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Del Carmen KJC, Du ALM and Kimseng KJN. Diagnostic Accuracy of the Neonatal Early Onset Sepsis Calculator in Screening for Early Onset Sepsis in Neonates More Than 35 Weeks Age of Gestation
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ORIGINAL ARTICLE

DIAGNOSTIC ACCURACY OF THE NEONATAL EARLY ONSET SEPSIS CALCULATOR IN SCREENING FOR EARLY ONSET SEPSIS IN NEONATES MORE THAN 35 WEEKS AGE OF GESTATION

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ABSTRACT

Background: Early-onset sepsis (EOS) is a leading cause of morbidity and mortality among neonates. Diagnosis of EOS can be difficult as clinical signs are subtle. The use of the Neonatal EOS Calculator (NEOSC) may help screen high-risk neonates for EOS and may result in a significant reduction in unnecessary antibiotic use.

Objective: To determine the diagnostic accuracy of the NEOSC in screening for EOS in neonates more than 35 weeks age of gestation.

Methodology: This was a retrospective, case-control study where 245 septic (cases) and 245 non-septic (controls) neonatal and maternal medical records were reviewed. The EOS risk classification from the NEOSC was compared with the actual clinical outcome. An online statistical software (*medcalc*.org) was used to compute for the sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and accuracy of the NEOSC.

Results: Based on the NEOSC, only 64 of 245 clinically septic neonates were truly positive for sepsis while 181 were falsely negative for sepsis. Of the 245 non-septic neonates, 3 were falsely positive for sepsis, while 242 were truly negative for sepsis. With a 95% confidence interval, the computed variables showed a Sn 26.12%, Sp 98.78%, PPV 76.12%, NPV 89.95%, PLR 21.33, and NLR 0.75. The accuracy of the NEOSC is 89.33%.

Conclusion: The NEOSC had poor sensitivity and is not recommended in screening for EOS in neonates more than 35 weeks age of gestation. It may be used as an adjunct in EOS diagnosis due to its high specificity and accuracy.

KEYWORDS: *Neonatal Early Onset Sepsis, Neonatal sepsis, Sepsis (EOS) Calculator*

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INTRODUCTION

Early-onset sepsis (EOS) is a leading cause of morbidity and mortality among neonates. The World Health Organization (WHO) data in 2016 showed that 46% of global deaths among children under 5 years of age were neonatal deaths. In the Philippines, it accounts for 18% of all causes of death.[1]

Physicians are confronted with the need to identify neonates at highest risk of infection as clinical signs of EOS are nonspecific and variable. Blood culture is considered the gold standard for diagnosis of EOS, however, only less than 1% of neonates are culture positive, with the incidence of culture-proven EOS in newborns ranging between 0.5 to 1.2 cases per thousand live births. [2-3] Due to the low incidence of culture-proven EOS but potentially high-mortality rates, EOS is frequently diagnosed based on clinical presentation.[2]

The Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) published guidelines that have been utilized by clinicians for the management of EOS. These recommend empiric antibiotic initiation for all neonates who appear to be clinically ill at birth or are born to women diagnosed with chorioamnionitis.[4] Empiric treatment of newborns at risk or with suspected EOS represents the main contributor to the use of antibiotics in early life. Unnecessary evaluations and antibiotic treatment are, however, not risk-free. Newborns are often admitted to a neonatal intensive care unit (NICU) which may interrupt parental bonding and breastfeeding. Moreover, long-term detrimental effects have been linked to antibiotic exposure which include alteration of the neonatal microbiome, asthma, inflammatory bowel disease, autoimmune disease, antibiotic resistance and mortality.[2] Optimizing antibiotic use in neonates is critical as they are vulnerable to their adverse effects.

Factors that increase the risk for infection include maternal Group B *Streptococcus* (GBS) colonization, maternal fever, chorioamnionitis, prolonged rupture of membranes (>18 hours) and inadequate intrapartum antibiotic administration before delivery.[5]

An online calculator known as the Neonatal Early Onset Sepsis Calculator (NEOSC) is a multivariate prediction model that could be used to predict the probability of EOS based on five objective maternal risk factors available at the time of birth.[6] Previous studies about the efficacy of the NEOSC was associated with reduced usage of antibiotics (from 6% to 1.4%), laboratory tests (from 15.5% to 2.5%) and admissions to neonatal units (from 19.1% to 5.4%).[7] Although this tool may serve to decrease unnecessary antibiotic treatment, its diagnostic accuracy has yet to be determined.

MATERIALS AND METHODS

Study Design

This was a retrospective case-control study where clinical outcomes of septic neonates (cases) and non-septic neonates (controls) were reviewed and compared with their classification in the NEOSC.

Study Setting

The study was conducted in a tertiary private hospital.

Study Population

Neonates more than 35 weeks of age of gestation (AOG) born at a tertiary private hospital from January 2019 up to March 2021 and admitted for at least 72 hours were included in the study.

Septic Neonates (Cases)

Septic neonates are neonates whose clinical course and final diagnosis on discharge are consistent with EOS as defined by the *Standards of Newborn Care.*[5]

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These cases presented as systemic inflammatory response syndrome (SIRS) secondary to infection occurring within 72 hours after birth. SIRS included the presence of 2 or more of the following: fever or hypothermia (>37.5˚C or <36.5˚C), tachycardia (HR ≥160bpm), tachypnea (RR ≥60cpm), an abnormally high or low white blood cell count (≤9 x 10^9 cells/L) and or elevated CRP (≥1.59 mg/dL) and isolation of a pathogen from blood culture, lumbar puncture or tracheal aspirate obtained immediately after endotracheal tube placement. Those with severe congenital malformations requiring surgical intervention and with concomitant diagnosis of Respiratory Distress Syndrome, Neonatal Pneumonia and Meconium Aspiration Syndrome were not included in the study.

Non-Septic Neonates (Control)

Non-septic neonates are neonates whose clinical course and final diagnosis on discharge are not consistent with EOS as defined by the *Standards of Newborn Care*.[5] These cases were clinically well with no persistent physiologic abnormalities recorded in the vital signs monitoring sheet (temperature, respiratory rate and heart rate) and with unremarkable laboratory results.

Scope and Limitations

The population was limited only to newborns at least 35 weeks AOG from a single tertiary institution who were admitted for EOS between January 2019 and March 2021. Data was gathered by review of maternal and neonatal medical records.

The prevalence rate of EOS in a particular setting would affect the statistical analysis used to compute the positive and negative predictive values as well as accuracy. A case-control study design was performed for this initial study as this was less invasive for a susceptible population such as neonates.

Data Collection and Analysis

After study approval by the Hospital Institutional Review Board (IRB), data collection commenced and was based on medical chart review. A master list of all neonates was taken from the hospital's Information Technology Service Team and a total of 245 records of septic neonates and 245 records of non-septic neonates were retrieved together with maternal medical records. Two research assistants (RA) were trained to collect the data. Each RA was assigned a specific list where each neonate had a corresponding unique patient number to maintain anonymity and avoid duplication. The neonatal outcome was obtained, as well as the temperature, heart rate, respiratory rate, and specific laboratory data (complete blood cell count, CRP and presence or absence of blood culture or CSF culture). The classification whether the neonate is septic or non-septic was based on the clinical course, laboratory results and diagnosis upon discharge and were verified by a neonatologist based on the definition of EOS in the *Standards of Newborn Care*.[5]

The following variables were entered into the NEOSC: AOG, highest maternal temperature during labor, duration of membrane rupture before delivery, GBS status at birth and intrapartum antibiotic treatment including the length of time before delivery. An incidence of 0.5 per 1000 live births (which is the CDC national incidence rate) was used as no local incidence rate was available. Based on the color code and clinical recommendation from the NEOSC, a *green* recommendation *(no culture and no antibiotics with routine vitals)* was considered negative for neonatal sepsis (nEOScalc) while those with *yellow* recommendation *(blood culture with vital signs every 4 hours every 24 hours)* and *red* recommendation *(empiric antibiotics with vitals per NICU recommendations*) were considered positive for neonatal sepsis (pEOScalc). Calculator scores whether a neonate was nEOScalc or pEOScalc from the NEOSC were noted and compared with the actual clinical outcome.

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An online statistical software *(www.medcalc.org)* was used to compute for the sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, and accuracy of the NEOSC.[8] A five-year (2016-2021) local prevalence of EOS in the study setting was computed and subsequently used in computing for the said variables. Clinically diagnosed EOS had a prevalence rate of 13% while culture-positive EOS had a prevalence rate of 0.34%. A table was used to show the clinically septic neonates who were pEOScalc and nEOScalc. A sub-analysis was done to show culture-positive septic neonates who were pEOScalc and nEOScalc. Data were compared with the results of the non-septic group.

RESULTS

A total of 3,318 neonates were born between January 2019 and March 2021. Of these, 245 septic neonates met the inclusion criteria and an equal number of 245 non-septic neonates were included as controls, as summarized in Table 1.

Table 1. Clinical Characteristics of Septic and Non-Septic Neonates

Clinical Characteristics		Septic Neonates n = 245	%	Non-Septic Neonates n = 245	%	p-value
Age of Gestation (AOG)	35-36 weeks	25	10.2	9	3.7	0.00*
	37-38 weeks	100	40.8	112	45.7	0.28
	39-40 weeks	111	45.3	122	49.8	0.32
	41-42 weeks	9	3.7	2	0.8	0.03*
Gender	Male	138	56.3	125	51	0.24
	Female	107	43.7	120	49	0.24
Birthweight	< 1500 g	1	0.4	0	0	0.32
	1500-2499 g	31	12.7	14	5.7	0.01*
	2500-3500 g	191	77.9	192	78.4	0.91
	>3500 g	22	9	39	15.9	0.02*
Apgar score at 5 minutes of life	<5	7	2.9	4	1.6	0.36
	>5	238	97.1	241	98.4	0.36

*Difference is Significant at Z-test for 2 sample proportions p-value <=0.05
Hypothesis tested using 2-tailed test

Neonates in both groups were between 39-40 weeks AOG. More septic neonates were noted in the 35-36 (p-value 0) and 41-42 (p-value 0.03) weeks group. There is a slight male preponderance in both groups with 56.3% (138) for the septic group and 51% (125) for the non-septic group, but this was not statistically significant (p-value 0.24). Birthweights mostly fell between 2500 to 3500 grams. Septic neonates were noted to have lower weight ranges with a significant difference in the 1500-2499 grams (p-value 0.01) group, while more non-septic neonates weighed >3500 grams. As for the APGAR score at 5 minutes of life, the septic neonates had lower scores, but this was not statistically significant (p-value 0.36).

Table 2. Maternal Risk Factors associated with EOS in Septic Neonates and Non-Septic Neonates

PARAMETER		Septic Neonates		Non-Septic Neonates		Total	Mean
Gestational Age	Weeks AOG	34 - 42 2/7		32 - 42 2/7		32– 42 2/7	-
Highest Maternal temperature	ºC	36.0 - 38.8		36.0 - 38		36.0 - 38.8	37.4
Duration of rupture of membranes	Minutes (m) – Hours (h)	3 m – 240 h		2 m – 28 h		2 m – 240 h	120 h
PARAMETER		n = 245	%	n = 245	%	n = 490	%
Group B streptococci colonization	Negative	41	16.7	43	17.6	84	7.1
	Positive	0	0	0	0	0	0
	Unknown	204	83.3	202	82.4	406	82.9
Type and duration of initiation of antibiotics prior to delivery	Broad spectrum > 4 hrs prior to birth	37	15.1	22	9	59	12
	Broad spectrum 2-3.9 hrs prior to birth	3	1.2	13	5.3	16	3.3
	GBS specific > 2 hrs prior to birth	81	33	24	9.8	105	21.4
	No or any < 2 hrs prior to birth	124	50.6	186	75.9	310	63.3

Table 2 provides the maternal characteristics and risk factors of mothers of both septic and non-septic neonates. The non-septic group had a wider gestational age range from 32 to 42 2/7 weeks compared with the septic group (34 to 42 2/7 weeks). The highest maternal temperature was noted in the septic group (38.8˚C), compared to 38˚C in the non-septic group. The duration of rupture of membranes was longer in the septic group (240 hours), compared to 28 hours in the non-septic group.

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For both groups, maternal GBS status was mostly unknown (82.9%) and majority had either no antibiotics or received the dose less than 2 hours before delivery (63.3%).

Table 3. Number of Culture Positive Sepsis

Blood Culture Positive Result	n = 15	%
Methicillin Resistant *Staphylococcus epidermidis*	6	40
Methicillin Sensitive *Staphylococcus epidermidis*	2	13.3
Methicillin Resistant *Staphylococcus haemolyticus*	2	13.3
Methicillin Resistant *Staphylococcus hominis*	1	6.7
Methicillin Resistant *Staphylococcus warneri*	1	6.7
Streptococcus mitis	1	6.7
Corynebacterium sp. (diphtheroids)	1	6.7
Pseudomonas stutzeri	1	6.7

Of the 245 septic neonates, only 15 had positive culture results (Table 3). The most common isolates are methicillin-resistant *Staphylococcus epidermidis* in 6 neonates (40%), methicillin-sensitive *Staphylococcus epidermidis in 2* (13.3%) and methicillin-resistant *Staphylococcus haemolyticus* (13.3%) in another 2.

Of the 245 septic neonates, six (2.45%) had an abnormal CBC and 14 (5.7%) had elevated CRP, but all had negative culture results. The non-septic neonates had normal CBC and CRP.

Based on the NEOSC, 64 (26%) of 245 clinically septic neonates were pEOScalc, while 181 (74%) were nEOScalc (Table 4). Of the 245 non-septic neonates, 3 (1.2%) were pEOScalc while 242 (98.8%) were nEOScalc. The calculated average EOS risk at birth is 0.24/1000 live births for the septic and 0.12/1000 live births for non-septic neonates.

Table 4. Comparison of the Septic Neonates and Non-Septic Neonates who were pEOScalc and nEOScalc in the NEOSC

EOS Calculator Outcome	Actual Clinical Outcome (Clinical Sepsis) *Gold standard				Total
	Septic Neonates		Non-Septic Neonates		
	n =245	%	n = 245	%	
pEOScalc	64	26	3	1.2	67
nEOScalc	181	74	242	98.8	423
Total	245	100	245	100	490

Based on the calculator, of the 15 culture positive septic neonates (Table 5), four (26.7%) were labeled positive for sepsis (pEOScalc) while 11 (73.3%) were negative (nEOScalc). The calculated average EOS risk at birth for culture-positive septic neonates is 2.87per 1000 live births.

Table 5. Number of Culture Positive Septic Neonates and Non-Septic Neonates who were pEOScalc and nEOScalc in the NEOSC

EOS Calculator Outcome	Actual Clinical Outcome (Culture positive)				Total
	Septic Neonates		Non-Septic Neonates		
	n =245	%	n = 245	%	
pEOScalc	4	26.7	3	1.2	7
nEOScalc	11	73.3	242	98.8	253
Total	15	100	245	100	260

With a 95% confidence interval (CI), the computed sensitivity (Table 6) is 26.12% (20.74% to 32.10%), specificity at 98.78% (96.46% to 99.75%), positive likelihood ratio at 21.33 (6.79 to 66.99) and negative likelihood ratio at 0.75 (0.69 to 0.81). Positive predictive value is at 76.12% (50.38% to 90.92%) while negative predictive value is at 89.95% (89.24% to 90.61%). The accuracy of the EOS risk calculator is 89.33% (86.25% to 91.92%).

Table 6. Calculated Outcome from the Online Statistical Medical Calculator using the Clinically Diagnosed Septic Neonates (Gold Standard) and Non-Septic Neonates

PARAMETER	95% CI	Value
Sensitivity	26.12%	20.74% to 32.10%
Specificity	98.78%	96.46% to 99.75%
Positive Likelihood Ratio	21.33	6.79 to 66.99
Negative Likelihood Ratio	0.75	0.69 to 0.81
Disease prevalence	13.00%	
Positive Predictive Value	76.12%	50.38% to 90.92%
Negative Predictive Value	89.95%	89.24% to 90.61%
Accuracy	89.33%	86.25% to 91.92%

*Available at Calculated via MedCalc

DISCUSSION

Globally, sepsis remains to be one of the major causes of morbidity and mortality in neonates, with EOS being 2.6-fold more common than late-onset sepsis (LOS).[9]

According to the WHO report on the epidemiology and burden of sepsis as of 2020, there are 1.3 to 3.9 million annual neonatal sepsis cases and 400,000 to 700,000 annual deaths worldwide. An estimated 84% of neonatal deaths due to infections could be prevented through early diagnosis and timely, appropriate clinical management.[9] Among the causes of death is EOS with an incidence of 7.1 to 38 per 1000 live births in Asia.[10]

Currently, blood culture is the gold standard for diagnosis of EOS, but only less than 1% of neonates are culture positive.[2] In addition, the incidence of culture-proven EOS in newborns only ranges between 0.5 to 1.2 cases per thousand live births.[3] Obtaining blood cultures may also result in infant discomfort and parental anxiety. With these limitations, EOS is frequently considered based on nonspecific clinical presentation.[2] In this study, only 15 of 245 septic neonates were culture positive; thus, the clinical diagnosis of EOS which is the actual outcome of the neonate (consistent with the description in the *Standards of Newborn Care)* is the substitute gold standard and was compared to the non-septic neonates (control).[5]

Based on the clinical characteristics of the septic and non-septic group, it was noted that more septic neonates were in the late preterm (35-36 weeks) and late-term (41-42 weeks) groups. More septic neonates were also noted to have lower weight ranges. These are consistent with literature showing that those born prematurely with lower birth weights are at a higher risk for infection. In contrast, there were more non-septic neonates who were >3500 grams and these were term neonates with fewer risk factors.

The EOS risk calculator, a risk-based prediction model for identifying neonates at risk for EOS, may dramatically reduce the number of infants who require extensive evaluation and antibiotic therapy. This in turn could lead to decreased healthcare costs associated with sepsis workups, antibiotic administration, and hospital stay.[2]

Based on available evidence, the NEOSC is a unique and promising tool which can be utilized in the newborn population as it allows healthcare providers to estimate the EOS risk score with a patient-specific probability to determine how to proceed in evaluating and empirically treating the neonate for EOS.

Several studies debated on the safety of applying the NEOSC to accurately recognize all EOS neonates, especially those who are asymptomatic. In a retrospective study done by He, *et al*. in Chongqing, China, the EOS calculator (sensitivity: 81.16%, specificity: 93.92%) has shown good predictive value and that alone or in combination with blood biomarkers can promote early and accurate recognition of EOS and help limit unnecessary antibiotic exposure.[11] On the other hand, a meta-analysis on the sensitivity of the EOS risk calculator by Pettinger, *et al*. demonstrated that the probability of the calculator missing a case of EOS was best case 0.19 [0.11-0.29] and worst case: 0.31 [0.17 - 0.49], and that a large proportion of true cases of EOS were missed by the calculator.[12]

Previous studies investigated the performance of the NEOSC which mostly involved well-developed and high-income countries where GBS screening of mothers is a standard.[4,12] With the GBS status of mothers being a major variable in the NEOSC, this study investigated if it will perform similarly when data about GBS status is not available. In our study it demonstrated poor sensitivity (Sn 26.12%) in detecting EOS. It failed to recommend treatment in at least 181/245 (74%) neonates with clinically diagnosed EOS and 11/15 (73.3%) neonates who were culture positive for EOS.

With its low sensitivity, it is not recommended as a screening tool as it would miss a significant number of septic neonates. However, with its high specificity (Sp 98.78%), the calculator may aid in the confirmation of EOS since non-septic or well-appearing neonates will be correctly identified through the calculator.

Additionally, it demonstrated a high positive likelihood ratio, which emphasizes that the calculator is to be used more for confirmation than for screening. With its negative likelihood ratio (0.75), positive predictive value (76.12%) and negative predictive value (89.95%), this tool can predict the probability of those truly not having sepsis with an accuracy calculated at 89.33%.

It is hard to quantify whether the benefits of reducing antibiotic use outweigh the occasional miss in the calculator since estimating the effects of widespread (over)use of antibiotics on individuals and populations is difficult. Kuzniewicz, *et al.* argued that any potential delays in treatment are far outweighed by the dramatic reduction in antibiotic use.[4]

The calculator may provide an objective assessment of symptomatic versus asymptomatic infants, but the ultimate decision is made by the physician. Studies reported several infants with culture-positive sepsis with an initially low sepsis risk score who clinically deteriorated beyond the 12th hour of life. This highlights the need to incorporate risk factors with continuous clinical monitoring in the first 24 hours of life.[2] No method for predicting EOS is perfect, and there is no substitute for clinical monitoring since there will inevitably be some neonates without identified risk factors for infection who develop sepsis.

Considering the global health burden associated with over-investigation and possible over-treatment of EOS, it is recommended for future studies to do modification of the variables and assessment of its accuracy in both high income and low to middle-income countries through multicenter research. One of the parameters in the NEOSC is the GBS status of mothers, which is not determined routinely in our setting; thus, a prospective study design could also be done to include this data. It is recommended to evaluate the predictive abilities of other maternal risk factors (e.g., Urinary Tract Infection, COVID-19, and Upper Respiratory Tract Infections).

A study to compare the diagnostic accuracy of the NEOSC with culture-positive neonates as the control group is also recommended.

CONCLUSION

The diagnostic accuracy of the NEOSC in screening for EOS in neonates more than 35 weeks age of gestation was 89.33%. In addition, the sensitivity demonstrated by the NEOSC in this study indicated that it is poor in identifying neonates at risk for EOS, thus limiting its use as a screening tool. The calculator appears more likely to miss cases and has failed to recommend treatment in at least 74% of clinically septic neonates and 73.3% of culture-positive septic neonates. The calculator may be used as an adjunct to clinical and laboratory parameters to support the diagnosis of neonatal sepsis since it has a high specificity (98.78%).

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