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# Validity of eosinophil count and monocyte-lymphocyte ratio for early detection of neonatal sepsis

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## Abstract

**Background:** Sepsis is a major cause of mortality in neonatal. Diagnosing neonatal sepsis is a challenge, as its clinical symptoms are not specific. Various studies have been conducted to identify infection markers for early identification of neonatal sepsis, but none have shown satisfactory results. Therefore, we aimed to determine the validity of eosinophil count and monocyte lymphocyte ratio (MLR) for the early detection of neonatal sepsis.

**Objective:** To determine the validity of eosinophil count and monocyte lymphocyte ratio (MLR) for the early detection of neonatal sepsis.

**Methods:** This study was a retrospective study with a diagnostic test. Data were collected from medical records of neonates with early-onset neonatal sepsis (EONS) or clinically EONS who were admitted to Neonatal Ward in Sanglah Hospital between April 2020 and December 2020. The ROC curve was used to determine the cut-off point of eosinophil count and MLR. Furthermore, a chi-squared test was used to determine sensitivity, specificity, PPV, and NPV

**Results:** The total sample was 100 subjects, and 28 subjects had positive blood culture (28%). The eosinophil count (cut-off of $0.16x10^3/\mu L$ or 160 cell/$mm^3$) produced a sensitivity of 57.14%, specificity of 65.28%, PPV of 39.02%, and NPV of 79.66%. At a cut-off value of 0.38, MLR had a sensitivity of 67.86%, specificity of 72.22%, PPV of 48.72%, and NPV of 85.25%.

**Conclusion:** Children with obesity were found to be significantly related to elevated blood pressure (hypertension).

**Keywords:** Eosinophil count; Monocyte-lymphocyte ratio; Neonatal sepsis; Sensitivity; Specificity

## 1. Introduction

Neonatal sepsis is a clinical condition due to the invasion of microorganisms into the bloodstream that can occur in the first month of life and is one of the main causes of death in neonates. The incidence of neonatal sepsis remains high, especially in developing countries, ranging from 1 to 5 neonates per 1000 live births worldwide, with mortality rates ranging from 11 to 19% [1,2]. The national incidence of neonatal sepsis in Indonesia is unknown. According to data from the Health Ministry of Republic of Indonesia's Fundamental Health Research in 2018, the mortality rate of neonates was around 12 neonates per 1000 live births [3]. The incidence of neonatal sepsis in Sanglah Hospital, Denpasar was 5%, with a mortality rate of 30.4% [4].

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Diagnosis of neonatal sepsis is a challenge because the symptoms and clinical signs are not specific. The clinical manifestations include hypothermia or hyperthermia, hypotension, poor tissue perfusion, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, lethargy, seizures, feeding intolerance, abdominal distension, jaundice, petechiae, purpura, and bleeding [2,5]. Although blood culture remains the gold standard for confirming sepsis, it is restricted by its low sensitivity, the length of time required to confirm a positive culture (often around 24 to 72 hours), and is not always effective at identifying microorganisms. Thus, a negative blood culture result does not always indicate an absence of microorganisms in the patients [2,6,7].

Leukocyte count, absolute neutrophil count, the ratio of immature to total neutrophil count (IT ratio), and platelet count are some of the laboratory parameters that can help diagnose neonatal sepsis. Other tests with good sensitivity and specificity for determining neonatal sepsis are serial C-reactive protein (CRP) and procalcitonin (PCT). Nonetheless, these tests are not available in all health facilities and require enormous costs [6,8]. Several studies have been conducted to identify early parameters of neonatal sepsis with good sensitivity, specificity, and low cost.

A complete blood count is a routine examination that is performed at an affordable cost in practically all health care facilities. Eosinophil, monocyte, and lymphocyte are parameters included in complete blood count. Eosinopenia can be used as an infection marker to detect sepsis. Research conducted by Wibrow et al. reported that eosinopenia (<10 cells/mm3) had a sensitivity of 54% and specificity of 56% in predicting the presence of bacterial infection in pediatric patients [9]. Another study by Shaaban et al. reported that eosinophil count <50 cells/$mm^3$ could predict sepsis in adult patients with a sensitivity of 81% and a specificity of 65% [10].

The monocyte-lymphocyte ratio (MLR) is obtained by dividing the absolute number of monocytes and lymphocytes in the complete blood count. Several studies have been conducted to identify patients at risk for influenza, malaria, and tuberculosis [11,12]. Naess et al. reported that the neutrophil-lymphocyte ratio and MLR were increased in patients with bacterial infection compared to viral infection [13]. Research on MLR in early-onset neonatal sepsis has not been conducted. Thus, we establish to assess the diagnostic value of eosinophils count and MLR in early detection of neonatal sepsis.

## 2. Material and methods

This retrospective study with a diagnostic testing design was conducted in the neonatal ward at Sanglah Hospital Denpasar. The data were taken from medical records of patients who were admitted between April 2020 and December 2020. The sample population is a population that meets the inclusion and exclusion criteria. The inclusion criteria are neonates with early-onset neonatal sepsis (EONS) or clinically EONS. Subjects will be excluded if the questionnaire data is incomplete and parents refused to participate and refused to sign the informed consent.

The inclusion criteria were neonates with early-onset neonatal sepsis (EONS) or clinically EONS. The exclusion criteria were neonates with incomplete medical records data, immunodeficiency disease, hematological disorders, congenital heart disease, and major congenital abnormalities.

Consecutive sampling was used to collect subjects who met the inclusion criteria until reaching the desired sample size. The minimum sample size was calculated to be 92 subjects using a diagnostic formula with sensitivity output, error rate set at 5% with Za=1.96, sensitivity set of 0.70, research precision of 15%, and disease prevalence of 0.347 [8].

The primary data of the study subjects were gender, gestational age, birth weight, delivery method, sepsis risk factors, and laboratory results in the form of eosinophils, monocytes, lymphocytes, MLR, and blood cultures. The operational definitions of the variables in this study were as follow:

- Early-onset neonatal sepsis (EONS) defined as a clinical syndrome in the form of at least one clinical symptom such as lethargy, rapid breathing, temperature instability that arises due to systemic accompanied by bacteremia that occurs in the first 72 hours of life than can be defined clinically and/or by positive blood cultures (nominal scale)
- Eosinophil, monocyte, and lymphocyte count were obtained from the result of complete blood count when the patient was diagnosed as neonatal sepsis diagnosis, expressed in units of $10^3/\mu L$ (numerical scale).
- Monocyte-lymphocyte ratio (MLR) is the value obtained from dividing the absolute number of monocytes and lymphocytes (numerical scale).
- Gender was the sex of the neonate based on phenotype, grouped into male and female (nominal scale).

- Gestational age was calculated from the first day of the mother's last menstruation until the baby was born or from ultrasound examination. Gestational age was grouped into <28 weeks, 28 weeks to <32 weeks, 32 weeks to <37 weeks, 37 weeks to 42 weeks (ordinal scale).
- Birth weight was neonatal body weight at birth who was weighed shortly after birth in grams. Birth weight was grouped into 4, namely: (ordinal scale)
  - Extremely low birth weight (ELBW) if <1000 grams.
  - Very low birth weight (VLBW) if 1000-1499 grams.
  - Low birth weight (LBW) if 1500-2499 grams.
  - Normal birth weight if >2500grams.
- The delivery method was the process of delivering the baby and placenta, membranes, and umbilical cord from the uterus. The delivery method is divided into cesarean section (surgical procedure), spontaneous (vaginal delivery), and vacuum/forceps.
- Referral is defined as case which was referred from other health workers/institutions (nominal scale).
- Sepsis risk factors were the risk factors of developing neonatal sepsis caused by maternal and neonatal risk factors. Sepsis risk factors include the history of maternal fever, premature rupture of membranes (PRM), chorioamnionitis, fetal distress, foul-smelling liquor, asphyxia, multiple pregnancies, maternal vaginal discharge, and maternal urinary tract infection.

All data was analyzed by IBM SPSS Statistics ver. 23.0. Descriptive analyzed were used to describe the characteristics of the data. Categorical variables are presented in terms of numbers and percentages. Numeric variables are presented in the form of mean and standard deviation if the data are normally distributed, or as medians and ranges if the data are not normally distributed. Processed data are presented in table and narrative form. Eosinophil count and MLR cut-off point was analyzed by Receiver operating characteristic (ROC) curve. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of eosinophil count and MLR in neonatal sepsis were determined by a chi-squared test. An assessment and statement of the ethical approved of this study was provided by the Research Ethics Commission of the Faculty of Medicine, Udayana University, Sanglah Hospital Denpasar with a permit number of 1429/UN14.2.2.VII.14/LT/2021.

## 3. Results

There were 137 neonates with suspected EONS admitted to Neonatology ward, Sanglah Hospital, during the study period. Nineteen neonates were excluded because of major congenital abnormalities, 15 neonates with congenital heart disease, and 3 neonates with incomplete medical record data. Thus, the total sample size was 100 subjects, 51 (51%) of whom were male. Blood culture results were positive in 28 subjects (28%). The characteristics of subjects and risk factors for infection based on the blood culture results group are described in Table 1 and Table 2.

**Table 1** Characteristics of blood count in relation to hospital course

| Characteristics | Blood cultures results | |
|---|---|---|
| | **Positive (n = 28)** | **Negative (n = 72)** |
| **Sex, n (%)** | | |
| Male | 11 (21.6) | 40 (78.4) |
| Female | 17 (34.7) | 32 (65.3) |
| **Gestational age, n (%)** | | |
| <28 weeks | 1 (33.3) | 2 (66.7) |
| 28-<32 weeks | 9 (30) | 21 (70) |
| 32-<37 weeks | 10 (31.3) | 22 (68.8) |
| 37-42 weeks | 8 (22.9) | 27 (77.1) |

| | | |
|---|---|---|
| **Birth weight, n (%)** | | |
| <1000 grams | 3 (50) | 3 (50) |
| 1000-1499 grams | 4 (21.1) | 15 (78.9) |
| 1500-2499 grams | 14 (31.1) | 31 (68.9) |
| 2500-4000 grams | 7 (23.3) | 23 (76.7) |
| **Delivery mode, n (%)** | | |
| Vaginal | 9 (23.1) | 30 (76.9) |
| Caesarian section | 19 (32.8) | 39 (67.2) |
| Vacuum/forceps | 0 (0) | 2 (100) |
| **Referral, n (%)** | | |
| Yes | 15 (36.6) | 26 (63.4) |
| No | 13 (22) | 46 (78) |

**Table 2** Neonatal sepsis risk factors

| **Characteristics** | **Blood cultures results** | |
|---|---|---|
| | **Positive (n = 28)** | **Negative (n = 72)** |
| History of maternal fever, n (%) | 4 (36.4) | 7 (63.6) |
| PRM 12-24 hours, n (%) | 4 (28.6) | 10 (71.4) |
| PRM more than 24 hours, n (%) | 3 (27.3) | 8 (72.7) |
| Chorioamnionitis, n (%) | 0 (0) | 1 (100) |
| Fetal distress, n (%) | 8 (33.3) | 16 (66.7) |
| Foul-smelling liquor | 2 (10) | 18 (90) |
| Asphyxia, n (%) | 20 (29.8) | 47 (80.6) |
| Multiple gestation, n (%) | 2 (16.7) | 10 (83.3) |
| Maternal vaginal discharge, n (%) | 8 (26.7) | 22 (73.3) |
| Maternal urinary tract infection, n (%) | 3 (30) | 7 (70) |

The median MLR value was significantly higher in the group with positive blood cultures than in the negative blood culture group ($p<0.001$). In contrast, the median value of eosinophils did not differ significantly between the two groups. The comparison of the number of absolute eosinophils, monocyte, lymphocyte, and MLR can be seen in Table 3.

**Table 3** The comparison of the number of absolute eosinophils, monocyte, lymphocytes, and MLR

| **Characteristics** | **Blood culture results** | | **p-value** |
|---|---|---|---|
| | **Positive (n = 28)** | **Negative (n = 72)** | |
| Eosinophils,[a] ($10^3/\mu L$) | 0.15 (0.03-1.07) | 0.22 (0.00-1.26) | 0.667 |
| Monocyte,[b] ($10^3/\mu L$) | 1.58 (0.58) | 1.28 (0.77) | 0.71 |
| Lymphocyte,[a] ($10^3/\mu L$) | 3.66 (0.96-9.93) | 4.48 (0.89-19.16) | 0.013* |
| MLR[a] | 0.51 (0.11-1.13) | 0.25 (0.00-0.93) | 0.000* |

[a] median(minimun-maximum), [b]mean (standard deviation), *

The ROC curve analysis revealed an eosinophil cut-off point of 0.16x10$^3$/µL or 160 cells/mm$^3$ for neonatal sepsis, with the area under curve (AUC) 0.528 (95%CI 0.39 to 0.66) (Figure 1). This cut-off point had 57.14% sensitivity, 65.28% specificity, 39.02% PPV, and 79.66% NPV (Table 4).

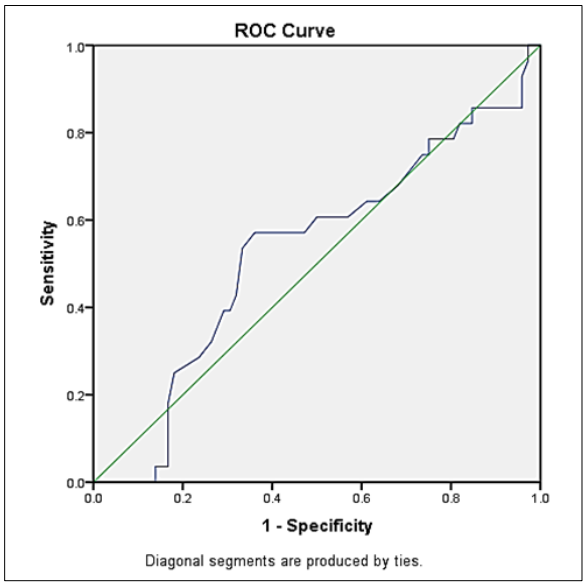


**Figure 1** ROC curve analysis of eosinophil count in detecting EONS

**Table 4** Diagnostic value of eosinophil count in neonatal sepsis

| Eosinophil counts, $10^3$/µL | Blood cultures | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| | Positive | Negative | | | | |
| ≤0.16 | 16 | 25 | 57.14 | 65.28 | 39.02 | 79.66 |
| >0.16 | 12 | 47 | | | | |

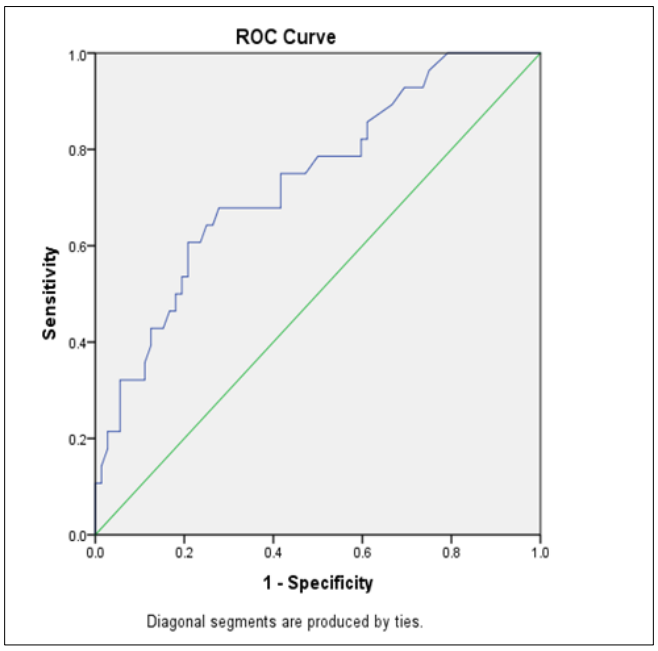


**Figure 2** ROC curve analysis of MLR in detecting EONS

While the MLR cut-off point in this study was 0.38 with the area under curve (AUC) 0.735 (95%CI 0.63 to 0.84). The ROC curve of MLR in neonatal sepsis can be seen in Figure 2. In this study, the use of the ROC curve obtained a cut-off point of 0.38 MLR with sensitivity, specificity, PPV, and NPV of 67.86%, 72.22%, 48.72%, and 85.25%, respectively. In addition, table 5 also showed the diagnostic values of MLR in neonatal sepsis.

**Table 5** Diagnostic value of MLR in neonatal sepsis

| MLR | Blood cultures | | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| | Positive | Negative | | | | |
| ≥0.38 | 19 | 20 | 67.86 | 72.22 | 48.72 | 85.25 |
| <0.38 | 9 | 52 | | | | |

## 4. Discussion

Early-onset neonatal sepsis (EONS) can occur due to a transplacental infection or a result of vertical infection transmitted from the mother during pregnancy to the infant during delivery. Blood culture remains the gold standard to diagnose neonatal sepsis. This test has high sensitivity, but it takes a long time, and only about 5-10% of patients with suspected sepsis are confirmed positive by blood culture [2]. That might be due to maternal use of antimicrobials, insufficient blood specimen volume for culture, and low levels of bacteremia [5,6]. A previous study reported that 33.3% of 174 infants with suspected neonatal sepsis had positive blood cultures [5]. Research conducted by Khoshdel et al. reported that 34.7% of 150 neonates with suspected EONS have positive blood cultures [8]. Similarly, another study obtained positive blood cultures in approximately 140 infants (40.7%) of the 344 neonates with suspected EONS (14). In this study, 28 subjects (28%) had positive blood cultures.

No significant difference in eosinophil and monocyte counts was seen between the two study groups (p=0.667 and p=0.71, respectively). This result contrasts the lymphocyte count and MLR, which show statistically significant differences between the two groups at a p-value <0.05. This disparity suggests that the lymphocyte count plays an essential role in providing a significant MLR value in neonatal sepsis.

Eosinophils are innate immune cells that contribute to the immune response to infection. Eosinophils can produce cytokines and growth factors related to immunomodulating functions. Sepsis results in a decrease in the eosinophil count (eosinopenia). The exact mechanism of eosinopenia in acute infection is unknown. However, it is thought to be affected by chemotactic substances, glucocorticoid hormones, and epinephrine [14,15]. In this study, the eosinophils count had an AUC of 0.562 (95%CI 0.39 to 0.660) to diagnosing neonatal sepsis.

Based on ROC curve analysis, we determine the eosinophil count cut-off point of $0.16x10^3/\mu L$ or 160 cell/$mm^3$. Forty-one subjects (41%) had eosinophils count ≤$0.16x10^3/\mu L$. This cut-off point has a sensitivity of 57.14% and a specificity of 65.28%. The results are distinct from those of previous research. A previous study established a significant eosinophil cut-off point of 140 cells/$mm^3$ (60% sensitivity; 90% specificity; AUC 0.835; p-value=0.001) [16]. This difference could be a result of the fact that the inclusion criteria and subject characteristics differ. Subjects with respiratory distress were excluded from the previous study. In addition, EONS was diagnosed by the laboratory examination and/or blood culture results [16]. Most of the research subjects are aterm babies (90%). In this study, EONS was diagnosed solely based on blood culture results, and 65% of subjects were premature babies.

In acute infection, the initial response to eosinopenia may be due to eosinophil sequestration in the peripheral circulation, suppression of eosinophil production, and suppression of mature eosinophil migration from the bone marrow. This sequestration process is associated with eosinophil migration to areas of inflammation as a result of chemotactic substances released during inflammation. C5a is one of the chemotactic substances responsible for the development of eosinopenia [17, 18].

Premature babies have an immature immune response. Thus, the eosinopenia response cascade process does not occur. Additionally, premature babies have more chemotactic factor inactivator (CFI), inhibiting complement and chemotactic activity. In acute infection conditions, the inability of premature babies to secrete adrenal hormones in response to corticotropin may also result in the absence of eosinopenia [15,19]. A previous study reported that neonates require high levels of corticotropin to produce an eosinopenia response [20].

This study found the PPV of eosinophil count was 39.02%, indicating that eosinophil cut-off point value of 0.16 x$10^3$/μL requires additional investigations in diagnosing neonatal sepsis, such as blood culture examination. The NPV of 79.66% is insufficient to rule out neonatal sepsis.

Lymphocytes and monocytes are various leukocyte cells that contribute to the immune system and are routinely examined throughout a complete blood count. Lymphocytes are responsible for the adaptive immune system. Previously, decreased lymphocyte counts or lymphocytopenia was used as indicators of bacteremia. Study conducted by De Jager et al. reported that lymphocyte count <1.0x$10^3$/μL can be used to differentiate the presence of bacteremia with a sensitivity of 73.9%, specificity of 57.6% PPV of 63.6%, NPV of 68.8% (p-value <0.001) [21]. In sepsis and septic shock, lymphocytopenia can occur due to lymphocytes margination and redistribution into the lymphatic system, as well as enhanced lymphocyte apoptosis [21,22].

Monocytes are a type of leukocyte that function as APCs (antigen-presenting cells) and produce cytokines in response to infection. Infection stimulates the immune system, resulting in an increase in monocytes and decreased lymphocytes [21,23]. As a result of this condition, the monocytes to lymphocytes ratio will be increased. In this study, the MLR cut-off point in neonatal sepsis was 0.38 with an accuracy of 73.5% (95% CI 62.7%-84.4%), sensitivity 67.86%, and specificity of 72.22%. Subjects who had MLR 0.38 were 39 subjects (39%). Naess et al. reported an increase in MLR associated with a bacterial infection in adult patients [13]. No research has been conducted on the MLR cut-off point in neonatal sepsis.

This study has several weaknesses. This study uses a retrospective design. In addition, the media used to grow blood culture microorganisms was only useful for bacteria and fungi. Other causes of neonatal sepsis such as viruses could not be detected. Future studies using a prospective design and blood culture media that can grow bacteria, fungi, or viruses need to be done to further assess the diagnostic value of eosinophil count and MLR in neonatal sepsis.

## 5. Conclusion

This study concludes that the MLR with a cut-off value of 0.38 has good sensitivity and specificity for early detection of neonatal sepsis. At the same time, the number of eosinophils is less sensitive and specific for the early detection of neonatal sepsis. Further research needs to be done using better blood culture media to get a better diagnostic value of eosinophil count and MLR in neonatal sepsis.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

There is no conflict of interests. The author reports no conflicts of interest in this work. By this statement, all authors who consist of Desmiyati Natalia Adoe and I Made Kardana have no conflict of interest regarding this manuscript publication.

### *Statement of informed consent*

Informed consent was obtained from the patient whose data mentioned in the study.

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