Original Article

Neonatal Early Onset Sepsis

Accuracy of Neonatal Early Onset Sepsis Calculator in Predicting EOS in Neonates ≥ 34 Weeks of Gestation

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ABSTRACT

Objective: To determine the accuracy of Early Onset Sepsis (EOS) risk calculator by following blood culture reports and CRP for predicting EOS in neonates with 34 weeks or more gestational age.

Study Design: prospective observational study

Place and Duration of Study: This study was conducted at the National Institute of Child Health, Karachi from April, 2022 to July, 2022.

Materials and Methods: All newborns with suspected EOS presented with 34 weeks or more gestational age of either gender on empiric antibiotics during past 3 days were enrolled. Early onset neonatal sepsis risk calculator was calculated using Kaiser Permanente calculator.

Results: Of 249 neonates, EOS risk calculator shows that 60 (24.1%) had clinical illness whereas 63 (25.3%) patients had well appeared status and 126 (50.1%) had equivocal status. A significantly higher risk of clinical illness was observed in low birth-weight neonates (p= 0.026), lower gestational age (p= 0.007), higher maternal temperature, having rupture of membrane (p= <0.001), higher duration of rupture of membrane (p= <0.001), GBS in any trimester (p= <0.001), >4 hours of broad-spectrum antibiotics (p= <0.001), lower oxygen saturation (p= <0.001), respiratory distress (p= 0.003), APGAR score <7 (p= <0.001), positive blood culture (p= <0.001), and positive CRP (p= <0.001).

Conclusion: EOS risk calculator has highlighted around one fourth of neonates with the high risk of clinical illness in neonates presented with ≥ 34 weeks of gestational age.

Key Words: Sepsis, Risk Calculator, Neonates

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INTRODUCTION

Neonatal sepsis continues to be a major source of morbidity and mortality around the globe [1]. Around seven thousand newborn deaths occur every day or 2.4 million children worldwide lost their lives in the first month of life in 2019.[2] Nearly a third of all neonatal deaths occur during the first day of life, and nearly three-quarters do so within the first week [2].

The safety of repeated physical examinations for neonates at risk for early onset of sepsis (EOS) is highly recommended as this method required fewer laboratory tests and exposure to medications without omitting any cases of early onset neonatal sepsis [3,4].

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The Kaiser Permanente early onset newborn sepsis at risk calculator has been designed with the objective of avoiding antibiotic overtreatment [5].

Taking into account objective maternal risk variables and the newborn's clinical presentation, the early onset neonatal sepsis risk calculator enables clinicians to evaluate a newborn's personal risk for developing EOS [5].

The rationale of this study is that as there is a lack of scientific literature on risk calculation of EOS among neonates born in developing countries. In country like Pakistan, where due to financial restrain and limited health care resources, there is a dire need of study that evaluate the outcome of early onset neonatal sepsis risk calculator to prevent the antibiotic resistance and related complications in neonates along with the reduction of extra financial burden.

MATERIALS AND METHODS

A prospective observational study was conducted from April 25 to July 31, 2022 at National Institute of Child Health (NICH). The NICH institutional review board granted its permission for the study's ethical conduct before it was carried out. In addition, before the study

began, all study participants' parents or guardians signed informed permission forms.

All newborns of either gender who received empiric antibiotics within seventy-two hours due to suspected early onset neonatal sepsis with 34 weeks or more gestation was included. Whereas neonates with incomplete maternal history, suspected neonates of sepsis not started empiric antibiotic within 72 hours after birth, proven viral illness, hypoxic ischemic encephalopathy, and severe congenital malformation/ genetic diseases were excluded.

Epi Info sample size was used for the estimation of sample size taking confidence interval 95%, margin of error 5% and reported prevalence of equivocal risk for early onset sepsis 20.4% 6. The estimated sample size came out to be 249.

Detailed maternal history was obtained from the mother and medical records. Furthermore, clinical evaluation was carried out and noted in a predesigned proforma along with the demographic characteristics.

Neonates who received antibiotics before culture reports and within 3 days age were labelled in EOS. Whereas early onset neonatal sepsis was labelled positive for EOS visited within 72 hours of life and blood or cerebrospinal fluid, or urine culture was positive for any bacteria.

EOS risk calculator was calculated using Kaiser Permanente calculator via online following links https://neonatalsepsiscalculator.kaiserpermanente.org/.

The variables used in the risk calculator included incidence of EOS risk, gestational age, highest maternal antepartum temperature, rupture of membrane, maternal group B streptococcus (GBS), and type of intrapartum antibiotics.

SPSS version 24 was used for the purpose of statistical analysis. Mean and standard deviation was calculated for quantitative variables like age, birth weight, gestational age, highest maternal antepartum temperature, duration of rupture of membrane, neonatal heart rate, neonatal respiratory rate, neonatal temperature, neonatal oxygen saturation, and CRP level. Frequency and percentages were calculated for qualitative variables like gender, mode of delivery, parity, gravida, GBS during any trimester, type of intrapartum antibiotic, respiratory distress (grunting/nasal flaring/coastal recessions), APGAR ≥7 at 5 min, EOS risk, and blood culture. The mean difference of quantitative variables with respect to EOS was explored using One-way ANOVA test. Whereas to see the association of EOS risk with independent variables, chi-square/Fisher-Exact test was applied. The p-value of ≤0.05 was taken as statistically significant.

RESULTS

Of 249 cases, the mean age was 1.67 ±0.81 days. The mean birth weight was 2.33 ±1.85 kg. The majority of the patients were presented with birth weight in between 1.5-2.5 kg, i.e., 174 (69.9%). The mean gestational age was 36.06 ±1.67 weeks. There were 156 (62.7%) patients with ≤37 weeks and 93 (37.3%) with >37 weeks of gestation. One hundred thirty-seven (55%) were males and 112 (45%) were females (male: female ratio 1.22:1). Vaginal delivery was observed in 174 (69.9%). (Table-1)

Table No.1: EOS Risk and General Characteristics of the Neonates (n=249)

		EOS Risk			
	Total	**Well Appearing (n=63)**	**Equivocal (n=126)**	**Clinical Illness (n=60)**	**p=**
Age, days	1.67 ±0.81*	1.68 ±0.78	1.62 ±0.78	1.78 ±0.92	0.438
Gender					
Male	137 (55.0)	31 (49.2)	69 (54.8)	37 (61.7)	0.380
Female	112 (45.0)	32 (50.8)	57 (45.2)	23 (38.3)	
Birth Weight, kg	2.33 ±1.85*	2.87 ±3.52	2.11 ±0.50	2.24 ±0.66	0.026
<1.5	25 (10.0)	3 (12.0)	14 (56.0)	8 (32.0)	0.066
1.5-2.5	174 (69.9)	40 (23.0)	91 (52.3)	43 (24.7)	
>2.5	50 (20.1)	20 (40.0)	21 (42.0)	9 (18.0)	
Gestational Age, weeks	36.06 ±1.67*	36.37 ±1.57	36.17 ±1.63	35.48 ±1.77	0.007
≤37	156 (62.7)	31 (49.2)	79 (62.7)	46 (76.7)	0.007
>37	93 (37.3)	32 (50.8)	47 (37.3)	14 (23.3)	
Mode of Delivery					
Vaginal	174 (69.9)	44 (69.8)	92 (73.0)	38 (63.3)	0.404
Cesarean	75 (30.1)	19 (30.2)	34 (27.0)	22 (36.7)	
Parity					
Nulliparous	85 (34.1)	18 (28.6)	47 (37.3)	20 (33.3)	0.688
Primiparous	64 (25.7)	20 (31.7)	29 (23.0)	15 (25.0)	
Multiparous	100 (40.2)	25 (39.7)	50 (39.7)	25 (41.7)	

Gravida					
Nulligravida	2 (0.8)	0 (0)	2 (1.6)	0 (0)	0.560
Primigravida	90 (36.1)	21 (33.3)	49 (38.9)	20 (33.3)	
Multigravida	157 (63.1)	42 (66.7)	75 (59.5)	40 (66.7)	

Table 2: Comparison of ESO risk with maternal characteristics (n=249)

		EOS Risk			
	Total	**Well Appearing (n=63)**	**Equivocal (n=126)**	**Clinical Illness (n=60)**	**p=**
Maternal temperature, ^{O}C	38.10 ±4.01	37.56 ±0.71	38.06 ±4.55	38.73 ±4.74	0.264
≤38	115 (46.2)	55 (87.3)	53 (42.1)	7 (11.7)	<0.001
>38	134 (53.8)	8 (12.7)	73 (57.9)	53 (88.3)	
Rupture of membrane					
Yes	193 (77.5)	26 (41.3)	107 (84.9)	60 (100)	<0.001
No	56 (22.5)	37 (58.7)	19 (15.1)	0 (0)	
Duration of rupture of membrane, hours (n=193)	20.89 ±17.69	7.00 ±10.45	17.36 ±13.61	33.20 ±19.45	<0.001
≤18	116 (60.1)	23 (19.8)	76 (65.5)	17 (14.7)	<0.001
>18	77 (30.9)	3 (3.9)	31 (40.3)	43 (55.8)	
GBS in any trimester (n=47)^					
Yes	16 (6.4)	0 (0)	0 (0)	16 (59.3)	<0.001
No	31 (12.4)	2 (100)	18 (100)	11 (40.7)	
Type of intrapartum antibiotic					
Broad spectrum antibiotics > 4 hrs	90 (36.1)	11 (17.5)	50 (39.7)	29 (48.3)	<0.001
Broad spectrum antibiotics 2-3.9 hrs	21 (8.4)	0 (0)	16 (12.7)	5 (8.3)	
GBS specific antibiotics > 2 hrs	16 (6.4)	0 (0)	0 (0)	16 (26.7)	
No antibiotics or any antibiotics < 2 hrs	122 (49.0)	52 (82.5)	60 (47.6)	10 (16.7)	

^In 202 neonates, GBS bacteria was unknown

Table No.3: Comparison of EOS risk with neonatal characteristics (n=249)

		EOS Risk			
	Total	**Well Appearing (n=63)**	**Equivocal (n=126)**	**Clinical Illness (n=60)**	**p=**
Heart Rate, beats/min	142.26 ±13.77	139.67 ±10.55	142.13 ±11.13	145.27 ±20.01	0.077
Respiratory rate, breaths/min	47.29 ±8.35	44.90 ±6.09	47.24 ±8.35	49.90 ±9.67	0.004
Temperature, ^{O}C	35.85 ±1.01	36.07 ±0.84	35.79 ±0.92	35.75 ±1.26	0.114
Oxygen Saturation, %	91.44 ±3.20	92.94 ±2.60	91.56 ±2.86	89.62 ±3.58	<0.001
Respiratory distress					
Yes	127 (51.0)	22 (34.9)	66 (52.4)	39 (65.0)	0.003
No	122 (49.0)	41 (65.1)	60 (47.6)	21 (35.0)	
APGAR <7					
Yes	119 (47.8)	46 (73.0)	65 (51.6)	8 (13.3)	<0.001
No	130 (52.2)	17 (27.0)	61 (48.4)	52 (86.7)	
Blood Culture					
Positive	157 (63.1)	13 (20.6)	84 (66.7)	60 (100)	<0.001
Negative	92 (36.9)	50 (79.4)	42 (33.3)	0 (0)	
CRP					
Positive	172 (69.1)	7 (11.1)	105 (83.3)	60 (100)	<0.001
Negative	77 (30.9)	56 (88.9)	21 (16.7)	0 (0)	

A significantly higher risk of clinical illness was observed among neonates with lower birth weight (p= 0.026), lower gestational age (p= 0.007), higher maternal temperature, having rupture of membrane (p= <0.001), higher duration of rupture of membrane (p= <0.001), GBS bacteriuria in any trimester (p= <0.001), >4 hours of broad-spectrum antibiotics (p= <0.001). (Table-2)

The mean heart rate, respiratory rate, temperature was 142.26 ±13.77 beats/minute, 47.29 ±8.35 breaths per minute, and 35.85 ±1.01 ºC. Respiratory distress was observed in 127 (51.0%), APGAR <7 was 119 (47.8%), positive blood culture 157 (63.1%), and positive CRP in 172 (69.1%) patients.

Early onset neonatal sepsis risk calculator shows that 60 (24.1%) had clinical illness, 63 (25.3%) patients had well appeared status and 126 (50.1%) had equivocal status. Blood culture was found positive in 157 patients. Of these 157 cases, 13 (20.6%) were well appearing, 84 (66.7%) were equivocal, and 60 (100%) had clinical illness. Whereas among 172 CRP positive cases, 7 (11.1%) were well appearing, 105 (83.3%) were equivocal, and 60 (100%) had clinical illness.

A significantly higher risk of clinical illness was observed among neonates with lower birth weight (p= 0.026), lower gestational age (p= 0.007), higher maternal temperature, having rupture of membrane (p= <0.001), higher duration of rupture of membrane (p= <0.001), GBS bacteriuria in any trimester (p= <0.001), >4 hours of broad-spectrum antibiotics (p= <0.001), lower oxygen saturation (p= <0.001), having respiratory distress (p= 0.003), APGAR score <7 (p= <0.001), positive blood culture (p= <0.001), and positive CRP (p= <0.001). (Table-3).

DISCUSSION

Neonatal sepsis is a significant problem that needs constant monitoring and stringent care guidelines. While neonatal sepsis is a global concern, it is mostly disregarded in places like Pakistan, where those who care about it must contend with significant financial hardships and a lack of access to high-quality medical treatment. In this cohort, the health of new-borns and babies is of special significance[7,8]. In critically ill and hospitalised patients, therapeutic care and early evaluation of sepsis risk are of highest significance in addition to morality, and morbidity. The overuse of antibiotics in this population leads to several health problems and puts further strain on the already impoverished healthcare systems in low- and middle-income countries [9-11].

In the current study, hospitalized neonates in neonatal intensive care were assessed to determine whether or not neonates who were born at less than 34 weeks of gestation need antibiotic support and are at risk of sepsis. The risk of EOS was evaluated using the Kaiser Permanente calculator. The findings of the study reported that early onset neonatal sepsis risk calculator revealed clinical illness in 24.1% neonates while 25.3% neonates were well-appeared, and half of the neonates had equivocal status. All the neonates who were found to have clinical illness on risk calculator had positive blood culture and CRP report showing the significance of using of early onset risk calculator in neonates admitted in intensive care.

Several previous studies have also reported supportive findings for EOS risk calculator in neonates [12-16]. Recently, Kopsidas et al. carried out a study to evaluate the potential advantages of implementing the Kaiser Permanente early-onset sepsis calculator across a network of newborn critical care units, in terms of antibiotic use and required laboratory testing. According to their study's findings, the calculator assisted management of neonates with well appearing sepsis could result in halting the need for empiric antibiotics and a significant reduction in the need for antibiotics. Furthermore, the EOS calculator has a high sensitivity for detecting newborns with positive blood cultures [12]. Another recent study by Rallis et al reported the positive findings of the use of early onset neonatal sepsis risk calculator. Similar to the current study, their study population also included neonates with more than 34 weeks of gestation. The authors claim that if the sepsis risk calculator had been used, five infants who later had clinical sepsis would have been overlooked, but roughly half of the infants who received antibiotics were unlikely to have received treatment. In addition, the author claimed that the use of the sepsis risk calculator resulted in a three percent reduction in the overall dose of antibiotics [13]. Morris et al. compared the National Institute for Health and Care Excellence (NICE) recommendation with the Kaiser Permanente neonatal EOS risk calculator in newborns with 34 weeks gestation who experienced EOS. While both methods performed poorly in detecting EOS within four hours, the investigators found that NICE performed better than the EOS risk calculator in detecting asymptomatic cases[14].

A significantly higher risk of clinical illness was observed in current study among neonates with lower birth weight, lower gestational age, higher maternal temperature, having rupture of membrane, higher duration of rupture of membrane, GBS in any trimester, >4 hours broad-spectrum antibiotics, lower oxygen saturation, having respiratory distress, APGAR score <7, positive blood culture, and positive CRP.

Previous studies from Pakistan also reported high prevalence of GBS in neonates with clinical illness [17,18]. Concerns concerning antibiotic exposure in neonates who are not ill have been expressed by clinicians. Early antibiotic exposure is linked to the development of antibiotic-resistant pathogenic germs and a decline in the diversity of gut microbes, which can lead to infections that are particularly challenging to cure [19].

Due to all of these factors, it's crucial to refrain from giving patients unneeded antibiotics in the first few postpartum weeks[20]. However, because many sepsis symptoms are nonspecific and can be seen alongside other non-infectious diseases, making a clinical diagnosis of sepsis can be difficult for neonatologists [9,21,22].

This study has highlighted the positive impact of EOS risk calculator in neonates. However, limited number of samples, inclusion of single center, and lack of follow-up are the few limitations of this study that needs to cover in the future studies on assessment of EOS risk calculator.

CONCLUSION

EOS risk calculator has highlighted around one fourth of neonates with the high risk of clinical illness in neonates presented with ≥ 34 weeks of gestational age. Moreover, all the neonates who had clinical disease on the risk calculator had positive blood cultures and CRP reports.

Author's Contribution:

Concept & Design of Study:	Bushra Qamar
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