



Clinical Risk Factors for Early-Onset Sepsis in Neonates: An International Delphi Study

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What's Known

- Understanding clinical risk factors for early-onset sepsis (EOS) is important to devise effective strategies for neonates at high risk of sepsis.
- Despite growing evidence, there is still uncertainty about potentially modifiable risk factors common to neonatal EOS.

What's New

- A set of clinical risk factors is developed for the diagnosis of EOS within the first few hours after birth.
- Neonatal-related risk factors were birth weight, one-min Apgar score, and prematurity. Maternal-related risk factors were gestational age and urinary tract infection. Delivery-related risk factors were premature rupture of membranes, chorioamnionitis, and intrapartum fever.

Abstract

Background: Despite growing evidence, there is still uncertainty about potentially modifiable risk factors for neonatal early-onset sepsis (EOS). This study aimed to identify potential clinical risk factors for EOS based on a literature review and expert opinions.

Methods: A literature search was conducted in PubMed (MEDLINE), Cochrane, Embase, and Scopus databases. Articles in English, published up to May 2021, on clinical risk factors for neonatal EOS were included. Initially, a questionnaire on risk factors for EOS was developed and validated. The fuzzy Delphi method (FDM) was used to formulate the final version of the questionnaire. The validity of the risk factors was assessed using the Chi square test. $P < 0.05$ was considered statistically significant.

Results: In the review phase, 30 risk factors were approved by two neonatologists and included in the FDM phase. In total, 25 risk factors met the consensus criteria and entered the validation phase. During the observational study, 114 neonates (31 with and 83 without EOS) were evaluated for two months. The results of the Chi square test showed that cesarean section was not a significant risk factor for EOS ($P = 0.862$). The need for mechanical ventilation and feed intolerance was observed in about 70% of neonates with EOS, and therefore considered significant risk factors for EOS ($P < 0.001$). Finally, 26 potential clinical risk factors were determined.

Conclusion: Neonatal-related risk factors for EOS were birth weight, one-min Apgar score, and prematurity. Maternal-related risk factors were gestational age and urinary tract infection. Delivery-related risk factors were premature rupture of membranes, chorioamnionitis, and intrapartum fever.

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Introduction

Neonatal sepsis is a major global health concern and the main cause of morbidity and mortality in newborns. Annually, 2,000 neonates die in the United States due to sepsis during the first month of life, most of which occur within the first week.¹ However, even those that survive may develop life-threatening complications. Sepsis within the first three days (72 h) after birth is defined as early-onset sepsis (EOS), which is difficult to diagnose early.^{2,3} Antimicrobial therapy and supportive care are the only effective treatments for

sepsis. The reproducibility and positive predictive value of diagnostic tests are not optimal, resulting in a low clinical suspicion index and increased empiric antimicrobial treatment. Although clinical suspicion is important to diagnose sepsis, some studies reported that only about 9% of blood cultures are positive for pathogenic bacteria.^{1, 3} Another study reported this percentage at 30%-40%.⁴ Understanding the risk factors for neonates at high risk of sepsis is essential to devise effective strategies for early-stage diagnosis. Despite growing evidence, there is still uncertainty about potentially modifiable risk factors common in neonatal EOS. A guideline for the management of neonates with EOS risk factors was published in August 2012, and updated in April 2021, by the National Institute for Health and Clinical Excellence (NICE).² NICE introduced a strategy for early diagnosis of neonatal sepsis based on 26 risk factors and clinical indicators. In addition, in 2010, the Centers for Disease Control and Prevention (CDC) published a guideline concerning the prevention of perinatal group B streptococcal disease.⁵ The CDC guideline defined 11 risk factors for neonatal sepsis.

Among the methods used to collect and distill expert opinions, the Delphi method is regarded as the best approach, since it allows participating experts to reach a consensus on important features of issues under investigation. It is an iterative process based on data collection and analysis techniques. It includes two or more rounds of questionnaires and is interspersed with a feedback mechanism.⁶ However, the traditional Delphi method has certain shortcomings, e.g., vagueness, ambiguity, and uncertainty in the decision-making dataset. These limitations lead to low convergence in retrieving results and a potential loss of important information. To overcome these, the traditional Delphi method is combined with the fuzzy set theory,⁷ called the fuzzy Delphi method (FDM).⁶

Unlike a recent study that reviewed risk factors for both EOS and late-onset sepsis,⁸ despite their different etiologies, we focused on neonatal EOS risk factors based on published literature and expert opinions. The risk factors were identified through a review of various databases, and the FDM was used to determine common risk factors for neonatal EOS. The validity of risk factors was assessed through a prospective observational evaluation of neonates, representative of the target population.

Materials and Methods

This study was conducted in 2020 in three

phases, namely literature review, obtaining expert opinions using the FDM, and external validation. The study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (code: IR.TBZMED.REC.1399.031).

Literature Review

The clinical risk factors for EOS were collected through a literature search in PubMed (MEDLINE), Cochrane, Embase, and Scopus databases. All articles in English, published up to May 2021, were included. Keywords used to search for relevant articles in each database are described below.

PubMed/Medline: ((newborn [mesh] OR newborn [Title/Abstract] OR Infant [Title/Abstract] OR Neonatal [Title/Abstract] OR neonate*[Title/Abstract]) AND (sepsis [mesh] OR sepsis [Title/Abstract] OR Infection* [mesh] OR "blood infection"[Title/Abstract] OR "blood infections" [Title/Abstract]) AND ("early onset" [Title/Abstract] OR "early-onset" [Title/Abstract]) AND (risk factor[mesh] OR "risk factors" [Title/Abstract]))

Cochrane: (newborn OR infant OR neonatal OR neonate*) AND (sepsis OR infection* OR "blood infection" OR "blood infections") AND ("early onset" OR "early-onset") AND ("risk factor" OR "risk factors")

Embase: (newborn: ti,ab,kw OR infant: ti,ab,kw OR neonatal: ti,ab,kw OR neonate*:ti,ab,kw) AND (sepsis: ti,ab,kw OR infection*:ti,ab,kw OR 'blood infection': ti,ab,kw OR 'blood infections': ti,ab,kw) AND ('early onset': ti,ab,kw OR 'early-onset': ti,ab,kw) AND ('risk factor': ti,ab,kw OR 'risk factors': ti,ab,kw)

Scopus: (newborn OR infant OR neonatal OR neonate) AND (sepsis OR infection* OR (blood infection) OR (blood infections)) AND (early onset) AND (risk factor)

The references of retrieved articles were reviewed for possible additional information. Articles whose full text was not accessible through the central library of Tabriz University of Medical Sciences, were excluded from the study. Two neonatologists evaluated the extracted risk factors and classified them into three categories, namely maternal, delivery, and neonatal.

Delphi Method

The Delphi method traditionally begins with open-ended questions to collect specific information in the field of expertise of the Delphi participants. However, in the first round, certain modifications (based on a comprehensive literature review) are permitted to develop a structured questionnaire.⁷

Development of the Initial Questionnaire: Clinical risk factors of EOS reported in at least two articles were used to formulate a structured questionnaire. The initial questionnaire consisted of three sections in which each risk factor was rated based on a five-point scale ranging from very unimportant to very important. In addition, a blank space was reserved for the experts to give additional recommendations and feedback on each risk factor. To assess the content validity ratio (CVR), the questionnaire was emailed to 10 neonatologists with at least 15 years of experience in the neonatal intensive care unit (NICU). Their responses were received within a week. The content validity index (CVI) was separately assessed by the experts based on three criteria, namely simplicity, appropriateness, and certainty. One week after receiving their responses, another email was sent to the experts requesting their feedback, based on which the test-retest reliability of the questionnaire was determined (Spearman correlation coefficient: 79%).

Participants: The purposive sampling method was used to identify internationally recognized neonatal experts. Potential participants were identified from publications on neonatal sepsis in Medline, CINAHL, and Scopus databases. The inclusion criteria were a minimum of two publications on neonatal sepsis during the previous 10 years and primary activity in the field of neonatology and pediatric infectious diseases. A total of 57 experts with an h-index of 3 to 57 in Scopus were identified. According to the Expertscape website (www.expertscape.com), 13 experts were ranked among the top 100 neonatologists with expertise in neonatal sepsis. All 57 experts were contacted by email to gauge their willingness to participate. Introductory information on the aim of the study, the questionnaire, and a timetable was attached. Based on the first round of FDM, the participants were requested to rank the 30 identified risk factors. Risk factors approved by more than 15% of the participants were added to the questionnaire for the second round of FDM. The updated questionnaire was emailed to the participants, requesting their response within a maximum of 21 days.

Fuzzification: Triangular fuzzy number (TFN)⁶ was used to convert the response from the experts. The five-point scale was then represented as very important (0.7, 0.9, 0.9), important (0.5, 0.7, 0.9), moderate (0.3, 0.5, 0.7), unimportant (0.1, 0.3, 0.5), very unimportant (0.1, 0.1, 0.3). Three values, namely minimum value (n_1), most sensible value (n_2), and maximum value (n_3) were considered for each response in

the fuzzification step, i.e., the score given by the participants was the three values of n_1 , n_2 , and n_3 . The mean of each fuzzy score for each risk factor was calculated as m_1 , m_2 , and m_3 .

Defuzzification: All risk factors were ranked in terms of importance to decide on their inclusion or rejection. The selection of risk factors based on importance was performed using the below formula.⁶

$$A_{max} = 1/3 (m_1 + m_2 + m_3)$$

The prerequisites for risk factor acceptance were threshold value (d), the consensus of participants $\geq 75\%$, and fuzzy score value $A_{max} \geq 0.5$. The threshold value indicates the consensus of participants for each risk factor. Based on the below formula, only a risk factor with $d \leq 0.2$ was accepted.⁶

$$d(\tilde{m}, \tilde{n}) =$$

$$\sqrt{1/3 [(m_1 - n_1)^2 + (m_2 - n_2)^2 + (m_3 - n_3)^2]}$$

$$\text{Threshold Value} =$$

$$\frac{\sum \text{Average Threshold Value, (d) for each risk factor}}{\text{Total participants} \times \text{Total risk factors in each category}}$$

Risk factors with a consensus of less than 75% were included in the second round of FDM. This process was repeated until full consensus was achieved for all risk factors or the results stabilized in consecutive rounds. Between the rounds, the results of the previous round were presented to the participants to evaluate their responses against that of their peers. Participants were asked to revise or qualify their responses after considering group opinions. To achieve a high response rate, two reminder emails were sent to the participants. Microsoft Excel 2016 (Microsoft, Redmond, Washington, USA) was used to manage the data.

Prospective Evaluation and External Validation: External validation was performed by conducting a two-month prospective observational study at the NICU of two tertiary hospitals in Iran. EOS risk factors were assessed in neonates admitted to the NICU within the first hours after birth and followed up until final diagnosis by the physician. Neonates born to mothers with some types of immunological deficiency and newborns with major congenital malformations were excluded from the study. Finally, the Chi square test (significant level $P \leq 0.05$) was used to determine group differences in terms of risk factors. All data were analyzed using SPSS software, version 23.0 (IBM Corp, Armonk, NY, USA).

Results

The flow diagram illustrating the search strategy and selection process of articles on clinical risk factors for sepsis is shown in figure 1.

In total, 35 articles were included in the review study (table 1). Out of the 41 risk factors extracted from the articles, 30 were approved by the two neonatologists and were included in the FDM phase. These risk factors were in the categories of neonatal (n=11), maternal (n=11), and delivery (n=8) (table 2). The CVR values for all items in the questionnaire ranged from 0.7 to 1. The CVI values for all items varied between 0.8 and 1. The calculated reliability of the questionnaire, using Cronbach's alpha coefficient, was 0.924.

Out of the 57 selected experts, 24 agreed to participate in the study (42% response rate). The number of participants in the second round of FDM was 23 (95% response rate); one participant withdrew without notice. In the first round of FDM, the participants suggested rephrasing one item from "X is a risk factor for neonatal EOS" to "neonatal EOS is more common in neonates with X". In the second round of FDM, the results of the first round together with an updated version of the questionnaire containing reformulated items and additional risk factors were emailed to the participants. Eventually, the participants reached a consensus about the items, and the questionnaire was approved (table 3). The threshold value was higher than 0.2 for all three categories. Out of a total of 34 risk factors, 25

met the consensus criteria. In the first round, all participants agreed on the EOS risk factors included in the neonatal categories (very low birth weight [VLBW], one-min Apgar <7, and prematurity). In addition, the maternal category (gestational age <37 weeks) and delivery category (premature rupture of membranes [PROM] >18, chorioamnionitis, and intrapartum fever >38 °C) were confirmed as EOS risk factors by all participants. During the first round of FDM, four additional risk factors were proposed by at least 15% of the participants, namely apnea, seizure, newborn temperature, and intrauterine growth restriction (IUGR). These were discussed in the second round of FDM, of which apnea, seizure, and neonate temperature met the consensus criteria. However, IUGR did not meet the criteria and was omitted.

During the observational study, 136 neonates were admitted to the NICU, out of which three neonates died within the first 72 h, five were transferred, and 14 were excluded, since they did not meet the inclusion criteria. Finally, 114 neonates (31 with and 83 without EOS) were included in the study. Among the neonates with EOS, 9.67%, 16.12%, and 74.19% had at least 1, 2, or ≥3 risk factors per category, respectively. In addition to the identified risk factors, the need for mechanical ventilation and feed intolerance were also observed in about 70% of neonates with EOS. However, these were not identified in the previous phases of the study. The risk factors related to EOS are presented in table 4.

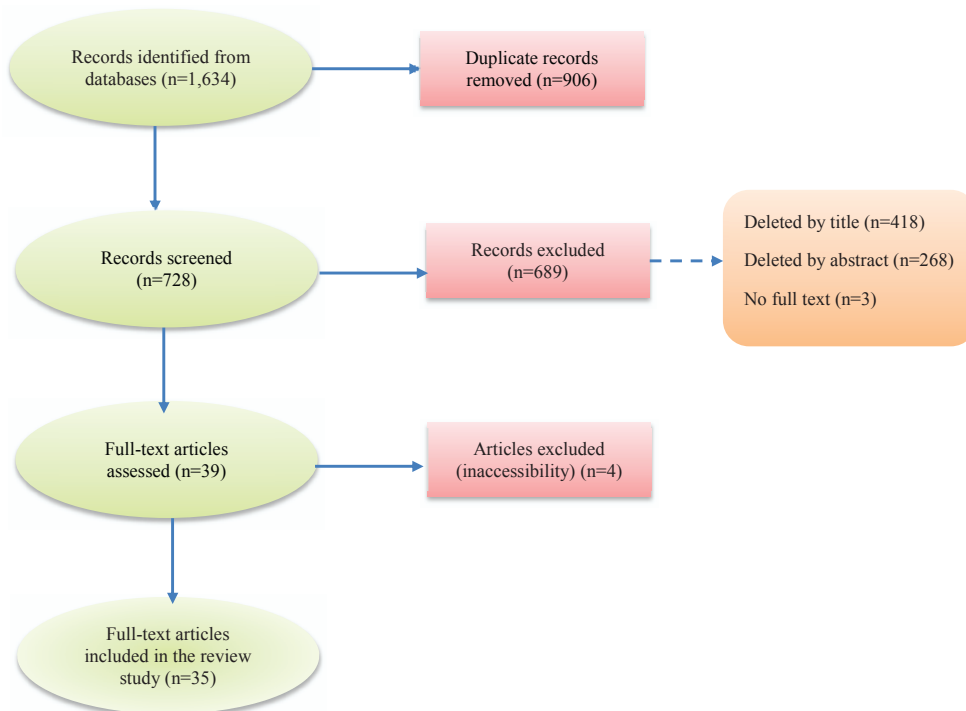


Figure 1: Flow diagram illustrates the search strategy and selection process of articles.

Table 1: Summary of the included articles

Author	Year	Study type	Country	Sample size	Method
Adatara et al. ¹	2019	Retrospective case-control	Ghana	900 neonates (103 cases, 797 controls)	Binary and multivariate logistic regression
Yismaw et al. ⁴	2019	Cross-sectional	Ethiopia	423 neonates	Bivariate and multivariable logistic regression
Adatara et al. ⁹	2018	Retrospective case-control	Ghana	383 Neonates (67 cases, 316 controls)	Univariate and multivariate logistic regression
Hayun et al. ¹⁰	2015	Retrospective cohort	Indonesia	221 neonates (62 cases, 159 controls)	Multivariate analysis and logistic regression
Polcwiartek et al. ¹¹	2021	Cohort	USA	1,197 neonates	Multivariable logistic regression
Akalu et al. ¹²	2020	Case-control	Ethiopia	231 neonates (77 cases, 155 controls)	Binary and multivariate logistic regression
Salem et al. ¹³	2006	Prospective observational	Bosnia and Herzegovina	200 neonates	Multivariable analysis
Gebremedhin et al. ¹⁴	2016	Case-control	Ethiopia	234 neonates (78 cases, 156 controls)	Binary logistic regression
Siakwa et al. ¹⁵	2014	Prospective case-control	Ghana	196 neonates (96 cases, 100 controls)	Logistic regression
Klinger et al. ¹⁶	2009	Population-based observational study	Israel	383 neonates	Multivariable analysis
Giannoni et al. ¹⁷	2018	Prospective population-based cohort	Switzerland	429 neonates	Multinomial logistic regression
Cizmeci et al. ¹⁸	2015	Case-control	Turkey	83 neonates (40 cases, 43 controls)	Logistic regression
Leal et al. ¹⁹	2012	Prospective cohort study	Mexico	11,790 neonates	Logistic regression
Utomo et al. ²⁰	2010	Case-control	Indonesia	97 neonates (31 cases, 66 controls)	Logistic regression
Schrag et al. ²¹	2012	Cohort	South Africa	8,129 neonates	Multinomial logistic regression
Schuchat et al. ²²	2000	Case-control	USA	101 neonates (41 cases, 61 controls)	Logistic regression
Gómez et al. ²³	2018	Case control	Colombia	549 neonates (183 cases, 366 controls)	Logistic regression
Kabwe et al. ²⁴	2016	Cross-sectional observational	Zambia	313 neonates	Multivariate analysis
Verstraete et al. ²⁵	2015	Prospective cohort	Belgium	5,134 neonates	Univariate and logistic regression
Boia et al. ²⁶	2010	Retrospective cohort	Romania	34 neonates	-
Babazono et al. ²⁷	2008	Retrospective cohort	Japan	871 neonates	Multiple logistic regression
Dutta et al. ²⁸	2010	Prospective cohort	India	601 neonates	Multivariable logistic regression
Palatnik et al. ²⁹	2019	Case-control	USA	779 neonates (73 cases, 706 controls)	Bivariate and multivariable logistic regression
Simarmata et al. ³⁰	2016	Observational and prospective basis	Indonesia	100 neonates	-
Mugalu et al. ³¹	2006	Prospective cohort	Uganda	293 neonates	Logistic regression
Ogunlesi et al. ³²	2011	Retrospective (2006-2007), Prospective (2008)	Nigeria	1,050 neonates	Descriptive and inferential statistics
Jiang et al. ³³	2013	Case-control	China	735 neonates (147 cases, 588 controls)	Univariate and multivariate logistic regression
Kawagoe et al. ³⁴	2001	Prospective cohort	Brazil	1,544 neonates	Univariate and multivariate
Puopolo et al. ³⁵	2011	Case-control	USA	1,413 Neonates (350 cases, 1,063 controls)	Multivariate analysis and split validation
Woldu et al. ³⁶	2017	Prospective cross-sectional	Ethiopia	306 neonates	Binary logistic regressions
Masanja et al. ³⁷	2019	Case-control	Tanzania	322 neonates (105 cases, 217 controls)	Bivariate and multiple logistic regression
Jabiri et al. ³⁸	2016	Cross-sectional	Tanzania	220 neonates	Logistic regression
Bayih et al. ³⁹	2021	Case-control	Ethiopia	246 neonates (82 cases, 164 controls)	Multivariable logistic regression
Agnche et al. ⁴⁰	2020	Cross-sectional	Ethiopia	352 neonates	Multivariable logistic regression
López et al. ⁴¹	2019	Case control	Colombia	555 neonates (186 cases, 368 controls)	Bivariate and logistic regression

Table 2: Results of the literature review on the risk factors associated with early-onset sepsis

Category	Risk factor	Reference number
Neonatal	One-min Apgar <7	1, 4, 9, 10, 12, 19, 33, 41
	Five-min Apgar <7	1, 9, 11, 14, 33
	Five-min Apgar <3	13
	Resuscitation at birth	12, 15, 16, 38-40
	Prematurity <37 weeks	18-21, 24, 29, 33, 35, 41
	VLBW <1500 g	9, 10, 16, 17, 21, 25-30, 33, 41
	LBW <2500 g	19, 20, 41
	Not crying	14, 15, 39
	Male sex	15, 27, 28, 30, 31, 40
	Jaundice	13, 33
	Asphyxia (ph<7, BE<-16 mmol/L)	19, 40
	Respiratory distress	19, 41
	Congenital anomaly	4
Maternal	Parity	1, 15
	GBS	11, 17, 22, 24, 34, 35
	UTI	12, 14, 15, 34, 36, 40
	Gestational age <32 weeks	26, 29, 30, 32
	Gestational age <34 weeks	17, 41
	Gestational age <30 weeks	28
	Gestational age <37 weeks	10, 15, 19, 39
	Age 31-40 years	15, 30, 38, 40
	Onset of sexual activity	41
	Bleeding disorder	40
	Gestational age 37-42 weeks	40
	Gestational age >42 weeks	40
	Gestational age <28 weeks	13
	Foul-smelling vaginal discharge	4, 15
	Multiple digital vaginal examinations>3	37, 40, 41
Level of education	23, 41	
Origin	23, 41	
Lower levels of cord-blood 25(OH)D	18	
Delivery	Cesarean section	1, 9, 11, 20, 33, 36, 41
	PROM >18 hours	12, 14, 22, 23, 32-35, 37, 39, 41
	PROM >24 hours	16, 19
	PROM >12 hours	4
	Chorioamnionitis	16, 28, 37, 41
	Intrapartum fever >38 °C	4, 12, 14, 15, 22, 23, 29, 35, 41
	Abnormal amniotic liquid	19, 33
	Abnormal placenta	33
	No intrapartum antibiotic prophylaxis	22, 28, 35
	MSAF	9, 12, 15, 20, 21, 29

VLBW: Very low birth weight; LBW: Low birth weight; GBS: Group B Streptococcus; UTI: Urinary tract infection; PROM: Premature rupture of membranes; MSAF: Meconium-stained amniotic fluid

Discussion

Of the 26 risk factors identified in this study, 14 were included in the NICE guideline, namely nine neonatal-related risk factors (prematurity, respiratory distress, apnea, fever, seizures, resuscitation at birth, jaundice, feed intolerance, and need for mechanical ventilation), one maternal-related risk factor (Guillain-Barré syndrome [GBS]), and four delivery-related risk factors (PROM >18, chorioamnionitis, intrapartum fever >38 °C, and PROM >24). Risk factors included in the CDC guideline were

prematurity, GBS, gestational age <34, PROM >18, chorioamnionitis, intrapartum fever >38 °C, and no intrapartum antibiotic prophylaxis. The other risk factors identified in our study were not included in the NICE and CDC guidelines.

Among the neonatal risk factors, consensus on VLBW was reached in the first round of FDM. It had the highest level of evidence as a risk factor in 13 (37.14%) articles. However, it was not viewed as a potential EOS risk factor in the NICE guideline. A review study reported a 10-fold increase in the incidence rate of EOS in infants with VLBW compared to those with normal birth weight.⁴²

Table 3: The results of the fuzzy Delphi method

Risk factor	First round FDM			Second round FDM			Rank	
	Consensus (%)	Average fuzzy number	Result	Consensus (%)	Average fuzzy number	Result		
Neonatal	VLBW	100	0.884	Accepted	100	0.884	Accepted	1
	One-min Apgar <7	100	0.884	Accepted	100	0.884	Accepted	1
	Prematurity <37 weeks	100	0.884	Accepted	100	0.884	Accepted	1
	Five-min Apgar <7 weeks	85	0.773	Accepted	98	0.772	Accepted	2
	Respiratory distress	79	0.768	Accepted	98	0.772	Accepted	2
	Apnea [#] -hypopnea index	53	0.756	-	98	0.763	Accepted	3
	Neonatal temperature [#]	34	0.728	-	91	0.758	Accepted	4
	Seizures [#]	46	0.746	-	90	0.752	Accepted	5
	Asphyxia (ph<7, BE<-16 mmol/L)	76	0.628	Accepted	87	0.72	Accepted	6
	LBW	79	0.653	Accepted	85	0.68	Accepted	7
	Resuscitation at birth	79	0.634	Accepted	90	0.68	Accepted	7
	Jaundice	76	0.502	Accepted	87	0.534	Accepted	8
	Not crying	76	0.401	Rejected	89	0.399	Rejected	0
	Male sex	56	0.399	Rejected	86	0.284	Rejected	0
	Maternal	Gestational age <32 weeks	100	0.884	Accepted	100	0.884	Accepted
UTI		78	0.752	Accepted	100	0.884	Accepted	1
GBS		75	0.742	Accepted	95	0.768	Accepted	2
Multiple digital vaginal examinations>3		75	0.501	Accepted	89	0.555	Accepted	3
Gestational age <34 weeks		73	0.545	Rejected	98	0.548	Accepted	4
Parity		75	0.543	Accepted	85	0.413	Rejected	0
Age (31-40) (Year)		65	0.532	Rejected	98	0.434	Rejected	0
Gestational age <37 weeks		73	0.44	Rejected	95	0.433	Rejected	0
Level of education		54	0.419	Rejected	91	0.398	Rejected	0
Origin		41	0.41	Rejected	88	0.418	Rejected	0
Foul-smelling Vaginal discharge		69	0.301	Rejected	86	0.3	Rejected	0
Delivery		PROM >18 hours	100	0.884	Accepted	100	0.884	Accepted
	Chorioamnionitis	100	0.884	Accepted	100	0.884	Accepted	1
	Intrapartum fever >38 °C	100	0.802	Accepted	100	0.884	Accepted	1
	No intrapartum antibiotic prophylaxis	75	0.732	Accepted	88	0.793	Accepted	2
	Abnormal amniotic liquid	78	0.752	Accepted	98	0.753	Accepted	3
	MSAF ⁶	75	0.698	Accepted	97	0.753	Accepted	3
	PROM >24 hours	75	0.461	Rejected	86	0.545	Accepted	4
	Cesarean section	75	0.432	Rejected	76	0.534	Accepted	5
	IUGR [#]	38	0.546	-	79	0.428	Rejected	0

[#]New risk factor suggested by <15% of the participants. VLBW: Very low birth weight; LBW: Low birth weight; GBS: Group B Streptococcus; UTI: Urinary tract infection; PROM: Premature rupture of membranes; MSAF: Meconium-stained amniotic fluid; IUGR: Intrauterine growth restriction; The threshold value (d) of risk factors associated with neonatal, maternal, and delivery categories in the first and second rounds of the fuzzy Delphi model (FDM) was 0.00, 0.01, and 0.02, respectively.

Table 4: Risk factors related to early-onset sepsis

Final risk factor		Case (N=31) N (%)	Control (N=83) N (%)	Chi square	P value
Neonatal	Birth weight <1,500 g	14 (45.1)	5 (6)	24.891	<0.001
	One-min Apgar <7	10 (32.2)	12 (14.4)	4.592	0.032
	Prematurity <37 weeks	17 (54.8)	4 (4.8)	37.577	<0.001
	Five-min Apgar <7	16 (51.6)	10 (12)	20.068	<0.001
	Respiratory distress	18 (58)	12 (14.4)	22.134	<0.001
	Apnea-hypopnea index	17 (54.8)	10 (12)	22.864	<0.001
	Fever	22 (70.9)	13 (15.6)	32.447	<0.001
	Seizures	12 (38.7)	9 (10.8)	11.663	0.001
	Asphyxia (ph<7, BE<-16 mmol/L)	20 (64.5)	13 (15.6)	26.190	<0.001
	Birth weight <2,500 g	13 (41.9)	16 (19.2)	6.109	0.013
	Resuscitation at birth	13 (41.9)	6 (7.2)	19.575	<0.001
	Jaundice	11 (35.4)	15 (6)	3.887	0.049
	Feed intolerance	22 (70.9)	12 (14.4)	34.437	<0.001
	Need for mechanical ventilation	21 (87.7)	6 (7.2)	45.726	<0.001
Maternal	Gestational age <32 weeks	12 (38.7)	1 (1.2)	31.424	<0.001
	UTI	18 (58)	12 (14.4)	22.134	<0.001
	GBS	13 (41.9)	9 (10.8)	14.010	<0.001
	Multiple digital vaginal examinations>3	27 (87)	34 (40.9)	19.309	<0.001
	Gestational age <34 weeks	11 (35.4)	10 (12)	8.249	0.04
Delivery	PROM>18 hours	18 (58)	10 (12)	25.794	<0.001
	Chorioamnionitis	19 (61.2)	5 (6)	41.477	<0.001
	Intrapartum fever >38 °C	15 (48.3)	11 (13.2)	15.825	<0.001
	No Intrapartum antibiotic prophylaxis	8 (25.8)	7 (8.4)	5.961	0.026
	Abnormal amniotic liquid	18 (58)	30 (36.1)	4.449	0.03
	MSAF	9 (29)	3 (3.6)	15.482	<0.001
	PROM >24 hours	7 (22.5)	2 (2.4)	12.629	0.001
Cesarean section	17 (54.8)	44 (53)	0.030	0.862*	

*Not a significant risk factor. UTI: Urinary tract infection; GBS: Group B Streptococcus; PROM: Premature rupture of membranes; MSAF: Meconium-stained amniotic fluid

Moreover, low birth weight (LBW) was considered a risk factor and ranked seventh in the FDM study. A meta-analysis of six cross-sectional and two cohort studies investigated the association between birth weight and EOS in 9,032 live births. A significant relationship between sepsis and LBW with an odds ratio (OR) of 1.42 (95% CI: 1.07-1.88) was reported, i.e., the OR of LBW for EOS is 1.42 times higher than the newborns with normal weight.⁴³

In our review, we found that eight studies reported a low one-min Apgar score as a risk factor for EOS (ranked first in the FDM). In addition, five other studies considered five-min Apgar as a risk factor for EOS (ranked second in the FDM). Whereas, this parameter is not directly considered a risk factor in the NICE guideline. During the second round of FDM, a participant commented: *“The evidence shows that one-min Apgar score depends on the cord blood hydrogen potential (pH) and intrapartum depression, whereas five-min Apgar score indicates a change in the condition of neonates upon resuscitation. Therefore, it is necessary to consider both Apgar scores in assessing the risk of EOS.”* Various studies showed that infants

with low Apgar scores have a 2.7-fold higher risk of EOS compared to other newborns.^{33, 41}

Apnea was indicated as a risk factor by 53% of the experts during the first round of FDM. A participant commented: *“Several studies demonstrated that immaturity of the respiratory center in the brain is the most common cause of apnea, and it may occur on days 2-7 after birth. However, apnea immediately after birth is indicative of another complication and could be a potential risk factor for EOS.”*

Fever and seizure were other risk factors identified by the experts. We noted that 48% of the experts categorized a body temperature >38 °C as fever. However, based on the NICE guideline, 32% of the experts considered newborn body temperature of <36 °C and >38 °C as abnormal.

Sexual dimorphism affects the human immune response. Women are less susceptible to infection than men due to more intense cellular and humoral immune responses to infection.⁴⁴ Six studies reported that boys are more likely to develop EOS than girls. However, this notion was ruled out by our experts.

In the maternal category, gestational age <32

weeks had the highest level of evidence as a risk factor and consensus on this topic was reached in the first round of FDM. However, CDC and NICE guidelines included a gestational age of <34 weeks and <37 weeks as a risk factor for sepsis⁵ and EOS,² respectively. A meta-analysis on the association between gestational age and EOS reported that neonates with gestational age <32 weeks were 3.36 times more likely to develop sepsis than other neonates.⁴⁵

Urinary tract infection (UTI) was also reported as a potential risk factor for EOS in six studies. Consensus on this risk factor was reached by the experts in the first round of FDM. However, NICE and CDC guidelines did not include UTI as a risk factor. A systematic review and meta-analysis of 27 studies assessing the effect of UTI and intrapartum fever on the risk of EOS reported that neonates born to mothers with UTI had a 3.55-fold higher risk of EOS (95% CI: 2.04, 5.06) than other infants.¹¹ A participant stated: *“UTI is an important risk factor for EOS, especially if not treated in the third trimester of pregnancy. Evidence indicates that EOS may be developed by infectious agents colonizing the birth canal.”*

In our review, vaginal examination ranked fourth among all EOS risk factors. The cervical canal is prone to infection due to vaginal organisms, even in sterile conditions. A vaginal examination can increase the risk of vaginal infection. However, some studies reported no significant relationship between vaginal examination and EOS.¹⁴ Such conflicting results could be attributed to different study settings and the difference in the quality of obstetrics and neonatal health care services between primary and referral hospitals.

All participants agreed that PROM, chorioamnionitis, and intrapartum fever are potential risk factors for EOS. Several studies indicated that PROM is a common and significant cause of preterm labor.^{12, 17} In line with NICE and CDC guidelines, in our review, 11 studies reported that PROM>18 h is a risk factor for EOS.^{2, 5} Since the birth canal is colonized with aerobic and anaerobic pathogens, it might cause ascending amniotic fluid and, as a result, infect the neonates at birth. These bacterial agents might transmit from mother to fetus in the uterus during labor and delivery, leading to EOS.¹² Chorioamnionitis was reported in four of the reviewed articles. A meta-analysis of 107 studies reported a positive correlation between chorioamnionitis and EOS (OR: 4.29, 95% CI: 3.63-5.06).³ Another meta-analysis of 55 studies also reported a relationship between chorioamnionitis and EOS (OR: 4.42, 95% CI: 2.68-7.29).⁴⁶ These results

were supported by NICE and CDC guidelines, indicating chorioamnionitis as a risk factor for EOS.^{2, 5} Intrapartum fever was reported in nine studies, and our experts were in full agreement on this. The results of a meta-analysis showed that intrapartum fever increased the risk of EOS by a factor of 3.36 (95% CI: 1.64-5.62).³⁹ During the first round of FDM, two participants stated: *“Evidence from studies indicate that fever is a clear sign of an infection, which can be transmitted to infants and cause EOS.”*

Some experts believed that EOS mainly develops as a result of vertical transmission and, consequently, a cesarean section cannot be a risk factor for EOS. The results of our Chi square test also showed that cesarean section was not a significant risk factor for EOS (P=0.862). Nonetheless, 76% of the experts considered cesarean section as a risk factor, since the normal flora in neonates could be affected by this procedure. Infants born by cesarian delivery have a lower amount of bifidobacteria, and the incidence of *Bacteroides* spp. is also lower.²⁹ Neonates with normal flora have a stronger immune system. A change in normal flora will lead to an increased risk of EOS. The latter was confirmed by the CDC guideline.

The main strength of our study is a comprehensive literature review of risk factors associated with neonatal EOS in terms of maternal, delivery, and neonatal categories. Another strength is related to the way FDM was conducted. The participants were selected based on strict requirements, namely knowledge and active engagement with the research topic, willingness to participate, readiness to dedicate time and effort to group sessions, and effective communication between the research team and experts. But above all, the selection of participating specialists was based entirely on their expertise. Each study round lasted 21 days and regular communication between the parties involved was ensured. We sought the opinion of leading experts from around the world, which in turn gave us confidence that we have identified the main risk factors for neonatal EOS. Last but not least, we took full advantage of FDM by effectively clarifying any ambiguities in the opinion of the experts, saving time by using a shortened questionnaire, and reducing costs compared to other methods (e.g., focus group discussion).

As the main limitation of the study, despite our effort to conduct FDM as fully as possible, some participants did not fully respond to the questionnaire and overlooked certain questions. In addition, we only considered risk factors related to the first few hours after birth and did

not include the risks associated with the quality of care and length of stay at the NICU. It is recommended to address these topics in future studies.

Conclusion

Neonatal-related risk factors for EOS were birth weight <1,500 g, one-min Apgar <7, and prematurity. Maternal-related risk factors were gestational age <32 weeks and UTI. In addition, delivery-related risk factors were PROM >18, chorioamnionitis, and intrapartum fever >38 °C. Our findings will facilitate accurate diagnosis of early-onset sepsis, prevent unnecessary use of antibiotics, and can be used to develop guidelines for the diagnosis and treatment of neonatal EOS.

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Authors' Contribution

N.M: Study concept and design, statistical analysis, and drafting; T.S.S: Statistical analysis, interpretation of data, and drafting; K.M: Study concept and design, and critical revision; A.E: Analysis and interpretation of data, and drafting; M.S.T: Analysis and interpretation of data, and critical revision; P.R.H: Study concept and design, and drafting; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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