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Laboratory and Clinical Manifestation Correlation of Neonatal Sepsis in Abdul Moeloek Hospital

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Abstract

Purpose: The prognosis of neonatal sepsis critically depends on early detection; however, its nonspecific clinical signs and variable laboratory findings often complicate the timely diagnosis. This study aimed to assess the correlation between clinical manifestations and laboratory results in neonatal sepsis cases, focusing on patients at Abdul Moeloek Hospital.

Methodology/approach: A cross-sectional approach was used to analyze the medical records of neonates diagnosed with sepsis between January and June 2024. All neonates admitted to the neonatal unit with suspected sepsis during this period were included in the study.

Results/findings: The majority of patients were male (65.1%) and 1 week old (58.7%). Hyperthermia (44.4%) was the most common symptom, followed by a normal heart rate (68.3%) and respiratory rate (81%). Most patients had normal hemoglobin (55.6%) and leukocyte levels (71.4%), low platelet counts (50.8%), and negative culture results (74.6%). Statistically significant correlations were found between heart rate (OR=0.4) and respiratory rate (OR=0.3) and laboratory findings ($p<0.05$), although the strength was weak to moderate. No significant correlation was observed with body temperature ($p=0.412$).

Conclusions: Heart and respiratory rates were significantly associated with sepsis-related laboratory results, whereas body temperature was not. Most affected neonates were male, one week old, and presented with hyperthermia but otherwise normal vital signs and blood cell counts.

Limitations: The limited sample size and study duration suggest the need for further research.

Contribution: These findings provide insights into improving the early detection and management of neonatal sepsis, particularly in pediatric care settings in Indonesia.

Keywords: *Clinical Diagnosis, Laboratory Results, Neonatal Sepsis*

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1. Introduction

Sepsis is one of the causes of morbidity and mortality in newborns. Neonatal sepsis is an invasive bloodstream infection characterized by the presence of bacteria in body fluids, such as blood, bone marrow, and urine (Kosim, 2018). Based on its onset, neonatal sepsis is divided into two, namely early-onset neonatal sepsis and late-onset neonatal sepsis. Early-onset neonatal sepsis is defined as an infection found in infants within 72 hours of delivery, while late-onset neonatal sepsis is defined as an infection found in infants after 72 hours or 3 days of birth in preterm infants and after 7 days of age in

full-term infants (Glaser, 2021).
According to a report by World Health Organization (WHO) in 2019, globally, there were 2.4 million infant deaths, of which neonatal sepsis is one of the leading causes with estimated more than 375,000 infant deaths due to neonatal sepsis (Pek, 2020). Surveys conducted worldwide in the period 1990–2017 estimated there were more than 25 million cases of sepsis, mainly neonates. Based on data from the Indonesian Ministry of Health in 2021, neonatal sepsis is one of the most common causes of death in neonates in Indonesia, namely around 3.4% (Rudd, 2020). Based on data from Abdul Moeloek Hospital from 2017-2019, there was an increase: in 2017 there were 193 incidents, in 2018 there were 242 incidents, and in 2019 there were 317 incidents of neonatal sepsis (Ervina, 2023). Newborn infants with premature birth or low birth weight, maternal infectious diseases, chorioamnionitis, and prolonged premature rupture of membranes are at a higher risk of neonatal sepsis (Glaser, 2021). Group B streptococcus (GBS), Escherichia coli (E. coli), Aerobactin, Listeria monocytogenes (L. monocytogenes), Haemophilus influenzae, S. aureus, Klebsiella spp, and non-typhoidal Salmonella bacteria are considered to be major microorganisms causing neonatal sepsis (Kim, 2020).

Current diagnostic criteria used in different studies vary substantially. Generally, sepsis diagnosis in neonates is typically based on a combination of risk factors, clinical presentation, and hematologic indices (Celik, 2022). However, early diagnosis of neonatal sepsis based on clinical presentation remains challenging as clinical manifestations can be subtle, non-specific, or even severe (Zea-Vera, 2015). Traditionally, the diagnosis of confirmed sepsis relies on conventional microbiologic culture. However, its time-consuming nature and low sensitivity challenge its value in the early diagnosis of neonatal sepsis. Few factors like intermittent bacteremia or maternal antibiotic exposure during labor that reduces pathogens detection through cultures (Tam, 2017). is the reason why hematology examination can be a reference for early diagnosis of neonatal sepsis (Niederman, 2021).

Recent research using molecular testing to diagnose neonatal sepsis patients has reported quite favorable results. A systematic review collected from 35 studies by Pammi, et al. (2017) stated that molecular assays has 90% sensitivity and 93% specificity in diagnosing neonatal sepsis. Molecular test such as Sepsis Flow Chip (SFC) demonstrated an overall sensitivity of 90% and specificity of 96% in detecting pathogens in neonatal sepsis patients and considerably produce faster results. SFC provide results in 4 to 6 hours, whereas blood culture takes 3-5 days. Despite this, the use of molecular approach in diagnosing neonatal or pediatric sepsis in Indonesia has not been adequately explored (Prasetyo, 2023).

European Medicines Agency (EMA)'s criteria (2010) were used in a few studies to diagnose neonatal sepsis. This criterion stated that diagnosis of probable sepsis was made when the neonate had ≥2 clinical and ≥2 laboratory signs of sepsis. And later, patient was diagnosed with culture-confirmed sepsis when there was ≥1 positive blood culture of a presumptive pathogen and ≥1 clinical or laboratory sign of sepsis (Toan, 2022). Clinical signs of sepsis include modified body temperature (core temperature greater than 38,5 □C, less than 36 □C and/or temperature instability), cardiovascular instability (bradycardia or tachycardia, rhythm instability, reduced urine output (less than 1 ml/kg/h), hypotension (mean arterial pressure less than the 5th percentile of age), mottled skin, or impaired peripheral perfusion), skin or subcutaneous lesions (petechial rash, sclerema), respiratory instability (apnoea or tachypnoea episodes or increased oxygen requirements or requirement for ventilation support), gastrointestinal (feeding intolerance, poor sucking, abdominal distension), and nonspecific manifestations (irritability, lethargy, hypotonia). On the other hand, laboratory signs of sepsis include WBC count (<4000 x 10^9 cells/L or >20.000 x 10^9 cells/L), immature to total neutrophil ratio (I/T ratio) greater than 0,2, platelet count <100.000 10^9 cells/L, C Reactive Protein (CRP) >15 mg/L or procalcitonin ≥2 ng/mL, and metabolic acidosis (base excess <-10 mEq/L or serum lactate > 2 mMol/L) (Medicines, 2010). The WBC count has long been recognized as a standard marker for detecting bacterial infections. (Setyoningrum, 2024). However, there have been no recent updates to the EMA criteria since 2010 and a study published in 2019 by (Tuzun, 2019) evaluated the EMA criteria and found that they had a sensitivity of only 44,2% and specificity of 64,4% in diagnosing neonatal sepsis, indicating that this criteria might not be sufficiently reliable for clinical use throughout

time.
A research conducted by (Hematyar, 2012) in Iran uses cross sectional descriptive prospective method to assess the role of clinical manifestations and laboratory findings in 110 infants with sepsis clinical manifestations showed that the most common clinical manifestations were respiratory distress (44,5%), jaundice (25,5%), vomiting (23,6%), and poor feeding (20.9%). And there are other clinical manifestations such as lethargy, decreased sucking reflex, fever, tremor, abdominal distension, and seizure. Meanwhile, for the laboratory findings, the most common were positive blood culture (100%), anemia (32,7%), positive C-reactive protein (CRP) (17.3%), positive urine culture (9,1%), leukocytopenia (1,8%), and thrombocytopenia (1,8%).

Previous research conducted in Northern Vietnam stated that there is no significant relationship between clinical characteristics and laboratory tests in full-term neonates with sepsis at National Children's Hospital (Nguyen, 2023). In other research, analysis of the relationship between eosinophils, basophils, neutrophils, lymphocytes, monocytes with mortality rates obtained a p value >0.05 which informs that there is no significant relationship between the type of count (eosinophils, basophils, neutrophils, lymphocytes, monocytes) with mortality rates (Fitriani, 2019). The prognosis of neonatal sepsis is closely tied to the timing of diagnosis. Early diagnosis of sepsis and proper management of sepsis can reduce mortality rates in sepsis patients. However, recent studies present differing opinions and views on which methods and their correlation are most appropriate for neonatal sepsis diagnosis. Particularly, clinical manifestations and hematology profile of neonatal sepsis are generally nonspecific and varied (Fitriani, 2019). Therefore, this study aimed to evaluate the conformity of laboratory results and clinical manifestations in neonatal sepsis.

2. Methodology

This research uses a cross-sectional method. All neonates (≤28 days) admitted to the neonatal unit and probable sepsis during this period January-June 2024 were included in the sampling method. This criterion was made when the neonate had ≥2 clinical and ≥2 laboratory signs of sepsis. Clinical signs of sepsis include modified body temperature (core temperature > 38,5 □C, < 36 □C and/or temperature instability), cardiovascular instability (bradycardia or tachycardia, rhythm instability, reduced urine output (< 1 ml/kg/h), hypotension (mean arterial pressure < the 5th percentile of age), mottled skin, or impaired peripheral perfusion), skin or subcutaneous lesions (petechial rash, sclerema), respiratory instability (apnoea or tachypnoea episodes or increased oxygen requirements or requirement for ventilation support), gastrointestinal (feeding intolerance, poor sucking, abdominal distension), and nonspecific manifestations (irritability, lethargy, hypotonia).

On the other hand, laboratory signs of sepsis include WBC count (<4000 x 10^9 cells/L or >20.000 x 10^9 cells/L), immature to total neutrophil ratio (I/T ratio) greater than 0,2, platelet count <100.000 10^9 cells/L, C Reactive Protein (CRP) >15 mg/L or procalcitonin □2 ng/mL, and metabolic acidosis (base excess <-10 mEq/L or serum lactate > 2 mMol/L). We excluded neonates whose parents declined to give informed consent and if the length of hospital stay was <24 hours. The data obtained were collected, then the results of the patients' laboratory and clinical features were grouped, and afterward the data was analyzed using chi square. In the multivariable analysis for Odds Ratio (OR), 95% Confidence Interval (95% CI), and p-values were estimated. Data analysis in this study used statistical software SPSS 26.0 and Microsoft Excel.

3. Results and Discussion

3.1. Results

Table 1. Clinical and laboratory characteristics

No	Parameter	Number	Percentage
1.	Age		
	1 Week	37	58.7%
	2 Weeks	13	20.6%
	3 Weeks	6	9.5%
	≥4 Weeks	7	11.1%

	Total	63	100%
2.	Sex		
	Male	41	65.1%
	Female	22	34.9%
	Total	63	100%
3.	Temperature		
	Hypothermia	9	14.3%
	Normal	26	41.3%
	Hyperthermia	28	44.4%
	Total	63	100%
4.	Heart Rate		
	Bradycardia	9	14.3%
	Normal	43	68.3%
	Tachycardia	11	17.5%
	Total	63	100%
5.	Respiratory Rate		
	Low	1	1.6%
	Normal	51	81%
	High	11	17.5%
	Total	63	100%
6.	Hemoglobin		
	Low	26	41.3%
	Normal	35	55.6%
	High	2	3.2%
	Total	63	100%
7.	Hematocrit		
	Low	32	50.8%
	Normal	31	49.2%
	High	0	0%
	Total	63	100%
8.	Leukocyte		
	Low	10	15.9%
	Normal	45	71.4%
	High	8	12.7%
	Total	63	100%
9.	Thrombocyte		
	Low	32	50.8%
	Normal	29	46.0%
	High	2	3.2%
	Total	63	100%
10.	Culture		
	Positive	16	25.4%
	Negative	47	74.6%
	Total	63	100%

Out of the 63 samples obtained, the characteristics of neonatal sepsis were classified based on 10 clinical and laboratory parameters, such as age, sex, temperature, heart rate, respiratory, hemoglobin, hematocrit, leucocyte, thrombocyte, and culture. Based on the results of the research, the characteristics of neonatal sepsis patients that the age group in the sample is divided into 4 groups, the 1 week age group totaling 37 (58.7%) samples, being the largest age sample group, followed by the 2 week age group with 13 (20.6%) samples. The 3 week age group obtained 6 (9.5%) samples, became the smallest age sample group. Meanwhile, the last age group ≥4 weeks obtained 7 (11.1%) samples. Then, on the gender variable in this study, the male gender group obtained 41 (65.1%) samples and became the largest number in the gender variable group. Meanwhile, the female gender group obtained 22 (34.9%) samples.

In the clinical variables of neonatal sepsis, the temperature variable was divided into 3 groups, namely the hypothermia group totaling 9 (14.3%) samples, the normal temperature group totaling 26 (41.3%) samples, and the hyperthermia group totaling 28 (44.4%) samples and became the largest number of samples in the temperature variable. Furthermore, the pulse variable was divided into 3 groups, the bradycardia group totaling 9 (14.3%), the normal pulse group totaling 43 (68.3%) and became the largest group in the pulse variable, and the tachycardia group totaling 11 (17.5%) samples. In the respiratory rate variable, it was found that in the low respiratory rate group there were 1 (1.6%) sample, in the normal respiratory rate group there were 51 (81%) and became the largest respiratory rate sample group, meanwhile high respiratory rate has 11 (17.5%) samples.

In the laboratory results variable of neonatal sepsis patients, there are 5 variables, namely Hemoglobin, Hematocrit, Leukocytes, Platelets, and Culture. In the hemoglobin variable, low hemoglobin was found in 26 (41.3%) samples, normal hemoglobin was found in 35 (55.6%) samples and became the largest sample group in the hemoglobin variable, and in the high hemoglobin group, 2 (3.2%) samples were obtained. Furthermore, in the hematocrit variable, the low hematocrit group was found in 32 (50.8%) samples and became the largest sample group in the hematocrit variable, normal hematocrit was found in 31 (49.2%) samples, and high hematocrit was found in 0 sample. In the leukocyte variable in this study, low leukocytes were found in 10 (15.9%) samples, normal leukocytes were found in 45 (71.4%) samples and became the largest sample group in the leukocyte variable, and high leukocytes were found in 8 (12.7%) samples. Then in the platelet variable, low platelets were found in 32 (50.8%) samples and became the largest sample group in the platelet variable, normal platelets were found in 29 (46%) samples, and high platelets were found in 2 (3.2%) samples. In the culture variable, positive culture results were obtained in 16 (25.4%) samples and negative culture results were obtained in 47 (74.6%) samples.

Table 2. Bivariate analysis of temperature and laboratory results

Temperature	**Culture**				**P-Value**
	Positive		**Negative**		
	n	**%**	**n**	**%**	
Abnormal	8	12.7 %	29	28.6%	0.412
Normal	8	12.7 %	18	41.9%	
Total	16	25.4 %	47	74.6%	

Table 3. Bivariate analysis of heart rate and laboratory results

Heart Rate	**Culture**				**P-Value**	**OR 95% CI**
	Positive		**Negative**			
	n	**%**	**n**	**%**		

Abnormal	11	17.5 %	9	14.3%	0.000	0,4
Normal	5	7.9%	38	60.3%		
Total	16	25.4 %	47	74.6%		

Table 4. Bivariate analysis of respiratory rate and laboratory results

Respiratory Rate	**Culture**				**P-Value**	**OR 95% CI**
	Positive (0)		**Negative (1)**			
	n	**%**	**n**	**%**		
Abnormal (0)	7	11.1 %	5	7.9%	0.004	0,3
Normal (1)	9	14.3 %	42	66.7%		
Total	16	25.4 %	47	74.6%		

Based on the data obtained, the results of the study showed the results of bivariate analysis on the three research variables, the temperature variable showed no correlation between laboratory results and the temperature of sepsis patients with the results of the bivariate analysis of 0.412 (OR=0,1). The bivariate analysis test of the correlation of laboratory results with heart rate p-value of 0.000 (OR=0,4) and the correlation variable of respiratory rate with laboratory results obtained a p-value of 0.004 (OR=0,3), this indicates that there is a relationship between laboratory results of sepsis patients with heart rate and respiratory rate. The correlation between laboratory results of sepsis patients with temperature and respiratory rate is weak. Meanwhile, the correlation between laboratory results of sepsis patients with heart rate is moderate.

3.2. Discussion

Neonatal sepsis is a clinical syndrome caused by bacteria, viruses, and fungi characterized by systemic symptoms and signs and showing positive blood cultures that occur in the first month of life (Jaya, 2019). Bacteria is the most common cause of infection, but can also be caused by fungi, viruses, or parasites. The immune response to bacteria can cause organ dysfunction. The most common primary infections organs are the respiratory system, nervous system, urogenital system, skin, and gastrointestinal system (Hadinegoro, 2018). Clinical manifestations of neonatal sepsis include respiratory disorders, lethargy, poor ability to suck breast milk, vomiting, bloating, and temperature instability. The diagnosis of neonatal sepsis is made clinically and in the laboratory. Clinically characterized by fever or hypothermia, or the presence of a focus of infection. In the laboratory, biomarkers of infection are used, namely: leukocyte count, Erythrocyte Sedimentation Rate, C Reactive Protein, and Procalcitonin (Hadinegoro, 2018).

First, based on age and sex parameters in this study, infants aged 1 week and male gender account for the highest percentage. This aligns with previous researches indicating that male neonates are at a significantly higher risk for developing sepsis compared to females and age under 7 days (Noah, 2022). Sepsis, particularly in infants under one week old, may be resulted from underdeveloped immune systems that are less capable of responding effectively to infections. Signs and symptoms of neonatal sepsis can range from nonspecific or vague symptoms to hemodynamic collapse. Early symptoms may include irritability, lethargy, or poor feeding. Others may quickly develop respiratory distress, fever, hypothermia, or hypotension with poor perfusion and shock. There are three parameters used in this study to assess the clinical manifestations of patients with neonatal sepsis, namely temperature, heart rate, and respiratory rate.

In this study, it was reported that high temperature (hyperthermia) places highest percentage in temperature parameters, although normal temperature has a percentage close to hyperthermia.

Previous studies stated that abnormal core temperature is a difficult criterion to interpret in the setting of neonatal sepsis, especially in preterm infants. Preterm neonates manifest a baseline lack of temperature maintenance due to physiologic immaturity that requires servo-controlled incubators. Thus, presentation of hypothermia in neonates may be secondary to inadequate provision of heat rather than sepsis (Wynn, 2014).

Heart rate is an easily obtained parameter that many clinicians use as an early marker of deterioration in children. Various hospitals have developed pediatric early warning systems. Sepsis has been reported to be associated with alterations in autonomic regulation, adaptability, and organization of heart rate. Tachycardia is the most prevalent finding in neonatal sepsis due to sympathetic nervous system activation and compensatory mechanisms to maintain cardiac output, but bradycardia and normal heart rates could also be found in infants with ongoing infections (Sullivan, 2022). Although heart rate is a convenient and easily accessed physiological parameter, there is a lack of consensus among warning scores on what constitutes significant and out of proportion tachycardia in a sick child. For instance, the normal heart rate of a 8-year-old child is between 80 to 120 bpm according to APLS guidelines, and PALS places the normal heart rate of a 8-year-old child at between 60 to 140 bpm (Wee, 2020).

In this study, normal respiratory rate infants have the highest percentage. Nevertheless, some studies express that sepsis generally presents itself with respiratory distress, although this symptom is also unspecific as many non-infected neonates display. During the first days of life, there is a dynamic adaption of different organ systems to extra-uterine life. Therefore, a single-point, clinical assessment to diagnose sepsis in neonates therefore seems impossible. Some guidelines suggest that a respiratory rate > 50 or 60/min may be suggestive of an infection (Klingenberg, 2018). Besides clinical manifestations, diagnosis of sepsis could also be supported by laboratory parameters. Few parameters in complete blood count that are usually assessed to be significant in diagnosing sepsis are leukocytes and platelet counts. Infants with sepsis usually show low (<5000/mm^3) or elevated (>20.000/mm^3) leukocyte count and low (<150.000/mm^3) platelet counts (Hornik, 2012). This study reported that normal leukocyte count and low platelet counts gain highest percentage. On the other hand, hemoglobin and hematocrit levels in neonatal sepsis are less frequently highlighted. In this study, the highest percentage is observed in infants with normal hemoglobin and low hematocrit.

Blood culture remains the gold standard for diagnosing neonatal sepsis, but it has low sensitivity. Within this research, negative blood culture has higher percentage (74.6%). A study suggested that 6 to 16 times more infants receive therapy for culture-negative sepsis due to the time-consuming nature of blood culture. On the other hand, some conditions such as inadequate blood volumes for cultures, maternal antimicrobial treatment prior to sampling, intermittent bacteremia or the possibility of infection with anaerobes could result in false-negative culture (Klingenberg, 2018). In our study, mother who were exposed perinatal antibiotherapy, were included. That's raising concerns about the accuracy of blood cultures and asymptomatic bacteremia.

The relationship between clinical manifestations and laboratory findings was assessed in this study using bivariate analysis, which revealed there is a relationship between heart rate and respiratory rate with laboratory results of neonatal sepsis. But, the correlation between heart rate with laboratory results of neonatal sepsis is moderate and weak for respiratory rate. Meanwhile, there is no correlation between laboratory results and body temperature. This highlights the need for greater consideration of heart rate and respiratory rate in diagnosing neonatal sepsis, rather than relying on body temperature. Although all those components are important, several studies suggest that heart rate and respiratory rate play a more significant role. (Sullivan, 2022) found that temperature instability in neonates is often caused by non-infectious or external factors, such as environmental conditions.

Low birth weight (LBW) neonates, particularly those born prematurely, are at significantly higher risk of experiencing temperature instability, specifically hypothermia, due to their limited body fat and underdeveloped thermoregulation systems (Primadevi, 2022). For instance, frequent holding of full-term infants can lead to elevated body temperature, while preterm infants might face hypothermia as

a result from inadequate external warmth. correlation between preeclampsia and low birth weight babies at the Batin Mangunang Regional General Hospital in Tanggamus Regency 2020 (Primadevi, 2022). Antenatal care (ANC) plays a crucial role in preventing, detecting, and managing preeclampsia (Sari, 2022); (Agata, 2022). Based on the study by Kristiana and Juliansyah (2017), which investigated risk factors for low birth weight (LBW) associated with Chronic Energy Deficiency (KEK), several significant contributors were identified (Hafid, 2024).

Current guidelines from WHO and CDC still identify heart rate, respiratory rate, and temperature as three key features essential for diagnosing neonatal sepsis. However, these correlation results and other discoveries from this research are intended to provide useful insights in the process of identifying which elements should be emphasized in diagnosing neonatal sepsis, leading to better management and improved patient care.

4. Conclusion

This study reports that there is correlation between heart rate and respiratory rate with sepsis laboratory results. Meanwhile, there is no correlation between neonatal sepsis laboratory results and body temperature. It was also mentioned that the majority of patients with neonatal sepsis were 1 week old, male, presented with hyperthermia, normal heart rate, normal respiratory rate, normal hemoglobin levels, low hematocrit levels, normal leukocyte levels, low platelets, and negative blood culture.

Limitations and Further Study

The limitations of this study include the lack of existing research samples and a short research period, which may restrict the ability to observe seasonal variations in neonatal infections. Additionally, the data in this research were collected retrospectively from medical records, which could result in inherent biases due to factors such as inconsistencies in diagnosis and or missing information. Factors such as selection bias and inaccuracies in lab results may also limit the study. In future research, the researcher suggests extending the research period, in effort to achieve larger sample size and greater variability. A prospective study could be considered in future research to minimize bias.

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