Current Science International
Volume: 13 | Issue: 01| Jan. - March| 2024

EISSN:2706-7920 ISSN: 2077-4435
DOI: 10.36632/csi/2024.13.1.8
Journal homepage: www.curresweb.com
Pages: 96-110

The Utility of Early Onset Sepsis Calculator and Procalcitonin in Prediction of Early Onset Neonatal Sepsis

Wafaa O. Ahmed[1], Mohamed A. Abd El Wahed[2], Walaa H. Ali[3], Heba E. Hashem[4] and Marwa S. Abo-Rageh[5]

[1]Assistant Professor of Pediatric, Faculty of Medicine, Ain Shams University, Egypt.
[2]Professor of Pediatric, Faculty of Medicine, Ain Shams University, Egypt.
[3]Assistant Professor Researcher, Child Health Department, National Research Centre, Cairo, Egypt.
[4]Lecturer of Clinical Pathology, Faculty of Medicine, Ain Shams University, Egypt
[5]Pediatric Resident, El-Gomhoreya General Hospital, Ministry of Health, Alexandria, Egypt.

Received: 08 June 2023 **Accepted:** 27 Dec. 2023 **Published:** 30 Jan. 2024

ABSTRACT

Objectives: Neonatal sepsis refers to an infection involving blood stream in newborn infants less than 28 days old. It continues to remain a leading cause of morbidity and mortality among infants, especially in middle and lower-income countries. Early onset sepsis (EOS) occurs before 72 hours. This study was designed to appraise the diagnostic and predictive role of proclcitonin and the role EOS calculator in tailoring the management of EOS and comparing between the ability of EOS calculator and Procalcitonin in Prediction of Early Onset Sepsis. **Methods:** This cross sectional study included 56 neonates with suspect EOS and other 16 healthy controls (age and sex matched). They were subjected to thorough history taking, full clinical examination and assessment of procalcitonin and EOS calculator score. **Results:** procalcitonin showed significant higher levels in neonates with EOS than healthy controls(P<0.001). Also, the EOS calculator were significantly higher in neonates with EOS (P<0.001). **Conclusion:** The present investigation provides a distinct evidence for the prominence of EOS burden. The EOS calculator aided in early detection with subsequent proper management of EOS. The EOS calculator provides a non invasive tool for detection of EOS.

Keywords: EOS, EOS calculator, procalcitonin.

1. Introduction

A neonatal's dysregulated reaction to infection results in sepsis, a potentially fatal organ failure. One of the most frequent causes of newborn morbidity and mortality in the preterm population is early onset neonatal sepsis (EONS). The age at which EONS manifested itself varied, with neonates experiencing bacteremia at less than 72 hours (Ognean *et al.*, 2017).

In the UK, the frequency of culture-positive sepsis is 9/1000 admissions and 0.9/1000 live births, according to the Neonatal Infection Surveillance Network. Even though early onset neonatal sepsis (EONS) is uncommon, if treatment for EONS is delayed, there is a substantial risk of death (Sgro *et al.,* 2019).

According to a recent study involving 400,000 newborns, the death rate from EONS remains at 16% even with neonatal intensive care. Infants with low birth weight and the most undeveloped are more vulnerable to mortality. 85% of newborns with EONS will exhibit symptoms during the first 24 hours of birth, despite the fact that clinical indicators of sepsis are inconsistent and unpredictable (Ohlin *et al.,* 2010, Singh *et al.,* 2022).

The bacteria that are most frequently linked to extracellular organic nitrogen syndrome (EONS) are Group B streptococcus (GBS), E coli, Coagulase-negative Staphylococcus, H influenzae, and L monocytogenes. There are several factors connected to the maternal factors and related to the neonatal factors that enhance the frequency of EONS (Chacko and Sohi, 2005).

Corresponding Author: Wafaa O. Ahmed, Assistant professor of Pediatric, Faculty of Medicine, Ain Shams University, Egypt. E-mail: - wafaaosman83@med.asu.edu.eg

A positive culture from a sterile location is the gold standard for diagnosing neonatal sepsis; however, preliminary inconclusive culture findings may not be available for 48 to 72 hours, and in these cases, competent clinical judgment is sometimes required for the beginning and maintenance of antimicrobials (Sorsa, 2019).

Blood tests should be carried out 6 to 12 hours after delivery to allow for an inflammatory response. These tests include the complete blood count and acute phase reactants, such as procalcitonin (PCT) and C-reactive protein (CRP). The entire blood count is time-dependent (Ruan *et al.,* 2018).

Under normal circumstances, the C cells of the thyroid gland create procalcitonin (PCT), which is the precursor of calcitonin hormone, in extremely small amounts. In bacterial sepsis, it is primarily generated as an acute-phase reactant. In response to bacterial lipopolysaccharide (LPS), a strong inducer of PCT into the bloodstream, it is produced by macrophages and monocytes of several organs during severe bacterial infection (AitOufella *et al.,* 2021).

The best time to measure PCT in neonatal sepsis, the ideal diagnostic values, and the cut-off level for differentiating neonatal sepsis are still up for debate, despite the fact that PCT is now used in many countries due to its quicker and more accurate diagnosis of the condition (Eichberger *et al.,* 2022).

The heterogeneities of the study methods (definitions of neonatal sepsis, timing of blood cultures and PCT sampling, as well as cut-off points) and the different population studies may have contributed to the variability in the PCT diagnostic values that had been observed in various sensitivity studies with a range of 60% to 100% and specificities of 79% to 100%. Regardless of the kind of microorganisms they had been infected with, the PCT levels were likewise shown to have been significantly greater in the culture positive group at all evaluation time points, as demonstrated by their respective PCT values of > 10 ng/mL (Hincu *et al.,* 2020 and walaa *et al.,* 2020).

Kaiser Permanente has released a new online tool called the Early Onset Sepsis Calculator. Based on maternal risk factors and neonatal examination, this publicly accessible online tool can be used to assess early onset sepsis in infants 34 weeks gestational age or more. By entering values for the designated maternal risk factors and the infant's clinical presentation, the interactive calculator calculates the chance of early onset sepsis per 1000 newborns (Neonatal early-onset sepsis calculator, 2021).

Although physical examinations of the children greatly enhanced the identification of EOS cases, 40% of EOS cases may not have been classified as high-risk at delivery. This gap was filled with additional recommendations from the online EOS Calculator that combined the multivariate model and clinical findings. These recommendations included "strongly consider antibiotics" for all infants exhibiting clinical signs of illness or performing more frequent vital signs and/or blood cultures for infants with intermediate risk estimates. A number of children with EOS in their cohort must have been found when ongoing examinations revealed postnatal development of clinical indications. The developers "recognized that a septic infant might appear well at birth and then develop symptoms later" (Joshi *et al.,* 2022).

Although this tool still needs to be validated, this work significantly advances our understanding of EOS ascertainment because standardized physical examinations add valuable information, ongoing clinical monitoring is crucial to identify infants with EOS who would not otherwise be identified, and known maternal risk factors alone are not sufficiently predictive (Benitz & Achten, 2020).

In this edition, Pettinger *et al.* (2020) use a set of published EOS cases for which there is enough data to compare case ascertainment using the calculator-based approach to ascertainment using NICE guidelines.

The Kaiser Permanente Calculator (KPC), a robust logistic regression model that provides individualized evaluations of early-onset sepsis risk in neonates ≥ 34 weeks gestation, was developed by researchers at Kaiser to reduce unnecessary hospital admission and antibacterial treatment to well-appearing infants (Kopsidas *et al.,* 2022).

Ultimately, around 40% of all newborns were exposed to antibiotics before to delivery as a result of suspected chorioamnionitis, maternal GBS intrapartum antibiotic prophylaxis (IAP) confirmed, and maternal surgical prophylaxis in cesarean deliveries (Miselli *et al.,* 2022).

Hence, in the absence of a culture-proven infection, neonatal health practitioners should weigh the benefits and risks of starting antibiotic therapy for neonates with suspected EOS as well as the length of the antibiotic course. To reduce the use of antibiotics, a combination of clinical techniques and evidence-based antibiotics programs may be helpful (Huseynova *et al.,* 2021).

Based on the level of risk, there are three categories for sepsis risk per 1000 live births at birth (Morris *et al.,* 2020). The newborn's developing clinical exam and this risk score are then used to suggest antibiotic treatment (Vaccina *et al.,* 2021).

2. Patient and Methods

This six-month cross-sectional study was place at the Neonatal Intensive Care Unit (NICU) of the Ain Shams University Maternity Hospital. Based on clinical signs and maternal risk factors, 56 infants who were born at 34 weeks or more gestational age and were suspected of having EOS were included in the study. If there is even one clinical sign, such as apnea, convulsions, cardiac resuscitation, mechanical ventilation, shock, or suspected or confirmed infection in another infant in the event of multiple pregnancies, the newborn is suspected of having EOS.

The study included babies with two risk factors or clinical indicators: confirmed prelabour rupture of membranes at term for more than 24 hours before the onset of labor; confirmed invasive group B streptococcal infection in a previous pregnancy or in the current one; preterm birth; intrapartum fever higher than 38°C; clinical diagnosis of chorioamnionitis; and confirmed rupture of membranes for more than 18 hours before a preterm birth.

A few other characteristics that were thought to be neonatal risk factors included altered muscle tone, feed intolerance, abnormal heart rate, signs of respiratory distress, hypoxia, jaundice within 24 hours of birth, abnormal temperature, altered glucose homeostasis, and metabolic acidosis. As controls, there were sixteen healthy newborns who were born at 34 weeks or more gestation and had no maternal risk factors. The study eliminated newborns who had congenital abnormalities, congenital infections, prenatal hypoxia, or signs of inborn metabolic problems within the first 12 hours of life.

Laboratory tests include blood culture, sensitivity, C-reactive protein (CRP), and complete blood count (CBC) with differential count. Serum procalcitonin measured 12 hours after delivery using the enzyme-linked immunosorbent test (ELISA). A risk calculator for early onset sepsis was developed at birth and following a clinical assessment. The gestational age, mother's highest antepartum temperature, ROM (hours), mother's GBS status, and the kind of intrapartum antibiotics are the predictors employed in the EOS calculator. The risk of EOS per 1000 births is then computed. The EOS risk is then recalculated based on the clinical assessment of the newborn. It provides therapy recommendations based on EOS risk and clinical evaluation, such as starting empirical antibiotics, waiting for blood culture findings, or just monitoring vital signs (Neonatal early-onset sepsis calculator, 2021).

The study was approved by the Research Ethics Committee at the Faculty of Medicine, Ain Shams Unversity, MS26/2023.

2.1. Statistical methods

IBM SPSS software package version 26.0 was used for analysis. First of all The Shapiro-Wilk and Kolmogorov-Smirnov tests were utilized to confirm that the distribution was normal. Numbers and percentages were used to describe the qualitative data. The terms range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR) were used to characterize quantitative data. The results were deemed significant at the 5% level. Fisher's Exact or Monte Carlo adjustment was used to compensate for chi-square when more than 20% of the cells had an anticipated count of less than 5 when using the chi-square test for categorical variables and comparing results between groups. The student t-test and the Mann Whitney test were utilized to compare the two groups under study for quantitative variables that were regularly distributed and abnormally distributed, respectively. Two quantitative variables that were normally distributed and one that was abnormally distributed were correlated using the Pearson and Spearman coefficients, respectively. The ability of various parameters to predict sepsis was evaluated using a receiver operating characteristic (ROC) curve, which was also used to identify different cutoff points at which sensitivity and specificity were maximized. Sensitivity, on the other hand, was used to express the test's capacity to correctly identify diseased individuals in a population of "TRUE POSITIVES." The number of undiscovered cases, or "false negatives," decreases with increasing sensitivity, but the ability of the test to accurately rule out those who are disease-free, or "TRUE NEGATIVES," is evaluated by specificity. There will be fewer "false positives" included the higher the specificity. PPV, or positive predictive value and Negative Predictive value (NPV) were used to describe the probability of the disease whether present or absent, among those with positive diagnostic test results respectively.

3. Results

Table 1: Comparison between the two studied groups as regards demographic data

		Patients		Test of sig.	P
		Cases (n=56)	**Controls (n=16)**		
Gender	Male	37 (66.1%)	8 (50.0%)	c^2= 1.371	0.242
	Female	19 (33.9%)	8 (50.0%)		
GA					
Min. – Max.		36.8 – 39.1	37 – 40		
Mean ± SD.		36 ± 2	38 ± 1	U= 156.5	0.06
Median (IQR)		38 (38 – 39)	38 (38 – 39)		

χ^2: **Chi-square test** U: Mann Whitney test p: p-value for comparing between the **two studied group.**
GA: Gestational age

Table 2: Comparison between the two studied groups as regards prenatal data

		Patients		Test of sig.	P
		Cases (n=56)	**Controls (n=16)**		
MOD	NVD	8 (14.3%)	3 (18.8%)	c^2= 0.192	FEp= 0.699
	CS	48 (85.7%)	13 (81.3%)		
Multiplicity	Single	54 (96.4%)	12 (75.0%)	c^2= 7.481	FEp= 0.020*
	Twin	2 (3.6%)	4 (25.0%)		
Maternal risk factors					
UTI	Yes	34 (60.7%)	4 (25.0%)	c^2= 6.369	FEp= 0.021
	No	22 (39.3%)	12 (75.0%)		
Vaginitis	Yes	29 (51.8%)	2 (12.5%)	c^2= 7.834	0.005*
	No	27 (48.2%)	14 (87.5%)		
Chorioamnionitis	Yes	15 (26.8%)	0 (0.0%)	c^2= 5.414	FEp= 0.031*
	No	41 (73.2%)	16 (100.0%)		
Maternal antepartum fever	Yes	6 (10.7%)	0 (0.0%)	c^2= 1.870	FEp= 0.327
	No	50 (89.3%)	16 (100.0%)		
ROM	<18 hr	17[a] (30.4%)	0[b] (0.0%)	c^2= 13.874	^{MC}p = 0.001*
	>18 hr	12[a] (21.4%)	0[b] (0.0%)		
	No	27[a] (48.2%)	16[b] (100.0%)		
GBS status	Negative	0 (0.0%)	0 (0.0%)	-	-
	Positive	0 (0.0%)	0 (0.0%)		
	Unknown	56 (100.0%)	16 (100.0%)		
Intrapartum antibiotics	Broad spectrum >4 hrs prior to birth	24 (42.9%)	5 (31.3%)	c^2= 1.491	^{MC}p = 0.417

	Broad spectrum 2-3.9 hrs prior to birth	30 (53.6%)	11 (68.8%)
	GBS specific >2 hrs prior to birth	2 (3.6%)	0 (0.0%)
	No antibiotics or any antibiotics <2 hrs prior to birth	0 (0.0%)	0 (0.0%)

χ^2: Chi square test, **MC**: Monte Carlo , FE: Fisher Exact p: p value for comparing between the studied groups.
*: Statistically significant at $p \leq 0.05$, MOD: Mode of delivery, ROM: Rupture of membrane, GBS: Group B streptococcus, UTI: Urinary tract infection

Table 3: Comparison between the two studied groups as regards vital signs.

		Patients		Test of sig.	P
		Cases (n=56)	**Controls (n=16)**		
HR	>160	26 (46.4%)	0 (0.0%)	c^2= 11.627	0.001*
	<160	30 (53.6%)	16 (100.0%)		
RR	>60	52 (92.9%)	0 (0.0%)	c^2= 53.486	FEp= <0.001*
	<60	4 (7.1%)	16 (100.0%)		
Temperature	Feverish	0 (0.0%)	0 (0.0%)	c^2= 3.710	FEp= 0.108
	Hypothermic	45 (80.4%)	16 (100.0%)		
	Normal temperature	11 (19.6%)	0 (0.0%)		

χ^2: Chi square test, FE: Fisher Exact, *: Statistically significant at $p \leq 0.05$. HR: Heart rate, RR: Respiratory rate

Table 4: Comparison between the two studied groups as regards respiratory support.

		Patients		Test of sig.	P
		Cases (n=56)	**Controls (n=16)**		
Need for O2	Yes	38 (67.9%)	0 (0.0%)	c^2= 22.992	<0.001*
	No	18 (32.1%)	16 (100.0%)		
Need for CPAP	Yes	33 (58.9%)	0 (0.0%)	c^2= 17.407	<0.001*
	No	23 (41.1%)	16 (100.0%)		

χ^2: Chi square test, FE: Fisher Exact, *: Statistically significant at $p \leq 0.05$. CPAP: Continuous positive airway pressure, MV: Mechanical ventilation

Table 5: Comparison between the two studied groups as regards associated complications

		Patients		Test of sig.	P
		Cases (n=56)	Controls(n=16)		
Apnea	Yes	6 (10.7%)	0 (0.0%)	c^2= 1.870	FEp= 0.327
	No	50 (89.3%)	16 (100.0%)		
Feeding intolerance	Yes	55 (98.2%)	0 (0.0%)	c^2= 66.555	<0.001*
	No	1 (1.8%)	16 (100.0%)		
Hypoglycemia	Yes	16 (28.6%)	1 (6.3%)	c^2= 3.438	FEp= 0.095
	No	40 (71.4%)	15 (93.8%)		
Hemodynamic instability	Yes	16 (28.6%)	0 (0.0%)	c^2= 5.878	FEp= 0.015*
	No	40 (71.4%)	16 (100.0%)		
Seizures	Yes	9 (16.1%)	0 (0.0%)	c^2= 2.939	FEp= 0.192
	No	47 (83.9%)	16 (100.0%)		

χ^2: Chi square test, FE: Fisher Exact, *: Statistically significant at $p \leq 0.05$.

Table 6: Comparison between the two studied groups as regards laboratory data

	Patients		Test of sig.	P
	Cases (n=56)	Controls (n=16)		
HB				
Min. – Max.	12.2 – 20.6	15.5 – 18.2		
Mean ± SD.	15.6 ± 1.9	16.6 ± 0.9	t= -3.058	0.003*
Median (IQR)	15.5 (14.1 – 17.0)	16.5 (16.0 – 17.5)		
WBC				
Min. – Max.	4300 – 54000	6300 – 13000		
Mean ± SD.	10499 ± 7416	8691 ± 1907	U= 407.5	0.583
Median (IQR)	8900 (7300 – 10700)	8000 (7550 – 9600)		
Neutrophils				
Min. – Max.	1600 – 20000	3000 – 10000		
Mean ± SD.	5145 ± 3146	5859 ± 2059	U= 303.5	0.05*
Median (IQR)	4300 (3470 – 6000)	5700 (4415 – 6350)		
CRP				
Min. – Max.	0.1 – 56.0	2.0 – 12.0		
Mean ± SD.	8.0 ± 9.7	3.9 ± 2.3	U= 351.5	0.186
Median (IQR)	4.0 (3.0 – 12.0)	3.5 (3.0 – 4.0)		

Procalcitonin					
Min. – Max.		0.20 – 30.90	0.15 – 1.50		
Mean ± SD.		5.62 ± 7.42	0.38 ± 0.32	U= 174.5	<0.001*
Median (IQR)		2.70 (0.32 – 6.75)	0.32 (0.20 – 0.43)		
Blood culture	Negative	18 (32.1%)	16 (100.0%)	c^2= 22.992	<0.001*
	Positive	38 (67.9%)	0 (0.0%)		
Type of blood culture	Acinetobacter	4 (10.5%)	0 (0.0%)		
	E. coli	13 (34.2%)	0 (0.0%)		
	Klebsiella	8 (21.1%)	0 (0.0%)		
	Pseudomonas	1 (2.6%)	0 (0.0%)		
	Streptococcus Pneumoniae	8 (21.1%)	0 (0.0%)		
	Staphylococcus	4 (10.5%)	0 (0.0%)		

χ^2: **Chi-square test,** U: Mann Whitney test, t: Student t-test

Table 7: Comparison between the two studied groups as regards EOS Calculator at birth

		Patients		**Test of sig.**	**P**
		Cases (n=56)	**Controls (n=16)**		
EOS risk calculator at birth					
Min. – Max.		0.25 – 205.10	0.01 – 0.01		
Mean ± SD.		19.3 ± 34.05	0.01 ± 0.00	U= 0	<0.001*
Median (IQR)		6.57 (1.05 – 20.95)	0.01 (0.01 – 0.01)		
Clinical recommendations	No cultures no antibiotics	13 (23.2%)	16 (100.0%)		
	Blood culture	9 (16.1%)	0 (0.0%)	c^2= 30.502	^{MC}p = <0.001*
	Empirical antibiotics	34 (60.7%)	0 (0.0%)		
Vitals	Routine vitals	13 (23.2%)	16 (100.0%)		
	Vitals /4 hrs for 24 hrs	9 (16.1%)	0 (0.0%)	c^2= 30.502	^{MC}p = <0.001*
	Vitals per NICU	34 (60.7%)	0 (0.0%)		

χ^2: **Chi-square test,** U: Mann Whitney test, t: Student t-test, **MC**: Monte Carlo EOS: Early onset sepsis

Table 8: Comparison between the two studied groups as regards EOS calculator at 12 hrs

		Patients		Test of sig.	P
		Cases (n=56)	**Controls (n=16)**		
EOS risk calculator at 12 hrs					
Min. – Max.		0.62 – 205.10	0.01 – 0.01		
Mean ± SD.		20.39 ± 33.68	0.01 ± 0.0	U= 0	<0.001*
Median (IQR)		9.20 (2.73 – 22.90)	0.01 (0.01 – 0.01)		
Clinical recommendations	No cultures no antibiotics	7 (12.5%)	16 (100.0%)		
	Blood culture	5 (8.9%)	0 (0.0%)	c^2= 43.826	^{MC}p = <0.001*
	Empirical antibiotics	44 (78.6%)	0 (0.0%)		
Vitals	Routine vitals	7 (12.5%)	16 (100.0%)		
	Vitals /4 hrs for 24 hrs	5 (8.9%)	0 (0.0%)	c^2= 43.826	^{MC}p = <0.001*
	Vitals per NICU	44 (78.6%)	0 (0.0%)		

χ^2: Chi-square test, U: Mann Whitney test, t: Student t-test, MC: Monte Carlo

Table 9: The predictive values of EOS risk calculator (at birth and 12 hrs) and procalcitonin for sepsis in the cases group

	P	AUC	95% C. I	Cut off	Sensitivity	Specificity	PPV	NPV
EOS (birth)	0.029*	0.682	0.527 – 0.837	≥ 6.57	60.5	72.2	82.1	46.4
EOS (12 hrs)	0.053	0.662	0.503 – 0.820	≥ 6.28	68.4	61.1	78.8	47.8
Procalcitonin	<0.001*	0.959	0.908 – 1.00	≥ 0.68	92.1	94.4	97.2	85

EOS (birth), Sensitivity was 60.5% Specificity was72.2%, P value=.029.
EOS (12 hrs), Sensitivity was 68.4% Specificity was 61.1%and P value=0.053. Procalcitonin, Sensitivity was92.1, Specificity=94.4 and P value=.001*

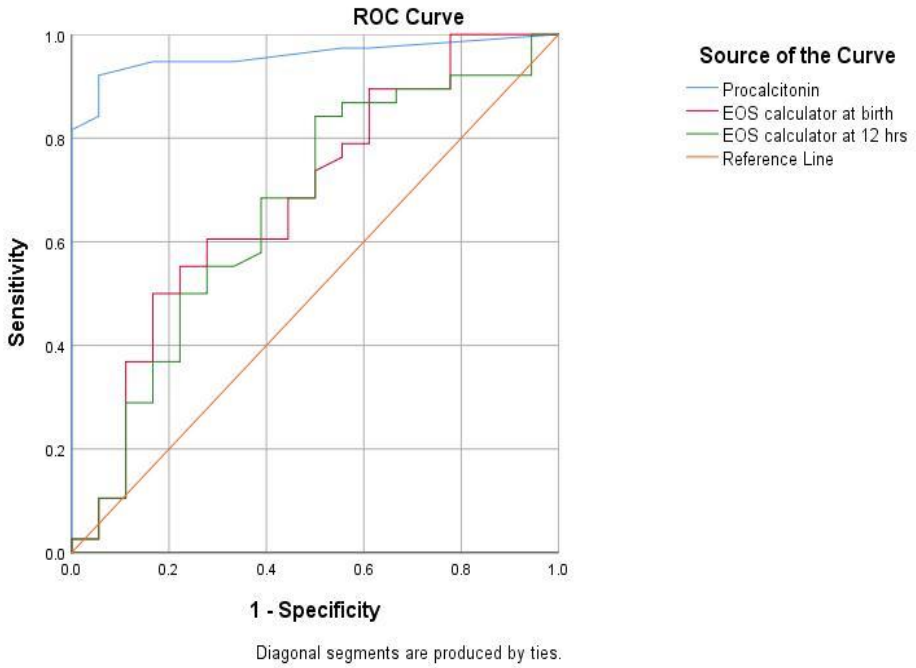

Fig. 1: ROC curve of EOS risk calculator (at birth and 12 hrs) and procalcitonin for prediction of sepsis in the cases group

Table 10: Correlation between procalcitonin and EOS risk calculator (at birth and 12 hrs)

	Procalcitonin	
	rho	**P**
EOS risk calculator (at birth)	0.475	<0.001*
EOS risk calculator (at 12 hrs)	0.464	<0.001*

*: Statistically significant at $p \leq 0.05$, rho: spearman correlation

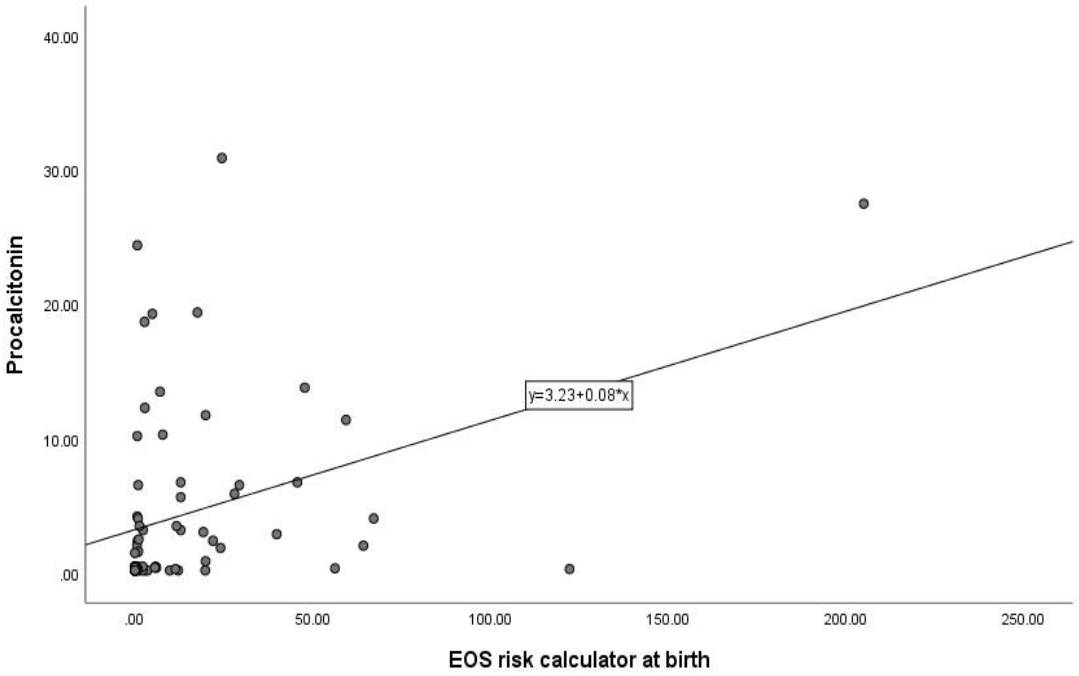

Fig. 2: Correlation between procalcitonin and EOS risk calculator at birth

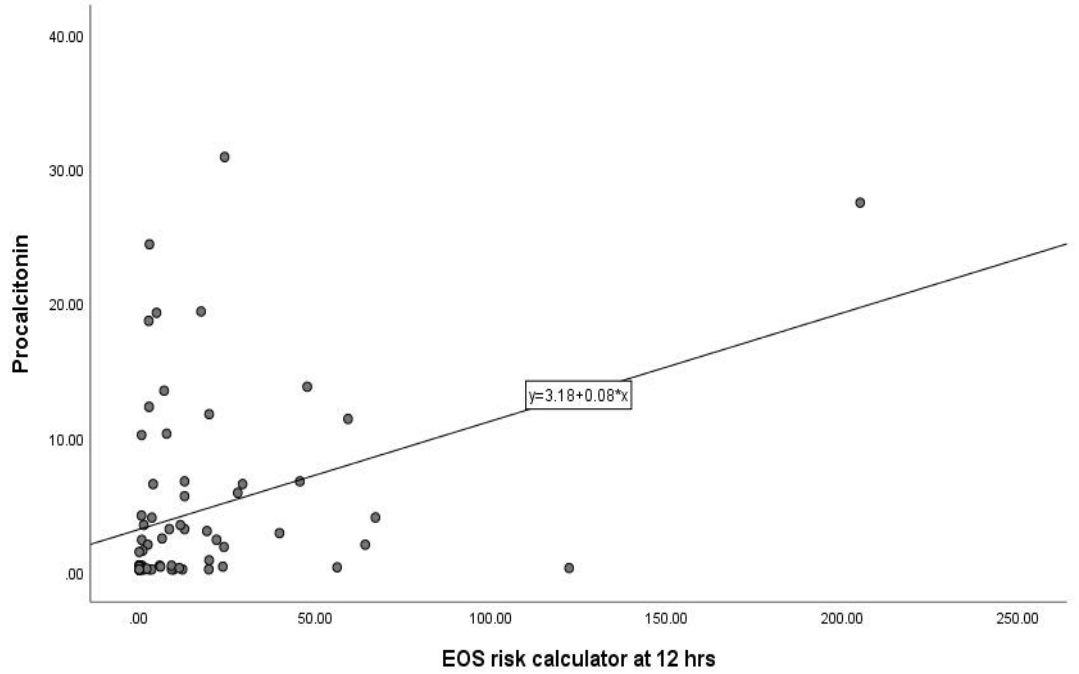

Fig. 3: Correlation between procalcitonin and EOS risk calculator at 12 hrs

4. Discussion

The purpose of this study was to assess procalcitonin's diagnostic use as an early onset sepsis (EOS) marker in newborn infants older than 34 weeks, as well as the diagnostic utility of the EOS calculator. This study was carried out in the Neonatal Intensive Care Unit (NICU) of Ain Shams University Maternity Hospital on newborns delivered at 34 weeks gestational age or more who had suspected EOS based on maternal risk factors and clinical indications.

Neonatal sepsis is the term used to describe a systemic illness that can be caused by bacteria, viruses, fungi, or parasites and is linked to hemodynamic abnormalities, various clinical symptoms, and significant morbidity and death (Shane *et al.,* 2017). One major factor contributing to newborn infants' morbidity and mortality is neonatal sepsis. According to Chauhan *et al*., there are two types of it: newborn late onset sepsis and neonatal early-onset sepsis (EOS) (Chauhan *et al.,* 2017).

Although some experts restrict the definition to infections that develop within the first 72 hours of life, neonatal EOS is defined as the onset of symptoms before 7 days of age (Can *et al.,* 2018).

Many sepsis biomarkers have been investigated for the purpose of early neonatal EOS identification; however, no one biomarker has been found to meet all of the necessary requirements. Since it accounts for both neutrophils and lymphocytes in its computation, the neutrophil to lymphocyte ratio (NLR) is thought to be somewhat more stable than absolute counts (Dirican *et al.,* 2015). According to studies, the NLR is a predictor of severity and clinical outcome in individuals with community-acquired pneumonia or bacteremia [(de Jager *et al.,* 2012), (Loonen *et al.,* 2014)]. The NLR and the platelet to lymphocyte ratio (PLR), two blood cell subtype ratios, have recently been described as helpful markers of systemic inflammation and prognostic predictors of cancer and unfavorable cardiovascular events (Lian *et al.,* 2015; Yodying *et al.,* 2016; Acet *et al.,* 2016; Yin *et al.,* 2016).

The peptide precursor of calcitonin is called PCT. Patients with bacterial infections have higher serum levels of it because parenchymal cells produce it in response to bacterial toxins. According to Hedegaard *et al*., a number of observational studies have indicated that PCT may be a helpful marker to identify infants who are infected (Hedegaard *et al.,* 2015).

Gender and age did not differ statistically significantly in the 56 cases and 16 control neonates born at 34 weeks or more in the current study (p value = 0.242, 0.06 correspondingly). Our findings corroborated those of Can *et al*., who discovered that there was no statistically significant difference in GA, age, gender, or mode of delivery between the patients and the controls (Can *et al.* 2018).

In our investigation, there was no discernible gender difference between the patient and control groups. This is consistent with the findings of Parajuli *et al.* and Xiao *et al*., who both arrived at the same conclusion. In the patient group, however, men dominated (63.3%). This male preponderance is seen in nearly every research on neonatal sepsis, including the Bohanon *et al.* study, which also revealed that male gender predominated in their investigations. This could be caused by a gene on the X chromosome that affects immunoglobulin synthesis or the activity of the Thymus gland [(Parajuli *et al.* 2017, Xiao *et al.* 2017), (Bianchi *et al.,* 2012), (Bohanon *et al.* 2017)].

Our findings concurred with those of He *et al*., who discovered no significant variations in the distribution of genders or modes of delivery, but rather notable variations in gestational age and birth weight (He *et al.,*2020).

Maternal risk factors for urinary tract infections were found in cases 60.7% of the time compared to controls (p=0.02). There was more severe evidence of vaginitis in patients (51.8%) compared to controls (p=0.005). Premature membrane rupture and chorioamnionitis were more common in cases than in controls. A 100% absence of membrane rupture was seen in the control group. As a result, mothers of instances received intrapartum antibiotics in reaction to infection and maternal antepartum fever.

Our findings were corroborated by Ikhsaniatun *et al*., who discovered that only mothers with PROM lasting longer than 18 hours significantly influenced the incidence of EOS (RR, 6.50; 95% CI: 0.87–48.34; P =.047). These mothers also ensured that the sepsis criteria according to WHO were met among the mothers having the risk factors of EOS, including the small gestational age, duration of PROM, history of fever, UTI, chorioamnionitis, and history of operative delivery (Ikhsaniatun *et al.,*2022).

Our findings are consistent with those of He *et al*., who discovered that the infected group had a statistically significant ($P < 0.05$) greater rate of meconium-stained amniotic fluid, PROM > 18 h, maternal fever, and GBS infection than the uninfected group (He *et al.,*2020).

According to our findings, there was a significant statistical difference (p value=.001) in the heart rate and respiratory rate between the two groups under study. There was no statistically significant difference in temperature between the two groups under investigation. It's interesting to note that patients' heart rate and respiratory rate were significantly higher than those of the controls group, which is consistent with Xiao *et al.,* However, the results did not agree with Can *et al.,* 2018, who concluded

that there was no discernible difference in heart rate and respiratory rate between the patient and control groups [(Xiao *et al.,* 2017), (Can *et al.,*2018)].

As per our findings, the cases group required O2 at a higher rate (67.9%) than the controls. Continuous positive airway pressure was required by the cases group more often than the controls (58.9%). Mechanical ventilation is required in the cases group (33.9%) higher than in the controls.

The demand for O2, CPAP, and MV showed very statistically significant differences between the two groups under study (p values <.001, <0.001, and 0.008, respectively).

Our findings concur with those of Can *et al.*, who discovered statistically significant variations in the need for oxygen assistance between patients and controls. As the p value was greater than 0.05, the current investigation did not find a statistically significant difference in apnea, hypoglycemia, or seizures between the two groups. In the patient group, apnea was (10.7%), seizures were (16.1%), hemodynamic instability was (28.6%), and feeding intolerance was (98.2%) among the cases. However, there was a statistically significant difference (p<.05) in hemodynamic instability and feeding intolerance between the two groups. This is consistent with the findings of Maharaja *et al.*, who discovered that respiratory distress affected most patients. Conversely, Can *et al.* discovered that bradycardia and apnea were the primary presenting sounds [(Can *et al.,*2018), (Maharaja et al. 2017)].

According to our findings, there was no statistically significant variation in WBC or CRP between the two groups. With respect to HB, the control group's mean ± SD was 16.6 ± 0.9, whereas the cases group's mean ± SD was 15.6 ± 1.9. In the case group, the mean ± standard deviation of neutrophils was 5145 ± 3146, while in the control groups, it was 5859 ± 2059. Procalcitonin Mean ± SD in the cases group was 5.62 ± 7.42, while in the control groups it was 0.38 ± 0.32. Between the two groups, there were highly statistically significant variations in HB, neutrophils, procalcitonin, and blood culture.

In line with Xiao *et al.*, there was no discernible difference in WBCs between the patient and control groups. A low WBC was reported to be more likely to be related with EOS by Jefferies, however Can *et al.,* showed no significant differences in WBCs and a statistically significant rise in Procalcitonin among patients compared to controls [(Xiao *et al.,* 2017), (Jefferies 2017), (Can *et al.,*2018)].

When compared to the controls group, we observed that the procalcitonin levels in the newborns in the sepsis group were considerably greater. This is consistent with research by Joram *et al.,* Leena *et al.* , and Steinberger *et al.*, which discovered that the sepsis group had a considerably greater procalcitonin level than the non-septic group. Additionally, in a recent study, procalcitonin levels were shown to be considerably greater in the patient group compared to the control group by Rashwan *et al.* 2019[(Joram *et al.,* 2012); (Leena *et al.* 2017), (Steinberger *et al.* 2014), (Rashwan *et al.* 2019)]

In the study by Sorsa *et al.* WBC was measured for each case. They discovered that 99 (32.7%) of the neonates with clinical sepsis had aberrant WBC counts; of these, 9 (2.9%) had leucopenia (WBC < 5,000/mm3) and 90 (29.8%) had leukocytosis (WBC >20,000/mm3). In contrast to our findings, newborns with culture-proven sepsis had a 5.7-fold higher likelihood of leuckocytosis [AOR 5.68(95%CI 3.415- 9.013) p<0.001] than those with negative results (Sorsa *et al.* 2019).

Our findings demonstrated that, with a p value of less than 0.05, there were highly statistically significant differences between the two groups with regard to the EOS risk calculator at birth, clinical recommendations, and vitals. The EOS risk calculator at birth mean ± SD for the cases group was 19.3 ± 34.05, while the control group's mean ± SD was 0.01 ± 0.00. In the meantime, the cases group was advised to use 60.7% of empirical antibiotics; the control group was not advised to use such antibiotics. While routine vitals were advised for the controls (100.0%), they were recommended for the cases group (23.2%).

One tool that is currently utilized to determine the risk of developing EOS in neonates born at 34 weeks or more of gestation is the EOS calculator. Numerous studies (both prospective and retrospective) have assessed how the EOS calculator can help cut down on the needless usage of lab tests and antibiotics. The EOS calculator would still be able to identify EOS even with lower antibiotic use if neonates were closely observed during their first 48 hours of life (Achten *et al.,* 2019).

According to our findings, the EOS risk calculator had a 60.5% sensitivity and a 72.2% specificity at birth (P value=.029). Sensitivity measured at 12 hours was 68.4%. P value was 0.053, and specificity was 61.1%. Procalcitonin displayed a 92.1% sensitivity, a 94.4 specificity, and a.001 P value.

Our findings concur with those of Can *et al.*, who discovered that procalcitonin (PCT) had a cut-off value of 1.04 ng/mL and had a sensitivity of 96.7% and specificity of 100%.

Our findings concur with those of Santuz *et al.* , who discovered that PCT had a reasonable level of accuracy when diagnosing EOS in infants who are at risk of infection. Specificity and sensitivity in our sample varied over time, ranging from 87% to 95% and 50% to 73%, respectively (Santuz *et al.* 2008).

Additionally, Santuz *et al.* discovered that the PCT had the best specificity at 100% at 24 hours (standard cut-off) and the best sensitivity at 58% at birth. In this investigation, the ROC curves were used to determine the ideal cut-off values for our population. The area under the curve (AUC) was 0.77 (CI 0.68–0.85) at birth, 0.77 (CI 0.67–0.85) at 24 hours, and 0.78 (CI 0.66–0.87) at 48 hours, respectively (Santuz *et al.* 2008).

According to He *et al.*, 501 neonates were examined, of which 353 were infected and 148 were not. When these predictors were compared, PCT had the best predictive value (sensitivity: 87.5%, specificity: 95.5%), closely followed by the EOS risk calculator (sensitivity: 81.16%, specificity: 93.92%). Thus, our results are consistent with their findings (He *et al.,*2020).

4. Conclusion

Study the diagnostic value of early onset sepsis (EOS) calculator and procalcitonin as markers of early diagnosis of early onset sepsis in newborn infants >34 weeks. The EOS risk calculator and PCT showed good predictive value compared to CBC and CRP. Risk scores from the EOS risk calculator strongly correlated with EOS, and the EOS risk calculator offered increased predictive value when used in combination with blood biomarkers. The EOS calculator can help predict EOS incidence and reduce unnecessary antibiotic use in neonate.

Procalcitonin, Sensitivity was 92.1, Specificity=94.4 and P value=.001 had best predictive value followed by EOS (12 hrs), Sensitivity was 68.4% Specificity was 61.1%and P value=0.053.

References

Acet, H., F. Ertaş, M.A. Akıl, et al., 2016. Relationship between hematologic indices and global registry of acute coronary events risk score in patients with ST- segment elevation myocardial infarction. Thrombosis/Hemostasis, 22(1): 60-68.

Achten, N.B., C. Klingenberg, W.E. Benitz, et al., 2019. Association of Use of the Neonatal Early-Onset Sepsis Calculator with Reduction in Antibiotic Therapy and Safety: A Systematic Review and Meta-analysis. JAMA Pediatr., 173(11):1032–1040. doi:10.1001/jamapediatrics.2019.2825.

AitOufella, H., P. Asfar, C. Aubron, E. Canet, G. Carteaux, A. Demoule, ... and N. Weiss, 2021. Proceedings of Reanimation 2021, the French Intensive Care Society International Congress. Annals of Intensive Care, 11(1): 001.

Ali, Walaa, et al., 2020. "The diagnostic role of soluble triggering receptor expressed on myeloid cells-1 and procalcitonin for early detection of neonatal sepsis." Journal of The Arab Society for Medical Research, 15(2):56.

Benitz, W.E., and N.B. Achten Technical assessment of the neonatal early-onset sepsis risk calculator. Lancet Infect Dis. 2021 May;21(5):e134-e140. doi: 10.1016/S1473-3099(20)30490-4. Epub 2020 Oct 29. PMID: 33129425.

Bianchi, I., A. Lleo, M.E. Gershwin, and P. Invernizzi, 2012. The X chromosome and immune associated genes. Journal of autoimmunity, 38(2-3): J187-J192.

Bohanon, F.J., O.N. Lopez, D. Adhikari, et al., 2017. Race, Income, and Insurance Status Affect Neonatal Sepsis Mortality and Healthcare Resource Utilization. The Pediatric infectious disease journal

Can, E., Ş. Hamilcikan, and C. Can, 2017. 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.

Chacko, B. and I. Sohi, 2005. Early onset neonatal sepsis. The Indian Journal of Pediatrics. 72(1):23-6.

Chauhan, N., S. Tiwari, and U. Jain, 2017. Potential biomarkers for effective screening of neonatal sepsis infections: An overview. Microb Pathog. Jun;107:234-242. doi: 10.1016/j.micpath.2017.03.042. Epub 2017 Apr 1. PMID: 28377234.

De Jager, C.P., P.C. Wever, E.F. Gemen, et al., 2012. The neutrophil-lymphocyte count ratio in patients with community- acquired pneumonia. PloS one, 7(10): e46561.

Dirican, A., B.B. Kucukzeybek, A. Alacacioglu, et al., 2015. Do the derived neutrophil to lymphocyte ratio and the neutrophil to lymphocyte ratio predict prognosis in breast cancer?. International journal of clinical oncology, 20(1): 70-81.

Eichberger, J., E. Resch, and B. Resch, 2022. Diagnosis of neonatal sepsis: the role of inflammatory markers. Frontiers in Pediatrics, 10.

Fitriani, I., H. Dwi, and G.M. Annang 2022. Early-Onset Sepsis Online Calculator as a Predictor of Early-Onset Sepsis in Neonates Born at ≥ 34 Weeks of Gestation Perinatology, 22(4):245.

Hedegaard, S.S., K. Wisborg and A.M. Hvas, 2015. Diagnostic utility of biomarkers for neonatal sepsis–a systematic review. Infectious Diseases, 47(3):117-124.

Hincu, M.A., G.I. Zonda, G.D.Stanciu, D. Nemescu, and L. Paduraru, 2020. Relevance of biomarkers currently in use or research for practical diagnosis approach of neonatal early-onset sepsis. Children, 7(12): 309.

Huseynova, R., L. Bin Mahmoud, F. Hamad Aljobair, O. Huseynov, H. Career, P.P. Jaganathan, A. Abdelrahim, and F.A. Abduljabar Alaklobi, 2021. Use of Early-Onset Sepsis Risk Calculator for Neonates ≥ 34 Weeks in a Large Tertiary Neonatal Centre, Saudi Arabia. Cureus, 13(4): e14620. https://doi.org/10.7759/cureus.14620.

Jefferies, A.L., 2017. Management of term infants at increased risk for early-onset bacterial sepsis. Paediatrics and child health, 22(4): 223-228.

Joram, N., J.-B. Muller, S.J.-L. Denizot, et al., 2012. Umbilical Cord Blood Procalcitonin Level in Early 1 Neonatal Infections: A 4- 2 year University Hospital Cohort Study Springer Verlag, 2011, 30 (8), pp.1005-1013. <10.1007/s10096- 011-1187-0>. <hal-00669195>.

Joshi, N.S., W.E. Benitz, and A. Frymoyer, 2022. Using Scientific Evidence to Narrow Practice Variation and Estimate the Warranted Performance Target: Antibiotic Stewardship for Early-Onset Sepsis. The Problem of Practice Variation in Newborn Medicine: Critical Insights for Evaluating and Improving Quality, 227-242.

Kopsidas, I., N.M. Molocha, E. Kourkouni, et al., 2022. Potential benefit from the implementation of the Kaiser Permanente neonatal early-onset sepsis calculator on clinical management of neonates with presumed sepsis. European journal of pediatrics, 181(3): 1001–1008. https://doi.org/10.1007/s00431-021-04282-x.

Leena, B.M., L.P. Hannah, Y. Ram, et al., 2017. Cord Blood Acute Phase Reactants Predict Early Onset Neonatal sepsis in preterm infants. Plos One DOI:10.1371/journal.pone.0168677 .

Lian, L., Y.Y. Xia, C. Zhou, X.M. Shen,et al., 2015. Application of platelet/lymphocyte and neutrophil/lymphocyte ratios in early diagnosis and prognostic prediction in patients with resectable gastric cancer. Cancer biomarkers, 15(6): 899-907.

Loonen, A.J., C.P. de Jager, J. Tosserams, et al., 2014. Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. PloS one, 9(1):e87315.

Maharaja, P. and V . Mangayakarasi, 2017. Clinical Profile And Risk Factors In Neonatal Septicaemia.Int. J. Pharm., Bio., 8(3): (B) 489-495

Miselli, F., R. Cuoghi Costantini, R. Creti, F. Sforza, S. Fanaro, M. Ciccia, ... and A. Berardi, 2022. Escherichia coli Is Overtaking Group B Streptococcus in Early-Onset Neonatal Sepsis. Microorganisms, 10(10): 1878.

Morris, R., S. Jones, S. Banerjee, A. Collinson, H. Hagan, H. Walsh, ... and J. Matthes, 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

Neonatal early-onset sepsis calculator. 2021. Available at: http://neonatalsepsiscalculator .kaiserpermanente.org. Accessed: Mar 18 2021

Ognean, M.L., A. Boicean, F.L. Șular and M. Cucerea, 2017. "Complete blood count and differential in diagnosis of early onset neonatal sepsis." Revista Romana de Medicina de Laborator, 25(1): 101-108.

Ohlin, A., M. Björkqvist, S.M. Montgomery and J. Schollin, 2010. Clinical signs and CRP values associated with blood culture results in neonates evaluated for suspected sepsis. Acta Paediatrica. 99(11):1635-40.

Parajuli, R., N.D. Pant, R. Bhandari, et al., 2017. Bacteriological Profile of Neonatal Sepsis and Antibiogram of the Isolates. Journal of Nepal Paediatric Society, 37(1): 5-9

Pettinger, K.J., K. Mayers, L. McKechnie, and B. Phillips, 2020. Sensitivity of the Kaiser Permanente early-onset sepsis calculator: a systematic review and meta-analysis. EClinicalMedicine, 19: 100227.

Rashwan, N.I., M.H. Hassan, Z.M.M. El-Deen, and A.E.A. Ahmed, 2019. V alidity of biomarkers in screening for neonatal sepsis–A single center– hospital based study. Pediatrics and Neonatology, 60(2): 149-155.

Ruan, L., G.Y. Chen, Z. Liu, Y. Zhao, G.Y. Xu, S.F. Li, et al., 2018. The combination of procalcitonin and C-reactive protein or presepsin alone improves the accuracy of diagnosis of neonatal sepsis: a meta-analysis and systematic review. Critical Care. 22(1):1-9.

Santuz, P, M. Soffiati, R.M. Dorizzi, M. Benedetti, F. Zaglia, P. Biban, 2008. Procalcitonin for the diagnosis of early-onset neonatal sepsis: a multilevel probabilistic approach. Clinical Biochemistry; 41(14-5):1150-5. [PubMed] [Google Scholar]

Sgro, M., D.M. Campbell, K.L. Mellor, K. Hollamby, J. Bodani, and P.S. Shah, 2019. Early-onset neonatal sepsis: Organism patterns between 2009 and 2014. Paediatrics and child health, 25(7): 425–431. https://doi.org/10.1093/pch/pxz073

Shane, A.L., P.J. Sánchez and B.J. Stoll, 2017. Neonatal sepsis. The Lancet.

Singh, M., M. Alsaleem, and C.P. Gray, 2022. Neonatal Sepsis. In StatPearls. StatPearls Publishing.

Sorsa, A., 2019. Epidemiology of neonatal sepsis and associated factors implicated: observational study at neonatal intensive care unit of Arsi University Teaching and Referral Hospital, South East Ethiopia. Ethiopian journal of health sciences. 29(3): 333-342.

Steinberger, E., N. Hofer, and B. Resch, 2014. Cord blood procalcitonin and interleukin-6 is highly sensitive and specific in the prediction of early-onset sepsis in preterm infants. Scand. J. Clin. Lab. Invest. 2014; 74:432Ð436.

Vaccina, E., A. Luglio, M. Ceccoli, M. Lecis, F. Leone, T. Zini, ... and A. Berardi, 2021. Brief comments on three existing approaches for managing neonates at risk of early-onset sepsis. Italian Journal of Pediatrics, 47(1): 1-5.

Xiao, T., L.P. Chen, H. Liu, et al., 2017. The Analysis of Etiology and Risk Factors for 192 Cases of Neonatal Sepsis. BioMed research international, 2017.

Yin, X., Y. Xiao, F. Li, S. Qi, Z. Yin, and J. Gao, 2016. Prognostic role of neutrophil-to- lymphocyte ratio in prostate cancer: a systematic review and meta- analysis. Medicine, 95(3).

Yodying, H., A. Matsuda, M. Miyashita, S. Matsumoto, et al., 2016. Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis. Annals of surgical oncology, 23(2): 646-654.