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Original Article

Hematology scoring model to predict sepsis in preterm neonates

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Abstract

Background Neonatal sepsis is a major cause of neonatal morbidity and mortality, especially in developing countries. Atypical clinical symptoms lead to delays in diagnosis and treatment. Scoring a combination of routine hematology parameters may be able to predict the occurrence of sepsis in preterm neonates.

Objective To formulate a new model for neonatal sepsis scoring from various complete blood count parameters to predict sepsis in preterm neonates.

Methods This analytical cross sectional study using secondary data from the Registry of the Neonatology Division was conducted at the RSUP Dr. Hasan Sadikin, Bandung, West Java. Subjects were neonates diagnosed with sepsis, of gestational age 28–36 weeks, who were born at the RSUP Dr. Hasan Sadikin from January to December 2021. Laboratory results of patients who met the inclusion criteria were recorded. Subjects were divided into either proven sepsis and probable sepsis groups, based on blood culture results.

Results Of 112 subjects, 35.7% had proven sepsis and 64.3% probable sepsis. In the proven sepsis group, 52.5% of subjects were male, median birth weight was 1,490 grams, median gestational age was 32 weeks, 90% were small for gestational age, and 60% were delivered normally. Multivariable analysis by multiple logistic regression revealed that the parameters associated with the incidence of neonatal sepsis were c-reactive protein (CRP) >0.18 mg/dL (score 6), hematocrit <40% (score 4), platelet-to-lymphocyte ratio (PLR) <19.623 (score 4); monocyte-lymphocyte ratio (MLR) <0.461 (score 2); and mean platelet volume (MPV) value >0 (score 2). Score >8 had a sensitivity of 85% and specificity of 70.8%, with area under the ROC curve of 0.865 (P<0.001). Scoring accuracy was 75.8%, with a positive predictive value of 61.8%, a negative predictive value of 89.5%, and Kappa index of 51.5% with moderate agreement.

Conclusion A hematological score >8 can be used as a predictor of sepsis in preterm neonates. **[Paediatr Indones. 2024;64:389-97; DOI: https://doi.org/10.14238/pi64.5.2024.389-97**].

Keywords: *preterm neonates; PLR; MLR; MPV; CRP*

Neonatal sepsis (NS) is still a major cause of death and morbidity in neonates, especially in developing countries. This medical condition causes long-term neurodevelopmental complications in those who survive it. Globally, around 40% of neonatal deaths are due to infection and 60% of infection occur within 3 days of life.[1] The incidence of NS is higher in preterm and very low birth weight (VLBW) neonates than in full term neonates.[2] In Indonesia, the incidence of NS in several hospitals was reportedly around 1.5-3.72%, with a mortality rate of 37.9-80%.[3] During the first trimester of 2022, the Maternal and Perinatal Audit of Dr. Hasan Sadikin Hospital (RSHS), Bandung, West Java, reported that almost 30% of neonatal deaths were caused by sepsis.[4]

In clinical practice, identifying newborns with sepsis is very challenging. Clinical signs are often non-specific in this age group, inconspicuous, and overlap with non-sepsis syndromes.[5] Non-specific clinical

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symptoms such as thermolability, respiratory distress, feeding intolerance, hypotonia, or "just not looking right" are difficult to distinguish from other symptoms due to prematurity.[6,7] The non-specific clinical symptoms in neonates and the lack of sufficiently accurate biomarkers can lead to delayed diagnosis and initiation of the therapy, unnecessary hospital admissions, and antibiotic resistance secondary to antibiotic misuse.[8] Blood cultures, the gold standard of diagnostic test, are only found in 30-40% of neonates with sepsis due to false negative results. The procedure is time-consuming, might not be available in many district hospitals, and have major drawbacks, even in high-resource settings.[2,5] Other tests for sepsis, like procalcitonin, presepsin, and haptoglobin are also not easily accessible.

A number of studies have explored the role of various parameters from a simple blood test on diagnosing neonatal sepsis, e.g., white blood cell count (WBC), absolute neutrophil count (ANC), immature/total leukocyte ratio (IT ratio), mean platelet volume (MPV), red cell distribution width (RDW), and platelet distribution width (PDW), but results varied extensively among studies.[9] Several studies found that a combination of these parameters was a more significant predictor than a single examination.[10-12] We aimed to formulate a new model of neonatal sepsis scoring from various complete blood count parameters to predict sepsis in preterm neonates.

Methods

This analytical cross sectional study using secondary data from the Registry of Neonatology Division in RSHS, Bandung, West Java, was conducted. The inclusion criteria were neonates diagnosed with sepsis, 28-36 weeks gestational age, and born at RSHS from January to December 2021. Neonates with APGAR scores <7 at 5 minutes, suffering from multiple congenital abnormalities, hemolytic anemia, or whose mothers had HIV, toxoplasmosis, cytomegalovirus, rubella, herpes, syphilis, or immunological disorders were excluded. Subjects were classified as either proven sepsis, if bacteria were found on blood culture or probable sepsis, based on negative blood culture with clinical symptoms suggestive of sepsis. Laboratory parameters from complete blood count noted were hemoglobin, hematocrit, red blood cell (RBC), total white blood cell (WBC) and IT differentiation, total platelet count, RDW, MPV, and PDW. We also calculated immature to total neutrophil ratio (IT ratio), neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR), RDW to platelet ratio (RDW/P), PDW to platelet ratio (PDW/P), MPV to platelet ratio (PDW/P), and C-reactive protein (CRP).

Data were analyzed using the Statistical Package for the *Social Sciences (SPSS) program for Windows, version 18*. Quantitative results were presented as the mean (SD) or median (range), while qualitative data were presented as frequency distribution (%). Mann-Whitney test was used to analyze means and Chi-square test was used to analyze categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal cut-off values, predictive performance of parameters and scores, and their sensitivities and specificities. Results with P values < 0.05 were considered to be statistically significant. This study was approved by the Research Ethics Commission of Dr. Hasan Sadikin Hospital, Bandung.

Results

In our study, 112 neonates met the inclusion criteria and were selected by total sampling. There were 40 (35.7%) neonates with proven sepsis, and 72 (64.3%) with probable sepsis. Characteristics of the two groups were similar, with regards to gender, birth weight, gestational age, or mode of delivery (P>0.05) (**Table 1**).

Of all hematology parameters collected, nine parameters showed statistically significant differences: hemoglobin, hematocrit, erythrocyte count, platelet count, PLR, MPV/P, RDW/P, PDW/P and CRP. Four other parameters had P values <0.25, which were included in the logistic regression analysis: RDW, MPV, PDW, and MLR (**Table 2**).

Table 3 shows the cut-off points of the significant hematological parameters (P<0.25 and P<0.05), which can be used as predictors of sepsis in preterm infants. The parameter with the highest sensitivity was quantitative CRP (92.5%); the specificity of CRP was

Table 1. General characteristics of subjects

Characteristics	Preterm infants		P value
	Proven sepsis (n=40)	Probable sepsis (n=72)	
Gender, n (%)			0.592*
Male	21 (52.5)	34 (47.2)	
Female	19 (47.5)	38 (52.8)	
Median birth weight (range), grams	1,490 (615-2,335)	1,532.5 (680-2,340)	0.340**
Median gestational age (range), weeks	32 (28-36)	32 (28-36)	0.743**
Gestational age category, n (%)			0.589*
SGA	36 (90)	66 (91.7)	
AGA	4 (10)	6 (8.3)	
Mode of delivery, n (%)			0.977*
Vaginal	24 (60)	43 (59.7)	
Cesarean section	16 (40)	29 (40.3)	

SGA=small for gestational age; AGA=appropriate for gestational age; *Chi-square test; **Mann-Whitney test

Table 2. Comparison of hematological parameters in study groups

Variables	Preterm infant		P value*
	Proven sepsis (n=40)	Probable sepsis (n=72)	
Hemoglobin, mg/dL	12.55 (8.3-18.3)	15.25 (6.9-21.5)	0.001
Hematocrit, %	35.7 (24.4-51.7)	44.4 (13.8-61.5)	0.001
Red blood cell, /mm^3	3.68 (2.5-5.1)	4.21 (2.05-40.3)	0.007
Leukocyte count, /mm^3	8.52 (0.82-56.96)	11.45 (0.99-49.95)	0.378
Platelet count, /mm^3	66.5 (2-578)	210.5 (5-920)	<0.001
RDW, %	60.0 (47.7-92.5)	63.05 (19.0-123.0)	0.184
MPV, fL	10.4 (0-13,3)	10.05 (0-13.3)	0.222
PDW	11.8 (9.3-20.1	11.0 (8.4-20.9)	0.182
IT ratio	0.04 (0.0-0.431)	0.03 (0.0-4.20)	0.539
NLR	2.36 (0.36-23.06)	20.30 (0.0-18.15)	0.347
PLR	34.27 (0.70-169.47)	61.12 (3.33-265.88)	0.007
MLR	0.41 (0.08-1.80)	0.48 (0.04-2.14)	0.120
MPV/P	0.14 (0.0-5.35)	0.04 (0.0-2.16)	0.001
RDW/P	1.0 (0.11-36.75)	0.32 (0.06-16,82)	0.001
PDW/P	0.13 (0.18-5.90)	0.05 (0.01-2.13)	0.006
CRP, mg/dL	3.48 (0.08-28.03)	0.23 (0.02-102.0)	<0.001

RDW=red cell distribution width; PDW=platelet distribution width; IT ratio=immature to total neutrophil ratio?; NLR=neutrophil to lymphocyte ratio; MPV/P=mean platelet volume to platelet count; RDW/P=red cell distribution width to platelet count; PDW/P=platelet distribution width to platelet count; *Mann-Whitney test

51.4%. The PDW had the lowest sensitivity (29.6%), but had the highest specificity (88.3%).

All hematological parameters were analyzed by multiple logistic regression to determine which factors had an influence on the incidence of proven sepsis in preterm infants. The final model of multiple logistic regression analysis is shown in **Table 4**. Of the 13 laboratory parameters, only five had an effect on the incidence of proven sepsis: hematocrit <40%, MPV >10, CRP level >0.18 ng/dL, PLR <19.263, and MLR < 0.461 (**Table 4**). The scoring model can be used to calculate the effect of hematological parameters on

Table 3. Cut-off points of the hematological parameters

Parameters	Cut-off	AUC	Sensitivity, %	Specificity, %	P value
Hemoglobin, mg/dL	≤13.5	0.695	75.0	66.767	<0.001
Hematocrit, %?	≤40	0.683	75.0	66.767	<0.001
RBC, /mm3?	≤3.94	0.639	65.0	68.106	0.013
Platelet, /mm3	≤110	0.721	67.5	69.44	<0.001
RDW, %	≤60.5	0.576	57.5	63.989	0.188
MPV, fL	>10	0.570	67.5	50.00	0.217
PDW	>14.3	0.595	29.6	88.106	0.144
PLR	≤19.623	0.654	47.5	83.33	0.005
MLR	≤0.461	0.589	67.5	55.656	0.122
MPV/P	>0.11	0.696	60.0	76.439	<0.001
RDW/P	>0.54	0.699	70.0	66.767	<0.001
PDW/P	>0.0513	0.683	81.5	53.03	0.003
CRP, mg/dL	>0.18	0.758	92.5	51.394	<0.001

Table 4. Multivariate analysis of factors that influence the incidence of proven sepsis in preterm infants based on multiple logistic regression (final model)

Variables	Coef B	SE (B)	ORadj (95%CI)*	Z score (B/SE (B)	Score**	P value
Hematocrit(≤ 40%)	1.541	0.524	4.669 (1.671 to 3.045)	2.941	4	0.001
MLR (≤ 0.461)	0.679	0.528	1.972 (0.704 to 5.526)	1.293	2	0.197
PLR (≤ 19.623)	1.551	0.578	4.714 (1.520 to 14.634)	2.683	4	0.007
MPV (>10)	0.748	0.524	2.113 (0.756 to 5.905)	1.427	2	0.154
CRP (>0.18)	2.724	0.737	15.249 (3.593 to 64.710)	3.696	6	<0.001

Model accuracy=79.5%; R2 (Nagelkerke)=0.504; *Odds ratio and 95%CI; **The lowest Z score was 2; the next score by dividing (Z score/1.293) x 2

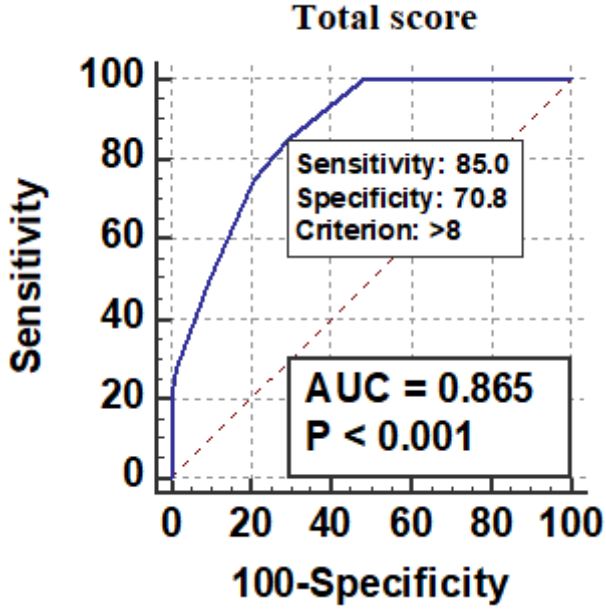

Figure 1. ROC area under the curve of the total score of hematology parameters studied

Table 5. Correlation between hematological score and proven sepsis

Cut-off point for total score, n (%)	Preterm infant		P values*
	Proven sepsis (n=40)	Probable sepsis (n=72)	
>8	34 (85.0)	21 (29.2)	<0.001
≤ 8	6 (15.0)	51 (70.8)	

Sensitivity=85.0%; specificity=70.8%; accuracy=75.9%; PPV=61.8%; NPV=89.5%. Kappa index=51.5%; OR (95%CI)=13.76 (5.03 to 37.62)

the incidence of proven sepsis, with the lowest Z value being MLR (score 2) and the highest score being CRP (score 6). The total score for all laboratory parameters was 18. The accuracy rate was 79.5% and coefficient of determination (R2) was 0.504.

The area under curve (AUC) of the ROC curve was used to determine the sensitivity and specificity of the total score >8 (**Figure 1**). The AUC was 0.865 with P<0.001. Total score > 8 had a sensitivity of 85.0% and specificity of 70.8%.

Table 5 shows that the total hematology score cut-off >8 had a sensitivity of 85.0%, a specificity of 70.8%, and a Kappa index of 51.5%, which is classified as a moderate agreement (according to Coch and Landis criteria). The PPV was 61.8% and NPV was 89.5% (OR 13.76; 95%CI 5.03 to 37.62). Based on this evidence, a scoring system formed from various hematological parameters can be used to predict proven sepsis in preterm infants.

Discussion

In neonatal sepsis, early diagnosis and therapy are crucial to prevent morbidity and mortality. However, an excellent biomarker has yet to be identified for diagnosis of NS. Many studies have evaluated the sensitivity and specificity of NS diagnostic markers (e.g., CRP, PCT, IT ratio, CBC parameters), but results varied extensively among studies.[13] As such, we aimed to develop a hematological score model to predict NS in preterm infants from feasible routine laboratory examinations.

Of 112 subjects, 40 (35.7%) neonates had positive blood cultures and 72 (64.3%) neonates had no bacterial growth from cultures. This finding was in agreement with previous studies which reported positive blood cultures in only 30-40% in NS.[2,14] Blood cultures can be influenced by several factors, such as the method of specimen collection, inadequate blood volume, blood culturing method, patient selection criteria, and previous use of antibiotics.[15]

The basic characteristics of our subjects were gender, birth weight, gestational age, appropriateness of gestational age, and mode of delivery. None of the characteristic data were significantly different between groups (P>0.05), so they were not considered to be confounding variables.

Systemic bacterial infections cause disturbances in the hemopoietic system, which affect the activity of leukocytes, erythrocytes, and platelets. Of the 16 parameters studied, only nine parameters had significant relationships with proven sepsis (P<0.05). The platelet parameters were has strong association to NS than other parameters. This finding was consistent with the function of platelets, since they play a role in inflammatory and infectious processes.[16] During infection, platelets are destroyed and their utilization increases, thus, the number of platelets in peripheral blood will decrease. Platelets also play a role in maintaining the integrity of blood vessels.[17] In 50% cases of bacterial infection, platelet count was found to be <100,000/mm^3, however, platelet levels are also decreased in viral infections, so thrombocytopenia alone is not specific as NS parameter.[18]

In our study, platelets were significantly different between the proven and probable sepsis groups. The platelet cut-off points in this study was <110,000/mm3. Many factors such as clinical conditions, improper sampling method, and timing of blood collection could be the reason for this difference between studies.

Mean platelet volume is stronger association in predicting sepsis than absolute platelet count.[19] A previous study found that an increase of MPV was associated with the risk of early onset sepsis (EOS).[10] Increased MPV indicates endothelial damage and its repair is indicated by platelet activation. During the

acute phase of sepsis, there is an increase in platelet consumption and MPV levels will increase rapidly as the disease progresses. Increased MPV indicates invasive, systemic, and severe infection.[20] We found no significant differences in MPV between study groups, but it was included in logistic regression analysis ($P<0.25$). The MPV/P ratio was significantly related to the occurrence of NS. Previous research found that the MPV/P ratio could be used as a predictor of progression and mortality in sepsis patients.[21] However, our final model of multiple logistic regression analysis revealed that MPV>10 had a higher risk of proven sepsis than probable sepsis.

We found significant differences in platelet counts, MPV/P ratio, and PDW/P ratio between the two groups, but no significant differences in MPV and PDW. This result differed from a meta-analysis which found that MPV levels were significantly higher in NS compared to that of healthy neonates.[22] MPV is more reflective of the size and function of platelets than the platelet alone.

Hemoglobin and erythrocytes were also significantly lower in the proven sepsis group than in the probable sepsis group. These results were in line with other studies which found decreases in hemoglobin, hematocrit, and erythrocyte levels in NS.[23,24] In sepsis, inflammatory cytokines cause dysregulation of erythropoiesis. The increase in oxidative stress associated with sepsis causes suppression of erythroid cells, decreasing the number of red blood cells in circulation and reducing the age of erythrocytes, thereby inducing the release of new red blood cells from the bone marrow. These actions cause a decrease in the number of erythrocytes and RDW.[25]

The RDW was not significantly different between our groups. Many studies have examined RDW as a predictor of sepsis, but results have varied. A previous study also did not find a significant relationship between RDW and proven sepsis, but they noted an increase in RDW as a predictor of death in sepsis.[26] Moreover, another study also found that the RDW was not significantly different between proven and suspected sepsis groups, but RDW was significantly different between suspected sepsis and healthy controls.[12] In contrast, a study of on 37 neonates found an association between increased RDW and sepsis in preterm neonates.[27] This difference may have been due to differences in study subjects and methodology. They compared RDW values in three subject types, namely, those with sepsis, suspected sepsis, and non-sepsis. Blood tests were performed at the time of sepsis diagnosis, using the Tollner score.[28]

During infection and inflammation, white blood cells (WBC) and neutrophils increase and lymphocytes decrease in response to bacterial infection.[29] Neutrophil colony-stimulating factor (NCSF) causes a decrease of granulocyte apoptosis, thereby, increasing the number of neutrophils in peripheral blood. At the same time, cytokines and chemokines inhibit lymphocyte proliferation and activation, causing a decrease in the number of lymphocytes.[30] Neutropenia is more common in sepsis than neutrophilia, due to increased use at sites of infection and number of attachments to endothelial cells.[31] Total neutrophil count has low sensitivity and specificity in predicting sepsis. The NLR and MLR are stronger association as a parameter of bacterial infection than levels of neutrophils, monocytes, or lymphocytes alone. Studies in full term neonates found positive correlations of NLR and PLR with early onset neonatal sepsis.[29,32]

The WBC parameters examined in our study were leukocyte count, IT ratio, NLR, MLR; there were no significant differences between the two study groups ($P>0.05$). The lack of a significant difference in leukocyte counts between groups could have been due to the wide range of gestational age (28-36 weeks). Normal WBC values vary greatly based on gestational age, so the absolute leukocyte count was never used as a parameter of infection in NS. A previous study also found no difference in the number of WBC and neutrophils in the sepsis group compared to that of the control group.[33]

Monocytes are an important component of the innate immune system as a link to the adaptive immune system through antigen presentation to lymphocytes.[34] The MLR is known to be increased in febrile patients with confirmed bacterial infection compared to febrile patients without evidence of bacterial infection.[32] Djordjevic *et al.*[34] found increased MLR in peritonitis patients with negative culture results. In our study, logistic regression analysis revealed that MLR near marginal significant as predictor of NS ($P=0.197$)

The PLR ratio is known to increase in adult patients with infection.[34] We found that PLR was

significantly lower in the proven sepsis group than in the probable sepsis group. These results are consistent with a study that found increased PLR in the neonatal sepsis group compared to the control group.[13] In addition, another study found a positive correlation between EOS and PLR.[29] In our final model of multiple logistic regression analysis, PLR was a significant predictor of the occurrence of NS.

C-reactive protein is a traditional parameter that has long been used as a diagnostic tool for sepsis. Currently, CRP is still relevant, despite its low sensitivity at the onset of sepsis and low specificity, because it is increased in other conditions.[35] We found that CRP was significantly increased in the proven sepsis group. The CRP cut-off obtained was very low compared to previous studies, at >0.18 mg/dl. Other studies reported significant CRP cut-off points of >7 and >10 mg/dL.[14,35] This difference may have been due to the fact that we did not include clinical conditions and did not perform serial CRP measurements. The final analysis, CRP had the highest score, which was 6 out of a total score of 18, with 92.5% sensitivity and 51.4% specificity.

Logistic regression analysis revealed five parameters near marginal significant to be predictors of NS: hematocrit, MLR, PLR, MPV, and CRP. The total score was maximum 18, with a cut-off of >8 to predict NS. The highest scoring was assigned to CRP (score 6) and the lowest were MLR and MPV (score 2 each), while hematocrit and PLR were 4 each. The scoring model had 85.0% sensitivity and 70.8% specificity, with AUC 0.865. This model can be used as a predictor of NS in preterm infants.

The scoring of the hematological parameters in our study is different from the *Hematology Scoring System* (HSS) developed by Rodwell *et al.*[36] The HSS uses seven parameters derived from simple routine blood tests and WBC differentiation. Their subjects were divided into full-term and preterm subgroups and blood tests were carried out on day 1 and day 2-30.[36]

Our results differ from previous studies with regards to neonatal sepsis scoring. We distinguished study subjects based only on blood culture, regardless of clinical condition. Infants with probable sepsis may have experienced sepsis, even though no bacteria were found in blood culture. Differences can also be caused by differences in methodology, subject criteria, timing of blood collection and laboratory analysis methods. We also did not distinguish between early and late onset sepsis, whereas other studies examined only EOS or LOS populations.[29,37,38] Many other factors can act as confounding factors, such as the unanalyzed onset of sepsis, use of antibiotics before and after delivery, differences in normal values between institutions, and risk factors for sepsis that were not taken into account which can lead to differences in results from previous studies. We used only laboratory parameters from secondary data without considering the clinical condition, which was also a limitation of our study. Not using a healthy normal population as controls was also a limitation of our study, which may have led to different results from previous hematological scoring.

In conclusion, the model of hematology scoring >8 can predict sepsis in preterm infants with moderate agreement. Further study is needed to test this model with the established scoring system.

Conflict of interest

None declared.

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