Elevated neutrophil - to - monocyte ratio as a prognostic marker for poor outcomes in neonatal sepsis

Xiaohong Xiaa,b,1, Yaman Wanga,b,1, Mengxiao Xiea,b, Shengfeng Qiua,b,**, Jun Zhoua,b,*

a Department of Laboratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China
b Branch of National Clinical Research Center for Laboratory Medicine, Nanjing, Jiangsu, China

ARTICLE INFO

Keywords:
- Monocyte
- Mortality
- Neonatal sepsis
- Neutrophil
- Prognosis

ABSTRACT

Objectives: Neonatal sepsis is one of the leading causes of neonatal death. The aim of this study was to evaluate the value of neutrophil - to - monocyte ratio (NMR) in predicting mortality in neonatal sepsis.

Methods: In this present retrospective study, a total of 134 neonates with sepsis were included. Baseline laboratory parameters were collected. The best cutoff value of NMR was determined by receiver operating characteristic (ROC) curve. Univariate and multivariate analysis were carried out to survey the predict value of NMR. Results from multivariate analysis showed that high NMR was an independent risk factor for neonatal sepsis (Hazard ratio (HR): 7.519, \(p = 0.001\)). ROC displayed that the area under curve (AUC) of NMR was 0.740, sensitivity and specificity of NMR were 80% and 65.8% when 7.65 was selected.

Conclusions: NMR could be a promising prognostic factor for neonatal sepsis.

1. Introduction

Neonatal sepsis is a serious infectious disease in the neonatal period, and it is the most common cause of morbidity and mortality for term and premature infants \([1, 2]\). Neonatal sepsis is the third leading cause of neonatal mortality and is a major public health problem, especially in developing countries \([3]\).

The clinical manifestation of sepsis is nonspecific in neonates, with different clinical features. It usually presents as decreased acceptance of feed, respiratory problems, temperature instability (hyperthermia and hypothermia), abnormal jaundice, coagulopathy, fussiness, lack of energy and necrotizing enterocolitis \([4, 5]\). These varied features which can be seen in other neonatal conditions increase the difficulty of diagnosis and may delay treatment, leading to a poor prognosis. Therefore, it is quite important to find a tool to predict infants who are more likely to experience worse clinical outcomes and provide them with closer monitoring and more active treatments.

There are variety of biomarkers that have been proved to be related to neonatal sepsis, including procalcitonin, C-reactive protein (CRP), serum amyloid A (SAA) and Interleukin 6 (IL-6) \([6, 7, 8, 9, 10]\). However, in the early stage of infection, these traditional biomarkers may be low, resulting in their limitations in clinical application \([11]\).

In addition, overexpression of inflammatory cytokines is associated with multisystem organ failure and mortality \([12]\). Conversely, immunoparalysis characterized by monocyte inactivation is also associated with adverse clinical outcomes of sepsis \([13]\). Therefore, the aim of this survey was to evaluate the value of neutrophil-to-monocyte ratio (NMR) in predicting mortality in patients with neonatal sepsis.

2. Methodology

2.1. Specimens and assays

The present retrospective study was conducted between January 2014 and November 2019 in the Jiangsu Women and Children Health Hospital. For this study, any infants diagnosed with possible or definite sepsis from birth to 28 days of age were included. Possible sepsis was diagnosed when a positive culture lacked signs indicating sepsis and 2 positive screening parameters (abnormal CRP, total white blood cell count, platelet count, absolute neutrophil count, or immature/total neutrophil ratio >0.2). Definite neonatal sepsis was the presence of

* Corresponding author.
** Corresponding author.
E-mail addresses: qiaoshengfengnj@163.com (S. Qiu), zhoujun5958@163.com (J. Zhou).

1 Authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2022.e11181
Received 29 March 2022; Received in revised form 31 July 2022; Accepted 17 October 2022
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potentially pathogenic organisms (bacteria or fungi) in sterile body fluids, such as blood, peritoneal, pleural and cerebrospinal fluid [14, 15]. When signs of sepsis were present but sepsis screening parameters and cultures were negative, it was considered that there is no sepsis. A total of 150 neonates who were admitted to the neonatal intensive care unit (NICU) and diagnosed with neonatal sepsis, younger than 28 days, were the sourced population. We ruled out the patients with unclear history and uncompleted laboratory tests were excluded. At last, 134 neonates were enrolled in this research. Sepsis-related death was defined as death within 28 days after sepsis.

The laboratory tests were evaluated on admission. Routine complete blood count (CBC) of peripheral blood from all participants was measured by using a Sysmex XE 2100 analyzer (Sysmex, Hyogo, Japan). All reagents used for testing were the original reagents of the instruments. The study was confirmed by the Ethics Committee of the local hospital and was in line with the Declaration of Helsinki (2019-SR-072). The PLR, NLR, SII, SIRI and NMR were calculated as follows: PLR = Platelet/Lymphocyte; NLR = Neutrophil/Lymphocyte; SII = (Platelet × Neutrophil)/Lymphocyte; SIRI = (Neutrophil × Monocyte)/Lymphocyte; NMR = Neutrophil/Monocyte.

2.2. Statistical analysis

Statistical analyses were performed by SPSS21.0 (SPSS Inc, Chicago, IL, USA) software. Variables are presented in mean ± standard deviation, median (range) or number. The Shapiro–Wilk test was used for normality assumption of the data. Receiver operating characteristic (ROC) curve analysis was created to assess the ability of NMR to predict neonatal sepsis mortality. Additionally, we performed chi-square and Mann–Whitney U-tests to determine statistically significant differences between survival and non-survival groups. Analysis of neonatal sepsis mortality was performed using univariate and multivariate analyses. A p-value < 0.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

A total of 134 neonates with sepsis were eligible for this study. Among the total patients, 20 neonates were dead. There were no significant differences in gender, age and weight between two groups. Concerning the gender of study patients, 79 were males, of which 67 were survived, while 55 neonates were females, of which 47 were survived. The median age is 2 days of non-survivor and 5 days of survivor. However, the subgroup with lower gestational age at birth and lower Apgar score had significantly higher mortality. Monocyte and platelet count in survival group were 0.92 (0.15, 16.97) vs. 1.24 (0.01, 52.37), 0.516 vs. 1.24 (0.12, 31.11), 0.173 vs. 0.12 (0.11, 31.11), 0.173 vs. 0.01 (0.22, 0.12), 0.844 vs. 0.185 (0.05, 0.63). There were no significant differences for CRP, WBC, RBC, lymphocyte count, neutrophil count, hemoglobin, red cell distribution width (RDW). Between two groups, NMR was significantly different between survival and non-survival group (12.43 (2.49, 44.03) vs. 5.80 (1.03, 133.54), p = 0.001), while PLR, NLR, SII, SIRI were not (PLR: 11.05 (5.02, 105.13) vs. 11.38 (2.21, 61.79), 0.099 vs. 0.025, 0.025 vs. 0.025, 0.099 vs. 0.025). NMR was higher compared with non-survival group (p = 0.024) and lymphocyte count (p = 0.030) were independent prognostic factors for neonatal sepsis.

3.2. Prognostic biomarkers predict survivor

Univariate analyses showed that NMR (p < 0.001), monocyte count (p = 0.013), platelet count (p = 0.024) and lymphocyte count (p = 0.030) were prognostic factors for neonatal sepsis. On the other hand, by multivariable adjustment, platelet count (HR:3.180, p = 0.031) and NMR (HR:7.519, p = 0.001) were independent prognostic factors for neonatal sepsis (Table 2).

Table 1. Baseline characteristics of study patients.

| Variables | Non-survivors (N = 20) | Survivors (N = 114) | p-value |
|-----------|------------------------|---------------------|---------|
| Gender (male/female), n | 12/8 | 67/47 | 0.920 |
| Median age (range), day | 2 (0.5, 28) | 5 (0.1, 28) | 0.329 |
| Gestational age at birth (weeks) | 33 (28, 37) | 36 (33, 39) | 0.011 |
| Weight (g) | 2100 (1175, 2387) | 2500 (1600, 3250) | 0.112 |
| WBC (×10^9/L) | 4.31 ± 0.77 | 4.61 ± 0.71 | 0.085 |
| Neutrophil (×10^9/L) | 201.15 ± 75.75 | 250.84 ± 105.16 | 0.045 |
| Monocyte (×10^9/L) | 382.07 (29.79, 4072.00) | 296.26 (10.27, 7777.78) | 0.516 |
| Hemoglobin (g/L) | 155.65 ± 29.43 | 163.03 ± 26.66 | 0.292 |
| Neutrophil/Lymphocyte | 5.71 (1.44, 78.64) | 5.11 (0.37, 51.35) | 0.158 |
| Monocyte/Lymphocyte | 3.180 (4.61, 61.79) | 6.19 (2.78, 105.16) | 0.076 |
| Neutrophil-to-lymphocyte ratio | 7777.78 | 7777.78 | 0.001 |
| Neutrophil-to-monocyte ratio | 5.80 (1.03, 133.54) | 5.11 (0.37, 51.35) | 0.099 |
| CRP (mg/L) | 16.60 ± 1.32 | 16.47 ± 1.53 | 0.714 |
| Neutrophil-to-lymphocyte ratio | 3.180 (4.61, 61.79) | 6.19 (2.78, 105.16) | 0.076 |
| Neutrophil-to-monocyte ratio | 5.80 (1.03, 133.54) | 5.11 (0.37, 51.35) | 0.099 |
| CRP: C-reactive protein; RBC: Red blood cell; RDW: red cell distribution width; WBC: white blood count; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: systemic inflammatory response index; NMR: neutrophil-to-monocyte ratio. Data are measured by using a Sysmex XE 2100 analyzer (Sysmex, Hyogo, Japan). Statistic analyses were performed by SPSS21.0 (SPSS Inc, Chicago, IL, USA) software. Variables are presented in mean ± standard deviation, median (range) or number. The Shapiro–Wilk test was used for normality assumption of the data. Receiver operating characteristic (ROC) curve analysis was created to assess the ability of NMR to predict neonatal sepsis mortality. Additionally, we performed chi-square and Mann–Whitney U-tests to determine statistically significant differences between survival and non-survival groups. Analysis of neonatal sepsis mortality was performed using univariate and multivariate analyses. A p-value < 0.05 was considered to be statistically significant. |
organ failure and mortality. Therefore, excessive anti-inflammatory stimulation may lead to a state of immunoparalysis [12, 23, 24]. Thus, it is quite important to balance pro-inflammatory and anti-inflammatory responses. Monocytes are the third largest component of leukocytes. Several studies have reported that monocytes are essential components of the inflammatory response and are involved in cytokine release [20]. In addition, in the present study, low monocyte count had something to do with a worse survival.

Blood analysis is a simple and easily accessible test, in which neutrophil count and monocyte count are commonly used clinical indicators. In the present study, we introduced a new index (NMR) based on neutrophil and monocyte, which was found to be significantly elevated in non-survivors compared with survivors of neonatal sepsis. In addition, we found that NMR is an independent factor with higher predicted value than these factors used alone. Our study shows that patients with NMR >7.65 represents lower survival rate.

In the present study, there was no significant difference for RDW between non-survivors and survivors of neonatal sepsis, which was the opposite of a study 14 [14]. It may be the reason of different regions and differences in the level of medical and health care. On the other hand, our sample size was much smaller, which may account for the difference.

However, the current study has several limitations. First, as a single-center retrospective analysis, selection biases associated with data collection may exist and some biomarkers may not included. Second, we also did not compare NMR with other valuable biomarkers in neonatal sepsis such as CRP, procalcitonin. Third, We did not verify the results in a verification cohort and check the performance of NMR in neonates with different age. So we expect to conduct a large, multi-center prospective study to verify our results.

5. Conclusion

In conclusion, our data shows that baseline NMR could play an important role in predicting mortality of neonatal sepsis, which is very important for the management of this high-risk infant population.

Declarations

Author contribution statement

Jun Zhou and Shengfeng Qiu - Conceived and designed the experiments; Analyzed and interpreted the data and Contributed reagents, materials, analysis tools or data.

Xiaohong Xia: Performed the experiments; Contributed reagents, materials, analysis tools or data and Wrote the paper.

Mengxiao Xie and Yaman Wang: Performed the experiments and Contributed reagents, materials, analysis tools or data.

Table 2. Analysis of in-hospital death.

| Variables | Univariate analyses | Forest Plot | Multivariate analyses | Forest Plot |
|-----------|---------------------|-------------|-----------------------|-------------|
|           | HR                  | 95% CI      | P-value               | HR         | 95% CI      | P-value |
| Age       | 2.700               | 0.920-7.925 | 0.087                 |             |             |         |
| WBC       | 2.695               | 0.949-7.633 | 0.069                 |             |             |         |
| Lymphocyte| 3.333               | 1.200-9.255 | 0.030                 |             |             |         |
| Monocyte  | 3.560               | 1.333-9.508 | 0.013                 |             |             |         |
| Platelet  | 3.307               | 1.222-8.946 | 0.024                 |             |             |         |
| NMR       | 7.692               | 2.404-24.390| <0.001                |             |             |         |

CI: Confidence interval; HR: Hazard ratio; WBC: white blood count. Bold values indicate statistical significance (p < 0.05).
Funding statement

This work was supported by grants from the National Natural Science Foundation of China (82101902) and Natural Science Foundation of Jiangsu Province (SBK2020042441).

Data availability statement

The datasets are available from the corresponding author on reasonable request.

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgement

None.

References

[1] A. Camacho-Gonzalez, P.W. Spearman, B.J. Stoll, Neonatal infectious diseases: evaluation of neonatal sepsis, Pediatr. Clin. 60 (2) (2013) 367–389.

[2] H. Wang, C.A. Liddell, M.M. Coates, M.D. Mooney, C.E. Levitz, A.E. Schumacher, et al., Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013, Lancet 384 (9947) (2014) 957–979.

[3] L. Liu, H.L. Johnson, S. Couzens, J. Perin, S. Scott, J.E. Lawn, et al., Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000, Lancet 379 (9832) (2012) 2151–2161.

[4] D. Gebremedhin, H. Berhe, K. Gebrekristos, Risk factors for neonatal sepsis in public hospitals of Mekelle City, North Ethiopia, 2015: unmatched case control study, PloS One 11 (5) (2016), e0154798.

[5] D. Sharma, P. Sharma, P. Soni, B. Gupta, Ralstonia picketti neonatal sepsis: a case report, BMC Res. Notes 10 (1) (2017) 28.

[6] M. Cernada, N. Badia, V. Modesto, R. Alonso, A. Mejias, S. Golombek, et al., Cord blood interleukin-6 as a predictor of early-onset neonatal sepsis, Acta Paediatr. 101 (5) (2012) e203–207.

[7] S.S. Hedegaard, K. Winborg, A.M. Hvas, Diagnostic utility of biomarkers for neonatal sepsis—a systematic review, Inf. Disp.(Lond) 47 (3) (2015) 117–124.

[8] A.Q. Ismail, A. Gandhi, Using CRP in neonatal practice, J. Matern. Fetal Neonatal Med. 28 (1) (2015) 3–6.

[9] D. Sharma, N. Farahbakhsh, S. Shastri, P. Sharma, Biomarkers for diagnosis of neonatal sepsis: a literature review, J. Matern. Fetal Neonatal Med. 31 (12) (2018) 1646–1659.

[10] M. Cetinkaya, H. Ozkan, N. Koksal, S. Celebi, M. Hacimustafaoglu, Comparison of serum amyloid A concentrations with those of C-reactive protein and procalcitonin in diagnosis and follow-up of neonatal sepsis in premature infants, J. Perinatol. 29 (3) (2009) 225–231.

[11] I.H. Celik, F.G. Demirel, N. Uras, O. Erdve, Z. Biyikli, et al., What are the cut-off levels for IL-6 and CRP in neonatal sepsis? J. Clin. Lab. Anal. 24 (6) (2010) 407–412.

[12] M.R. Pinkly, J.L. Vincent, J. Deviere, M. Alegre, R.J. Kahn, E. Dupont, Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality, Chest 103 (2) (1993) 565–575.

[13] H.D. Volk, P. Reinke, D. Krausch, H. Zuckermann, K. Assadullah, J.M. Muller, et al., Monocyte deactivation-rational for a new therapeutic strategy in sepsis, Intensive Care Med. 22 (Suppl 4) (1996) S474–481.

[14] D.M. Ellahony, M.S. El-Mekkawy, M.M. Farag, A study of red cell distribution width as a predictor of neonatal sepsis, Pediatr. Emerg. Care 35 (8) (2020) 379–383.

[15] C. Polinski, The value of the white blood cell count and differential in the prediction of neonatal sepsis, Neonatal Netw 15 (7) (1996) 13–23.

[16] A.L. Shane, P.J. Sanchez, B.J. Stoll, Neonatal sepsis, Lancet 390 (10104) (2017) 1770–1780.

[17] C. Fleischmann-Struzek, D.M. Goldfarb, P. Schlattmann, L.J. Schlapbach, M.E. Monighetti, T. Wild, D. Lastovica, et al., The value of leukocyte-to-lymphocyte ratio as predictive biomarkers for early-onset neonatal sepsis, a systematic review, J. Perinatol. 29 (3) (2009) 225–230.

[18] S. Dessu, A. Habte, T. Melis, M. Gebremedhin, Survival status and predictors of mortality among newborns admitted with neonatal sepsis at public hospitals in Ethiopia, Int. J. Pediatr. 2020 (2020), 8327028.

[19] A.I. Omoigbemaker, W.E. Sadoh, D.U. Nwaneri, A 4 year review of neonatal outcome at the university of Benin teaching hospital, Benin City, Niger. J. Clin. Pract. 13 (3) (2010) 321–325.

[20] W.F. Fang, Y.M. Chen, Y.H. Wang, C.H. Huang, K.Y. Hung, Y.T. Fang, et al., Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality, Chest 103 (2) (1993) 565–575.

[21] S. Zhang, X. Luan, W. Zhang, Z. Jin, Platelet-to-Lymphocyte and neutrophil-to-monocyte ratio as predictive biomarkers for early-onset neonatal sepsis, Pediatr. Emerg. Care 36 (8) (2020) 378–383.

[22] S. Zarb, B. Gupta, R. Arens, K. Reinhart, N. Kissoon, The global burden of paediatric and neonatal sepsis: a systematic review, Lancet Respir. Med. 6 (3) (2018) 223–230.

[23] S. Xu, X. Luan, L. Li, J. Guo, J. Wang, J. Zhang, et al., The value of white blood cell count and differential in the prediction of neonatal sepsis, Neonatal Netw 31 (12) (2012) 7650713.

[24] S.E. Perry, S.M. Mostafa, R. Wenstone, A. Shenkin, P.J. McLaughlin, Is low monocyte HLA-DR expression helpful to predict outcome in severe sepsis? Intensive Care Med. 29 (8) (2003) 1245–1252.