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Original Article

Scoring model to predict early-onset bacterial sepsis at Dr. Mohammad Hoesin Hospital, Palembang

Lilik Fitriana, Afifa Ramadanti, Indrayady

Abstract

Background Early-onset bacterial neonatal sepsis (bacterial EONS) is one of the most common causes of death and illness in newborns. Assessment of risk factors is important to identify infants who are more susceptible to bacterial EONS. A scoring model based on maternal and infant risk factors would be useful for predicting bacterial EONS.

Objective To develop a scoring model to predict bacterial EONS by examining maternal and neonatal risk factors.

Methods This diagnostic test study was conducted at Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera, between January-September 2021 using various maternal and infant risk factors. Subjects were newborns suspected of having early-onset bacterial sepsis with birth weight >1000 grams. The potential risk factors evaluated consisted of premature rupture of membranes >18 hours, greenish-thick-and-foul-smelling amniotic fluid, maternal body temperature >38°C, maternal leukocytosis >15.000/μL, gestational of <37 weeks, birth weight of <2500 grams, and APGAR score of <7 at 1 minute. One hundred sixty-two subjects were selected consecutively. Analyses included odds ratio, logistic regression test, and ROC curve to assess sensitivity and specificity of each risk factor.

Results Premature rupture of membranes >18 hours, greenish-thick-and-foul-smelling amniotic fluid, male sex, and gestation of <37 weeks were risk factors for bacterial EONS. In the multivariate analysis, premature rupture of membranes >18 hours had an OR of 5.94 (95%CI 1.69 to 20.86, P=0.005), greenish-thick-and-foul-smelling amniotic fluid had an OR of 3.74(95%CI 1.16 to 12.02, P=0,027), male sex had an OR of 4.28 (95%CI 1.14 to 16.02, P=0.031), and gestation of <37 weeks had an OR of 3.1 (95%CI 0.82 to 11.72, P=0.094). In the scoring model, each of these four risk factors were assigned a score of 2 (for maternal risk factors) and 1 (for neonatal risk factors). Using a cut-off score of 2.5 to predict bacterial EONS, the scoring system had a sensitivity of 80% and specificity of 47%.

Conclusion Our scoring model of maternal and infant risk factors can be used to screen for possible bacterial EONS at an earlier stage of illness, although with limited specificity. **[Paediatr Indones. 2023;63:29-36; DOI: 10.14238/pi63.1.2022.29-36**].

Keywords: *early-onset neonatal sepsis; scoring system*

Early-onset bacterial neonatal sepsis (bacterial EONS) is one of the most common causes of death and morbidity in neonates. The *National Institute of Child Health and Human Development* (NICHD) *Neonatal Research Network* (NRN) estimated an overall bacterial EONS incidence of 0.98 cases per 1,000 live births, with an even higher rate in premature infants.[1] Bacterial EONS is a systemic clinical disease syndrome accompanied by bacteremia that occurs in the first 72 hours after birth.[2-4] The diagnosis of neonatal sepsis is based on clinical symptoms as well as physical and laboratory examinations, with blood culture as the gold standard. However, not all health care centers have adequate facilities for the bacterial confirmation of EONS diagnosis. Routine administration of antibiotics results in their excessive use in neonates, while increasing the rate of antibiotic resistance.[5]

Takkar *et al.*[6] classified neonatal bacterial sepsis into three degrees based on the following risk factors: cloudy and foul-smelling amniotic membranes, non-sterile vaginal examination, labor of >24 hours, first minute APGAR score ≤6, ruptured membranes of

From the Department of Child Health, Universitas Sriwijaya Medical School/Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera, Indonesia.

Corresponding author: Afifa Ramadanti. Department of Child Health, Universitas Sriwijaya Medical School/Dr. Mohammad Hoesin Hospital. Jalan Jenderal Sudirman KM 3,5 Palembang, South Sumatera, Indonesia. Telp. +62 81368527264; Fax. +62 711 376445; Email: afifa.ramadanti@gmail.com

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>24 hours, birth weight of <2,000 g, or gestational age of <37 weeks. Rodwell *et al.*[7] also carried out a scoring model based on several laboratory parameters, and Spector *et al.*[8] reported a scoring model using a combination of clinical features and investigations to elucidate a sepsis diagnosis. Thus, a scoring model that uses maternal and infant risk factors may predict EONS so that antibiotics can be administered as early as possible. Such a scoring model would also benefit health facilities in areas with limited support facilities. In this study, we aimed to devise a scoring model incorporating maternal and neonatal risk factors, in the hope to identify bacterial EONS cases in a timely manner and limit the irrational use of antibiotics.

Methods

This diagnostic test study was conducted from January to September 2021 in mothers and newborns rooming-in at the Neonatal Ward or newborns admitted to the NICU of Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera. All mothers were asked to sign an informed consent prior to participation in the study. Various maternal and infant risk factors were used to develop the scoring model to predict bacterial EONS. Subjects were consecutively selected infants suspected of having infection, with or without clinical sepsis. A minimum required sample size of 162 subjects was calculated based on the sample size formula for estimation of sensitivity, with a Zα of 1.96, sensitivity of 80%, proportion of 0.42, and drop-out possibility of 10%. Inclusion criteria were neonates suspected of having early-onset bacterial sepsis with birth weight of >1000 grams. Neonates with intrauterine growth retardation (IUGR), gestational age of <28 weeks, or major congenital abnormalities or syndromes (e.g., Down syndrome) were excluded. The maternal and neonatal risk factors assessed were gestational age <37 weeks, birth weight <2,500 grams, APGAR score <7 on the first minute, premature rupture of membranes >18 hours before birth, maternal body temperature >38°C intrapartum, maternal blood leukocytes >15,000/μL, greenish-thick-and-foul-smelling amniotic fluid, duration of labor >24 hours, use of intrapartum antibiotics, and twin pregnancies.

Bacterial EONS was defined as a systemic clinical disease syndrome, with bacteremia that occurring in the first 72 hours after birth. Proven sepsis was evidenced by bacteria in blood cultures with clinical and/or laboratory evidence of sepsis. Probable sepsis was defined as the presence of signs or symptoms of neonatal sepsis supported by two or more septic markers, but without evidence of bacteria in blood culture. Clinical sepsis was defined as the presence of at least two clinical symptoms of neonatal sepsis, but with neither laboratory signs nor positive blood culture. Suspected infection was defined as the presence of risk factors for neonatal infection without any signs or symptoms of clinical sepsis.

For the scoring model, we calculated odds ratios and performed logistic regression and receiver-operator characteristics (ROC) curve analysis to determine the cut-off score for optimal sensitivity and specificity. Variables with a P value of <0.2 were incorporated in the multivariate analysis. Multivariate analysis was done using *SPSS version 21.0* (*IBM*, Armonk, New York). This study had been approved by the Health Research Ethics Committee of Universitas Sriwijaya Faculty of Medicine/Mohammad Hoesin Hospital, Palembang.

Results

We included 162 neonates; 87 (53.7%) were male. Most deliveries (122/162; 75.3%) were performed by Caesarean section (CS). The majority of infants (101/162; 62.4%) had gestational age <37 weeks, with a median gestational age of 37 (range 28-42) weeks. Subjects' median birth weight was 2,735 (range 1,020-4,600) grams, while 93/162 (57.4%) had birth weights of >2500 g. Most subjects (134/162; 82.7%) had first-minute APGAR scores of >7.

Median duration of premature rupture of membranes was 14 (range 0-48) hours; 95/162 (58.6%) and 67/162 (41.4%) subjects had premature rupture of membranes of ≤18 and >18 hours, respectively. Greenish-thick-and-foul-smelling amniotic fluid was found in 45/162 (27.8%) subjects; the rest had clear amniotic fluid. The duration of labor from the time of membrane rupture to delivery was ≥24 hours for 25/162 (15.4%) subjects. Only 10/162 (6.2%) subjects were not given intrapartum antibiotics. Two (1.2%) subjects were twins. Subject characteristics are shown in **Table 1**.

Table 1. Characteristics of subjects (N=162)

Variables	n (%)
Sex	
Male	87 (53.7)
Female	75 (46.3)
Type of delivery	
Caesarean section (CS)	122 (75.3)
Vaginal	40 (24.7)
Gestational age	
<37 weeks	101 (62.3)
≥37 weeks	61 (37.7)
Median (range)	37 (28-42)
Birth weight	
<2,500 g	69 (42.6)
≥2,500 g	93 (57.4)
Median (range)	2,735 (1,020-4,600)
APGAR score	
<7	28 (17.3)
≥7	134 (82.7)
Premature rupture of membranes	
>18 hours	67 (41.4)
≤18 hours	95 (58.6)
Median (range)	14 (0-48)
Amniotic fluid characteristics	
Green-thick-and-smelly amniotic fluid	45 (27.8)
Clear	117 (72.2)
Maternal body temperature	
≥38°C	5 (3.1)
<38°C	157 (96.9)
Median (range)	36.7 (35.8-38.9)
Duration of labor	
<24 hours	137 (84.6)
≥24 hours	25 (15.4)
Intrapartum antibiotic use	
Yes	152 (93.8)
No	10 (6.2)
Twin pregnancy	
Yes	2 (1.2)
No	160 (98.8)

Table 2. Bacterial EONS distribution (N=162)

EONS	n (%)
Probable sepsis	3 (1.9)
Proven sepsis	15 (9.3)
Gram negative	4 (27)
Gram positive	11 (73.1)
Clinical sepsis	50 (30.9)
Suspected Infection	94 (58)

In our study, 15/162 (9.3%) subjects had bacterial EONS proven by positive blood cultures. Most subjects (95/162; 58%) had suspected infection, and 3/162 (1.9%) had probable sepsis (**Table 2**). Out of the 15 subjects with positive blood cultures, four showed Gram-negative bacteria (*Pseudomonas aeruginosa* and *Acinetobacter baumannii*) and 11 showed Gram-positive bacteria (*Staphylococcus epidermidis* and *Staphylococcus hemolyticus*).

Bivariate analysis to examine relationships between independent variables (risk factors) and the dependent variable (proven EONS) is shown in **Table 3**. Of the maternal risk factors, only premature rupture membranes >18 hours was significantly associated with bacterial EONS (OR 4.46; 95%CI 1.35 to 14.71; P=0.008). Of the neonatal risk factors, male sex (OR 3.84; 95%CI 1.04 to 14.17; P=0.032) and gestational age <37 weeks (OR 4.35; 95%CI 0.94 to 20.02; P=0.041) were statistically significant risk factors for bacterial EONS.

Multivariate analysis results are shown in **Tables 4** and **5**. The maternal factors significantly associated with bacterial EONS were premature rupture of membranes >18 hours (OR 5.94; 95%CI 1.69 to 20.86; P=0.005) and greenish-thick-and-foul-smelling amniotic fluid (OR 3.74; 95%CI 1.16 to 12.02; P=0.027). The neonatal factors associated with bacterial EONS was male sex (OR 4.28; 95%CI 1.14 to 16.02; P=0.031). We decided to include gestational age <37 weeks (OR 3.111; 95%CI 0.82 to 11.72; P = 0.094) in the final scoring model because its p value was <0.1.

We then performed combined multivariate analysis incorporating all four variables (**Table 6**). We then divided the beta coefficient with the standard error (B/SE); the smallest value of B/SE was used as a divisor of all B/SE values to arrive at the variable scores. Based on this, we assigned a score of 2 for each positive maternal risk factor (premature rupture of membranes >18 hours and greenish-thick-and-foul-smelling amniotic fluid) and a score of 1 for each positive neonatal risk factor (male sex and gestational age of <37 weeks), resulting in a scoring model with a maximum possible total score of 6 (indicating maximum risk) to predict bacterial EONS (**Table 7**).

Figure 1 shows the ROC curve with an area under the curve (AUC) value of 0.762. We determined the optimal cut-off point for bacterial EONS based on

Table 3. Maternal and neonatal risk factors for bacterial EONS (N=162)

Variables	EONS		OR	95%CI	P value
	Positive (n=15)	Negative (n=147)			
Premature rupture of membranes, n (%)					
>18 hours	11	56 (38.1)	4.46	1.35 to 14.71	0.008[b]
≤18 hours	4	91 (61.9)			
Amniotic fluid characteristics, n(%)					
Green-thick-and-smelly amniotic fluid	7	38 (25.9)	2.51	0.85 to 7.38	0.127[a]
Clear	8	109 (74.1)			
Maternal body temperature, n(%)					
≥38˚C	0	5 (3.4)	1	1.05 to 1.16	0.611[a]
38˚C	15	142 (96.6)			
Leukocytes, n(%)					
>15,000/mm^3	11	90 (61.2)	1.74	0.53 to 5.73	0.357[b]
≤15,000/mm^3	4	57 (38.8)			
Maternal intrapartum antibiotic use, n(%)					
Yes	15	137 (93.2)	1.9	0.85 to 2.95	0.601[a]
No	0	10 (6.8)			
Type of labor, n(%)					
Vaginal	5	35 (23.8)	1.60	0.51 to 4.99	0.529[b]
CS	10	112 (76.2)			
Twin pregnancy, n(%)					
Yes	0	2 (1.4)	1.10	1.05 to 1.16	1[a]
No	15	145 (98.6)			
Sex, n(%)					
Male	12	75 (51.0)	3.84	1.04 to 14.17	0.032[b]
Female	3	72 (49.0)			
Gestational age, n(%)					
<37 weeks	13	88 (59.9)	4.35	0.94 to 20.02	0.041[b]
≥37 weeks	2	59 (40.1)			
Birth weight, n(%)					
<2500 g	8	61 (41.5)	1.6	0.55 to 4.67	0.377[b]
≥2500 g	7	86 (58.5)			
Apgar score, n(%)					
<7	2	26 (17.7)	0.72	0.15 to 3.37	1[a]
≥7	13	121 (82.3)			

[a]Fisher's exact test, [b]Chi-square test; P<0.05 was considered to be statistically significant

Table 4. Multivariate analysis of maternal risk factors for bacterial EONS (N=162)

Variables	B	S.E.	Wald	OR	95%CI	P value
Premature rupture of membranes >18 hours	1.782	0.641	7.724	5.940	1.691 to 20.868	0.005
Green-thick-and-smelly amniotic fluid	1.319	0.596	4.906	3.740	1.164 to 12.021	0.027
Constant	-3.759	0.637	34.855	0.023		0.000

*Multivariate logistic regression test

Table 5. Multivariate analysis of neonatal risk factors for bacterial EONS (N=162)

Variables	B	S.E.	Wald	OR	95% CI	P value
Male sex	1.455	0.673	4.675	4.286	1.146 to 16.029	0.031
Gestational age <37 weeks	1.135	0.677	2.810	3.111	0.825 to 1.726	0.094
Constant	-4.050	0.826	24.012	0.017		0.000

*Multivariate logistic regression test

the optimal sensitivity and specificity. A score of 2.5 had 80% sensitivity and 47% specificity (P=0.001).

Table 6. Combined multivariate analysis of maternal and neonatal risk factors to predict bacterial EONS

Variables	B	S.E.	Wald	OR	95% CI	P value
Premature rupture of membranes >18 hours	1.632	0.675	5.855	5.115	1.364 to 19.189	0.016
Green-thick-and-smelly amniotic fluid	1.456	0.638	5.218	4.290	1.230 to 14.968	0.022
Male sex	1.307	0.706	3.430	3.694	0.927 to 14.729	0.064
Gestational age <37 weeks	1.113	0.717	2.409	3.042	0.747 to 12.395	0.121
Constant	-5.415	1.107	23.911	0.00		0.000

B=beta coefficient, S.E.= standard error

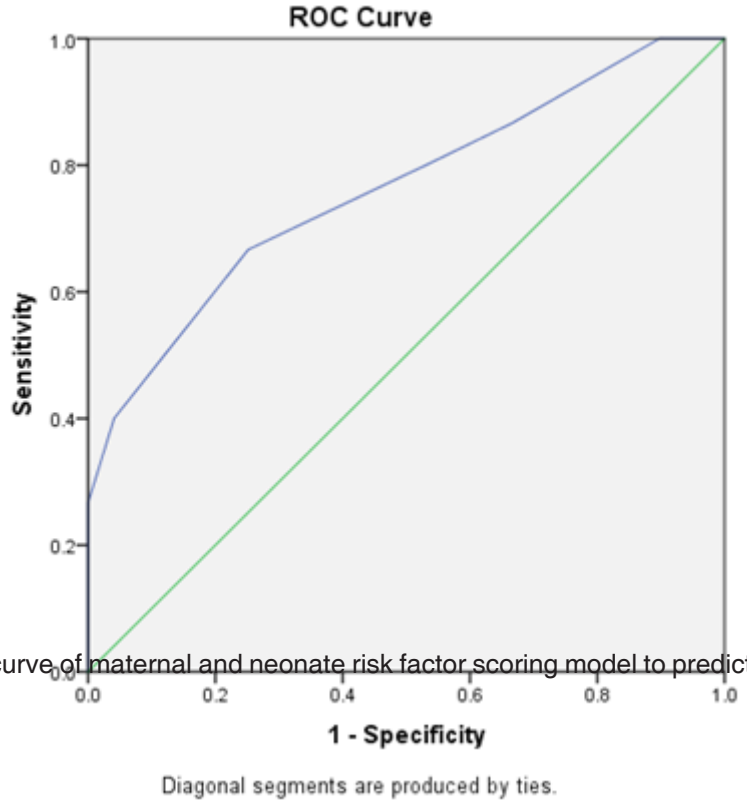

Figure 1. ROC curve of maternal and neonate risk factor scoring model to predict bacterial EONS

Table 7. Maternal and neonatal risk factor scoring model for bacterial EONS

Variables	B	S.E.	B/S.E.	(B/S.E.):1.55	Score
Premature rupture of membranes >18 hours	1.632	0.675	2.42	1.56	2
Green-thick-and-smelly amniotic fluid	1.456	0.638	2.28	1.47	2
Male sex	1.307	0.706	1.85	1.19	1
Gestational age <37 weeks	1.113	0.717	1.55	1	1

B=beta coefficient, S.E.= standard error

Discussion

In our study, 15/162 (9.3%) subjects had proven bacterial EONS, 94/162 (58%) had suspected infection, and 3/162 (1.9%) had probable sepsis. A previous study identified 429 infants infant with blood culture-proven sepsis, 20% of whom had EONS and 62% of whom had late-onset neonatal sepsis.[9] Another study found that the incidence of bacterial EONS was 32% among 402 infants.[10] The incidence of bacterial EONS found by Moges *et al.*[11] was 117 (46.6%) of 251 subjects. In 901 neonates admitted to the NICU, Sorsa *et al.*[12] found a prevalence of bacterial EONS of 34%.

We used bivariate analysis to analyze for possible associations between risk factors and bacterial EONS. Of maternal risk factors, premature rupture of membranes had 4.4 times higher risk for the occurrence of bacterial EONS (P<0.05). A similar study found that among 251 mothers whose newborns had bacterial EONS, 12% had a labor duration of >24 hours, 12.8% had intrapartum fever, 51.3 delivered pervaginam and 44.4% had a Caesarean section, 4.3% had instrumentation during delivery, and 21.4 had urinary tract infection.[11] Sorsa *et al.*[13] found that maternal risk factors of prolonged delivery, urinary tract infection, premature birth, and ruptured membranes >18 hours were associated with bacterial EONS.

We found that male sex and gestational age <37 weeks had ORs of 3.8 and 4.3 for bacterial EONS, respectively. Our findings were consistent with a previous study which concluded that male sex and gestational age <37 weeks were strongly correlated with the incidence of bacterial EONS.[13] Another study noted that in addition to gestational age <37 weeks, APGAR score < 5, male sex, and low birth weight (<2,500 g) were also associated with EONS. Neonates with bacterial EONS showed symptoms of fever/hypothermia, vomiting, diarrhea, irritability, lethargy, breathing problems, low blood sugar, jaundice (jaundice), weak suction reflex, and seizures.[11]

Multivariate analysis of maternal risk factors revealed that premature rupture of membranes >18 hours and greenish-thick-and-foul-smelling amniotic fluid had ORs of 5.9 and 3.7 for bacterial EONS. A multivariate study by Gandra *et al.*[14] found that twin birth carried a triple increase in the risk of experiencing EONS, while ruptured membranes >18 hours brought a 6-fold increased risk of experiencing EONS. A case-control study in Tanzania found the following maternal risk factors to be associated with bacterial EONS: chorioamnionitis (OR 1.9), HIV (OR 2.9), premature rupture of membranes >18 hours (OR 2.8), cloudy amniotic fluid (OR 3.2), foul-smelling amniotic fluid (OR 4.2), and vaginal examination during the delivery process (OR 5.9). The neonatal risk factors associated with EONS were <37 weeks gestational age (OR 1.5), newborn's weight risk (OR 1.5), fetal distress (OR 1.6), and perinatal asphyxia (OR 6.7).[15]

In our study, analysis of neonatal risk factors revealed that male sex and gestational age of <37 weeks had fourfold and threefold increased risk for the occurrence of bacterial EONS, similar to results from Murthy *et al.*[13] Consistent with previous study, Gianoni *et al.*[9] found that newborns weighing <2,500 grams had a 1.7 times higher risk and male babies had 1.8 times higher risk for bacterial EONS, while female babies tend to be protected from bacterial EONS (OR=0.9). Moreover, the presence of clinical symptoms put infants at 2.4 times higher risk of having bacterial EONS.

Our scoring model to predict bacterial EONS had four parameters based on the multivariate logistic regression analysis results: premature rupture of membranes >18 hours, greenish-thick-and-foul-smelling amniotic fluid, male gender, and gestational age <37 weeks. The first two risk factors each were assigned a score of 2, while the two latter each were assigned a score of 1, yielding a scoring system with a maximum total score of 6 to predict bacterial EONS. This scoring model is quite easy to use as a screening tool to predict bacterial EONS in neonates. ROC analysis revealed the optimal cut-off point score of 2.5. This cut-off point had reasonably high sensitivity (80%), so a total score of >2 can be said to predict bacterial EONS.

A study compared two guidelines for prediction of EONS: the *National Institute for Health and Care Excellence* (NICE) guidelines and the *Kaiser Permanente Sepsis Risk Calculator* (SRC). The study concluded that these two guidelines had similar results and increased the appropriate use of antibiotics. While the NICE guidelines focused on maternal risk factors in mothers and clinical symptoms in newborns, the

SRC focused on recommendations based on maternal risk factors and infant risk factors towards actions such as normal care checks, vital signs, culture, and administration of antibiotics.[16]

A technical assessment of an EONS risk calculator identified gestational age, maternal temperature, time from membrane rupture until delivery, membrane characteristics, and maternal history of urinary tract infection during pregnancy as risk factors for EONS. The use of the calculator results in a fairly high accuracy value to predict sepsis, with recommendations for further examination related to bacterial EONS.[17] In a case-control study done in Thailand, the reported incidence of proven late-onset neonatal sepsis was 1.4%. The study devised a predictive model for late-onset neonatal sepsis which included feeding refusal, elevated heart rate, and abnormalities in temperature, oxygen saturation, leukocyte count, and pH as significant predictive factors, with a sensitivity of 88.5% and specificity of 90.4%.[18]

The present study has several advantages. We knew the potential maternal and neonatal risk factors before carrying out additional examinations. This study was a cohort study, so that factors other than those that influenced the occurrence of bacterial EONS sepsis could be controlled. A weakness of our study was that the cut-off point for premature rupture of membranes and gestational age was determined at the beginning of the study. In addition, this scoring model has not yet been validated, so further validation with a larger sample size is needed.

In conclusion, premature rupture of membranes >18 hours, greenish, thick, and foul-smelling amniotic fluid, gestational age of <37 weeks, and male sex are significant predictors of bacterial EONS. A scoring model devised based on these four risk factors has a sensitivity of 80% and a specificity of 47% to predict bacterial EONS.

Conflict of interest

None declared.

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