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ARTICLE

Predictors of early-onset neonatal sepsis or death among newborns born at <32 weeks of gestation

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Abstract

Objective To develop a predictive model for early-onset neonatal sepsis or death among infants born at less than 32 weeks of gestation.

Study design This was a case-control study of all deliveries <32 weeks between 2011 and 2015 in a single tertiary care center. Cases were defined as neonates diagnosed with early-onset sepsis based on a blood or cerebrospinal fluid culture or neonates who expired during the first week of life. Controls consisted of neonates without these outcomes. Variables previously identified to be associated with neonatal sepsis or death were abstracted from the medical record. Bivariable analyses and multivariable logistic regression were used to determine independent risk factors for early-onset neonatal sepsis or death. An ROC curve was created and AUC calculated to estimate the predictive capacity of these associations.

Results Of 779 eligible neonates, early-onset neonatal sepsis or death occurred in 73 (9.4%). In bivariable analyses, mothers whose neonates were diagnosed with early-onset sepsis or death were more likely to be obese, have an intrapartum fever, and have meconium-stained amniotic fluid, and were less likely to have received betamethasone or antepartum/intrapartum antibiotics. Gestational age at delivery and birth weight was significantly lower among neonates diagnosed with neonatal sepsis or death. In multivariable analyses, factors remaining independently associated with neonatal sepsis or death were earlier gestational age at the time of delivery (specifically <28 weeks), intrapartum fever, presence of meconium-stained amniotic fluid, and lower birth weight. The AUC for this regression was 0.81 (95% confidence interval 0.77–0.83).

Conclusion Earlier gestational age at the time of delivery, intrapartum fever, meconium, and lower birth weight are independently associated with early-onset neonatal sepsis or death among deliveries occurring at <32 weeks of gestation; these factors can be used to create a model with fair predictive capability.

Introduction

Early-onset neonatal sepsis (EOS) has been defined as sepsis that manifests within the first 72 h of life and is usually due to vertical transmission through contaminated amniotic fluid or during vaginal delivery [1, 2]. EOS is a common complication among preterm and very low birth infants [3–5]. Diagnosis of neonatal sepsis in this population is associated with poor neurodevelopmental outcome, growth impairment, and neonatal death [6–9]. In the past few years, although the incidence of late-onset sepsis, defined as sepsis that presents at or beyond 3–7 days of life, has decreased among preterm infants, the incidence of EOS in preterm or very low birth weight infants has remained stable [5].

Several investigators have described risk factors associated with neonatal sepsis [2, 10–13]. These include delivery at <37 weeks of gestation [10], maternal Group B

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Streptococcal (GBS) infection [2], prolonged rupture of membranes ≥18 h [13], and chorioamnionitis [11]. Despite these known risk factors, diagnosis of EOS is difficult, especially in the population of <32 weeks infants, due to nonspecific clinical presentation. Contemporary studies have focused on developing a predictive model for either late-onset neonatal sepsis only [14–16] or EOS in term and late preterm neonates (≥34 weeks) [17, 18]. Therefore, the objective of this study was to identify predictors of EOS in early preterm infants <32 weeks. Identifying particular maternal characteristics and intrapartum factors that may facilitate earlier accurate prediction of which preterm neonates would experience EOS may help to prevent sepsis or treat it earlier.

Materials and methods

This was a case-control study of all pregnancies complicated by preterm birth <32 weeks of gestation at Northwestern Memorial Hospital (NMH) between January 2011 and June 2015. The source population was all women delivering at NMH, which is a large tertiary care urban center. The population includes a sociodemographically diverse group of women who received care both at prenatal care sites affiliated with this institution as well as women who were transferred to this institution for advanced obstetric care. The care for women in this population is provided by a multidisciplinary team including maternal-fetal medicine subspecialists and general obstetrician specialists, as well as obstetrics and gynecology residents and maternal-fetal -medicine fellows.

Inclusion criterion for this case-control study was singleton or twin gestation delivering at $23^{1/7}$–$31^{6/7}$ weeks. Neonates transferred to this hospital from outside institutions were not included. Cases were defined as neonates diagnosed with EOS on a blood or a cerebrospinal fluid culture during the first 72 h of life or neonates who expired during the first week of life. Neonates delivered during this gestational age window without diagnosis of sepsis constituted the control group. All neonates delivered prior to 32 weeks who met inclusion criteria and did not experience primary outcome were included in the control group. Exclusion criteria were pregnancies complicated by major fetal anomaly and deliveries with no intent for neonatal resuscitation. Matching between cases and controls was not done as we analyzed all deliveries at $23^{1/7}$–$31^{6/7}$ weeks that met inclusion criteria. Additionally, as the sample size was constrained, a power calculation was not performed.

Medical records were abstracted for sociodemographic and clinical characteristics, including maternal age, race and ethnicity, body mass index (BMI) at the time of delivery, type of insurance, obstetric history, including parity, GBS status, presence of preterm prelabor rupture of membranes (PPROM), and antepartum hospital stay (i.e., any hospital admission to the antepartum unit prior to labor and delivery). Clinical factors also included antepartum or intrapartum administration of antibiotics, defined as receipt of Penicillin for GBS prophylaxis, corticosteroids, and magnesium sulfate. Delivery variables collected included presence of intrapartum fever (≥38.0 °C) without an explicit clinical diagnosis of chorioamnionitis, presence of clinical diagnosis of chorioamnionitis (as defined by the treating obstetrician), rupture of membranes in labor >18 h, clinical diagnosis of placental abruption, mode of delivery, presence of meconium-stained amniotic fluid at delivery, performance of delayed cord clamping, and birth weight.

Cases and controls were compared in bivariable analysis using Student's *t*-test, x^2, Fisher's exact test, and Mann-Whitney U test as appropriate. Factors that were significantly associated with neonatal sepsis or death ($P < 0.05$) were retained for further analyses, which included models of multivariable logistic regression for the outcome of neonatal sepsis. As the combination of prematurity and birth weight is known to increase the likelihood of EOS, we tested for interaction between these two risk factors towards the risk of EOS, entering the gestational age into the interaction model both as a continuous variable and as categorical variable. We performed three different regression models: model 1 included continuous variable of gestational age at delivery, continuous variable of birth weight, and the interaction between these two variables. Model 2 included gestational age at delivery as continuous variable, birth weight dichotomized by very low birth weight (<1500 g), and the interaction between these two variables. Model 3 included gestational age as a categorical variable dichotomized by delivery <28 weeks of gestation, birth weight as a continuous variable, and interaction between the two variables. The gestational age of 28 weeks was chosen as it is a clinically significant point after which neonatal outcomes generally are improved, and it is the natural midpoint of the gestational age range in this study. We did not construct a fourth model for categorical variables of gestational age <28 weeks and birth weight <1500 g as all neonates delivered prior to 28 weeks have birth weight <1500 g.

A receiver operating characteristic (ROC) curve analysis was performed for each regression model. The area under the curve (AUC) was calculated to estimate the predictive capacity of the logistic regression. An AUC of 0.80 was considered minimally necessary for the model to have clinical applicability [19, 20]. The Hosmer-Lemeshow goodness of fit test was done to examine how well each of the models fit the data. The higher the *P* value is in the goodness of fit test, the model passes the test of fit. *P* value <0.05 will lead to model rejection. All analyses were

performed with Stata version 12.0 (StataCorp College Station, TX). All tests were two-tailed and $P < 0.05$ was used to define significance. Approval for this study was obtained from the Northwestern University Institutional Review Board.

Results

During the study period, 779 neonates met inclusion criteria. EOS ($n = 40$) or death ($n = 33$) occurred in 73 (9.4%) of the neonates born at <32 weeks of gestation. Nine of the neonates experienced both outcomes. Maternal and neonatal characteristics, stratified by EOS or death, are shown in Table 1. Women whose neonates experienced EOS or death had higher BMI and were more likely to be obese (53.5 versus 37.7%, $p = 0.009$), were more likely to deliver prior to 28 weeks (66.7 versus 23.6%, $p < 0.001$), and were less likely to receive antibiotics before delivery (82.2 versus 91.5%, $p = 0.009$), at least one dose of corticosteroids (74.0 versus 87.6%, $p = 0.001$) or magnesium sulfate (81.9 versus 90.5%, $p = 0.024$) prior to delivery. During labor, these women were more likely to experience fever ≥38.0 °C (12.3 versus 5.4%, $p = 0.018$) and meconium-stained amniotic fluid (9.6 versus 3.3%, $p = 0.007$). Neonates who experienced EOS or death had lower birth weight and were more likely to have a very low birth weight (87.5 versus 65.1%, $p < 0.001$).

In the multivariable analysis, model 1, using gestational age at delivery and birth weight as continuous variables, demonstrated that after adjusting for potential confounding variables (maternal obesity, receipt of antibiotics prior to delivery, receipt of one corticosteroids prior to delivery, magnesium sulfate in labor, fever in labor of ≥38.0 °C, presence of meconium, gestational age at birth, and birth weight), factors that remained independently associated with EOS or death were presence of meconium, fever in labor, and lower gestational age and birth weight (Table 2). Model 2 showed that only gestational age at birth was associated with EOS or death. Model 3 demonstrated that presence of meconium, fever in labor, gestational age at delivery <28 weeks, and lower birth weight was significantly associated with EOS or death. There was no significant interaction between gestational age at birth and birth weight in all three models with regard to the risk of EOS or death (Table 2). Sensitivities, specificities, positive predictive, and negative predictive values were calculated for all three models. All three models had low sensitivity and positive predictive value and high specificity and negative predictive value (Table 2).

Additional analysis was performed to assess the performance of each model towards prediction of each individual component of the composite outcomes, EOS (Table 3) and death (Table 4). In addition to factors associated with the primary outcome in the composite analysis, administration of antibiotics in labor was significantly associated with lower rates of EOS in all three models.

Table 1 Baseline characteristics stratified by neonatal sepsis or death

Characteristics	Neonatal sepsis or death ($n = 73$)	Control ($n = 706$)	P
Maternal age	31.2 ± 7.1	31.8 ± 6.5	0.458
Race			0.417
NonHispanic white	30 (41.1)	329 (46.4)	
NonHispanic black	23 (31.5)	162 (22.8)	
Hispanic	7 (9.6)	76 (10.7)	
Other	4 (5.5)	67 (9.5)	
Declined	9 (12.3)	75 (10.6)	
BMI at delivery (kg/m^2)	30.7 ± 7.1	29.2 ± 6.3	0.044
Obesity (BMI >30(kg/m^2))	38 (53.5)	264 (37.7)	0.009
Nulliparity	48 (65.8)	428 (60.6)	0.392
Insurance			0.165
Medicaid	27 (37.0)	206 (29.2)	
Private	46 (63.0)	500 (70.8)	
Twin gestation	31 (42.5)	231 (32.4)	0.084
Antepartum admission	57 (78.1)	571 (80.9)	0.565
Preeclampsia	13 (17.8)	170 (24.1)	0.229
Diabetes	2 (7.1)	50 (2.7)	0.157
Preterm labor at presentation	43 (58.9)	336 (47.6)	0.066
PPROM	31 (42.5)	276 (39.1)	0.575
Gestational age at delivery	26.8 ± 2.4	29.3 ± 2.3	<0.001
Gestational age <28 weeks at delivery	48 (66.7)	162 (23.6)	<0.001
Antibiotics given before delivery	60 (82.2)	646 (91.5)	0.009
Group B Streptococcus status			0.115
Positive	9 (12.3)	99 (13.9)	
Negative	23 (31.5)	302 (42.4)	
Unknown	41 (56.2)	311 (43.7)	
Placental abruption	8 (11.0)	79 (11.2)	0.952
ROM >18 h	21 (28.8)	210 (29.8)	0.862
Chorioamnionitis	8 (11.0)	53 (7.5)	0.296
Fever in labor ≥38.1 °C	9 (12.3)	38 (5.4)	0.018
Cesarean delivery	38 (52.1)	378 (53.5)	0.809
Operative vaginal delivery	1 (1.4)	13 (1.8)	0.710
Received at least one course of BMTZ	54 (74.0)	620 (87.6)	0.001
Received magnesium sulfate	59 (81.9)	618 (90.5)	0.024
Meconium-stained amniotic fluid	7 (9.6)	23 (3.3)	0.007
Birth weight (g)	910 ± 408	1,350 ± 450	<0.001
Very low birth weight (<1500 g)	63 (87.5)	448 (65.1)	<0.001
Male gender	36 (50.0)	372 (52.5)	0.690
Received DCC	9 (13.4)	118 (17.3)	0.423
Emergent delivery	13 (18.8)	90 (13.4)	0.209

All data presented as mean ± standard deviation or N (%)

BMI body mass index, *PPROM* preterm prelabor rupture of membranes, *ROM* rupture of membranes, *BMTZ* betamethasone, *DCC* delayed cord clamping

Table 2 Factors associated with early-onset neonatal sepsis or death analyzed by three regression models

	Model 1		Model 2		Model 3	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Obesity (BMI ≥30 kg/m^2)	1.69	0.98–2.94	1.70	0.98–2.95	1.56	0.90–2.72
Administration of magnesium sulfate	0.82	0.35–1.94	0.84	0.36–1.95	0.86	0.37–2.00
Presence of meconium-stained amniotic fluid at delivery	**2.80**	**1.01–7.81**	2.64	0.95–7.41	**3.08**	**1.13–8.37**
Antibiotics administration in labor	0.51	0.22–1.17	0.52	0.23–1.14	0.49	0.21–1.12
Fever in labor ≥38 °C	**2.59**	**1.05–6.35**	2.31	0.96–5.52	**2.69**	**1.11–6.58**
Gestational age at delivery	**0.68**	**0.48–0.96**	**0.64**	**0.56–0.74**	–	–
Gestational age at delivery <28 weeks	–	–	–	–	**2.38**	**1.13–5.01**
Birth weight	0.99	0.97–1.01	–	–	**0.99**	**0.997–0.999**
Birth weight <1500 g	–	–	0.78	0.32–1.89	–	–
Interaction term between gestational age at delivery and birth weight	1.00	0.99–1.00	0.91	0.60–1.39	0.99	0.96–5.51
AUC for each model	0.82	0.73–0.85	0.81	0.73–0.85	0.81	0.73–0.85
Hosmer–Lemeshow *P* value	0.119		0.556		0.543	
Sensitivity	11.6%		9.9%		13.1%	
Specificity	99.1%		99.1%		99.4%	
Positive predictive value	57.1%		53.8%		60.0%	
Negative predictive value	91.7%		91.3%		91.8%	

BMI body mass index, *AUC* area under the curve

Table 3 Factors associated with early-onset neonatal sepsis by three regression models

	Model 1		Model 2		Model 3	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Obesity (BMI ≥30 kg/m^2)	1.05	0.48–2.30	1.12	0.53–2.40	1.02	0.47–2.24
Administration of magnesium sulfate	0.57	0.20–1.60	0.56	0.21–1.55	0.56	0.20–1.54
Presence of meconium-stained amniotic fluid at delivery	**3.63**	**1.04–12.65**	2.64	0.94–11.10	**4.13**	**1.20–14.19**
Antibiotics administration in labor	**0.32**	**0.11–0.89**	**0.32**	**0.12–0.86**	**0.30**	**0.11–0.86**
Fever in labor ≥38 °C	**3.38**	**1.07–10.69**	2.92	0.96–8.87	**3.43**	**1.08–10.90**
Gestational age at delivery	0.75	0.45–1.26	**0.57**	**0.35–0.93**	–	–
Gestational age at delivery <28 weeks	–	–	–	–	7.86	0.24–261.37
Birth weight	0.99	0.98–1.01	–	–	0.99	0.996–1.00
Birth weight <1500 g	–	–	0.03	0.007–111.90	–	–
Interaction term between gestational age at delivery and birth weight	1.00	0.99–1.00	1.12	0.66–1.88	0.99	0.99–1.00
AUC for each model	0.81	0.73–0.88	0.81	0.73–0.88	0.81	0.73–0.87
Hosmer–Lemeshow *P* value	0.760		0.525		0.897	

BMI body mass index, *AUC* area under the curve

The AUCs for the ROC curves generated using each model are shown in Table 2 and Fig. 1. All three models had AUCs above 0.80, demonstrating reasonable prediction of the outcome of EOS or death. The Hosmer–Lemeshow *P* values for all three models were high demonstrating that the models fit the data.

Discussion

In this analysis, we attempted to predict occurrence of EOS in neonates delivering at <32 weeks of gestation. In this population, we identified the following significant risk factors for EOS or death: earlier gestational age at delivery

Table 4 Factors associated with death during the first week of life by three regression models

	Model 1		Model 2		Model 3	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Obesity (BMI ≥30 kg/m^2)	1.32	0.87–2.02	1.33	0.87–2.03	1.32	0.86–2.02
Administration of magnesium sulfate	1.20	0.38–3.81	1.23	0.39–3.91	1.22	0.39–3.85
Presence of meconium-stained amniotic fluid at delivery	**1.90**	**0.52–6.89**	1.97	0.54–7.24	**2.00**	**0.55–7.25**
Antibiotics administration in labor	0.86	0.27–2.73	0.87	0.27–2.75	0.81	0.26–2.56
Fever in labor ≥38 °C	**1.76**	**0.57–5.46**	1.80	0.57–5.60	**1.78**	**0.57–5.52**
Gestational age at delivery	**0.84**	**0.56–1.27**	**0.86**	**0.66–1.13**	–	–
Gestational age at delivery <28 weeks	–	–	–	–	3.03	0.18–51.40
Birth weight	1.00	0.99–1.01	–	–	0.99	0.99–1.00
Birth weight <1500 g	–	–	0.47	0.10–2.18	–	–
Interaction term between gestational age at delivery and birth weight	0.99	0.99–1.00	0.69	0.32–1.50	0.99	0.99–1.00
AUC for each model	0.75	0.66–0.83	0.74	0.66–0.82	0.75	0.66–0.83
Hosmer–Lemeshow *P* value	0.602		0.370		0.376	

BMI body mass index, *AUC* area under the curve

and specifically less than 28 weeks, presence of meconium-stained amniotic fluid at delivery, maternal fever ≥38 °C in labor, and lower birth weight. Combining these factors into a prediction model provided reasonable accuracy in predicting occurrence of EOS or death. Finally, when examining the risks factors for EOS separately from the risk of death, use of antibiotics in labor was found to be a protective factor against EOS.

One of the models examined in our study (Model 2) showed that gestational age was the only significant risk factor for EOS or death among newborns born at <32 weeks. Although this model was the most simple out of the three models examined, the information derived from it is not clinically useful. It is already established that earlier gestational age confers higher risk of EOS. Furthermore, the decision to initiate empiric antibiotic therapy is not based solely on gestational age. Since the goal of this study was to develop risk prediction model for this high-risk preterm neonatal group, Models 1 and 3 provide specific risk factors that can be used in clinical practice.

Early preterm infants, compared to late preterm and term infants, are at higher risk for developing sepsis [6, 9–11]. Early preterm infants have immune dysfunction due to absence of maternal transplacental transfer of IgG that occurs during the third trimester [21]. They also lack mature skin and mucosal barriers and require prolonged IV access, endotracheal intubation, and other invasive procedures [22, 23]. All of these risks factors predispose preterm infants to sepsis. On the other hand, preterm infants have low blood culture volumes and are frequently exposed to previous antimicrobial therapy [24]—these circumstances may be responsible for false-negative results of sepsis work-up. Because of these challenges, diagnosing sepsis in this population is difficult and predictive models such as the model described in our paper are particularly clinically needed.

Antepartum and intrapartum characteristics provide important information about exposure to infectious diseases and inform neonatologists about obstetric risk factors for neonatal infection [9, 12, 13, 17]. Puopolo et al. designed a prediction model for EOS for infants born at ≥34 weeks gestation using objective clinical data available at the time of birth [17]. They found that the two most important predictors are gestational age and maternal fever. Their model performed well with AUC of 0.807, which was similar to AUC derived from our study. In contrast, existing models that looked for risk factors for neonatal sepsis among early preterm infants were conducted a few decades ago, before the widespread screening and prophylaxis for GBS and in a context of different management practices for PPROM [25, 26]. In addition, majority of the studies looking at predictive models for sepsis among preterm infants focused on prediction of late and not early-onset sepsis [14–16], looking at variables related to exposure in the NICU [22, 23], blood biomarkers [27, 28], and physical exam of the newborn [14–18]. Our study adds to this body of literature by specifically addressing early preterm newborns and examining how maternal risks factors and delivery characteristics can help identify EOS in this contemporary cohort.

We did not find a significant reduction in the risk of EOS or death with the use of antibiotics before delivery. However, when EOS was analyzed as a separate outcome, administration of antibiotics had a protective effect in all

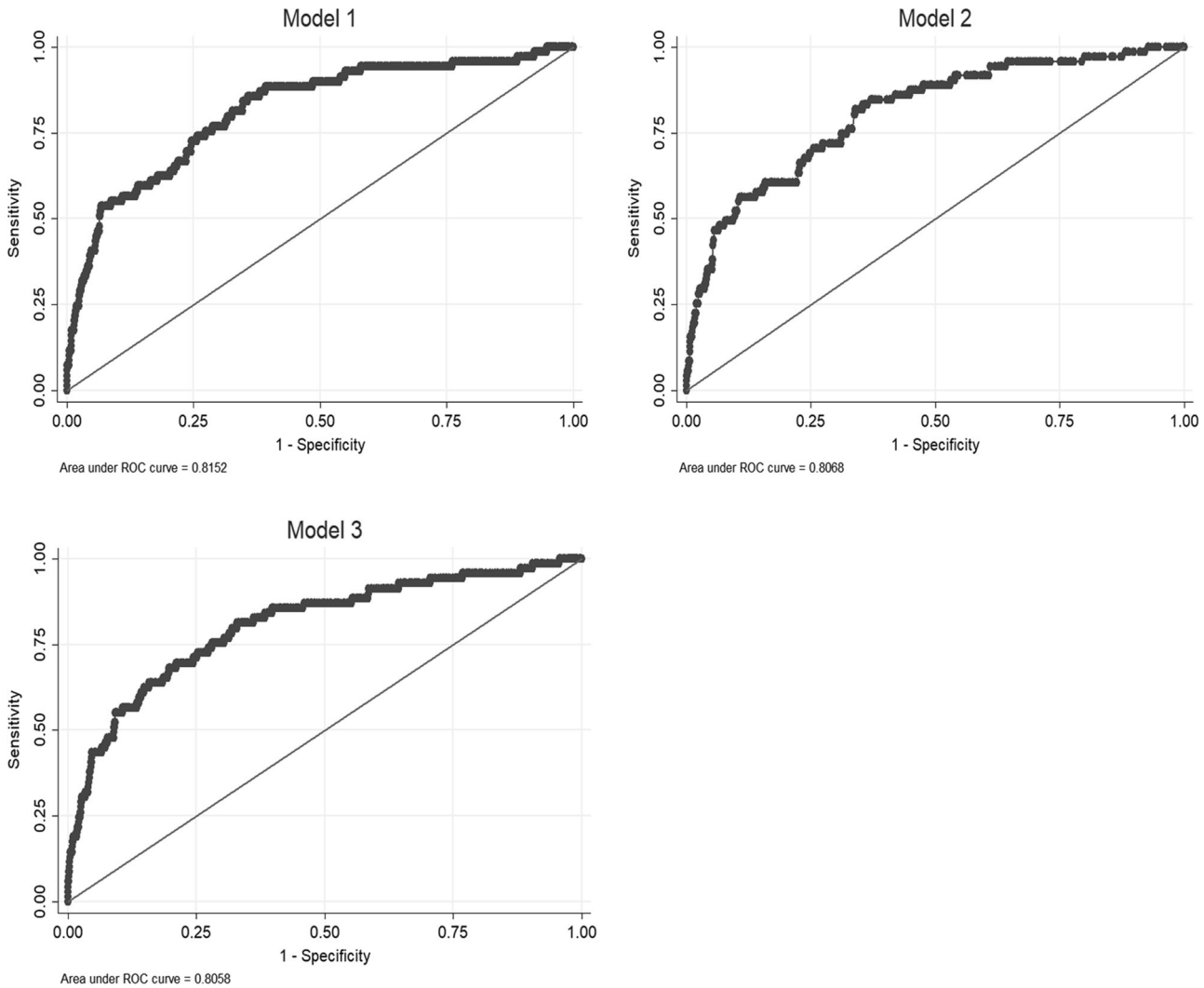

Fig. 1 Receiver-operating characteristic curves for three prediction models of early-onset neonatal sepsis at <32 weeks

three models. In addition, we did not find a difference in maternal GBS colonization between neonates diagnosed with EOS or death and controls. This is likely due to the high number of patient with unknown GBS status prior to delivery. In addition, although GBS remains the most frequent pathogen for EOS, there has been a shift from GBS to Escherichia coli as the most important pathogen causing EOS in preterm and very low birth weight infants [2, 9].

Our study is not without limitations. First, as we used only information available in the antepartum and intrapartum period, our prediction model performed well for prediction of early but not late neonatal sepsis. This was an intentional approach, as the goal of the analysis was to identify factors known prior to birth that may be clinically useful in the prediction of EOS; thus, factors such as Apgar scores were not included. Second, our prediction model did not include newborn clinical exam. Physical exam in preterm neonates can be challenging in sepsis prediction, as these neonates have more respiratory distress than term neonates, such as chest retraction and grunting, more feeding intolerance, and temperature instability [16, 29, 30]. Nevertheless, clinical signs can augment sepsis prediction models when used in conjunction with other risk factors [18]. Additionally, some potentially clinically relevant maternal information, such as history of a prior neonate affected by GBS sepsis or history of invasive procedures such as amniocentesis, was unavailable for this analysis; however, we expect the impact of these factors to be low, given the infrequency of these events.

In conclusion, in this study we developed a fair prediction model for the risk of EOS among infants born at <32 weeks of gestation that may be of benefit in clinical practice when deciding regarding administration of broad spectrum antibiotics. Significant risk factors available at delivery were gestational age <28 weeks, maternal fever >38.0 °C, presence of meconium-stained amniotic fluid at

delivery, and lower birth weight. Future directions for this work will be to incorporate these antepartum and intrapartum risk factors into a prediction model that will include clinical evaluation of the preterm newborn.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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