR. AOR, adjusted odds ratio; CI, confidence interval; NICU, neonatal intensive care unit; NLR, neutrophil-lymphocyte ratio; OR, odds ratio; PLR, platelet-lymphocyte ratio; SNAP, the score for neonatal acute physiology.

Table 6 Predictive ability of risk factors for NICU mortality

Variables	AUC	95% CI	P value	Cut-off value	Sensitivity, %	Specificity, %
Low birth weight, g	0.75	0.65–0.85	<0.001	1,640.0	65.7	80.2
SNAP, score	0.69	0.61–0.78	<0.001	9.5	57.1	71.6
Low PLR	0.63	0.51–0.75	0.010	40.8	51.4	85.5
Combination[a]	0.77	0.69–0.85	<0.001	N/A		
Combination[b]	0.70	0.60–0.79	<0.001	N/A		
Combination[c]	0.79	0.72–0.86	<0.001	N/A		

[a], combination of PLR with birth weight; [b], combination of PLR with SNAP; [c], combination of PLR with birth weight and SNAP. AUC, area under the curve; CI, confidence interval; N/A, not applicable; NICU, neonatal intensive care unit; PLR, platelet-lymphocyte ratio; SNAP, the score for neonatal acute physiology.

risk of AKI in leucopenia could be related to lymphopenia and monocytopenia (14). Unfortunately, in critically ill neonates, the counts of neutrophil and lymphocyte are substantially influenced by postnatal age and depend strongly on the underlying conditions and the severity of the illness (18,19).

Interestingly, a negative correlation of the PLR with AKI and outcome was observed in the study, implying that the lower the PLR value, the higher the risk of AKI and mortality in critically ill neonates. Although a high PLR has been associated with an increased risk of AKI or mortality in previous studies conducted in a specific clinical setting, such as in adult patients undergoing contrast-induced AKI (15) or in selected sepsis patients (16), the negative correlation in our study is in line with a previous report conducted on 10,859 critically ill patients with AKI, where a U-shaped relationship was observed between the PLR and increased all-cause mortality, namely, not only high PLR but low PLR is correlated with increased mortality (10). Thus, the correlation between the PLR and the risk of AKI and outcome is diverse, which is determined by the difference in age, underlying conditions, and illness severity, as well as the stage of inflammation. The neonates in this study were critically ill in the early acute stage of illness. The lower PLR might result from the presence of thrombocytopenia that has been demonstrated to be associated with higher AKI and mortality risk in previous studies (25,26).

In this study, the AUC value for the PLR alone to predict AKI was less than 0.70, suggesting that the PLR on admission, similar to SCr, cannot effectively discriminate AKI that developed during the first week after NICU admission by itself in critically ill neonates. The poor

results derived from a mixed heterogeneous NICU population might be related to the low specificity of PLR or SCr for AKI. Indeed, we know that SCr levels reflect the creatinine levels of the mother during the first few days after birth and are unstable during the postnatal period, and the percentages of lymphocyte and platelet in the blood routine examination change with postnatal age (18,19). Nevertheless, we identified that the combination of the PLR with birth weight, SNAP, and SCr was much better than any individual marker alone for early prediction of AKI in heterogeneous critically ill neonates. The significant difference in birth weight and SNAP between neonates with and without AKI has been reported by our previous study and in research conducted by others (4,27). Our finding suggests that the additional predictive value of combining PLR on admission with birth weight, SNAP, and SCr improves the quantification of the risk for prediction of neonatal AKI.

A similar situation was observed in prognosis. The combination of the PLR with body weight and SNAP appeared to be the best predictive model for death in critically ill neonates, with an AUC of 0.79. Gestational age, birth weight, and illness severity are well known to contribute independently to the risk of death in critically ill neonates (28,29). In the study, the body weight and SNAP displayed superior predictive performance to that of other perinatal risk factors, which is accordance with our previous study (4). Our data indicate that the PLR, as an early marker calculated based on easily available parameters found in a CBC, could add predictive value to other previously described perinatal risk factors for death.

This study has several limitations. Firstly, AKI diagnosis was made on the basis of SCr and urine output. Although the urine output is of great value in improving the diagnostic rate of AKI, the criteria of urine output for neonatal AKI are still ambiguous or even controversial (2,30). Secondly, the primary aim of the study was to evaluate the early predictive value of these ratios. The CBC was collected for analysis only on NICU admission rather than through serial measurements, which might affect the predictive power of the PLR. Thirdly, the study included neonates from a single center, only 16 (3.6%) neonates were born at less than 29 weeks of gestational age and the illness severity of the neonates assessed by the SNAP was less severe. Our findings may not be generalizable to neonates with extremely low gestational age or with more severe conditions, suggesting that the PLR needs to be validated as a diagnostic and prognostic marker in multiple centers before they can be extrapolated to other populations.

Conclusions

Our study indicates that low PLR on NICU admission is associated with increased risk for AKI and NICU mortality in critically ill neonates. Although the PLR alone is not predictive of AKI and NICU mortally, it adds predictive value to other risk factors for the prediction in the population.

Acknowledgments

We thank the staff in the biochemistry laboratory for their technical assistance.
Funding: This work was supported by grants from the National Natural Science Foundation of China (No. 81971432) and Jiangsu Province Science and Technology Support Program (No. BE2020660). The funders had no role in study design, data collection, preparation of the manuscript, or decision to publish.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1075/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1075/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1075/coif). YL reports that this work was supported by grants from the National Natural Science Foundation of China (No. 81971432) and Jiangsu Province Science and Technology Support Program (No. BE2020660). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The parents or guardians of all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by the Ethics Committee of Children's Hospital of Soochow

University (No. 2015LW005).

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Cite this article as: Chen Z, Dai X, Li Y. Addition of platelet-lymphocyte ratio to risk factors to improve the early prediction of acute kidney injury and mortality in critically ill neonates. Ann Palliat Med 2023;12(3):538-547. doi: 10.21037/apm-22-1075

Supplementary

Table S1 Correlation analysis of the NLPR, NLR and PLR with clinical variables

Variables	NLPR[a]		NLR[a]		PLR[a]	
	r	P value	r	P value	r	P value
Gestational age, weeks	0.385	<0.001	0.427	<0.001	0.056	0.236
Birth weight, g	0.377	<0.001	0.438	<0.001	0.065	0.172
Male	−0.032	0.501	−0.026	0.580	−0.005	0.917
SNAP, score	−0.134	0.005	−0.205	<0.001	−0.194	<0.001
AKI	−0.026	0.586	−0.100	0.036	−0.125	0.008
Apnea[b]	−0.079	0.099	−0.168	<0.001	−0.052	0.274
Sepsis[b]	−0.008	0.862	−0.078	0.103	−0.012	0.796
RDS[b]	−0.197	<0.001	−0.198	<0.001	−0.013	0.787
HIE[b]	0.139	0.003	0.120	0.012	−0.033	0.484
CPAP[b]	−0.083	0.083	−0.110	0.020	−0.057	0.233
MV[b]	−0.085	0.074	−0.136	0.004	−0.170	<0.001
Surfactant[b]	−0.230	<0.001	−0.231	<0.001	−0.093	0.051
Inotrope[b]	−0.075	0.115	−0.125	0.008	−0.174	<0.001
NICU mortality	−0.090	0.059	−0.184	<0.001	−0.123	0.010
Serum sodium[c], mmol/L	−0.030	0.535	−0.038	0.435	−0.089	0.066
Serum potassium[c], mmol/L	0.016	0.736	0.018	0.704	−0.007	0.889
Serum glucose[c], mmol/L	0.064	0.182	0.120	0.013	0.173	<0.001
Serum bicarbonate[c], mmol/L	0.002	0.963	−0.003	0.953	0.012	0.806
Serum creatinine[c], μmol/L	0.244	<0.001	0.229	<0.001	0.005	0.919
BUN[c], mmol/L	0.228	<0.001	0.203	<0.001	0.046	0.339
Neutrophil[a], 10^9/L	0.736	<0.001	0.813	<0.001	0.009	0.853
Lymphocyte[a], 10^9/L	−0.465	<0.001	−0.517	<0.001	−0.779	<0.001
Platelet[a], 10^9/L	−0.358	<0.001	0.019	0.694	0.547	<0.001

r, spearman's correlation coefficient. AKI was developed during the first 7 days after NICU admission. [a], obtained on NICU admission; [b], developed during NICU stay; [c], the first available laboratory results during the first 24 h after admission. AKI, acute kidney injury; BUN, blood urea nitrogen; CPAP, continuous positive air way pressure; HIE, hypoxic ischemic encephalopathy; MV, mechanical ventilation; NICU, neonatal intensive care unit; NLPR, neutrophil, lymphocyte, and platelet ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; RDS, respiratory distress syndrome; SNAP, the score for neonatal acute physiology.

https://dx.doi.org/10.21037/apm-22-1075

Table S2 Comparisons of the demographic and clinical characteristics and laboratory results between survivors and non-survivors

Variables	Survivors, n=407	Non-survivors, n=35	P value
Neonatal characteristics			
Gestational age, weeks	35.1 [32.7–38.1]	31.4 [29.4–35.9]	<0.001
26–28	10 (2.5)	6 (17.1)	<0.001
29–32	99 (24.3)	16 (45.7)	0.006
33–36	159 (39.1)	7 (20.0)	0.025
37–42	139 (34.2)	6 (17.1)	0.040
Birth weight, g	2,305.0 [1,800.0–3,100.0]	1,500.0 [1,100.0–2,000.0]	<0.001
Male	253 (62.2)	22(62.9)	0.935
SNAP, score	7.0 [5.0–10.0]	10.0 [7.0–12.0]	<0.001
Apnea[a]	62 (15.2)	18 (51.4)	<0.001
AKI	39 (9.6)	10 (28.6)	0.002
Sepsis[a]	27 (6.6)	9 (25.7)	0.001
RDS[a]	55 (13.5)	12 (34.3)	0.003
HIE[a]	23 (5.7)	3 (8.6)	0.449
CPAP[a]	128 (31.4)	20 (57.1)	0.003
MV[a]	59(14.5)	19 (54.3)	<0.001
Surfactant[a]	44 (10.8)	7 (20.0)	0.161
Inotrope[a]	58 (14.3)	10 (28.6)	0.031
Serum sodium[b], mmol/L	135.6 [133.0–138.0]	135.0 [132.0–138.2]	0.292
Serum potassium[b], mmol/L	4.6 [4.2–5.1]	4.6 [4.2–5.1]	0.994
Serum glucose[b], mmol/L	3.4[2.5–4.3]	3.9 [2.3–5.1]	0.412
Serum bicarbonate[b], mmol/L	19.3 [17.5–21.2]	18.3 [16.6–20.5]	0.064
Serum creatinine[b], μmol/L	58.2 [48.9–69.9]	59.0 [44.3–72.3]	0.891
BUN[b], mmol/L	3.8 [3.1–4.9]	4.0 [3.2–5.8]	0.512
NLPR[c]	0.9 [0.5–1.7]	0.7 [0.3–1.2]	0.059
NLR[c]	2.2 [1.2–3.6]	1.6 [0.7–2.0]	<0.001
PLR[c]	67.0 [50.9–93.1]	40.7 [30.6–99.2]	0.010
Maternal characteristics			
Hypertension[d]	34 (8.4)	4 (11.4)	0.527
Diabetes[d]	23 (5.7)	2 (5.7)	0.990
Prenatal steroids	46 (11.3)	5 (14.3)	0.581

Values are median [interquartile range] or number (percentage). AKI was developed during the first 7 days after NICU admission. [a], developed during NICU stay; [b], the first available laboratory results during the first 24 hours after NICU admission; [c], obtained on NICU admission; [d], diagnosed during the pregnancy. AKI, acute kidney injury; BUN, blood urea nitrogen; CPAP, continuous positive air way pressure; HIE, hypoxic ischemic encephalopathy; MV, mechanical ventilation; NICU, neonatal intensive care unit; NLPR, neutrophil, lymphocyte, and platelet ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; RDS, respiratory distress syndrome; SNAP, the score for neonatal acute physiology.

https://dx.doi.org/10.21037/apm-22-1075

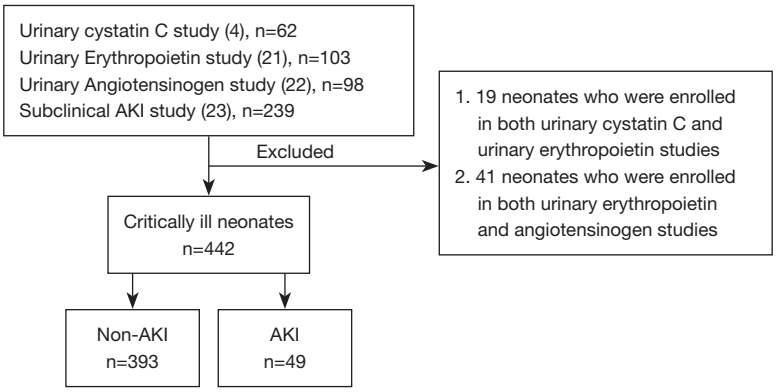

Figure S1 Study flow diagram. AKI, acute kidney injury.

https://dx.doi.org/10.21037/apm-22-1075