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Original article

Impact of neonatal sepsis calculators on diagnostic accuracy and antimicrobial stewardship: A systematic review and meta-analysis

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Abstract. *Background and Aim:* Early-onset neonatal sepsis (EOS) is a life-threatening infection occurring within the first 72 hours of life, requiring timely treatment to optimize outcomes. Although group B streptococcus screening and intrapartum antibiotic prophylaxis have reduced EOS incidence, concerns regarding antibiotic overuse persist. The neonatal sepsis calculator, developed by Kaiser Permanente Northern California, is a risk-based prediction tool designed to improve antibiotic stewardship. This systematic review and meta-analysis evaluate its diagnostic accuracy and impact on antibiotic use. *Methods:* A systematic literature search was conducted across PubMed, Scopus, Web of Science, ScienceDirect, and ProQuest (up to July 1, 2024), following the PRISMA guidelines (PROSPERO ID 567269). Studies assessing the neonatal sepsis calculator against blood culture results were included. Data on antibiotic usage with and without calculator implementation were extracted. Meta-analysis of diagnostic accuracy was performed using STATA 16.0 to determine pooled sensitivity, specificity, diagnostic odds ratio (DOR), and area under the curve (AUC). Proportional and binary meta-analysis using RStudio 4.4.1 summarized antibiotic usage changes. *Results:* From 1,523 records, 21 observational studies were included. The neonatal sepsis calculator showed a pooled sensitivity of 68% (95% CI 49–82%) and specificity of 78% (95% CI 57–90%), with an AUC of 0.79 (95% CI 0.75–0.82) and a DOR of 7.25 (95% CI 2.49–21.08). Its implementation significantly reduced antibiotic use (OR 0.045, 95% CI 0.009–0.236, p=0.001). *Conclusion:* The neonatal sepsis calculator demonstrates good diagnostic accuracy and supports antibiotic stewardship. Future refinements incorporating neonatal factors may enhance its predictive performance. (www.actabiomedica.it)

Key words: neonatal sepsis calculator, early-onset neonatal sepsis, antibiotic stewardship, diagnostic accuracy, meta-analysis, neonatal infection, sepsis, antimicrobial stewardship, neonatal sepsis diagnosis, early detection of neonatal sepsis, meta-analysis in sepsis, sepsis diagnostic tools

Introduction

Early-onset neonatal sepsis (EOS) is a systemic infection occured at ≤72 hours in infants hospitalized in the neonatal intensive care unit, which is characterized by bacteremia or bacterial meningitis (1, 2). EOS is primarily caused by organisms that colonize the maternal genitourinary tract, which includes *Group B Streptococcus* (GBS) and *Escherichia coli*, constitutes 70% of infections combined (3). These pathogens may contaminate the amniotic fluid, placenta, cervix, or vaginal canal during pregnancy or labor. A recent study indicated that the approximate EOS incidence is 2,496 per 100,000, which was more common than late-onset neonatal sepsis (4). Despite modern treatment strategies, EOS carries a significant mortality burden, with reported rates reaching up to 54% (5). The high incidence of EOS is a major concern due to the significant challenge of diagnosis. It is because EOS has broad clinical manifestations, which make it difficult to definitively identify the disease and potentially leading to overreliance on antibiotics (6). However, the overall incidence of EOS has decreased about 55% because of universal GBS screening and intrapartum antibiotic prophylaxis (7). Despite a significant decline in EOS incidence due to GBS screening and intrapartum antibiotic prophylaxis, concerns about overuse of antibiotics persist. Overuse and prolonged use of antibiotics in infants who are not suffering from sepsis can result in extended hospitalization. Longer hospitalization increases healthcare costs and mother-infant separation which hinder early bonding and may compromise successful breastfeeding (8). Moreover, prolonged antibiotic exposure is associated with the emergence of antibiotic-resistant bacteria, which heightens the risk of subsequent infections with multidrug-resistant organisms (9, 10). The neonatal sepsis risk calculator (SRC), developed by Kaiser Permanente Northern California, provides an early-onset sepsis risk estimate for each neonate, aiming to improve antibiotic stewardship by reducing unnecessary treatments. The calculator based on the five objective maternal risk factors and infant's clinical presentation (11). Studies has shown that applying the calculator has been shown to decrease antibiotic use in late preterm or full-term preterm infants by approximately 40%, without increasing the risk of false negative results (12, 13). Despite the decrease of antibiotic use, some studies have shown that neonatal SRC failed to predict empirical antibiotic use, which resulted in potential delay in antibiotic use (14-16). The delays in antibiotic administration could result in increased risk factor for both mortality and longer hospitalization days (17). Current meta-analyses have included too few studies and primarily focused on the reduction of antibiotic use rather than the accuracy of neonatal SRC (Desmukh; Achten, Rohsiswatmo) (18-20). To date, no meta-analysis has thoroughly examined the predictive accuracy of empiric antibiotic use on the first day of life using neonatal SRC, nor have they comprehensively evaluated the factors influencing this accuracy. Therefore, this systematic review and meta-analysis aim to assess the accuracy of neonatal SRC and their broader implications for enhancing antibiotic stewardship programs.

Methods

Study design

This systematic review and meta-analysis was conducted in accordance to PRISMA-DTA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis of Diagnostic Test Accuracy Studies) (21) and Cochrance Handbook for Systematic Reviews of Diagnostic Test Accuracy v.2 Collaboration recommendations (22). Our study protocol has been registered International Prospective Register of Systematic Reviews (PROSPERO). The registration number is CRD42024567269. The completed PRISMA 2020 Checklist can be accessed in Table S1.

Search strategy and study selection

A comprehensive literature search was performed across literature databases (ProQuest, PubMed, ScienceDirect, Scopus, and Web of Science) without restrictions on time frame or language, up to July 3rd, 2024. A list of main keywords was formulated: "neonatal", "sepsis risk calculator", and "diagnostic". Subsequently, Medical Subject Headings (MeSH) terms and related text terms were incorporated to create database-specific

search terms. Detailed search terms for each database are provided in Table S2. Search results were retrieved and organized using Google Sheets (https://docs.google.com/spreadsheets/) (Google LLC, Mountain View, CA, USA). Duplicate entries were manually removed on Google Sheets. The remaining studies were screened based on the study title and abstract. Subsequently, full-text availability was then assessed, and eligible studies were evaluated aginst pre-defined inclusion and exclusion criteria. Reasons for exclusion at each screening stage were documented in spreadsheet as appropriate and presented in PRISMA Flow Diagram. The literature searches and overall study selection process were independently performed by three authors (VIV, FMA, and JOH). Any discrepancies resolved through group discussion.

Eligibility criteria

Eligibility criteria were developed by adapting the Population, Index Test, Comparator, Outcome (PICO) framework (Table S3) (23). To be included in this systematic review and meta-analysis, studies had to met all the following inclusion criteria: (1) study population comprised newborn diagnosed with early-onset sepsis; (2) sepsis detection was confirmed through culture-based methods; (3) evaluated the diagnostic accuracy of neonatal SRC in estimating the risk of sepsis; and (4) employed an observational design (case-control, cross-sectional, or cohort studies). We excluded studies if: (1) studies categorized as review article, case report, case series, or conference abstract; or (2) the full text was irretrievable.

Data extraction and quality assessment of individual studies

Data extraction process was performed independently by three investigators (VIV, FMA, and JOH) using a pre-specified template designed and tabulated within the spreadsheet. Extracted data were cross verified for accuracy and eligibility, with disagreements were resolved immediately. Extracted information included study characteristics (authors, publication year, study location (country and continent), study design, population characteristics (inclusion and exclusion criteria), gestational age, gestational weight, female percentage, study sample size, incidence sepsis in country/1000 lives birth, antibiotic use for pre post implementation study or approach comparison study, and diagnostic accuracy parameters of SRC (true positive [TP], true negative [TN], false positive [FP], false negative [FN], sensitivity, specificity, area under the curve [AUC]), and sample size cultured). Afterwards, the extracted characteristics and outcomes of each included study were then presented in tabular format. Three reviewers (VIV, FMA, and JOH) independently evaluated the quality assessment in each included study using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (24). Incongruity in judgements was reconciled with the involvement of a fourth reviewer (BSW). Risk of bias and applicability concerns were categorized as "low", "uncertain", or "high" based on the responses and further visualized using RevMan version 5.4.0 (The Cochrane Collaboration, USA)

Statistical analysis

Data analysis were conducted using STATA version 16.0 (Stata Corporation, College Station, TX, USA) and RStudio version 4.4.1 (Posit, Boston, MA, USA). For the primary outcome, a diagnostic test accuracy meta-analysis was performed to evaluate the performance of SRC in identifying neonatal sepsis. A secondary meta-analysis was undertaken to compare the Odds Ratio (OR) and Proportion of antibiotic usage between the sepsis calculator and standard care approaches. Heterogeneity among studies was assessed using the Cochran's Q statistic and quantified with the Higgins' I2 statistic, with the thresholds of 0%, 25%, 50%, and 75% indicating negligible, low, moderate, and high heterogeneity, respectively. A p-value of < 0.05 was used to indicate statistical significance in all analysis. A bivariate model for diagnostic accuracy meta-analysis was used to calculate pooled sensitivity, specificity, diagnostic odds ratio (DOR), and area under the summary receiver operating characteristics (AUSROC) curve with 95% confidence intervals (CIs). The AUSROC was interpreted in alignment with AUC, where 0.5 indicates that SRC have no ability to distinguish neonates with and without sepsis,

while 0.7 to 0.8 is considered an acceptable diagnostic power, 0.8 to 0.9 is considered excellent, and more than 0.9 suggests an outstanding discriminatory power (25). The publication bias analysis for diagnostic test accuracy meta-analysis was assessed using the Deeks' funnel plot.

Meta-proportion analysis also conducted using generalized linear mixed models (GLMM) models (26). These analysis estimate population-averaged proportions and differ from traditional treatment comparison meta-analysis, which focus on estimating relative effects such as odds ratios, risk ratios, or risk differences (27). An odds ratio (OR) meta-analysis was performed to compare the proportions between groups.

Result

Study selection process

Figure 1 shows a PRISMA flow diagram of the overall study selection process. The initial database search across five datasets yielded a total of 1523 records. Before the screening process, 534 duplicate records and 368 records marked as non-article, non-human, and non-newborn records were removed. The 621 remaining studies were then assessed based on their title and abstract, resulting in 505 and 55 studies being excluded, respectively. The availability of full-text access was then investigated, resulting in six

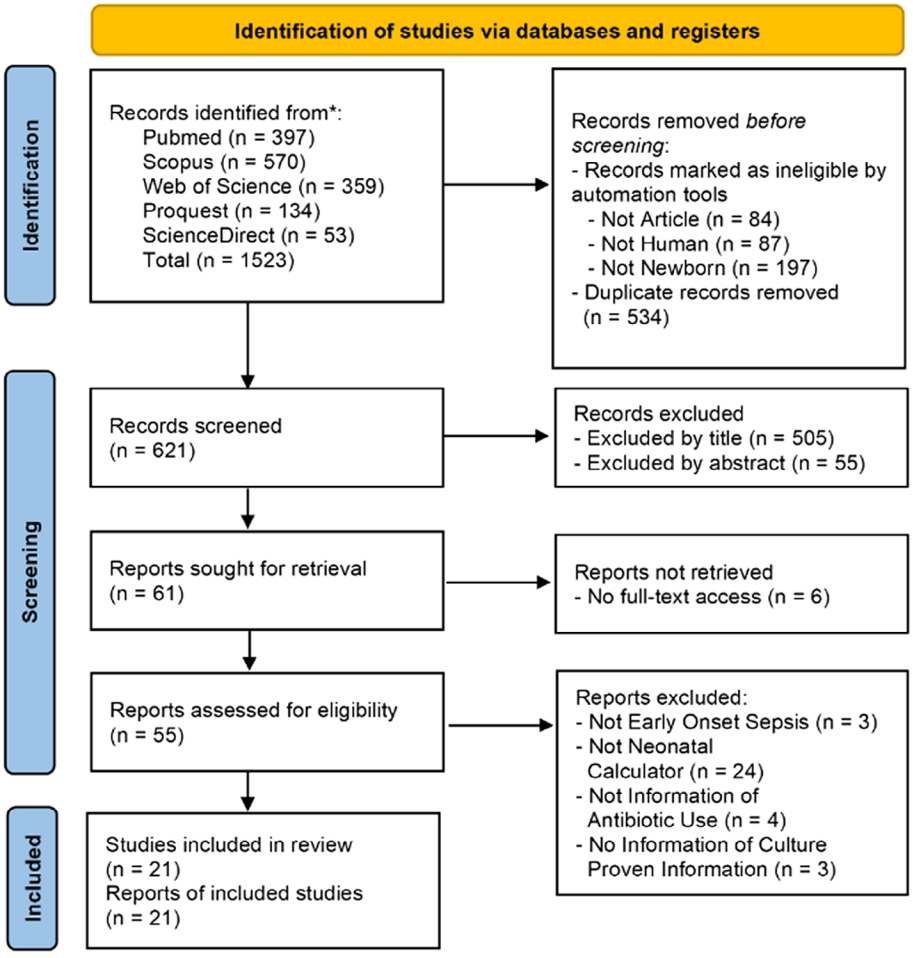

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) fow diagram of the study selection process.

studies to be excluded. Lastly, a comprehensive review was performed in the last 55 studies, and 34 studies were subsequently excluded due to the following reasons: not assessing early onset sepsis (n = 3), not investigating the accuracy of neonatal calculator (n = 24), no information of antibiotic use (n = 4), and not giving culture proven information (n = 3). Eventually, the whole screening process resulted in the inclusion of 21 eligible studies in this systematic review and meta-analysis (12, 13, 28-46).

Characteristics of included studies

Table 1 provides the characteristics of each included study. In this systematic review and meta-analysis, all 21 included studies are Cohort studies. The female neonates accounts for 47.02% of the study population. The gestational age ranged from 36.5 weeks to 39.6 weeks, averaging 38.58 weeks, while the gestational weight averaged 3195.6 grams. More than half of the studies were located in America, while the remaining studies were located in Europe (n = 5), Asia (n = 2), and Australia (n = 1).

Quality assessment of included studies

The risk of bias and applicability concern of each included study is presented in Figure 2. Regarding the risk of bias, eight studies rated low risk in all domains, giving a low overall risk of bias. Twelve studies were rated as having a moderate risk of bias since there were some concerns in one or two domains. Concerning applicability concerns, eight, ten, and three studies were considered to have low, moderate, and high concerns, respectively.

Accuracy of neonatal sepsis calculator in detecting early onset sepsis

The diagnostic test accuracy meta-analysis included 8474 neonates from eleven studies. Data analysis from Figure 3 showed that neonatal SRC has the potential to detect early onset sepsis with a pooled sensitivity of 68% (95% CI [49%-82%]) and specificity of 78% (95% CI [57%-90%]).

The AUSROC curve from Figure 4 shows a value of 79% (95% CI [75%-82%]). This AUSROC value indicates an acceptable power of neonatal SRC. High heterogeneity was found in both sensitivity (I2 = 98.40%) and specificity (I2 = 99.95%). However, the Deeks' funnel plot analysis indicated a potential publication bias (p = 0.04) (Figure 5).

Subgroup and meta-regression analyses

The results of subgroup analysis are presented in Table 2. The subgroup analysis showed significant differences in the sensitivity and specificity of neonatal SRC between studies conducted in America, Europe, and Asia (p < 0.001). Table 3 displays the results of meta-regression analyses. Meta-regression analyses on mean gestational week (p < 0.001), mean birth weight (p < 0.001), gender (p < 0.001), and incidence reported in the study (p < 0.001) showed significant results, indicating that these covariates affected the pooled diagnostic accuracies of neonatal SRC. The incidence use in calculator, proved not to influence the pooled sensitivity and specificity.

Meta-analysis on proportion antibiotic used

A total of 18 studies were included in the meta-analysis. Three studies by Quintero-Carreñom (2023) (43), Yi He (2019) (36), and Carola (2018) (12) were omitted because the proportion of antibiotics used was not reported. Table 4 demonstrated a lower proportion of antibiotics used in neonatal SRC with a proportion of 11% (95% CI [5%-21%]) compared to standard of care (Proportion = 83%, 95% CI [36%-98%]). This analysis was also statistically significantly lower in the neonatal SRC group (Odds Ratio = 0.04, 95% CI [0.01-0.24], p = 0.001). Subgroup analysis on the study region revealed no statistically significant difference in the proportion of antibiotics used between studies conducted in America and Europe (p = 0.816). The results of meta-regression analyses of meta-proportion are displayed in Table 5. Meta-regressions on all covariates, mean gestational week (p = 0.70), mean birth weight (p = 0.82), gender distribution (p = 0.80), incidence use in calculator (p = 0.88), and incidence

Table 1. Characteristics of included studies

Author, Year	Location (Country, Continent)	Study Design	Gestational Age, week (Mean (SD))	Gestational Weight, gram (Mean (SD))	Female Percentage (%)	Study Sample Size*	Incidence Sepsis in Country / 1000 Lives Birth	Incidence Sepsis in Study / 1000 Lives Birth
Alhindi, 2024 (28)	Saudi Arabia, Asia	Cohort	N/A	3000 (500)	47.7	770	1.5	0.3
Arora, 2019 (29)	USA, America	Cohort	37.28	2940	42.8	190/276	0.5	N/A
Begnaud, 2021 (30)	USA, America	Cohort	N/A	N/A	41.64	193	0.5	N/A
Carola, 2018 (12)	USA, America	Cohort	39.4 (1.35)	3384 (508)	51.6	147	0.5	
Fowler, 2019 (31)	USA, America	Cohort	N/A	N/A		1000	0.5	N/A
Dhudasia, 2018 (32)	USA, America	Cohort	39.35 (1.25)	N/A	48.54	6090	0.7	0.5
Fernandes, 2022 (33)	UK, Europe	Cohort	38.14 (0.76)	3269 (757)	N/A	60	0.5	N/A
Goel, 2019 (34)	UK, Europe	Cohort	N/A	N/A	N/A	3593	0.5	1.4
Joshi, 2019 (37)	USA, America	Cohort	N/A	3357 (447)	44.5	319	0.6	0.4
Kopsidas, 2021 (38)	Greece, Europe	Cohort	36.50 (2.45)	2793 (589)	41.60	262	1.8	1.8
Zayek, 2017 (39)	USA, America	Cohort	39.4 (1.3)	3385 (497)	49.2	56261	0.5	2
Money, 2017 (41)	USA, America	Cohort	39.5 (1.2)	3431 (438)	49.5	362	0.5	2.3
Piyasena, 2023 (42)	UK, Europe	Cohort	38.9 (1.7)	3156 (562)	60	3297/42952	0.6	0.6
Quintero-Carreñom, 2023 (43)	Colombia, America	Cohort	37.24 (2.56)	2701 (532)	41.7	470	0.5	0.3
Shakib, 2014 (44)	USA, America	Cohort	N/A	N/A	N/A	455/698	0.5	1.4
Sharma, 2019 (45)	USA, America	Cohort	39.6 (1.4)	3435 (484)	44.4	180	0.35	3.5
Sloane, 2020 (46)	USA, America	Cohort	39.4 (1.3)	3370 (460)	48.1	1257	0.6	0.3
Snoek, 2022 (47)	Netherland, Europe	Cohort	38.98 (2.33)	3360 (670)	42	88/81	0.6	N/A
Stipelman, 2019 (48)	USA, America	Cohort	N/A	N/A	N/A	5009	0.3	0.3
Strunk, 2018 (13)	Australia, Australia	Cohort	N/A	3315 (541)	48.4	2502	0.44	0.4
Yi He, 2019 (36)	China, Asia	Cohort	37.86 (2.36)	3038 (777)	50.69	501	0.6	2.2

*One study can give difference sample size for accuracy and antibiotic reduction study. The data presented by sample size for accuracy / antibiotic reduction study. N/A: Not Available

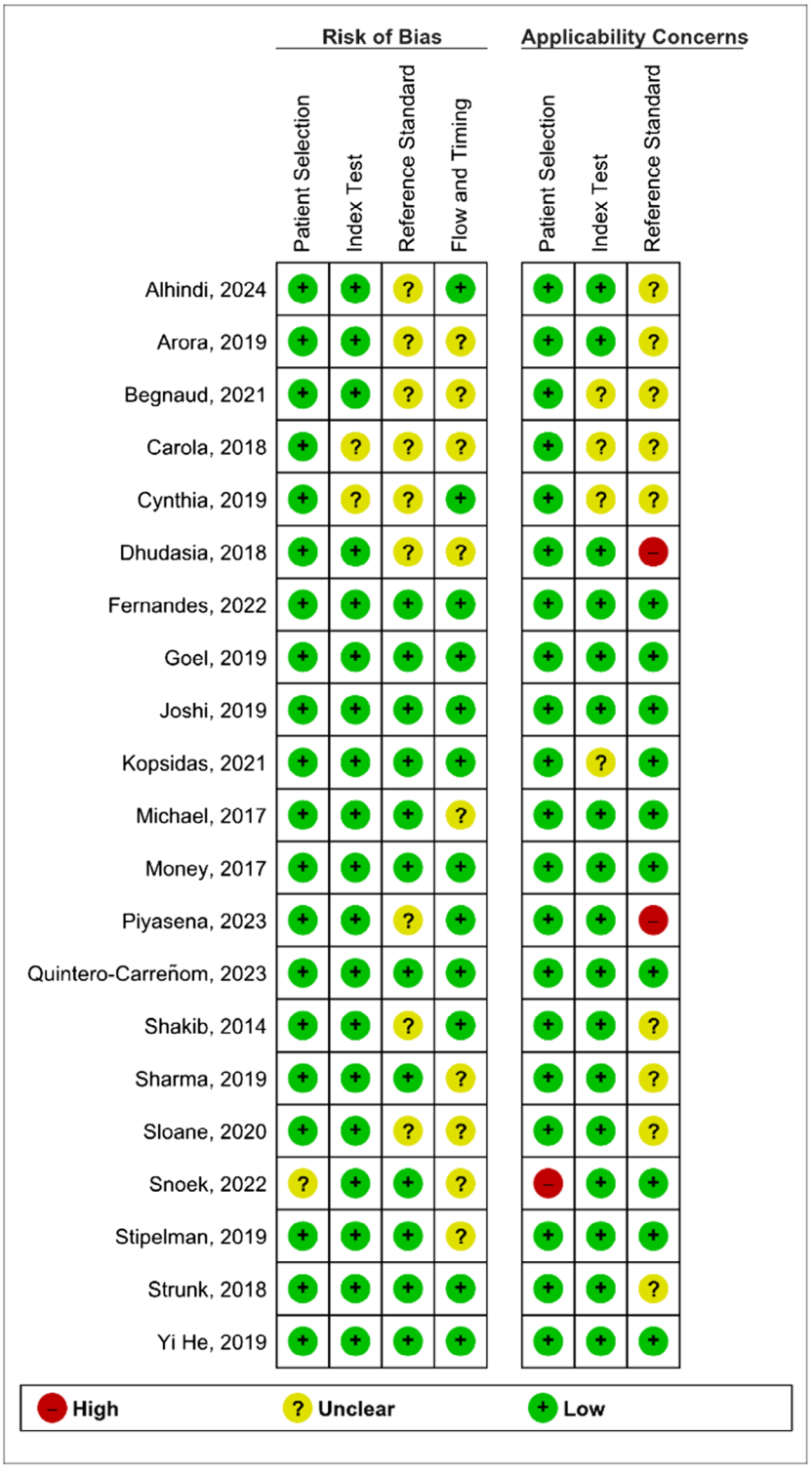

Figure 2. QUADAS-2 risk of bias and applicability concerns summary

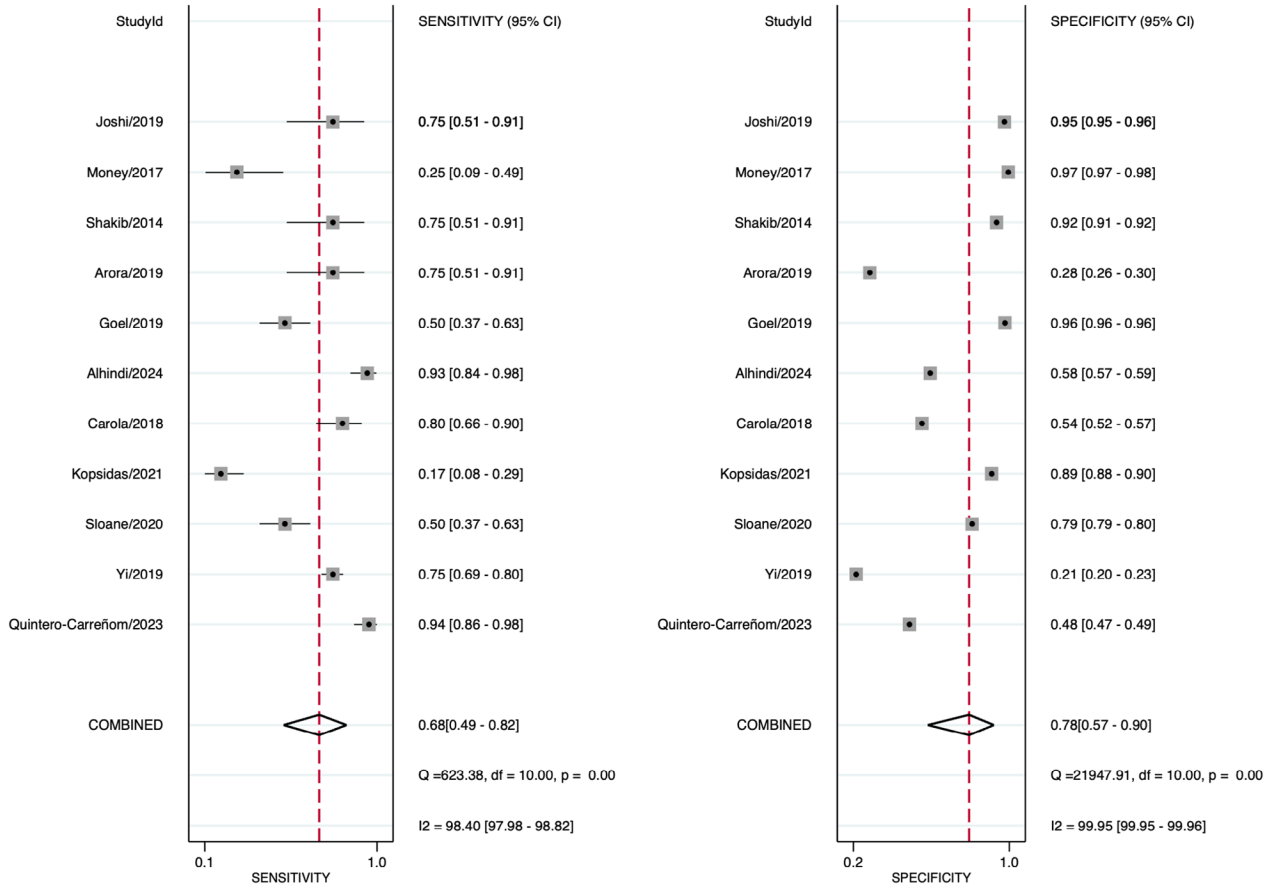

Figure 3. Forest plots of the pooled sensitivity and specificity of neonatal SRC

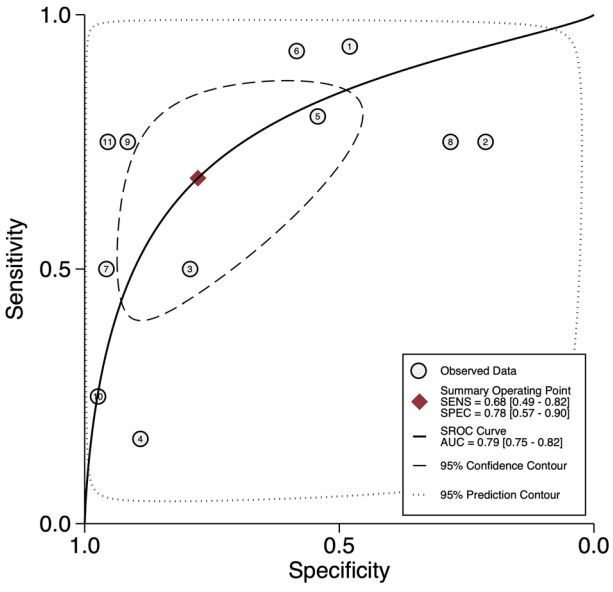

Figure 4. Area under the summary receiver operating characteristic (AUSROC) curves of neonatal SRC

reported in study (p = 0.32) unveiled non-significant results, suggesting that these covariates not affect the proportion of antibiotics used.

Discussion

Main findings

The neonatal SRC achieves sufficient accuracy, but suboptimal sensitivity and specificity. The neonatal SRC may not be considered a primary diagnostic tool in comparison to culture-based methods. Nonetheless, due to its notable capacity for generating true negative results, the neonatal SRC can serve as an effective screening tool aimed at mitigating unnecessary antibiotic administration (28). It is important to note that the neonatal SRC recommendations for neonates who have

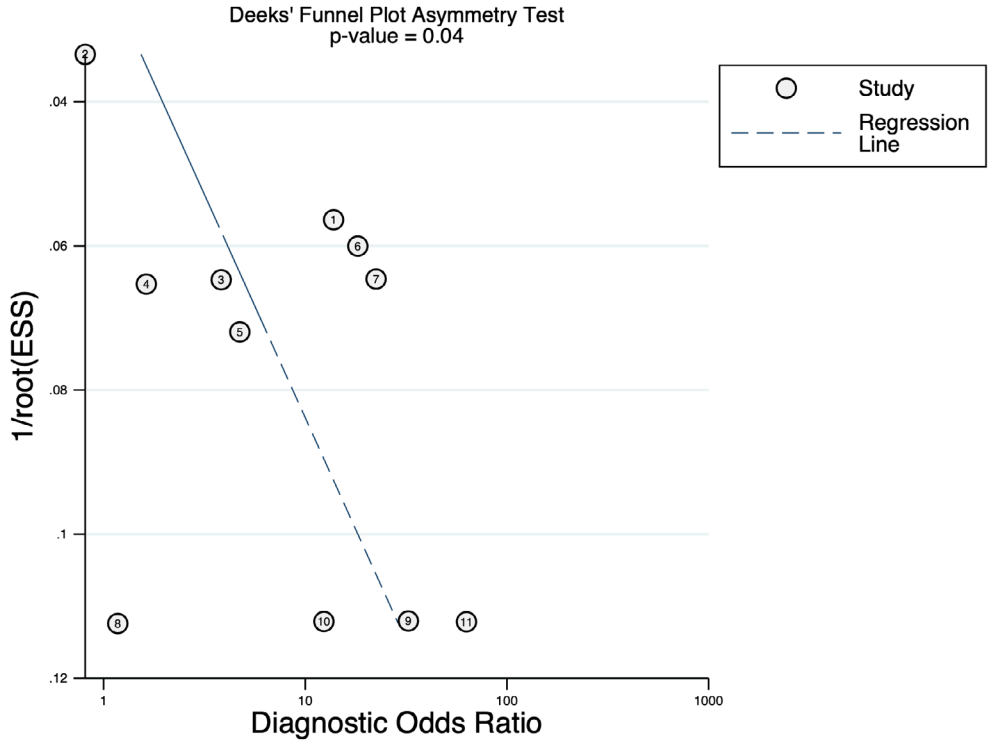

Figure 5. Deeks' funnel plot asymmetry test of neonatal SRC

Table 2. Total and subgroup analysis of sensitivity and specificity of neonatal SRC

Total and Subgroup Analysis	Studies (n)	% Sensitivity (95% CI)	% Specificity (95% CI)	*p*-value
Overall Result	11	67 (41–86)	78 (57–90)	
Subgroup Analysis: Region				
America	7	71 (55–88)	80 (62–97)	ref.
Europe	2	31 (1–62)	93 (80–100)	< 0.001
Asia	2	85 (67–100)	38 (9–86)	< 0.001

Table 3. Meta-regression analysis of sensitivity and specificity of neonatal SRC

Regression Analysis	Studies (n)	*p*-value
Mean Gestational Age (week)	7	< 0.001
Mean Birth Weight (gram)	9	< 0.001
Percentage of Female (%)	9	< 0.001
Incidence use in Calculator	11	0.68
Incidence reported in Study	9	< 0.001

not been given antibiotics remain divided into two categories, those that do not require either a culture or antibiotics, and those that still require a blood culture (40). Consequently, the assessment conducted in this study was limited to evaluating the accuracy of the neonatal SRC in postponing the administration of antibiotics on the first day. The actual accuracy of the neonatal SRC may prove higher under broader evaluation conditions.

Regional

Significant differences in the accuracy of early neonatal sepsis calculators across America, Europe, and Asia can be attributed to various regional factors, including disparities in healthcare practices, epidemiology, and antibiotic usage (49). In high-resource settings like America and Europe, routine interventions such as risk-based antibiotic prophylaxis during labor and advanced neonatal care significantly reduce sepsis-related mortality (50). Neonatal mortality due to sepsis in low-mortality regions (e.g., <15 per 1,000 live births)

Table 4. Total and subgroup analysis of antibiotic used proportion

Total and Subgroup Analysis	Studies (n)	Proportion of Antibiotic Used (95% CI)		OR (95% CI)	*p*-value
		Sepsis Risk Calculator	Standard of Care		
Overall Result	18	0.11 (0.05–0.21)	0.83 (0.36–0.98)	0.04 (0.01–0.24)	0.001
Subgroup Analysis: Region*					
America	11	0.08 (0.03–0.19)	0.83 (0.22–0.99)	0.03 (0.00–0.34)	ref
Europe	5	0.16 (0.04–0.45)	0.93 (0.12–1.00)	0.04 (0.00–3.06)	0.816

*2 studies, 1 from Asia and 1 from Australia were excluded in subgroup analysis.

Table 5. Meta-regression analysis of antibiotic used proportion

Regression Analysis	Studies (n)	Estimate	SE	*p*-value
Mean Gestational Age (week)	10	0.48	1.23	0.70
Mean Birth Weight (gram)	12	0.00	0.01	0.82
Percentage of Female (%)	13	0.06	0.23	0.80
Incidence use in Calculator	13	-0.17	1.11	0.88
Incidence reported in Study	13	-2.20	2.17	0.32

accounts for 9.1%-15.3% of neonatal deaths, primarily linked to nosocomial infections and complications of prematurity (49). In this area, the healthcare systems emphasize antimicrobial stewardship, resulting in calculators with higher specificity but lower sensitivity. This contrasts with high-mortality regions such as parts of Asia, where sepsis accounts for 22.5%-27.2% of neonatal deaths due to limited access to these interventions and delayed diagnosis (51). Therefore, the implementation of EOS calculators is designed with high sensitivity to minimize the risk of missed diagnoses. This approach reflects the limitations in rapid diagnostic tools and the higher baseline prevalence of neonatal sepsis in the region. Additionally, the component of calculation such as unscreened maternal infections still limited in Asia compared to the Americas or Europe (52). The difference on the antibiotic usage patterns also illustrate regional differences. Prior study assesing early-life antibiotic exposure along with EOS incidence reported significant higher antibiotic days per year in Australia (491) and Canada (230) compared to rest Europe countries and USA (53). High antibiotic usage in countries like Australia aligns with a higher percentage of treated neonates (12.45%) compared to Europe or USA, reflecting a preventive rather than reactive approach. Clinical decision making in the USA often withholding antibiotics for neonates presenting isolated respiratory distress without other risk factors resulted in a 95% to 41% reduction in empirical treatment rates without missing cases of early-onset sepsis (EOS) (54).

Gender and birthweight

The subgroup analysis revealed that gender significantly influenced the accuracy of the neonatal SRC. Furthermore, meta-regression analysis identified weight difference as a significant determinant affecting the accuracy of the neonatal SRC. These findings suggest that these two variables should be included in further development of neonatal SRC. This phenomenon can be attributed to the inherent susceptibility which renders infants more vulnerable to this condition (1, 55). Prior meta-analysis synthesized data from 15 studies to investigate neonatal sepsis risk factors in India. They reported male sex (OR 1.3; 95% CI 1.02–1.68) and low birthweight (OR 2.05; 95% CI 1.40–2.99) as significant risk of EOS (56).

Studies have consistently demonstrated that male neonates exhibit higher rates of respiratory and circulatory complications during the early neonatal period, contributing to their increased susceptibility to sepsis (57, 58). Male neonates are more likely to require mechanical ventilation, inotropic support, and

exhibit chronic lung disease. Previous study reported that 36.2% of male preterm neonates developed CLD compared to 9.8% of females (p = 0.004), while inotropic support was needed by 67.1% of male ELBW infants versus 50.6% of females (p = 0.028) (58). Several factors underscore a multifactorial etiology for the increased susceptibility of male neonates to sepsis. The differential catecholamine response during labor, which preterm male infants exhibit lower catecholamine release during labor, likely contributes to their worser outcomes following hypoxic events compare to preterm female infants (59). Male infants not only require more postnatal catecholamine support (60) but also display vulnerabilities on severe intraventricular hemorrhage, sepsis, and subsequent long-term neurodevelopmental impairments (61). The vulnerability on preterm male infant is due to cumulatively disadvantage on hormonal, genetic, and immunological differences (62). Lower birth weight is a significant risk factor for EOS in preterm infants. Low birth weight infants have a 3–10 times higher incidence of infection than full-term neonates due to factors such as an immature immune system by limited transplacental IgG transfer, inadequate thermoregulation, feeding challenges, and a heightened susceptibility to hypoglycemia (5, 63). Further supporting this link, Lee et al (64). demonstrated that very low birth weight infants with sepsis exhibited lower gut microbial diversity at birth, and PCR analysis revealed that 40% of these infants had pathogenic bacteria colonizing their gut prior to the onset of sepsis. Moreover, the frequent morbidity in low birth weight infant given them more susceptible to develop sepsis (65). Together, these findings underscore the critical need for adding the estimated fetal birth weight to support early identification of EOS in low-birth-weight neonates.

Antibiotic utilization

The neonatal SRC has consistently demonstrated its effectiveness in significantly reducing antibiotic utilization across diverse populations and clinical settings, regardless of factors such as birth weight, gender, or geographical location. The implementation of the neonatal SRC demonstrates a substantial reduction of antibiotic utilization, potentially decreasing by as much as 1/20. This will greatly support antibiotic stewardship efforts aligned with World Health Organization's (WHO) antibiotic use program (66). Additionally, the widespread adoption of the SRC offers ancillary benefits, including cost savings and shorter treatment durations, making it a valuable screening tool with a clear and universal benefit.

Strength and limitation

The strength of this study is that it provides a comprehensive assessment of the accuracy of neonatal SRC with a sufficient number of patients. Several important limitations exist in this study. First, the standard diagnosis of sepsis in this study is culture results. It is well established that a substantial proportion of neonates with clinical sepsis are culture-negative, relying solely on culture results may underestimate the true incidence of sepsis and lead to missed opportunities for timely intervention. Second, this study has not adequately explored the clinical decision-making involved in withholding empirical antibiotics. In resource-limited settings where advanced diagnostic tools are scarce, there is a critical need to balance the risk of overtreatment against the potential harm of delaying therapy. Third, most of the current evidence supporting the SRC is derived from populations of larger, term infants (above 37 weeks' gestation). The management strategies for smaller or preterm neonates are different and not included in this study. Future research should aim to include more diverse populations and settings, especially from underrepresented regions such as Asia and Africa, to enhance the global applicability of neonatal SRC findings.

Conclusion

The neonatal SRC demonstrates promising accuracy in predicting the need for antibiotic use in culture-proven sepsis cases, making it a valuable tool for enhancing clinical decision-making. Its integration into routine neonatal care can significantly improve antibiotic stewardship efforts, reducing unnecessary antibiotic exposure and mitigating the risk of antibiotic resistance. However, the current studies highlight

gaps in understanding the influence of critical factors such as neonatal birth weight, sex, and regional epidemiology on its predictive accuracy. Future research should focus on refining the calculator by incorporating these variables, expanding its applicability across diverse populations, and validating its use in resource-limited settings. By addressing these areas, the neonatal sepsis calculator has the potential to become a globally effective screening tool, fostering safer and more targeted neonatal care.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article".

Authors' contribution: VIV, FMA, JOH, MTA, and BSW: conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft/review and editing. MTU, RIE, DIA, KDH, WUA, ABI, RID, MUR, SDL, and ATP: supervision, formal analysis, writing – review and editing. All authors contributed to the article and approved the final submitted version.

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Annex

Table S1. PRISMA-DTA Checklist Item

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE / ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	2
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	3
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	3
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	3

Table S1 (*Continued*)

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	3
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	4
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	4
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	5
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	5
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	7
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	N/A

Table S2. Search strategies.

Database	Keywords
PubMed	1. neonate[MeSH Terms] OR infants, newborn[MeSH Terms] OR "Newborn"[Title/Abstract] OR "Newborns"[Title/Abstract] OR "Infant"[Title/Abstract] OR "Infants"[Title/Abstract] OR "Neonate"[Title/Abstract] OR "Neonates"[Title/Abstract] OR "Neonatal"[Title/Abstract] 2. sepsis[MeSH Terms] OR chorioamnionitis[MeSH Terms] OR "Sepsis"[Title/Abstract] OR "Chorioamnionitis"[Title/Abstract] OR "Funisitis"[Title/Abstract] OR "Septicemia"[Title/Abstract] OR "Septicemias"[Title/Abstract] 3. "Scoring"[Title/Abstract] OR "Score"[Title/Abstract] OR "Calculator"[Title/Abstract] OR "Kaiser"[Title/Abstract] 4. "Diagnostic"[Title/Abstract] OR "Diagnosis"[Title/Abstract] OR "Diagnose"[Title/Abstract] OR "Sensitivity"[Title/Abstract] OR "Specificity"[Title/Abstract] OR "Accuracy"[Title/Abstract] 5. #1 AND #2 AND #3 AND #4
Scopus	1. TITLE ("Newborn" OR "Newborns" OR "Infant" OR "Infants" OR "Neonate" OR "Neonates" OR "Neonatal") 2. TITLE ("Sepsis" OR "Chorioamnionitis" OR "Funisitis" OR "Septicemia" OR "Septicemias") 3. TITLE ("Scoring" OR "Score" OR "Calculator" OR "Kaiser") 4. TITLE ("Diagnostic" OR "Diagnosis" OR "Diagnose" OR "Sensitivity" OR "Specificity" OR "Accuracy") 5. ABS ("Newborn" OR "Newborns" OR "Infant" OR "Infants" OR "Neonate" OR "Neonates" OR "Neonatal") 6. ABS ("Sepsis" OR "Chorioamnionitis" OR "Funisitis" OR "Septicemia" OR "Septicemias") 7. ABS ("Scoring" OR "Score" OR "Calculator" OR "Kaiser") 8. ABS ("Diagnostic" OR "Diagnosis" OR "Diagnose" OR "Sensitivity" OR "Specificity" OR "Accuracy") 9. (#1 AND #2 AND #3 AND #4) OR (#5 AND #6 AND #7 AND #8)
Web of Science	1. TITLE= ("Newborn" OR "Newborns" OR "Infant" OR "Infants" OR "Neonate" OR "Neonates" OR "Neonatal") 2. TITLE= ("Sepsis" OR "Chorioamnionitis" OR "Funisitis" OR "Septicemia" OR "Septicemias") 3. TITLE= ("Scoring" OR "Score" OR "Calculator" OR "Kaiser") 4. TITLE= ("Diagnostic" OR "Diagnosis" OR "Diagnose" OR "Sensitivity" OR "Specificity" OR "Accuracy") 5. ABSTRACT= ("Newborn" OR "Newborns" OR "Infant" OR "Infants" OR "Neonate" OR "Neonates" OR "Neonatal") 6. ABSTRACT= ("Sepsis" OR "Chorioamnionitis" OR "Funisitis" OR "Septicemia" OR "Septicemias") 7. ABSTRACT= ("Scoring" OR "Score" OR "Calculator" OR "Kaiser") 8. ABSTRACT= ("Diagnostic" OR "Diagnosis" OR "Diagnose" OR "Sensitivity" OR "Specificity" OR "Accuracy") 9. (#1 AND #2 AND #3 AND #4) OR (#5 AND #6 AND #7 AND #8
ProQuest	1. mesh.Exact("neonate" OR "infants, newborn") 2. noft("Newborn" OR "Newborns" OR "Infant" OR "Infants" OR "Neonate" OR "Neonates" OR "Neonatal") 3. mesh.Exact("sepsis" OR "chorioamnionitis") 4. noft("Sepsis" OR "Chorioamnionitis" OR "Funisitis" OR "Septicemia" OR "Septicemias") 5. noft("Scoring" OR "Score" OR "Calculator" OR "Kaiser") 6. noft("Diagnostic" OR "Diagnosis" OR "Diagnose" OR "Sensitivity" OR "Specificity" OR "Accuracy") 7. (#1 OR #2) AND (#3 OR #4) AND (#5) AND (#6)
Science Direct	1. (Newborn OR Infant OR Neonatal) 2. (Sepsis OR Chorioamnionitis) 3. (Score OR Calculator) 4. (Diagnostic OR Sensitivity) 5. #1 AND #2 AND #3 AND #4

Table S3. PICO framework.

Components of PICO	Definition
Population	Newborns diagnosed with early-onset sepsis
Indeks Test	Neonatal sepsis risk calculator
Comparison	Culture-proven sepsis
Outcome	Diagnostic accuracy parameters & proportion of antibiotic used

Abbreviations: PICO, Population, Indeks Test, Comparison, Outcome, and Study Design

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