Early Detection of Sepsis in Neonates: A Literature Review

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A B S T R A C T

Sepsis in neonates is a very serious problem and contributes to morbidity and mortality among the newborns. Signs and symptoms of its infection are hardly detected early. They are only detected in a severe sepsis, increasing the death incidence. An effective early detection method is needed for early treatment and will prevent the mortality in neonates. This study used electronic databases of Pub Med, Science Direct, EBSCO Host, and Pro Quest. The articles taken are those issued in the last 5 years. Based on the review, there are several methods used to detect sepsis in neonates early. They are SNAP II, SNAPPE II, SRC (Sepsis Risk Calculator), NICE guideline CG49, and laboratory results (procalcitonin, CRP, NLR, PLR, thromboelastometry, interleukin-6). SNAP II and SNAPPE II scores are not significantly associated with blood culture results. SRC recommends blood culture examination in neonates with a moderate risk. Procalcitonin can predict neonate sepsis with a sensitivity of 73.6% and specificity of 38.6%, while CRP has a sensitivity of 50.9% and specificity of 28.7%. NLR and PLR have a sensitivity of 97.4%, and specificity of 100%. Interleukin-6 has greater potential to detect early onset sepsis (EOS) than late onset sepsis (LOS).

A B S T R A K

Sepsis pada neonatus merupakan masalah yang sangat serius dan berkontribusi terhadap morbiditas dan mortalitas pada neonatus. Tanda dan gejala infeksi sering tidak terdeteksi sejak awal, dan terdeteksi sudah dalam kondisi sepsis berat, hal ini meningkatkan insiden kematian pada neonatus. Metode deteksi dini sepsis yang efektif dapat mendeteksi secara lebih cepat terjadinya sepsis, sehingga dapat dilakukan tindakan penanganan lebih awal dan mencegah semakin bertambahnya angka mortalitas pada neonatus karena sepsis. Pencarian artikel menggunakan *database* elektronik diantaranya *Pub Med, Science Direct, Ebsco Host,* dan *Pro Quest.* Artikel yang digunakan yaitu 5 tahun terakhir. Berdasarkan 7 artikel yang terpilih didapatkan beberapa metode yang digunakan untuk mendeteksi sepsis secara dini pada neonatus, diantaranya, SNAP II, SNAPPE II, SRC (*Sepsis Risk Calculator*), NICE guideline CG49, dan hasil laboratorium (procalcitonin, CRP, NLR, PLR, thromboelastometry, interleukin-6). Skor SNAP II dan SNAPPE II tidak ditemukan hubungan yang signifikan dengan hasil kultur darah. SRC merekomendasikan pemeriksaan kultur darah pada neonatus dengan resiko sedang. Procalcitonin dapat memprediksi sepsis neonatus dengan sensitifitas 73,6% dan spesifisitas 38,6% sedangkan CRP sensitifitas sebesar 50,9% dan spesifisitas 28,7%. NLR dan PLR memiliki sensitifitas sebesar 97,4%, spesifisitas 100%. Interleukin-6 berpotensi lebih besar untuk mendeteksi *early onset sepsis* (EOS) dari pada *late onset sepsis* (LOS).

INTRODUCTION

Sepsis in neonates is a very serious problem and contributes to newborn morbidity and mortality, especially in developing countries such as Indonesia. In 2021, the problem of infection ranks 4th in contributing to the most deaths in neonates, which is 4% (Kemenkes RI., 2021). The mortality rate of the sepsis in neonates in Indonesia varies in each referral hospital, ranging from 11.56% - 49.9%.

Sepsis neonatorum is a clinical syndrome of bacteremia, with systemic signs and symptoms in the first 28 days of the newborn (Pal et al., 2020). Sepsis in neonates is the most significant factor of morbidity and mortality in newborns. Sepsis in neonates is divided into two, namely Early Onset Sepsis (EOS) and Late Onset Sepsis (LOS). EOS is the occurrence of sepsis within the first 72 hours of life. The cause of EOS is infection during pregnancy either from placental transmission or other transmission such as the entry of bacteria into the uterus through the vagina due to rupture of the amniotic membrane (Can, Hamilcikan, & Can, 2018). Risk factors for neonate sepsis in the perinatal phase include a history of premature rupture of membranes, fever in the laboring mother, intraamniotic infection and chorioamnionitis (Sokou et al., 2018). Suwarna et al., (2022) stated that infection is the main cause of neonatal sepsis which is obtained vertically from bacterial colonization identified in pregnant women until childbirth.

Signs and symptoms of infection frequently are not detected early; they are mostly identified in severe sepsis, which further complicates treatment and increases the incidence of death in neonates (Samanta et al., 2020). In their research, Sokou et al., (2018), mentioned that sepsis in neonates shows changes in clinical symptoms including body temperature instability, indigestion, flatulence, hepatomegaly, respiratory disorders (apnea, dyspnea, chest retraction, use of oxygen support), bradycardia or tachycardia, poor peripheral perfusion, hypotension, irritability, lethargy, hypotonia, jaundice, and petechiae. Laboratory results showed leukopenia, immature total neutrophil (I/T ratio > 0.2), thrombocytopenia, absolute neutrophil count (ANC) < 1500/mm³, C-reactive Protein (CRP) > 3 mg/L. The gold standard for establishing the diagnosis of sepsis using blood cultures (Meena et al., 2020).

One of the goals in the Sustained Development Goals is to end preventable deaths in neonates and under-fives by 2030. The target to be achieved is to reduce the neonate mortality rate in 2030 by 12 per 1000 births in neonates. Early-onset neonatal sepsis is a major cause of death in neonates especially preterm infants, and is an emergency problem in neonates. In Indonesia, the mortality rate of neonatal sepsis is still high; this shows that the prevention program of neonatal sepsis has not run well, especially early-onset sepsis. Early onset sepsis prevention measures require early detection quickly, precisely and accurately. Research on screening methods or tools to detect sepsis in neonates has been widely conducted, but no one has conducted a systematic study to analyze and compare several methods to determine the most effective detection of sepsis in neonates. With the effective detection tool or method, it is hoped that early treatment can be taken to prevent the increasing the mortality rate due to sepsis.

Based on the background, it is very critical to conduct a literature review related to early detection of sepsis in neonates, to analyze the most effective and efficient detection tools or methods to be applied in Indonesia, especially at Prof. Dr. Margono Soekarjo Hospital.

The purpose of this study is to determine the early detection used to determine sepsis in neonates based on Evidence Based Research. Another purpose is to identify the types of early detection methods in sepsis neonates and their effectiveness, and finally to determine the most effective and efficient sepsis early detection method.

METHOD

The design of this article is a literature review employing the Preferred Reporting Items for Literature Review and Meta Analysis (PRISMA). The clinical questions of this literature review applied the PICO format, P (patient, population and problem), namely neonates with sepsis, I (intervention, prognostic, factor, exposure) by using techniques or methods of sepsis detection in neonates, C (comparison, control) this review does not use any comparator, and O (outcome), namely early detection of sepsis cases in neonates.

Strategy of literature searching

The literature search in this review used several databases, including Pub Med, Science Direct, EBSCO Host, and Pro Quest. The results of the search from the databases are as follows: Pub Med (n = 27), Science Direct (n = 435), EBSCO Host (n = 25) and Pro Quest (n = 35). The keywords used are "Early Detection AND Sepsis AND Neonate".

Inclusion and exclusion criteria

The inclusion criteria in this study were neonate patients (term and preterm), all early detection techniques in neonate sepsis, articles with a publication period of 2017 to 2022 and in international language (English). While the exclusion criteria were articles that could not be accessed, and those do not have any full text available.

Article quality assessment

The article quality assessment was done by applying The Joanna Briggs Institute (JBI) checklist for cohort studies, checklist for case control studies, and checklist for analytical cross-sectional studies. The JBI questionnaire contained several questions to assess the quality of the studies by giving the answers of 'yes', 'no', 'unclear' or 'not applicable' to each item.

RESULTS

The results of the literature search in Pub Med, Science Direct, EBSCO Host, and Pro Quest found 7 articles to be reviewed. They were selected from 522 articles matching the keywords. The articles were published during the period 2017 to 2022. The flow of article search, using PRISMA, can be seen in detail in Figure 1, and their summaries are presented in Table 1.
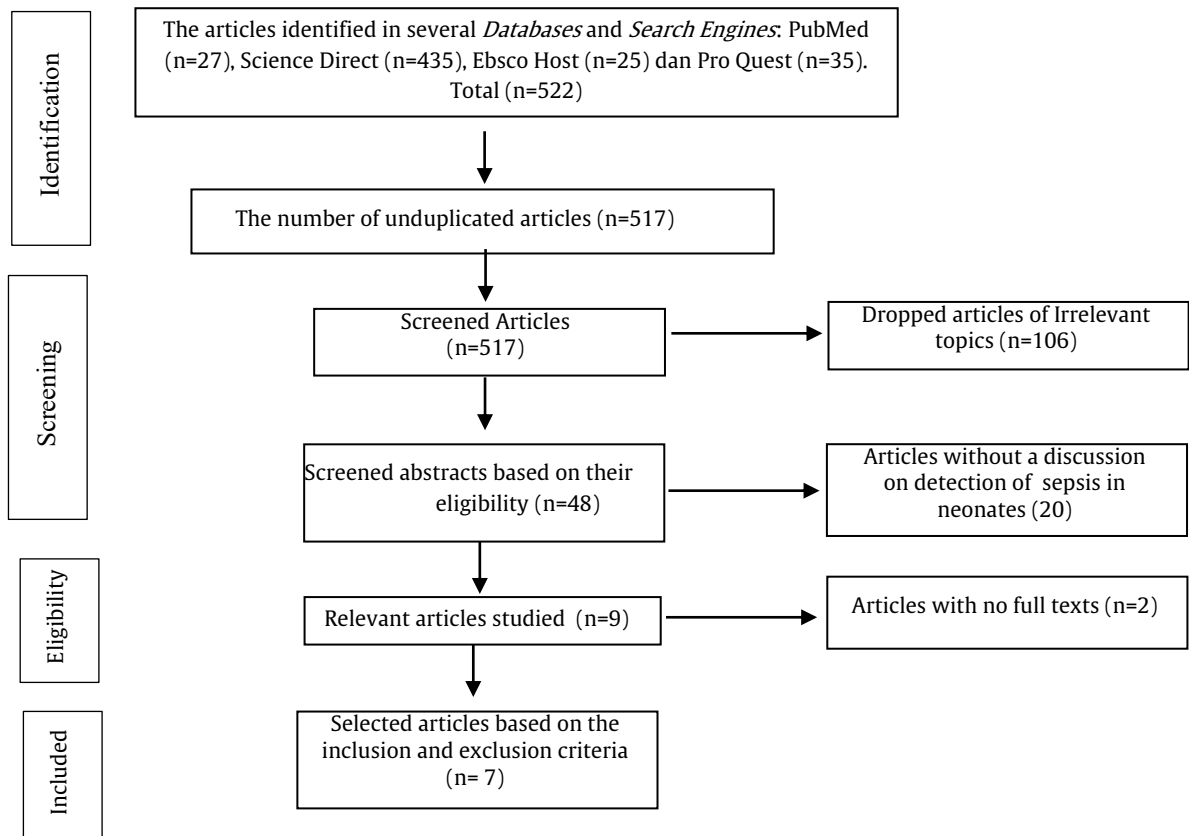
Figure 1. Chart of article selection using PRISMA

Table.1
A review result of the selected articles

Title & Author(s)	Research Design, Sample, and Sampling Techniques	Results	Research Limitation
Performance of SNAPPE II score in neonatal sepsis: an experience from a tertiary care center. Authors: Moumita Samanta, et.al Doi: 10.24953/turkjped.2020.02.004	The researcher used a prospective observational research design. A sample of 225 neonates with gestational age between 28-40 weeks with clinically suspected sepsis. The sampling technique used is purposive sampling.	There was no significant relationship between SNAPPE II scores and positive blood cultures (25.16 ± 15.6 in positive cultures vs 24.49 ± 15.6 in negative cultures).	The sample size is small, resulting in difficult subgroups to analyze. Late onset sepsis has not been included as a confounding variable.
The Value of Neutrophyl to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early Onset Neonatal Sepsis. Authors: Emrah Can, Sahin Hamilcikan dan Ceren Can Doi: 10.1097/MPH.0000000000001059	The study used a prospective observational method. The sample is 122 term neonates, 78 babies diagnosed with early onset sepsis, and 44 babies are the control group (healthy babies). The sampling technique used is purposive sampling.	Neonates in the sepsis group had significantly higher neutrophil, NLR, PLR, CRP and procalcitonin values than the non-septic neonates.	This study was only conducted on term neonates. The small number of the samples limited its results.
Comparison of NICE guideline CG149 and the sepsis risk calculator for the management of early onset sepsis on the postnatal ward Authors: Jessica Alexandra K, et.al Doi: 10.1159/000518059	The study used a prospective, multicenter observational method. The sample is 1066 of the 8856 total population of neonates. The sampling technique was purposive sampling.	The application of the SRC method to EOS incidents reduced the use of antibiotics from 601 (using the NICE guidelines) to 55 babies. In conclusion, that SRC can reduce the use of antibiotics by 74% compared to the use of NICE.	The study was only conducted on neonates with gestational age ≥ 34 weeks.

Thromboelastometry for diagnosis of sepsis associated coagulopathy: an observational study Authors: Rozeta Sokou, et.al Doi:10.1007/s00431-017-3072-z	The study used a single center observational, cohort study. The sample is 365 neonates, which are divided into; 35 diagnosed with sepsis, 56 neonates with suspected sepsis, and 274 healthy babies as the control group. The sampling technique was purposive.	ROTEM (Rotational Thromboelastometry) parameters consisting of CT (Clotting time), CFT Clot Formation Time), and MCF (Maximal clot Firmness) show a clearer hypocoagulant profile in septic neonates with hemorrhagic diathesis. ROTEM can be a useful tool in the early detection of sepsis in neonates.	It used a relatively small sample size, which can affect its diagnostic accuracy. The variation in measurement time and lack of serial measurements can also affect its test results.
Predicting outcome in neonates with possible clinical sepsis by estimating an early score for neonatal acute physiology II (SNAP II) Authors: Somalika Pal, et.al Doi: 10.1093/tropej/fmz076	The study used a cohort prospective observational study. Samples were 100 neonates, with weights ranging from 1000 g, with gestational ages ranging from 28 weeks. The sampling technique used purposive sampling technique.	SNAP II and its parameters have high sensitivity and specificity in predicting the probability of sepsis in neonates and can predict the severity of disease progression.	The sample in the study is still small, thus limiting its result.
Interleukin-6 a biomarker of early onset neonatal sepsis Authors: Cortes Jose,S., et.al Doi: 10.1055/s-0040-1710010	The study used an observational study, a case control study. Total sample 93 newborns consisted of 31 cases and 62 controls. The sampling technique used convenience sampling technique.	Interleukin-6 has greater potential to detect early onset sepsis (EOS) than late onset sepsis (LOS). Meanwhile, CRP shows greater potential in detecting late onset sepsis (LOS).	The sample size is still inadequate, because the small number of patients treated with a clinical history of chorioamnionitis during pregnancy. The presence of amniotic fluid mixed with meconium, the presence of hypotension or hypoperfusion during neonatal care makes its low accuracy in the confidence interval.
Comparison of procalcitonin versus C reactive protein in the detection of neonatal sepsis Authors: Wahid Ali, et.al Doi:10.51253/pafmj.v72i1.2478	This is a cross sectional study. The sample consisted of 154 infants with an average age of 6.1 ± 3.8 days. The sampling technique used a convenient sampling technique.	C Reactive Protein (CRP) has a sensitivity of 50.9% and a specificity of 28.7%. While procalcitonin has a sensitivity value of 73.6% and a specificity of 38.6%. In conclusion, procalcitonin has higher sensitivity and specificity than CRP in the diagnosis of early onset neonatal sepsis or EOS.	Larger studies are needed to assess the diagnostic benefit of the tests under investigation.

DISCUSSION

Early detections of sepsis in neonates refer to methods and tools used to detect early the presence of risk factors and signs of infection in newborns up to 28 days. Blood culture is the gold standard for diagnosing septicemia in neonates, but this examination takes a long time, so it can cause delays in intervention and management, having an impact on increasing the incidence of morbidity and mortality (Ali et al., 2022). Therefore, a method is needed to predict the presence of sepsis in neonates quickly and accurately. Many studies have studied methods that can detect sepsis early, either in the form of methods to assess the physical symptoms of sepsis or from the laboratory values of sepsis markers or biomarkers. The methods used include SNAPPE II score, Sepsis Risk Calculator (SRC), and laboratory tests such as procalcitonin, C Reactive Protein (CRP), thrombo-elastometry, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and interleukin-6.

SNAP II and SNAPPE II

Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE II) developed and validated by Richardson et.al in 2001, is one of the scores to predict morbidity and mortality in sick neonates in the hospital. In 2007 for the first time the SNAPPE II score was used to detect early onset sepsis, by applying SNAPPE II in the first 12 hours of the newborn. SNAPPE II consists of 6 parameters, namely Mean Artery Pressure (MAP), body temperature, PaO2/FiO2, blood pH, seizures, and urine output. The more severe the physical symptoms of each parameter are, the higher the scores will be. The best score has a value of 0 and the highest score is 115. A research of Samanta et al., (2020) showed that there was no significant relationship between SNAPPE II scores and blood culture results; there was a significant relationship between mortality in neonatal sepsis and an increase in SNAPPE II scores. In his study, it was also found that the performance of SNAPPE II score was very sensitive in

predicting the mortality rate of sepsis neonates at gestational age between 32-36 weeks. However, it could not predict well in neonates with gestational age less than 32 weeks. It is possible that prematurity and asphyxia of neonates were confounding factors, resulting in a biased effect in the study. The sensitivity value of the SNAPPE II score in the study (Samanta et al., 2020) was 74.5%, specificity of 48.3%, PPV of 27.6% and NPV of 87.7% at a cut-off value of ≥ 20. Another study (Pal et al., 2020), indicated that the Score for Neonatal Acute Physiology (SNAP II) limit was ≥44 which could predict mortality due to sepsis in neonates, with a sensitivity value of 99.99%, and specificity of 75%. Different results were conveyed by Anne et al., (2023) in their study that delta SNAP II (results of serial assessment of SNAP II scores) does not have a good discriminatory ability to predict mortality in neonates with severe sepsis. Some parameters in this SNAPPE II score, i.e. blood PH and PaO2/FiO2 ratio, require blood gas analysis examination. In Indonesia, the implementation of blood gas analysis examination is limited to type A and B hospitals or referral hospitals, so that the use of SNAPPE II score cannot be applied thoroughly.

SRC and NICE CG149

One of the interventions in neonates suspected of sepsis is empirical antibiotic administration. Sepsis Risk Calculator (SRC) is an instrument used to assess and to evaluate the risk of Early Onset Sepsis (EOS) in neonates; it is used as a guideline in giving empirical antibiotics. The SRC was developed by the Kaiser Permanente research group. The aim of its development was to reduce the proportion of antibiotic use in neonates. Based on the research of Kimpton et al., (2021), it explained that the use of SRC can reduce the use of antibiotics from 601 recommended by NICE CG149 to 55 neonates who received antibiotics according to SRC guidelines, meaning a 90.8% reduction.

This study was limited to neonates with gestational age ≥ 34 weeks. They were treated using antibiotics in the postpartum room. It did not examine the neonates treated in the NICU room. The application of SRC method needs to be applied with better observation, and more care because it relates to antibiotic administration in neonates. Then, the study recommends to provide resources to conduct a clinical monitoring and evaluation of EOS cases being observed. SRC was adopted in clinical practice in the UK for screening and management of EOS because it has been shown to potentially reduce antibiotic use interventions in full-term neonates and can increase early discharge from hospital by > 50% Goel et al., (2020) and (Goel et al., 2022). The other study was conducted by Snoek et al., (2022), comparing the sensitivity between SRC, the Dutch and NICE. SRC recommended the use of less antibiotics (36%) in neonates suspected of sepsis, compared to the Dutch (50%) and NICE (55%). However, SRC recommended a further treatment in neonates suspected of sepsis at a greater rate (52%) compared to the Dutch (31%) and NICE (30%). The SRC method recommends blood culture examination in neonates with a moderate risk. Different statement was conveyed by Morris et al., (2020) that between SRC and NICE had poor results in identifying EOS in neonates

Procalcitonin (PCT) and C- reactive protein (CRP)

In addition to physical signs that can indicate sepsis in neonates, some laboratory tests can also detect its early signs. Procalcitonin (PCT) and CRP are the most commonly used biomarkers to detect neonate sepsis. Procalcitonin is a peptide precursor of the hormone calcitonin which is produced in response to endotoxins due to bacterial infection and is related to the severity of the infection. CRP is a protein compound secreted by the liver and is produced in large quantities during infection. In their research, Ali et al., (2022) compared procalcitonin and CRP in detecting early onset sepsis in neonates. Based on the results of the study, the sensitivity value of procalcitonin was 73.6% and its specificity was 38.6%. Meanwhile the CRP had a sensitivity value of 50.9% and a specificity of 28.7%. Thus, the procalcitonin detects more accurately the presence of early-onset sepsis in neonates compared to CRP. The same statement was conveyed by Morad et al., (2020), namely PCT has better characteristics in detecting neonatal sepsis compared to CRP and interleukin-6, with a sensitivity value of 97.6%, specificity of 89% and accuracy of 96%. Frerot et al., (2019) examined the association of umbilical vein blood procalcitonin levels with the incidence of early-onset sepsis in very premature neonates. They concluded that procalcitonin levels with a threshold value of 0.7 µg/L had a sensitivity value of 69% and specificity of 70%. The study was conducted on neonates born with gestational age between 24 to 27 weeks, with signs of early onset sepsis, including leukopenia (leukocyte value < 5000/mm³), leukocytosis (leukocyte value ≥ 21,000/mm³), CRP value > 10 mg/dL, and clinical signs such as lethargy, hypothermia, indigestion, apnea, cyanosis, desaturation, bradycardia, poor perfusion and hypotension. Harsanti et al., (2016) also conducted a study using procalcitonin and tollner scores in detecting sepsis in neonates, obtained the results of an increase in procalcitonin levels comparable to an increase in tollner scores. Despite of its higher cost than CRP, procalcitonin is more ideal for diagnosing sepsis in neonates. Hakiem et al., (2020) argued that there was a significant relationship between CRP values and the incidence of sepsis in neonates, especially premature neonates. With a cut off value of 0.64 mg/dl, it has a sensitivity value of 90% and a specificity of 86.7%. Neonate with CRP value > 0.64 mg/dl has 32 times potential to experience neonate sepsis. This study recommends CRP examination to detect the presence of sepsis in premature neonates in the meantime waiting a confirming result of blood culture examination. The same statement was conveyed by Aydemir et al., (2018) in their study that PCT and CRP rates are significantly higher in preterm neonates with sepsis. Beltempo et al., (2018) also stated that the combination of CRP and complete blood count (CBC) can be used to detect LOS, especially in neonates with very low birth weight. For developing countries, with low socioeconomic conditions, procalcitonin is the main choice to detect sepsis more quickly and precisely, so as to reduce the cost of care and treatment.

Neutrophil Lymphosyte Ratio (NLR) and platelet Lymphosyte Ratio (PLR)

The body's physiological immune response to infectious agents and processes is to increase the total number of leukocytes and neutrophils and decrease the number of lymphocytes (Can, Hamilcikan, & Cen, 2018). In their research, Can, et al. (2018) investigated the Neutrophil Lymphocyte Ratio (NLR), and Platelet Lymphocyte Ratio (PLR) to predict the incidence of sepsis in neonates. The results showed that NLR and PLR were significantly associated with the incidence of early onset sepsis in neonates, with the same sensitivity NLR (cut off value 6.76) and PLR (cut off value 94.05) of 97.4%, specificity 100%. NLR and PLR do not require additional costs, because these values

are obtained from routine blood tests. The same thing was conveyed by Alkan Ozdemir et al., (2018) in their research, which stated that NLR together with CRP is more effective in detecting sepsis in neonates, with an easy, cheap, simple, and fast method. NLR with a cut off value of 1.42 with a probability ratio of 5.5 has a sensitivity of 88% and specificity of 84% in predicting EOS in neonates (Karabulut & Alatas, 2021). The shortcomings this study is its limited samples of full-term or term neonates; it had not been carried out in less-month or preterm neonates. In addition to high neutrophil values or neutrophilia, a sign of sepsis in neonates is a decrease in neutrophil content or what is referred to as neutropenia. This condition is often associated with immunocompromised conditions. In their research, Beaulieu et al., (2017) stated that neutropenia taken from cord blood samples was significantly associated with early-onset sepsis in neonates with good specificity value, but low sensitivity value. A similar research was conducted by Arcagok & Karabulut, (2019) using the results of PLR, CRP, PCT, WBC (White Blood Cell) and I/T ratio (Immature to Total neutrophil) as parameters to predict sepsis in neonates. The results of their study indicated that PLR has higher sensitivity and specificity compared to other biomarkers in predicting sepsis in neonates. PLR value in neonates suspected of sepsis has a sensitivity of 88.9% and specificity of 94.7% with a cut off value of 39.5. In EOS positive neonates, the PLR value with a cut off of 57.7 had a sensitivity of 91.4% and specificity of 97.6%. Arcagok & Karabulut, (2019) also recommended PLR as a biomarker to detect sepsis in neonates. In addition to having better sensitivity and specificity, it is more efficient in terms of cost and blood to test, and it is easy to do and to measure.

Thromboelastometry (EXTEM)

Another laboratory value parameter used to detect sepsis in neonates is thromboelastometry with the Extrinsically Activated Thromboelastometry (EXTEM) method. The variables measured in thromboelastometry examination are Clotting Time (CT), Clot Formation Time (CFT), and Maximal Clot Firmness (MCF). CT is the latency time from the addition of reagent into the blood until the clot starts to form. CFT is the time from CT until the clot firmness point reaches 20 mm. This parameter indicates the speed of clot formation, mainly influenced by platelet function. MCF or maximum clot firmness indicates the absolute strength of the fibrin and platelet clot. Of several extem parameters, A10 is the strongest variable for detecting sepsis in neonates, besides extem 10 is independently and significantly associated with an increased risk of death in neonates with severe illness (Sokou et al., 2022). According to Sokou et al., (2018), thromboelastometry values were used to detect coagulopathy in sepsis neonates. Hypocoagulation was found more in sepsis neonates with hemorrhagic diathesis. The ability of thromboelastometry test to detect coagulopathy induced by the presence of sepsis, can be used to detect sepsis in neonates. The disadvantage of this study is that the time of thromboelastometry test implementation still varies. There is no certain indicator of the right time to do the test, so that a serial test is required.

Interleukin-6

In neonate sepsis, immune cells will be activated by bacterial or pathogenic products coming into the body such as lipopolysaccharides which stimulate the secretion of interleukins including IL-1 β, IL-6 and IL-10. IL-6 is the most commonly found and studied cytokine in neonate sepsis. IL-6 levels will increase in number at 2 to 6 hours from the onset of infection and will decrease in the following 24 to 48 hours (Sharma et al., 2018). Hence, IL-6 can be used in detecting sepsis in neonates early. An increase in IL-6 will induce an increase in CRP synthesis in the liver so that it will increase its level in the blood. Cortés et al., (2021) explained that interleukin-6 has greater potential to detect early onset sepsis (EOS) than late onset sepsis (LOS), with a cut off value of 0.6869 pg/ml and the optimal limit is 17.75 pg/ml. This occurred because the sampling time with the onset of symptoms was not appropriate, while IL-6 will decrease rapidly in number after 24-48 hours after the infection onset. Qiu et al., (2018) also stated that interleukin-6 is one of the sensitive and specific markers of neonatal sepsis, especially in neonates with premature rupture of membranes. A similar study conducted by Tessema et al., (2020) in their research recommends that the combined use of interleukin-6 and CRP can increase sensitivity in detecting sepsis in neonates.

Based on the neonatal service guidelines (IDAI, 2018), supporting examinations of neonatal sepsis include I/T ratio, total neutrophil value, leukocyte count, platelet count, blood culture, lumbar puncture, and biomarkers including CRP, procalcitonin, serum amyloid-A, interleukin 1 (IL-1), IL-2, IL-8, interferon gamma and surface antigen cells. The laboratory examination can be adjusted to the ability and availability of facilities in the hospital. In Indonesia, there are three strata of Comprehensive Emergency Obstetric and Newborn Care facilities, namely intermediate, main and complete (Kemenkes, RI, 2022). There are 16 complete, 34 main and 320 intermediate facilities in Indonesia. The standard criteria for laboratory examination of blood culture and identification of bacterial species are provided in the complete hospitals. However, many hospitals with the primary level are also able to perform blood culture and bacterial identification. Several methods can be applied to detect sepsis in neonates while waiting for blood culture results. However, its implementation can be adjusted to the resources available. In RSUD Prof. Dr. Margono Soekarjo, the detection method of sepsis incidence in neonates can be applied by CRP, PLR, NLR, and sepsis calculator as they have been available.

RESEARCH LIMITATIONS

The limitation of this study is its nature as a literature review, not a meta-analysis. The research designs in the articles used are cohort study, case control study and cross-sectional study. The number of articles analyzed is still few, which may affect the quality of the results.

CONCLUSIONS AND SUGGESTIONS

Early detection ways of sepsis in neonates include methods and tools to detect early the presence of risk factors and signs of infection in newborns up to 28 days. Many studies have investigated methods that can detect sepsis early, either in the form of methods to assess physical symptoms of sepsis or from laboratory values of sepsis markers or biomarkers. Although blood culture is the gold standard for diagnosing sepsis, some methods can detect sepsis earlier and faster. Thus, an early intervention can be done and can reduce morbidity and mortality of neonates

with sepsis. SNAP II with a cut off value of ≥44 can predict mortality due to sepsis in neonates, with a sensitivity value of 99.99%, and specificity of 75%. The SRC method recommends blood culture examination in neonates with a moderate risk. For developing countries, with low socio-economic conditions, procalcitonin is the main choice to detect sepsis more quickly and precisely, thus reducing the cost of care and treatment. Neutropenia taken from cord blood samples is significantly associated with early-onset sepsis in neonates with good specificity, but low sensitivity. The ability of thromboelastometry test to detect coagulopathy induced by the presence of sepsis, can be used to detect sepsis in neonates, but there is no certainty of the right time to do the test. Interleukin-6 has a greater potential to detect early onset sepsis (EOS) than late onset sepsis (LOS). Some of these methods can be applied to detect sepsis in neonates in Indonesia, but the implementation can be adjusted to the resources available in each hospital. In RSUD Prof. Dr. Margono Soekarjo, the detection methods of sepsis incidence in neonates can be done by CRP, PLR, NLR, and sepsis calculator methods because it has the resources to implement them.

REFERENCES

Ali, W., Shirazi, H., Gul, S., Halim, A., Ain, Q. U., & Zaman, Q. (2022). *Comparison of Procalcitonin Versus C Reactive Protein in The Detection of Neonatal Sepsis. 72*(1), 131–136.

Alkan Ozdemir, S., Arun Ozer, E., Ilhan, O., & Sutcuoglu, S. (2018). Can neutrophil to lymphocyte ratio predict late-onset sepsis in preterm infants? *Journal of Clinical Laboratory Analysis*, *32*(4), 4–8. https://doi.org/10.1002/jcla.22338

Anne, R. P., Sundaram, V., & Kumar, P. (2023). Change in Score for Neonatal Acute Physiology-II Measurements for Prediction of Mortality in Severely Septic Preterm Neonates. *Indian journal of pediatrics*, *90*(4), 348–354. https://doi.org/10.1007/s12098-022-04190-4

Arcagok, B. C., & Karabulut, B. (2019). Platelet to lymphocyte ratio in neonates: A predictor of early onset neonatal sepsis. *Mediterranean Journal of Hematology and Infectious Diseases*, *11*(1), 1–8. https://doi.org/10.4084/MJHID.2019.055

Aydemir, C., Aydemir, H., Kokturk, F., Kulah, C., & Mungan, A. G. (2018). The cut-off levels of procalcitonin and C-reactive protein and the kinetics of mean platelet volume in preterm neonates with sepsis. *BMC Pediatrics*, *18*(1), 1–12. https://doi.org/10.1186/s12887-018-1236-2

Beaulieu, E., Massé, E., & Dallaire, F. (2017). Cord blood neutropenia is an independent predictor of early sepsis. *Journal of Perinatology*, *37*(11), 1204–1209. https://doi.org/10.1038/jp.2017.115

Beltempo, M., Viel-Thériault, I., Thibeault, R., Julien, A. S., & Piedboeuf, B. (2018). C-reactive protein for late-onset sepsis diagnosis in very low birth weight infants. *BMC Pediatrics*, *18*(1), 1–8. https://doi.org/10.1186/s12887-018-1002-5

Can, E., Hamilcikan, Ş., & Can, C. (2018). The Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio for Detecting Early-onset Neonatal Sepsis. *Journal of Pediatric Hematology/Oncology*, *40*(4), e229–e232. https://doi.org/10.1097/MPH.0000000000001059

Cortés, J. S., Losada, P. X., Fernández, L. X., Beltrán, E., DeLaura, I., Narváez, C. F., & Fonseca-Becerra, C. E. (2021). Interleukin-6 as a Biomarker of Early-Onset Neonatal Sepsis. *American Journal of Perinatology*, *38*(S 01), e338–e346. https://doi.org/10.1055/s-0040-1710010

Frerot, A., Baud, O., Colella, M., Taibi, L., Bonacorsi, S., Alberti, C., Mohamed, D., & Biran, V. (2019). Cord blood procalcitonin level and early-onset sepsis in extremely preterm infants. *European Journal of Clinical Microbiology & Infectious Diseases : Official Publication of the European Society of Clinical Microbiology*, *38*(9), 1651–1657. https://doi.org/10.1007/s10096-019-03593-0

Goel, N., Shrestha, S., Smith, R., Mehta, A., Ketty, M., Muxworthy, H., Abelian, A., Kirupaalar, V., Saeed, S., Jain, S., Asokkumar, A., Natti, M., Barnard, I., Pitchaikani, P. K., & Banerjee, S. (2020). Screening for early onset neonatal sepsis: NICE guidance-based practice versus projected application of the Kaiser Permanente sepsis risk calculator in the UK population. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, *105*(2), F118–F122. https://doi.org/10.1136/archdischild-2018-316777

Goel, N., Cannell, S., Davies, G., Natti, M. S., Kirupaalar, V., Abelian, A., Saeed, S., Smith, R., Manikonda, R., Pitchaikani, P. K., Davies, D., Morris, R. M., Edwards, L., Govindaraju, R., Creese, K., Jones, J., Choudhary, J., Rowley, S., Sethuraman, C., Muxworthy, H., … Banerjee, S. (2022). Implementation of an adapted Sepsis Risk Calculator algorithm to reduce antibiotic usage in the management of early onset neonatal sepsis: a multicentre initiative in Wales, UK. *Archives of disease in childhood. Fetal and neonatal edition*, *107*(3), 303–310. https://doi.org/10.1136/archdischild-2020-321489

Hakiem, F., Susanah, S., & Yuniati, T. (2020). Hubungan antara Nilai C–Reactive Protein, Immature To Total Neutrophil Ratio, dan Red Cell Distribution Width dengan Kejadian Sepsis Neonatorum Bayi Prematur. *Sari Pediatri*, *21*(4), 218. https://doi.org/10.14238/sp21.4.2019.218-25

Harsanti, A., Sekarwana, N., & Rusmil, K. (2016). Perbedaan Skor Sepsis Modifikasi Tollner dan Kadar Procalsitonin Serum Sebelum dengan Setelah Pemberian Antibiotik Empiris pada Sepsis Neonatorum. *Sari Pediatri*, *16*(3), 178. https://doi.org/10.14238/sp16.3.2014.178-82

IDAI. (2018). *BUKU PANDUAN PELAYANAN NEONATAL UKK NEONATOLOGI PP IDAI Edisi pertama Penyunting : Adhi Teguh Perma Iskandar Kartika Darma Handayani Rocky Wilar Setyadewi Lusyati Tetty Yuniati Toto Wisnu Hendrarto Tunjung Wibowo.*

Karabulut, B., & Alatas, S. O. (2021). Diagnostic Value of Neutrophil to Lymphocyte Ratio and Mean Platelet Volume on Early Onset Neonatal Sepsis on Term Neonate. *Journal of Pediatric Intensive Care*, *10*(02), 143–147. https://doi.org/10.1055/s-0040-1715104

Kemenkes RI. (2016). *Profil Kesehatan Indo-nesia*. https://pusdatin.kemkes.go.id/resources/download/pusdatin/profil-kesehatan-indonesia/Profil-Kesehatan-indonesia-2019.pdf

Kimpton, J. A., Verma, A., Thakkar, D., Teoh, S., Verma, A., Piyasena, C., & Battersby, C. (2021). Comparison of NICE Guideline CG149 and the Sepsis Risk Calculator for the Management of Early-Onset Sepsis on the Postnatal Ward. *Neonatology*, *118*(5), 562–568. https://doi.org/10.1159/000518059

Meena, R., Meena, K. K., Athwani, V., Gothwal, S., Bairwa, G. S., & Sitaraman, S. (2020). Umbilical Cord Blood Culture in Diagnosis of Early Onset Neonatal Sepsis. *Indian Journal of Pediatrics*, *87*(10), 793–797. https://doi.org/10.1007/s12098-020-03345-5

Morad, E. A., Rabie, R. A., Almalky, M. A., & Gebriel, M. G. (2020). Evaluation of Procalcitonin, C-Reactive Protein, and Interleukin-6 as Early Markers for Diagnosis of Neonatal Sepsis. *International Journal of Microbiology*, *2020*. https://doi.org/10.1155/2020/8889086

Morris, R., Jones, S., Banerjee, S., Collinson, A., Hagan, H., Walsh, H., Thornton, G., Barnard, I., Warren, C., Reid, J., Busfield, A., & Matthes, J. (2020). Comparison of the management recommendations of the Kaiser Permanente neonatal early-onset sepsis risk calculator (SRC) with NICE guideline CG149 in infants ≥34 weeks' gestation who developed early-onset sepsis. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, *105*(6), 581–586. https://doi.org/10.1136/archdischild-2019-317165

Pal, S., Jain, A., Garg, M., & Sekhar, J. C. (2020). Predicting Outcome in Neonates with Possible Clinical Sepsis by Estimating an Early Score for Neonatal Acute Physiology-II (SNAP-II). *Journal of Tropical Pediatrics*, *66*(4), 377–384. https://doi.org/10.1093/tropej/fmz076

Qiu, X., Zhang, L., Tong, Y., Qu, Y., Wang, H., & Mu, D. (2018). Interleukin-6 for early diagnosis of neonatal sepsis with premature rupture of the membranes A meta-analysis. *Medicine (United States)*, *97*(47), 1–8. https://doi.org/10.1097/MD.0000000000013146

Samanta, M., Biswas, C., Pal, N. K., Sarkar, S., Goswami, A., Hazra, A., Bhowmik, A., & Sabui, T. K. (2020). Performance of SNAPPE-II score in neonatal sepsis: an experience from a tertiary care center. *The Turkish Journal of Pediatrics*, *62*(2), 191–198. https://doi.org/10.24953/turkjped.2020.02.004

Sharma, D., Farahbakhsh, N., Shastri, S., & Sharma, P. (2018). Biomarkers for diagnosis of neonatal sepsis: a literature review. *Journal of Maternal-Fetal and Neonatal Medicine*, *31*(12), 1646–1659. https://doi.org/10.1080/14767058.2017.1322060

Snoek, L., van Kassel, M. N., Krommenhoek, J. F., Achten, N. B., Plötz, F. B., van Sorge, N. M., Brouwer, M. C., van de Beek, D., & Bijlsma, M. W. (2022). Neonatal early-onset infections: Comparing the sensitivity of the neonatal early-onset sepsis calculator to the Dutch and the updated NICE guidelines in an observational cohort of culture-positive cases. *EClinicalMedicine*, *44*, 101270. https://doi.org/https://doi.org/10.1016/j.eclinm.2021.101270

Sokou, R., Giallouros, G., Konstantinidi, A., Pantavou, K., Nikolopoulos, G., Bonovas, S., Lytras, T., Kyriakou, E., Lambadaridis, I., Gounaris, A., Douramani, P., Valsami, S., Kapsimali, V., Iacovidou, N., & Tsantes, A. E. (2018). Thromboelastometry for diagnosis of neonatal sepsis-associated coagulopathy: an observational study. *European Journal of Pediatrics*, *177*(3), 355–362. https://doi.org/10.1007/s00431-017-3072-z

Sokou, R., Ioakeimidis, G., Piovani, D., Parastatidou, S., Konstantinidi, A., Tsantes, A. G., Lampridou, M., Houhoula, D., Iacovidou, N., Kokoris, S., Vaiopoulos, A. G., Gialeraki, A., Kopterides, P., Bonovas, S., & Tsantes, A. E. (2022). Development and validation of a sepsis diagnostic scoring model for neonates with suspected sepsis. *Frontiers in Pediatrics*, *10*(October), 1–15. https://doi.org/10.3389/fped.2022.1004727

Suwarna, N. O., Yuniati, T., Cahyadi, A. I., Achmad, T. H., & Agustian, D. (2022). Faktor Risiko Kejadian Sepsis Neonatorum Awitan Dini di Rumah Sakit Umum Pusat Dr. Hasan Sadikin Bandung. *Sari Pediatri*, *24*(2), 99. https://doi.org/10.14238/sp24.2.2022.99-105

Tessema, B., Lippmann, N., Willenberg, A., Knüpfer, M., Sack, U., & König, B. (2020). The diagnostic performance of interleukin-6 and c-reactive protein for early identification of neonatal sepsis. *Diagnostics*, *10*(11), 1–12. https://doi.org/10.3390/diagnostics10110978