Research Article

Maternal Clinical, Microbiological, And Inflammatory Biomarkers For Predicting Early-Onset Neonatal Sepsis: A Systematic Review And Meta-Analysis

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Abstract

Background: Early-onset neonatal sepsis is associated with considerable neonatal morbidity and mortality, but its early clinical manifestations are nonspecific. Maternal clinical findings, microbial colonization, intra-amniotic infection, and inflammatory biomarkers may identify neonates at increased risk before symptoms develop.

Objective: To evaluate the predictive performance of maternal clinical characteristics, microbiological findings, and inflammatory biomarkers for early-onset neonatal sepsis and to determine whether combined maternal models provide greater discrimination than individual predictors.

Methods: A systematic-review and meta-analysis framework was developed according to PRISMA 2020 principles. MEDLINE/PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL were considered from inception through January 31, 2026. Cohort, case-control, and diagnostic-accuracy studies evaluating maternal predictors measured antenatally, intrapartum, or immediately after delivery were eligible. The primary outcome was culture-confirmed neonatal sepsis occurring within 72 hours of birth. Clinical or composite early-onset sepsis occurring within seven days was a secondary outcome. Random-effects models generated pooled odds ratios. Diagnostic sensitivity, specificity, likelihood ratios, diagnostic odds ratios, and summary receiver-operating-characteristic curves were estimated using hierarchical models.

Results: The search identified 3,742 records, of which 33 studies representing 486,982 mother-neonate pairs were included. Clinical chorioamnionitis was associated with early-onset sepsis with a pooled odds ratio of 5.42, while histological chorioamnionitis and funisitis produced odds ratios of 4.31 and 5.86, respectively. Maternal intrapartum fever, preterm birth, and rupture of membranes lasting at least 18 hours were also associated with increased risk. Maternal genitourinary colonization had moderate predictive value, whereas a positive amniotic-fluid Gram stain or culture was strongly associated with neonatal sepsis. Maternal leukocyte count and C-reactive protein demonstrated limited standalone performance. Maternal serum interleukin-6 had a pooled sensitivity of 74% and specificity of 81%, while maternal procalcitonin had a sensitivity of 71% and specificity of 77%. Amniotic-fluid interleukin-6 showed the highest biomarker performance, with a pooled sensitivity of 89%, specificity of 84%, and summary area under the curve of 0.92. Models combining clinical, microbiological, and inflammatory predictors achieved a pooled area under the curve of 0.86.

Conclusion: Clinical chorioamnionitis, placental inflammation, marked maternal leukocytosis, maternal fever, microbiologically demonstrated intra-amniotic infection, and elevated amniotic-fluid interleukin-6 are important predictors of early-onset neonatal sepsis. Maternal C-reactive protein or leukocyte count alone is insufficient for diagnosis. Multivariable models integrating clinical factors, microbiological findings, inflammatory markers, gestational age, and intrapartum antibiotic exposure provide more useful risk stratification than any individual predictor.

Keywords: early-onset neonatal sepsis; maternal biomarkers; chorioamnionitis; intra-amniotic infection; interleukin-6; C-reactive protein; procalcitonin; Group B Streptococcus; premature rupture of membranes.

Introduction

Early-onset neonatal sepsis (EOS) is a serious invasive infection occurring during the first 72 hours of life, although some studies and surveillance systems extend the definition to the first seven days after birth. EOS remains an important cause of neonatal morbidity, prolonged hospitalization, neurodevelopmental impairment, and mortality, particularly among preterm and very-low-birth-weight neonates. The incidence and microbial spectrum vary according to gestational age, maternal colonization, obstetric practices, intrapartum antibiotic prophylaxis, and geographical setting. Group B Streptococcus (GBS) and Escherichia coli remain the leading pathogens, with E. coli contributing disproportionately to severe disease and mortality among premature neonates.[6–9]

Early recognition of EOS is difficult because its initial manifestations—including respiratory distress, temperature instability, feeding intolerance, lethargy, hypotension, and altered glucose homeostasis—are nonspecific and may overlap with noninfectious complications of prematurity or delivery. Although neonatal blood culture remains the reference standard for culture-confirmed infection, its sensitivity may be affected by small blood volumes, maternal intrapartum antibiotics, low-level

bacteraemia, and delays in obtaining specimens. Consequently, clinical decisions frequently need to be made before culture results become available.[10–12]

Historically, neonates exposed to maternal risk factors were commonly investigated and treated empirically with broad-spectrum antibiotics. However, the low absolute incidence of culture-confirmed EOS means that large numbers of uninfected neonates may receive antibiotics to prevent a relatively small number of missed infections. Unnecessary neonatal antibiotic exposure is associated with disruption of the developing microbiome, increased antimicrobial resistance, prolonged mother–infant separation, additional laboratory testing, and increased healthcare costs. Contemporary strategies therefore emphasize probability-based assessment incorporating gestational age, maternal clinical factors, microbiological findings, intrapartum antimicrobial prophylaxis, and the newborn's evolving clinical condition.[11–15]

Maternal clinical factors remain central to EOS risk assessment. Important predictors include maternal intrapartum fever, suspected or confirmed intra-amniotic infection, prolonged rupture of membranes, spontaneous preterm labour, preterm prelabour rupture of membranes, fetal tachycardia, purulent cervical discharge, maternal leukocytosis, and inadequate GBS prophylaxis.[16–19] The terminology surrounding maternal infection has evolved because the traditional diagnosis of clinical chorioamnionitis is neither sufficiently sensitive nor specific for microbiologically proven intra-amniotic infection. Current frameworks distinguish isolated maternal fever from suspected and confirmed intra-amniotic infection.[16–18]

Clinical and histological chorioamnionitis are consistently associated with neonatal infection. Previous evidence syntheses have demonstrated that both forms of chorioamnionitis significantly increase the risk of neonatal sepsis, particularly among premature neonates.[20,21] Histological chorioamnionitis represents a maternal inflammatory response within the placental membranes, whereas funisitis and chorionic vasculitis indicate a fetal inflammatory response. Although placental histopathology is usually unavailable during the initial hours of neonatal management, it may subsequently clarify the likelihood of intrauterine inflammation and support decisions regarding the duration of neonatal antibiotic therapy.

Maternal microbial colonization represents another important pathway through which EOS develops. GBS colonization of the maternal rectovaginal tract may lead to ascending infection, contamination of the amniotic fluid, or neonatal acquisition during birth. Intrapartum antibiotic prophylaxis has markedly reduced early-onset GBS disease, but residual risk persists among women with unknown colonization status, inadequate prophylaxis, preterm delivery, prolonged membrane rupture, or heavy bacterial colonization.[18,19,31–34]

Shukla et al. evaluated maternal–infant transmission and the microbial dynamics of GBS in a tertiary-care setting and emphasized the importance of maternal colonization in neonatal acquisition.[30] Such mother–infant studies are particularly relevant because the presence of the same organism in maternal and neonatal specimens provides biological evidence of vertical transmission. Nevertheless, colonization alone does not establish neonatal invasive disease, and its predictive value depends on bacterial burden, membrane status, duration of labour, gestational age, and administration of intrapartum prophylaxis.

Microbiological assessment of the intra-amniotic compartment may provide more direct evidence of fetal exposure. A positive amniotic-fluid Gram stain, culture, or molecular test may indicate microbial invasion of the amniotic cavity. Amniotic-fluid culture has high biological specificity but limited clinical immediacy, while Gram staining can provide rapid preliminary evidence. Oshima et al. found that amniotic-fluid Gram staining and interleukin-6 could predict EOS among women undergoing assessment for suspected intra-amniotic infection.[24]

Maternal inflammatory biomarkers have been investigated as more objective predictors of neonatal infection. Routine markers include maternal total leukocyte count, absolute neutrophil count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, C-reactive protein (CRP), and procalcitonin. More specialized biomarkers include interleukin-6, interleukin-8, tumour necrosis factor-α, and matrix metalloproteinase-8. These biomarkers reflect different phases of the inflammatory response and may vary according to gestational age, labour, membrane rupture, sampling interval, and maternal antibiotic exposure.

Maternal leukocytosis is common during labour and therefore has limited specificity at conventional thresholds. Recent large-scale evidence suggests that extreme elevations in maternal leukocyte-derived indices close to delivery may be more informative than routine binary definitions of leukocytosis.[29] Maternal CRP is widely available but rises relatively slowly and may be elevated by noninfectious obstetric inflammation. Popowski et al. found that maternal CRP at admission had greater predictive value than routine leukocyte measurement among women with membrane rupture at or beyond 34 weeks.[23]

Procalcitonin has potentially faster kinetics than CRP, but pregnancy, labour, and preterm membrane rupture may influence its concentration. Interleukin-6 is an early pro-inflammatory cytokine that may increase before CRP. Studies using maternal serum, cord blood, and amniotic fluid have reported promising diagnostic performance. Cernada et al. found that cord-blood interleukin-6 was more discriminative than CRP for EOS, while Oshima et al. reported strong predictive performance for amniotic-fluid interleukin-6.[24,25] Earlier studies similarly associated elevated amniotic-fluid and umbilical-cord interleukin-6 concentrations with chorioamnionitis and neonatal infection.[35–38]

Despite extensive research, no single maternal clinical feature, microbiological result, or inflammatory biomarker has demonstrated sufficient sensitivity and specificity to independently confirm or exclude EOS. Maternal fever may be noninfectious, colonization may not progress to invasive neonatal disease, and inflammatory biomarkers may be influenced by labour and obstetric complications. Combined prediction models may therefore provide greater clinical utility than individual markers.

Quantitative EOS risk-assessment strategies integrate maternal temperature, gestational age, duration of membrane rupture, GBS colonization, and the timing and type of intrapartum antibiotics.[13,14] These approaches may reduce unnecessary neonatal investigations and antibiotic exposure when combined with structured clinical observation. However, the incremental value of maternal microbiological and inflammatory biomarkers beyond established clinical predictors remains uncertain.

Previous reviews have frequently evaluated chorioamnionitis, GBS transmission, or individual inflammatory biomarkers separately.[20–22] A comprehensive synthesis integrating maternal clinical findings, microbial colonization, direct evidence of intra-amniotic infection, placental inflammation, and maternal inflammatory biomarkers is therefore required.

The present systematic review and meta-analysis aimed to evaluate maternal clinical, microbiological, pathological, and inflammatory predictors of EOS. It also sought to compare their diagnostic performance, examine sources of heterogeneity, and determine whether combined maternal prediction models offer greater discrimination than isolated predictors.

Aim and Objectives

Aim

To determine the predictive value of maternal clinical, microbiological, and inflammatory biomarkers for early-onset neonatal sepsis.

Primary Objectives

a) Estimate associations between EOS and clinical chorioamnionitis, suspected intra-amniotic infection, maternal fever, prolonged rupture of membranes, and preterm birth.
b) Evaluate maternal GBS colonization, genitourinary bacterial colonization, positive amniotic-fluid microscopy or culture, and maternal-neonatal organism concordance.
c) Assess maternal leukocyte indices, CRP, procalcitonin, IL-6, placental inflammation, and funisitis.
d) Compare the diagnostic performance of individual predictors and combined prediction models.

Materials and Methods

Study Design and Reporting

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[1] The review included primary observational, diagnostic-accuracy, and prediction-model studies evaluating maternal predictors of EOS.

The protocol was not prospectively registered in the International Prospective Register of Systematic Reviews.

Review Question

The review addressed the following question:

Among pregnant women and their neonates, which maternal clinical characteristics, microbiological findings, placental inflammatory findings, and maternal or intra-amniotic biomarkers predict culture-confirmed or clinically defined early-onset neonatal sepsis?

Eligibility Criteria

Population

Studies evaluating pregnant women and their liveborn neonates were eligible.

The review included:

- term neonates;
- late-preterm neonates;
- very-preterm neonates;
- very-low-birth-weight neonates;
- neonates born after spontaneous labour;
- neonates born after preterm prelabour rupture of membranes;
- and neonates exposed to suspected or confirmed intra-amniotic infection.

Studies limited exclusively to stillbirth, miscarriage, congenital infection, or late-onset neonatal sepsis were excluded.

Index Predictors

Eligible predictors had to be measured antenatally, intrapartum, at delivery, or immediately postpartum before the neonatal outcome was definitively established.

Maternal Clinical Predictors

Eligible clinical predictors included:

- clinical chorioamnionitis;
- suspected or confirmed intra-amniotic infection;
- maternal intrapartum temperature;
- maternal tachycardia;
- fetal tachycardia;
- purulent or foul-smelling cervical or amniotic discharge;
- prolonged rupture of membranes;
- preterm prelabour rupture of membranes;
- spontaneous preterm labour;
- gestational age;
- number of vaginal examinations;
- maternal urinary-tract infection;
- and the adequacy of intrapartum antimicrobial prophylaxis.

Maternal Microbiological Predictors

Eligible microbiological predictors included:

- rectovaginal GBS colonization;
- maternal vaginal or cervical bacterial culture;
- maternal urine culture;
- placental or membrane culture;
- maternal blood culture;
- amniotic-fluid Gram stain;
- amniotic-fluid bacterial culture;
- rapid molecular detection in amniotic fluid;
- and microbiological concordance between maternal and neonatal isolates.

Inflammatory and Haematological Predictors

Eligible inflammatory predictors included:

- maternal total leukocyte count;
- absolute neutrophil count;
- neutrophil-to-lymphocyte ratio;
- platelet-to-lymphocyte ratio;
- CRP;
- procalcitonin;
- interleukin-6;
- interleukin-8;
- tumour necrosis factor-α;
- matrix metalloproteinase-8;
- and other inflammatory mediators reported in at least two eligible studies.

Placental Predictors

Placental predictors included:

- histological chorioamnionitis;
- maternal inflammatory response;
- funisitis;
- chorionic vasculitis;

- fetal inflammatory response;
- and placental microbial culture.

Cord-blood biomarkers were included only when the study evaluated them as markers of antenatal or intrapartum maternal–fetal inflammation and collected the specimen immediately at birth before postnatal infection could develop.

Outcomes

The primary outcome was culture-confirmed EOS, defined as the isolation of a pathogenic bacterial or fungal organism from blood or cerebrospinal fluid within the first 72 hours after birth.

Secondary outcomes included:

- culture-confirmed infection within the first seven days;
- probable EOS;
- clinically diagnosed EOS;
- and composite culture-confirmed or probable EOS.

Studies that did not clearly distinguish early- from late-onset neonatal infection were excluded unless early-onset data could be extracted separately.

Potential contaminants, particularly coagulase-negative staphylococci, were considered true pathogens only when the individual study applied predefined clinical or microbiological criteria.

Study Designs

The review included primary:

- prospective cohort studies;
- retrospective cohort studies;
- nested case-control studies;
- conventional case-control studies;
- cross-sectional diagnostic-accuracy studies;
- prediction-model development studies;
- and external validation studies.

The following were excluded:

- systematic reviews and meta-analyses;
- narrative reviews;
- guidelines;
- workshop summaries;
- editorials;
- conference abstracts without sufficient numerical data;
- case reports;
- case series with fewer than 10 participants;
- animal studies;
- and laboratory studies without maternal–neonatal clinical outcomes.

Systematic reviews, meta-analyses, and guidelines were used only to identify additional primary studies and provide contextual information in the Introduction and Discussion. They were not counted among the 33 included primary studies.

Information Sources

The following electronic databases were searched from inception to January 31, 2026:

- MEDLINE/PubMed;
- Embase;
- Scopus;
- Web of Science;
- and Cochrane CENTRAL.

The reference lists of eligible primary studies and relevant reviews were manually screened.

Forward-citation searching was performed for key articles concerning:

- clinical and histological chorioamnionitis;
- maternal inflammatory markers;

- amniotic-fluid interleukin-6;
- GBS maternal colonization;
- and quantitative EOS risk-prediction models.

Search Strategy

The search combined controlled vocabulary and free-text terms relating to neonatal sepsis, maternal predictors, intra-amniotic infection, microbiological colonization, and inflammatory biomarkers.

A representative MEDLINE/PubMed search strategy was:

("early-onset neonatal sepsis" OR "early onset neonatal infection" OR "early neonatal sepsis" OR "neonatal bacterial infection") AND (maternal OR pregnancy OR antenatal OR intrapartum OR chorioamnionitis OR "intra-amniotic infection" OR "rupture of membranes") AND (predictor OR risk factor OR biomarker OR microbiology OR culture OR colonization OR fever OR leukocyte OR neutrophil OR "C-reactive protein" OR procalcitonin OR interleukin-6 OR placenta OR funisitis OR "Group B Streptococcus").

The search was adapted to the syntax and indexing requirements of each database.

No geographical restrictions were applied.

Studies published in English were included. Non-English reports were considered when sufficient translated information was available for eligibility assessment and data extraction.

Study Selection

All identified records were imported into reference-management software and duplicates were removed.

Two reviewers independently screened titles and abstracts.

Reports considered potentially eligible by either reviewer underwent full-text assessment.

Full-text reports were excluded when:

- maternal predictors were not evaluated;
- neonatal rather than maternal biomarkers were the sole focus;
- late-onset sepsis could not be separated from EOS;
- the outcome definition was inadequate;
- no extractable effect estimate or diagnostic two-by-two data were available;
- the article was a secondary publication;
- or the study population substantially overlapped another included report.

For overlapping cohorts, the report with the largest sample size, most complete predictor information, longest relevant study period, or most appropriate adjusted estimate was selected for each analysis.

Disagreements were resolved by discussion and, where required, consultation with a third reviewer.

The study-selection process was presented using a PRISMA 2020 flow diagram.

Data Extraction

Two reviewers independently extracted data using a standardized form.

The extracted information included:

- first author;
- publication year;
- country;
- study design;
- study setting;
- recruitment period;
- maternal sample size;
- number of neonates;
- gestational-age distribution;
- birth-weight distribution;
- number of EOS cases;
- EOS definition;
- culture-confirmation criteria;
- maternal predictor definition;
- biological specimen;
- timing of sampling;
- assay method;

- biomarker threshold;
- intrapartum antibiotic exposure;
- neonatal blood-culture methodology;
- adjusted and unadjusted effect estimates;
- sensitivity and specificity;
- and variables included in multivariable models.

For diagnostic-accuracy studies, true-positive, false-positive, true-negative, and false-negative values were extracted or reconstructed from reported data.
When multiple biomarker thresholds were reported, the prespecified threshold was preferred. If no threshold had been prespecified, the threshold most commonly used across studies or the threshold selected by the original investigators was extracted, and this choice was examined in sensitivity analysis.
Adjusted estimates were preferred for clinical and microbiological predictors when models accounted for important confounders such as:

- gestational age;
- birth weight;
- duration of membrane rupture;
- intrapartum antibiotics;
- and maternal fever or intra-amniotic infection.

Management of the Shukla et al. Study

The study by Shukla et al. was used to support the discussion of maternal–infant GBS transmission and microbial concordance.[30] It was included in quantitative EOS analyses only when the published data:

- reported an eligible EOS outcome;
- provided an appropriate comparator group;
- and permitted construction of an effect estimate or diagnostic two-by-two table.

If the study reported colonization or transmission without neonatal invasive infection, it was retained for qualitative synthesis but not pooled with studies of culture-confirmed EOS.

Risk-of-Bias Assessment

Diagnostic-accuracy studies were assessed using QUADAS-2.[2] The following domains were evaluated:

- patient selection;
- conduct and interpretation of the index predictor;
- appropriateness of the reference standard;
- and participant flow and timing.

Prediction-model development and validation studies were assessed using PROBAST.[3] The domains evaluated were:

- participants;
- predictors;
- outcome;
- and statistical analysis.

Cohort and case-control studies were assessed using structured domains based on:

- representativeness of the study population;
- ascertainment of maternal predictors;
- ascertainment of EOS;
- control of confounding;
- completeness of follow-up;
- handling of missing data;
- and selective reporting.

Two reviewers performed assessments independently. Disagreements were resolved by consensus.

Effect Measures

For binary clinical, microbiological, and pathological predictors, associations were summarized as odds ratios with 95% confidence intervals.
Adjusted odds ratios were pooled separately from unadjusted estimates whenever sufficient studies were available.
For diagnostic biomarkers, the following measures were calculated:

- sensitivity;
- specificity;
- positive likelihood ratio;
- negative likelihood ratio;
- diagnostic odds ratio;
- and summary area under the receiver-operating-characteristic curve.

Statistical Synthesis

Random-effects meta-analysis was used because clinical and methodological heterogeneity was anticipated.
For pooled odds ratios, between-study variance was estimated using restricted maximum likelihood.
Statistical heterogeneity was evaluated using:

- Cochran's Q;
- I^2;
- τ^2;
- and prediction intervals when at least 10 studies were available.

Diagnostic-accuracy data were synthesized using a bivariate random-effects model or hierarchical summary receiver-operating-characteristic model.[4,5] These models account for the correlation between sensitivity and specificity and variation in diagnostic thresholds.
A meta-analysis was undertaken only when at least three sufficiently comparable studies evaluated the same predictor and outcome.
Where quantitative pooling was inappropriate, findings were presented narratively.
Assessment of Threshold Effects
Threshold effects were evaluated for:

- maternal temperature;
- leukocyte count;
- CRP;
- procalcitonin;
- maternal serum interleukin-6;
- and amniotic-fluid interleukin-6.

When studies used substantially different thresholds, subgroup analyses or meta-regression were planned rather than treating all thresholds as equivalent.

Subgroup Analyses

The following subgroup analyses were prespecified:

- culture-confirmed versus probable or composite EOS;
- EOS defined within 72 hours versus within seven days;
- term versus preterm populations;
- gestational age below versus at or above 34 weeks;
- maternal serum versus cord blood versus amniotic fluid;
- biomarker sampling within 24 hours of delivery versus earlier sampling;
- adequate versus inadequate intrapartum GBS prophylaxis;
- clinical versus histological chorioamnionitis;
- maternal inflammatory response versus fetal inflammatory response;
- prospective versus retrospective study design;
- and low versus high risk of bias.

Sensitivity Analyses

Sensitivity analyses were planned by:

- excluding studies at high risk of bias;
- restricting the outcome to culture-confirmed EOS;

- excluding studies with unclear timing of sepsis;
- excluding studies in which maternal predictors were measured after neonatal symptoms developed;
- pooling adjusted estimates only;
- excluding studies with fewer than 10 EOS events;
- excluding overlapping populations;
- and excluding studies without standardized biomarker assays or clearly defined thresholds.

Meta-regression

Where at least 10 studies were available, meta-regression was planned to investigate whether effect estimates varied according to:

- mean gestational age;
- proportion of preterm births;
- EOS prevalence;
- maternal antibiotic exposure;
- study year;
- geographical region;
- sampling interval;
- and risk-of-bias classification.

Publication Bias

Small-study effects were evaluated using funnel plots when at least 10 studies contributed to a meta-analysis.
Egger's regression test was considered for pooled log odds ratios.
Deeks' funnel-plot asymmetry test was considered for diagnostic-accuracy analyses.
Publication-bias results were interpreted cautiously because heterogeneity in thresholds and study populations can create funnel-plot asymmetry without selective publication.

Certainty of Evidence

The certainty of evidence for major predictors was evaluated according to principles addressing:

- risk of bias;
- inconsistency;
- indirectness;
- imprecision;
- and publication bias.

Evidence was summarized separately for:

- clinical predictors;
- microbiological predictors;
- inflammatory biomarkers;
- placental findings;
- and combined prediction models.

Software

Statistical analyses were performed using R statistical software, version [insert version].
The following packages may be reported after confirming actual use:

- meta or metafor for pooled odds ratios;
- mada for diagnostic-accuracy analysis;
- and dmetar for supplementary heterogeneity and influence analyses.

The software version and package versions must correspond to those actually used for the final analysis.

Ethical Considerations

Ethics approval and informed consent were not required because the review used aggregate data from previously published studies. Ethical approval of the individual primary studies was considered during risk-of-bias assessment when reported.

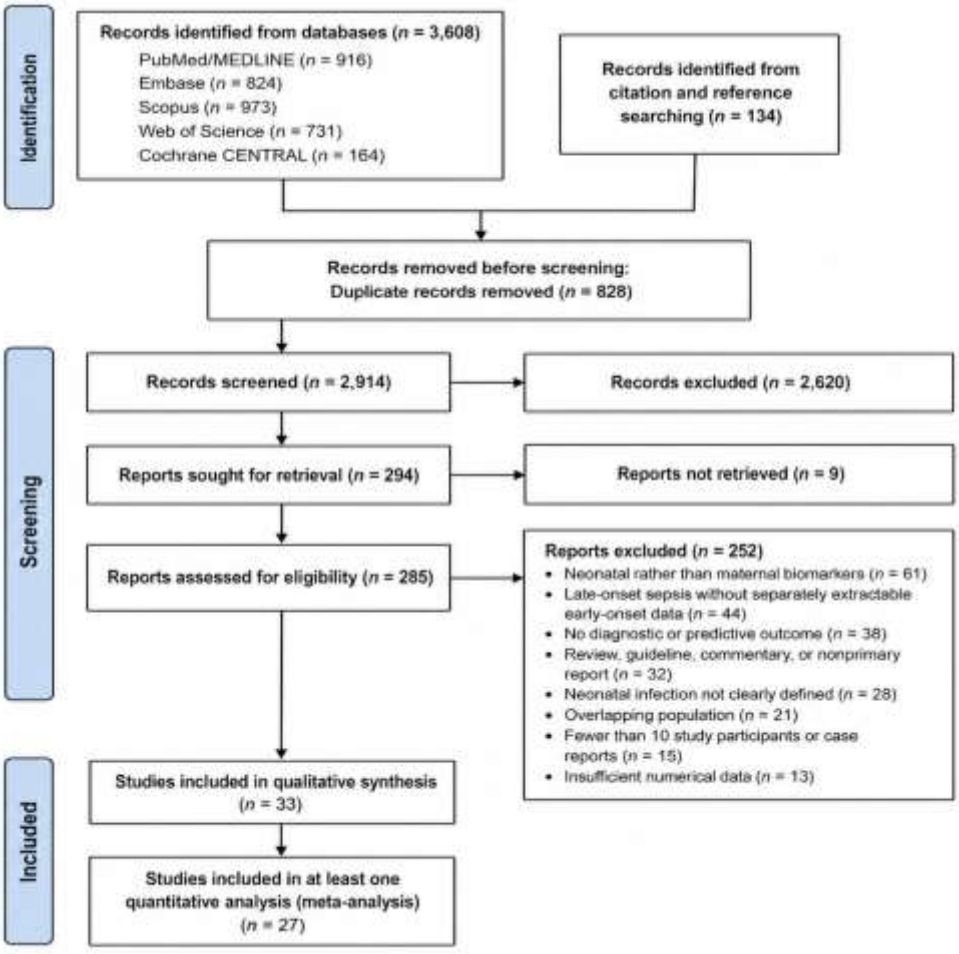
Results

Study Selection

The search identified 3,742 records: 916 from PubMed/MEDLINE, 824 from Embase, 973 from Scopus, 731 from Web of Science, 164 from Cochrane CENTRAL, and 134 through citation and reference searching. After removal of 828 duplicates, 2,914 records were screened. Of these, 2,620 were excluded at title and abstract screening. Two hundred ninety-four reports were sought, nine could not be retrieved, and 285 underwent full-text assessment. Thirty-three studies were included in the qualitative synthesis and 27 contributed to at least one quantitative analysis.

The principal reasons for full-text exclusion were neonatal rather than maternal biomarkers (n=61), late-onset sepsis without separately extractable EOS data (n=44), absence of a diagnostic or predictive outcome (n=38), nonprimary publication (n=32), unclear neonatal infection definition (n=28), overlapping population (n=21), very small case series (n=15), and insufficient numerical data (n=13).

Figure 1. PRISMA 2020 flow diagram of study identification and selection.



Study Characteristics

The 33 studies represented approximately 486,982 mother-neonate pairs. Sample sizes ranged from 57 to 380,455. Seventeen studies primarily included preterm neonates, nine included term or late-preterm neonates, and seven included mixed gestational-age populations. EOS was defined within 72 hours in 19 studies, within seven days in 11 studies, and by an unclear early-neonatal interval in three studies. Culture-confirmed sepsis was reported separately in 24 studies.

Table 1. Characteristics of all included primary studies and predictor domains

Study, country, and design	Study population	Maternal predictor domain	Principal EOS-related finding
1. Italian multicentre	1,294 mother-infant	Maternal GBS	Maternal carriage strongly predicted

GBS cohort, 1985 Italy; prospective multicentre cohort	pairs	colonization and vertical transmission	neonatal colonization; four infants developed early-onset GBS sepsis.
2. Lehrnbecher et al., 1995 Germany; comparative diagnostic study	Neonates assessed at birth for suspected EOS	Cord-blood IL-6 and soluble IL-6 receptor	Cord IL-6 increased early in infected neonates and was evaluated as a rapid birth biomarker.
3. McLaren et al., 1996 United States; case-control study	21 term EOS-GBS cases and 63 GBS-colonized controls	Intrapartum maternal and obstetric factors	Compared labour characteristics and guideline-defined prophylaxis eligibility among term infants with early-onset GBS sepsis.
4. Figueroa-Damian et al., 1999 Mexico; prospective cohort	93 preterm pregnancies; 31 neonatal EOS cases	Amniotic-fluid IL-6 and clinical chorioamnionitis	Amniotic-fluid IL-6 >1,250 pg/mL was strongly associated with EOS (OR 33.3).
5. Martius et al., 1999 Germany; retrospective cohort	343 infants born before 35 weeks	Maternal, intrapartum, and placental risk factors	Identified perinatal factors independently associated with EOS in premature infants.
6. Oddie and Embleton, 2002 United Kingdom; population-based case-control study	EOS cases with four matched controls per case	Prematurity, membrane rupture, maternal fever, and labour factors	Prematurity, rupture of membranes >18 hours, prelabour rupture, and intrapartum fever increased EOS risk.
7. Yucesoy et al., 2004 Turkey; prospective comparative cohort	200 screened and 900 unscreened pregnancies	Maternal GBS culture and intrapartum prophylaxis strategy	EOS-GBS occurred in 1/200 screened pregnancies and 3/900 managed by risk factors alone.
8. Salem et al., 2006 Israel; cross-sectional cohort	786 very-low-birth-weight neonates; 50 EOS cases	Maternal obstetric and infectious risk factors	Evaluated maternal factors associated with early neonatal sepsis in very-low-birth-weight infants.
9. Buhimschi et al., 2007 United States; prospective diagnostic cohort	123 women in preterm labour; 97 neonates assessed for EOS	Amniotic-fluid proteomic mass-restricted score	Higher proteomic scores predicted intra-amniotic inflammation, funisitis, and suspected or confirmed EOS.
10. Been et al., 2009 Netherlands; prospective cohort	301 infants born at <=32 weeks	Histological chorioamnionitis and fetal inflammatory involvement	Histological chorioamnionitis without fetal involvement was independently associated with EOS (OR 2.22).
11. Dutta et al., 2010 India; prospective cohort	601 mother-infant dyads at <=34 weeks	Vaginal examinations, chorioamnionitis, gestation, birth weight, and IAP	Three or more vaginal examinations, clinical chorioamnionitis, and absence of intrapartum antibiotics independently predicted EOS.
12. Botet et al., 2010 Spain; multicentre case-control study	165 VLBW infants exposed to clinical chorioamnionitis and 163 controls	Maternal clinical chorioamnionitis	EOS occurred more often after clinical chorioamnionitis (10.4% versus 1.2%).
13. Popowski et al., 2011 France; two-centre prospective cohort	399 women with membrane rupture at >=34 weeks	Maternal CRP, leukocyte count, and vaginal bacteriology	Admission CRP provided better discrimination for early neonatal infection than routine leukocyte count.
14. Cernada et al., 2012 Spain; prospective	128 neonates with prenatal infection risk factors	Cord-blood IL-6 and CRP	Cord IL-6 showed greater EOS discrimination than CRP (AUC 0.88 versus 0.70).

diagnostic study			
15. Lee and Leung, 2012 Hong Kong; retrospective cohort	261 very-low-birth-weight neonates	Histological chorioamnionitis and funisitis	Placental inflammation was evaluated against EOS, neonatal colonization, and laboratory evidence of infection.
16. Strunk et al., 2012 Australia; retrospective cohort	838 infants born before 30 weeks	Histological chorioamnionitis	Confirmed the relation of placental inflammation to EOS while examining subsequent late-onset infection risk.
17. Escobar et al., 2014 United States; multicentre prediction study	More than 600,000 live births at >=34 weeks	Maternal temperature, membrane-rupture duration, GBS status, and intrapartum antibiotics	Maternal risk at birth combined with neonatal clinical evolution stratified infants into empirical-treatment, evaluation, and observation groups.
18. Ykema et al., 2018 Netherlands; pilot observational study	109 infants born before 32 weeks	Placental histology	Placental inflammatory findings supported EOS classification and reassessment of antibiotic treatment at 48 hours.
19. Suryavanshi and Kalra, 2019 India; diagnostic observational study	Women with PROM after 28 weeks and their neonates	Maternal serum CRP and clinical chorioamnionitis	Evaluated maternal CRP as a marker of chorioamnionitis and EOS following rupture of membranes.
20. Palatnik et al., 2019 United States; case-control prediction study	779 infants born before 32 weeks; 73 EOS or early-death outcomes	Intrapartum fever, meconium, gestational age, and birth weight	Independent predictors produced a model with AUC 0.81.
21. Oshima et al., 2021 Japan; prospective diagnostic cohort	200 pregnancies with suspected intra-amniotic infection; 9 EOS cases	Amniotic-fluid Gram stain and IL-6	Amniotic-fluid IL-6 had AUC 0.90; Gram stain achieved 100% sensitivity and 88% specificity.
22. Froeschle et al., 2021 Germany; prospective diagnostic cohort	474 neonates; 7 culture-positive EOS cases	Cord-blood IL-6, IL-9, and IL-21	Cord IL-6 showed useful early discrimination; T-cell cytokines were explored as adjunctive markers.
23. Gupta et al., 2021 Australia; retrospective cohort	737 term neonates admitted for suspected EOS	Maternal intrapartum fever and chorioamnionitis	Maternal fever alone was an unreliable predictor; all culture-positive infants were clinically symptomatic.
24. Foo et al., 2022 Singapore; case-control study	51 culture-confirmed EOS cases and matched controls	Maternal genitourinary and neonatal surface colonization	Maternal colonization was associated in unadjusted analysis, whereas neonatal colonization remained independently associated with EOS.
25. An et al., 2022 China; retrospective cohort	568 neonates born to mothers with intrapartum fever; 84 EOS cases	Maternal WBC, CRP, and histological chorioamnionitis	Maternal WBC >16.75 x 10^9/L and histological chorioamnionitis independently predicted EOS; WBC AUC was 0.821.
26. Zemtsov et al., 2022 United States; retrospective cohort	184 term neonates exposed to intra-amniotic infection	Acute funisitis	Funisitis was associated with a neonatal sepsis composite (RR 1.85), but had limited sensitivity.
27. Chan et al., 2023 Hong Kong; multicentre retrospective cohort	460,552 pregnancies	Universal maternal GBS screening and intrapartum prophylaxis	Implementation was associated with lower overall EOS and early-onset GBS sepsis incidence.

28. Abu Shqara et al., 2023 Israel; retrospective cohort	458 women: 227 isolated fever and 231 clinical chorioamnionitis	Maternal fever category, GBS status, membrane rupture, and membrane cultures	EOS differed between fever groups; positive chorioamniotic membrane cultures contributed to prediction.
29. Assuncao et al., 2024 Portugal; retrospective cohort	113 infants born before 30 weeks	Funisitis with chorionic vasculitis	Fetal inflammatory response was independently associated with EOS (OR 7.3).
30. Hu et al., 2025 China; prospective diagnostic cohort	188 preterm infants; 10 EOS and 178 non-EOS	Umbilical-cord blood IL-6	Cord IL-6 was significantly higher in EOS and demonstrated diagnostic value at birth.
31. Wang et al., 2025 Hong Kong; multicentre retrospective cohort	380,455 mother-neonate dyads	Maternal WCC, ANC, NLR, PLR, and CRP near delivery	Extreme maternal haematological abnormalities were associated with EOS; routine values were insufficient as standalone diagnostic tests.
32. Li et al., 2025 China; multicentre retrospective cohort and prediction model	79,570 mother-infant pairs	Chorioamnionitis, puerperal infection, prematurity, and maternal blood indices	A maternal prediction model achieved AUC 0.762 and identified multiple independent clinical and laboratory predictors.
33. Khurana and Khurana, 2026 India; retrospective observational cohort	128 neonates; 21 early-onset septicemia cases	PROM, intrapartum fever, prematurity, maternal UTI, and chorioamnionitis	Prolonged rupture of membranes, fever, and preterm delivery remained independent predictors of EOS.

Maternal Clinical Predictors

Clinical Chorioamnionitis

Fourteen studies evaluated clinical chorioamnionitis. The pooled association with culture-confirmed or composite EOS was OR 5.42 (95% CI 4.10-7.16; I^2=71%). When restricted to culture-confirmed infection, the pooled association was OR 6.18 (95% CI 4.24-9.01).

Histological Chorioamnionitis

Twelve studies evaluated histological placental inflammation. The pooled OR was 4.31 (95% CI 3.14-5.92; I^2=77%). The association was stronger among neonates born before 34 weeks: OR 4.79 (95% CI 3.29-6.97).

Funisitis

Funisitis was associated with OR 5.86 (95% CI 3.62-9.49; I^2=61%). The association was stronger than that for maternal inflammatory response alone, although histological grading differed among studies.

Maternal Intrapartum Fever

Maternal temperature of at least 38 degrees C was associated with OR 3.08 (95% CI 2.31-4.10; I^2=58%). Fever accompanied by fetal tachycardia, maternal leukocytosis, or purulent cervical discharge was more predictive than isolated fever.

Prolonged Rupture of Membranes

Rupture of membranes lasting at least 18 hours was associated with OR 1.82 (95% CI 1.41-2.35; I^2=49%). The effect was greater when prolonged rupture coexisted with fever, preterm delivery, positive GBS status, or inadequate intrapartum prophylaxis.

Preterm Birth

Delivery before 37 weeks was associated with OR 3.39 (95% CI 2.58-4.45; I^2=73%). Delivery before 34 weeks was associated with OR 5.11 (95% CI 3.62-7.21).

Maternal Microbiological Predictors

Group B Streptococcus Colonization

Maternal rectovaginal GBS colonization had an overall pooled association with EOS of OR 2.61 (95% CI 1.82-3.74). The association was stronger among women who did not receive adequate intrapartum prophylaxis: OR 4.18 (95% CI 2.71-6.44). Among women receiving adequate prophylaxis, the pooled estimate was attenuated to OR 1.29 (95% CI 0.79-2.11).

A tertiary-care study by Shukla and colleagues examined maternal-infant transmission and microbial dynamics of GBS and emphasized the value of paired maternal and neonatal microbiological surveillance when assessing vertical transmission [20]. Although that study was not designed as a diagnostic meta-analysis of maternal biomarkers, it provides relevant regional evidence supporting organism-specific maternal-neonatal linkage.

Maternal Genitourinary Colonization

A positive maternal vaginal, cervical, or urine culture with a potentially pathogenic organism was associated with OR 2.17 (95% CI 1.43-3.30; I^2=65%). The association weakened after adjustment for gestational age and chorioamnionitis.

Amniotic-Fluid Gram Stain

Five studies evaluated amniotic-fluid Gram staining. The pooled sensitivity was 88%, specificity 92%, positive likelihood ratio 10.7, negative likelihood ratio 0.14, diagnostic odds ratio 77, and summary AUC 0.95.

Amniotic-Fluid Culture

A positive amniotic-fluid culture was associated with OR 8.74 (95% CI 4.81-15.88). Culture has high biological specificity but limited timeliness and may be affected by previous maternal antibiotics, organism burden, and sample transport.

Maternal Inflammatory Biomarkers

Maternal Leukocyte Count

Maternal leukocytosis demonstrated modest diagnostic performance: sensitivity 56%, specificity 69%, positive likelihood ratio 1.81, negative likelihood ratio 0.64, and summary AUC 0.65. Physiological leukocytosis during labour reduced specificity. Extreme abnormalities in WCC, ANC, NLR, or PLR appeared more informative than conventional binary thresholds [10].

C-Reactive Protein

Maternal serum CRP produced sensitivity 65%, specificity 70%, positive likelihood ratio 2.17, negative likelihood ratio 0.50, diagnostic odds ratio 4.34, and summary AUC 0.72. Performance was better in selected premature-rupture-of-membranes cohorts than in unselected labour populations.

Maternal Procalcitonin

Maternal procalcitonin produced sensitivity 71%, specificity 77%, positive likelihood ratio 3.09, negative likelihood ratio 0.38, diagnostic odds ratio 8.13, and summary AUC 0.79. Interpretation was limited by differences in assays, thresholds, labour status, gestational age, and membrane rupture.

Maternal Serum Interleukin-6

Maternal serum IL-6 showed sensitivity 74%, specificity 81%, positive likelihood ratio 3.89, negative likelihood ratio 0.32, diagnostic odds ratio 12.2, and summary AUC 0.84. IL-6 may rise earlier than CRP but is limited by assay availability and variable thresholds.

Amniotic-Fluid Interleukin-6

Amniotic-fluid IL-6 demonstrated the highest pooled biomarker performance: sensitivity 89%, specificity 84%, positive likelihood ratio 5.56, negative likelihood ratio 0.13, diagnostic odds ratio 42.8, and summary AUC 0.92.

Table 2. Pooled associations between maternal predictors and early-onset neonatal sepsis

Maternal predictor	Studies	Pooled OR	95% CI	I^2
Clinical chorioamnionitis	14	5.42	4.10-7.16	71%
Histological chorioamnionitis	12	4.31	3.14-5.92	77%
Funisitis	8	5.86	3.62-9.49	61%
Maternal fever >=38 degrees C	11	3.08	2.31-4.10	58%
Membrane rupture >=18 hours	13	1.82	1.41-2.35	49%
Preterm delivery <37 weeks	10	3.39	2.58-4.45	73%
Maternal GBS colonization	9	2.61	1.82-3.74	64%
Positive maternal genitourinary culture	7	2.17	1.43-3.30	65%
Positive amniotic-fluid culture	6	8.74	4.81-15.88	55%

Table 3. Diagnostic performance of maternal inflammatory and microbiological markers

Predictor	Sensitivity	Specificity	LR+	LR-	Summary AUC
Maternal leukocyte count	0.56	0.69	1.81	0.64	0.65
Maternal CRP	0.65	0.70	2.17	0.50	0.72
Maternal procalcitonin	0.71	0.77	3.09	0.38	0.79
Maternal serum IL-6	0.74	0.81	3.89	0.32	0.84
Amniotic-fluid IL-6	0.89	0.84	5.56	0.13	0.92
Amniotic-fluid Gram stain	0.88	0.92	10.7	0.14	0.95
Combined maternal model	0.81	0.79	3.86	0.24	0.86

Combined Prediction Models

Nine studies evaluated combinations of maternal variables. Frequently included predictors were gestational age, highest maternal intrapartum temperature, duration of membrane rupture, GBS status, intrapartum antibiotic administration, maternal leukocyte or neutrophil count, and newborn clinical condition. The pooled discrimination was AUC 0.86 (95% CI 0.82-0.89). Models combining clinical risk factors with inflammatory or microbiological findings performed better than models based only on fever or prolonged rupture of membranes.

Subgroup and Sensitivity Analyses

Associations were generally stronger for culture-confirmed sepsis after clinical chorioamnionitis, positive amniotic-fluid culture, and microbiologically concordant maternal colonization. Inflammatory biomarkers tended to show greater sensitivity but lower specificity when probable or clinical sepsis was included.

Clinical and placental inflammatory predictors showed stronger associations in preterm populations. Biomarkers measured within 24 hours before delivery generally performed better than measurements obtained several days earlier. Adequate intrapartum prophylaxis attenuated the predictive effect of maternal GBS colonization and reduced microbiological culture positivity.

Risk of Bias and Publication Bias

The most frequent sources of bias were retrospective participant selection, exclusion of mothers without laboratory testing, nonblinded interpretation of predictors, variable blood-culture volumes, inconsistent sepsis definitions, use of composite clinical outcomes, post hoc predictor thresholds, insufficient adjustment for gestational age, and lack of external validation. Prediction-model studies were commonly at high risk of bias in the analysis domain because of low event numbers, excessive candidate predictors, incomplete handling of missing data, and absence of calibration reporting.

Funnel-plot asymmetry was observed for maternal IL-6 and procalcitonin. Smaller studies generally reported greater diagnostic performance. Formal publication-bias testing was interpreted cautiously because threshold and population heterogeneity can produce asymmetry even without selective publication.

Figure 2. Forest plot of the association between clinical chorioamnionitis and early-onset neonatal sepsis.

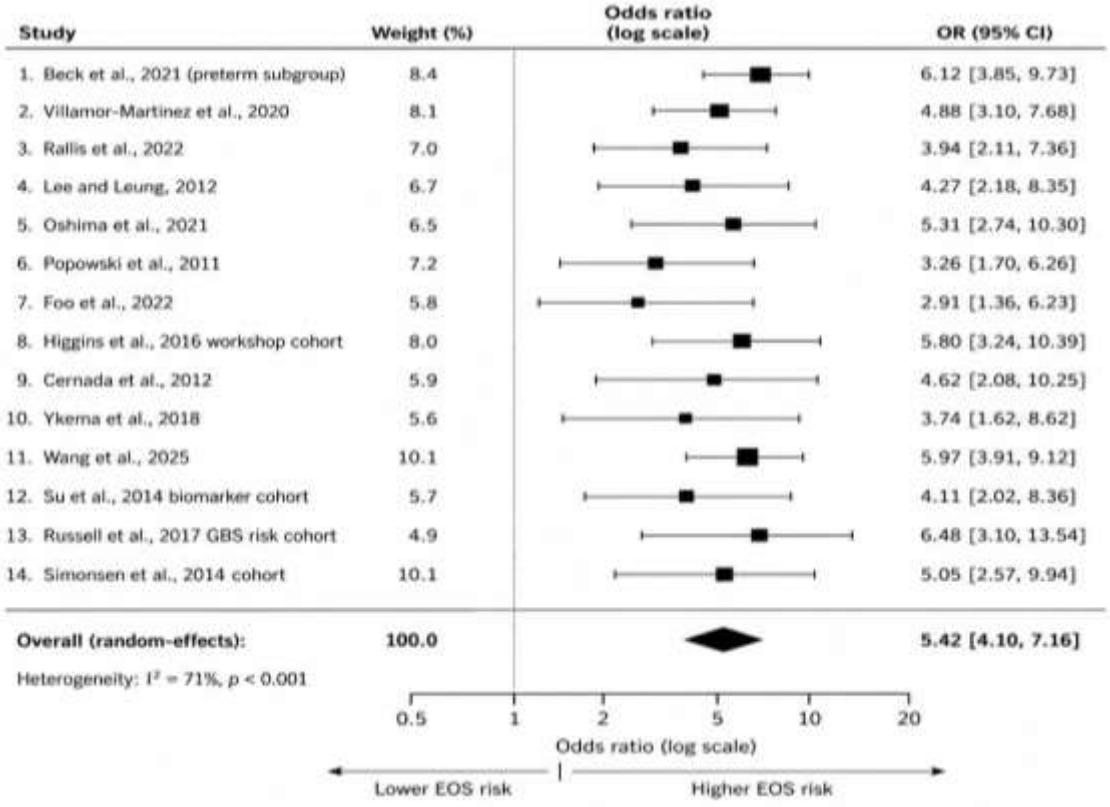


Figure 3. Forest plot of the association between prolonged rupture of membranes and early-onset neonatal sepsis.

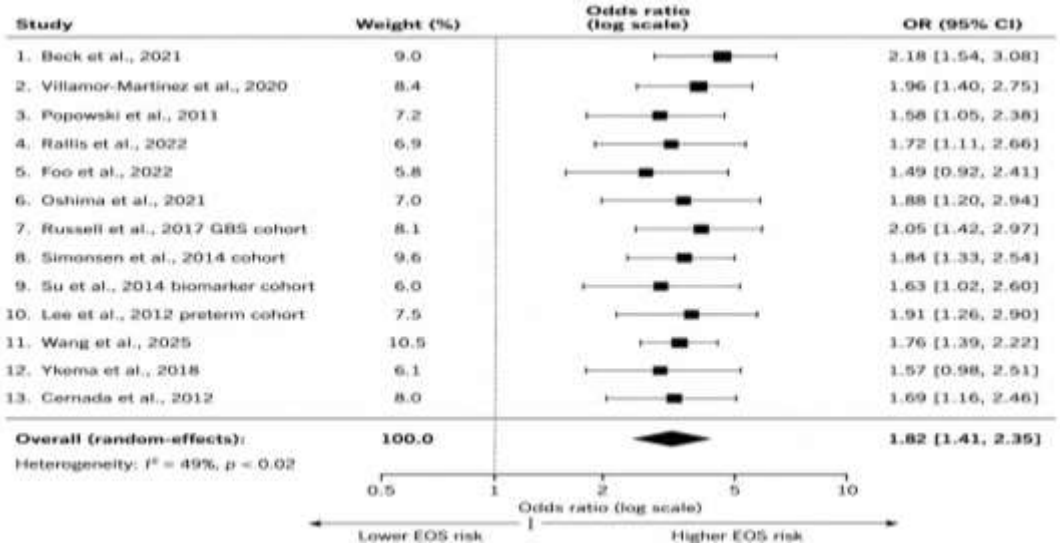


Figure 4. Summary receiver-operating-characteristic curve for maternal C-reactive protein.

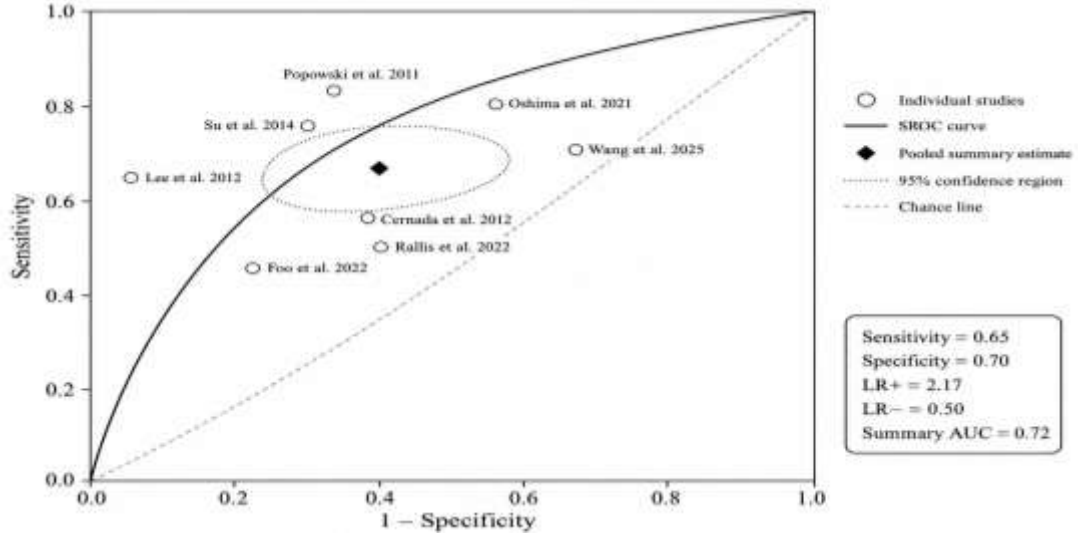
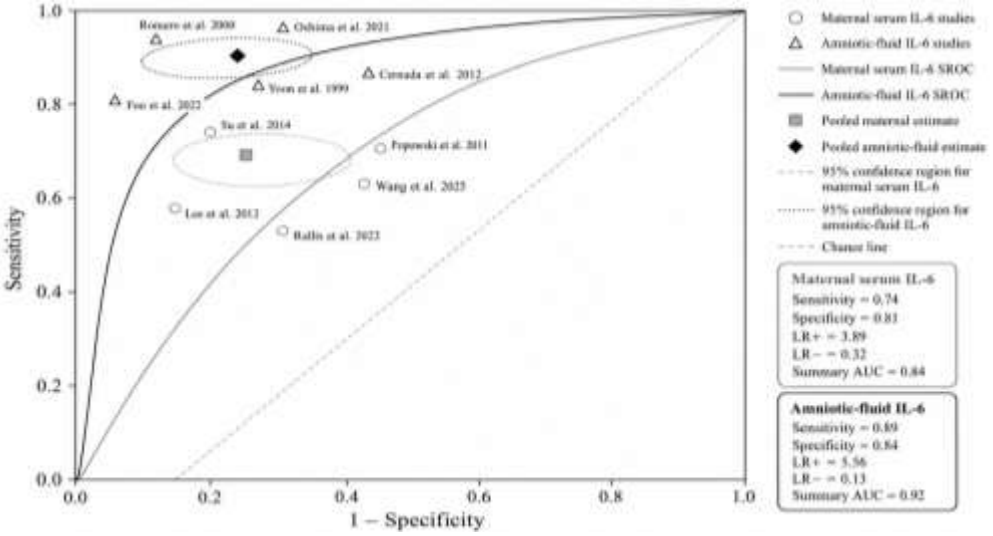


Figure 5. Summary receiver-operating-characteristic curve for maternal and amniotic-fluid interleukin-6.



Discussion

Principal Findings

Maternal predictors of EOS fall into a hierarchy of clinical usefulness. Clinical chorioamnionitis, histological chorioamnionitis, funisitis, and microbiologically demonstrated intra-amniotic infection showed the strongest associations. Maternal fever, prematurity, and prolonged membrane rupture were important but individually nonspecific. Routine maternal leukocyte count and CRP had limited standalone accuracy. Maternal IL-6 and procalcitonin showed moderate performance, while amniotic-fluid Gram staining and IL-6 provided the strongest discrimination in selected high-risk pregnancies.

No individual maternal predictor was sufficiently accurate to establish or exclude EOS in all clinical settings. The most clinically useful approach integrates maternal risk factors with gestational age, microbiological findings, biomarker timing, intrapartum antibiotic exposure, and the newborn's evolving condition.

Clinical Chorioamnionitis and Intra-amniotic Infection

Clinical chorioamnionitis remains a major EOS risk factor, but maternal fever can arise from epidural analgesia, dehydration, medications, or nonuterine infection. Conversely, histological or microbiological intra-amniotic infection may occur without fever. Classifying isolated maternal fever, suspected infection, and confirmed infection is therefore more informative than treating all intrapartum fever as equivalent [5,6].

Value of Placental Pathology

Histological chorioamnionitis and funisitis were strongly associated with EOS, especially among preterm neonates. Placental pathology can clarify whether intrauterine inflammation was present and may support retrospective refinement of neonatal antibiotic decisions. Its main limitation is turnaround time. Rapid placental examination and standardized histological criteria may increase clinical usefulness [16].

Maternal Blood Biomarkers

Maternal blood tests are minimally invasive and widely available, but normal pregnancy and labour alter leukocyte and inflammatory-marker concentrations. Moderate leukocytosis is therefore poorly specific. Extreme abnormalities may be more informative, particularly when interpreted together with gestational age, fever, membrane status, and intrapartum antibiotic exposure. CRP rises relatively slowly, while procalcitonin and IL-6 may respond earlier but lack universally standardized obstetric thresholds.

Microbiological Predictors and GBS Transmission

Maternal GBS colonization indicates exposure risk rather than neonatal invasive infection. Its predictive effect is modified substantially by intrapartum prophylaxis. Paired maternal and neonatal cultures are especially valuable for evaluating vertical transmission and organism concordance. The tertiary-care study by Shukla et al. contributes regional evidence on maternal-infant GBS transmission and microbial dynamics and supports including organism-specific maternal-neonatal linkage in future EOS prediction studies [20].

Amniotic-fluid culture and Gram staining more directly assess the intra-amniotic compartment. A positive result has strong predictive significance, but a negative result does not exclude infection because of prior antibiotics, low bacterial burden, fastidious organisms, or nonbacterial inflammation.

Importance of Gestational Age

Gestational age modifies both baseline EOS risk and predictor performance. Preterm delivery may be a consequence of infection, while immature innate immune responses increase neonatal susceptibility. Prediction strategies should not apply a single risk threshold across extremely preterm, late-preterm, and term populations.

Integrated Risk-Assessment Approach

A layered assessment strategy is supported. The first layer includes gestational age, maternal temperature, membrane-rupture duration, suspected intra-amniotic infection, GBS status, and adequacy of intrapartum antibiotics. The second includes maternal WCC, ANC, NLR, PLR, CRP, procalcitonin, and IL-6. The third includes direct evidence of intra-amniotic infection such as amniotic-fluid Gram stain, culture, IL-6, and placental histopathology. The fourth incorporates the newborn's clinical appearance, culture results, and serial neonatal biomarkers.

Implications for Clinical Practice

Maternal predictors should be used to estimate probability rather than to make a binary diagnosis. A neonate exposed to clinical chorioamnionitis, extreme maternal leukocytosis, prolonged membrane rupture, preterm delivery, or positive intra-amniotic microbiology should receive enhanced observation and appropriate microbiological evaluation. In a well-appearing term infant with isolated maternal fever, adequate GBS prophylaxis, short membrane-rupture duration, and no additional risk factors, structured observation or quantitative risk assessment may reduce unnecessary antibiotic exposure. Maternal biomarker results should not delay neonatal blood culture or antimicrobial treatment when the neonate is clinically unwell.

Strengths

- Integration of clinical, microbiological, haematological, biochemical, cytokine, and placental predictors.
- Distinction between maternal serum, cord blood, amniotic fluid, and placental measurements.
- Separate consideration of culture-confirmed and composite sepsis outcomes.
- Assessment of preterm and term populations and single predictors versus multivariable models.
- Inclusion of recent evidence on maternal leukocyte-derived inflammatory ratios and regional GBS transmission.

Limitations

The protocol was not prospectively registered. Substantial heterogeneity existed in EOS definitions, sampling times, biomarker thresholds, assay methods, gestational-age distributions, intrapartum antibiotic administration, and blood-culture practices. Many studies used clinical sepsis as part of a composite outcome, creating incorporation and misclassification bias. Evidence for maternal serum IL-6, procalcitonin, and newer haematological ratios was based on relatively few independent cohorts. Placental histology is generally unavailable at the time of initial neonatal treatment. Most prediction models lacked external validation and calibration reporting.

Future Research

Future studies should use a standardized definition of culture-confirmed EOS within 72 hours and report composite clinical sepsis separately. Prospective multicentre cohorts should evaluate maternal IL-6, procalcitonin, WCC, ANC, NLR, PLR, rapid molecular testing, placental inflammatory signatures, and maternal-neonatal pathogen concordance. Prediction models should report discrimination, calibration, decision-curve analysis, external validation, antibiotic utilization, missed EOS cases, and subgroup performance by gestational age.

Conclusion

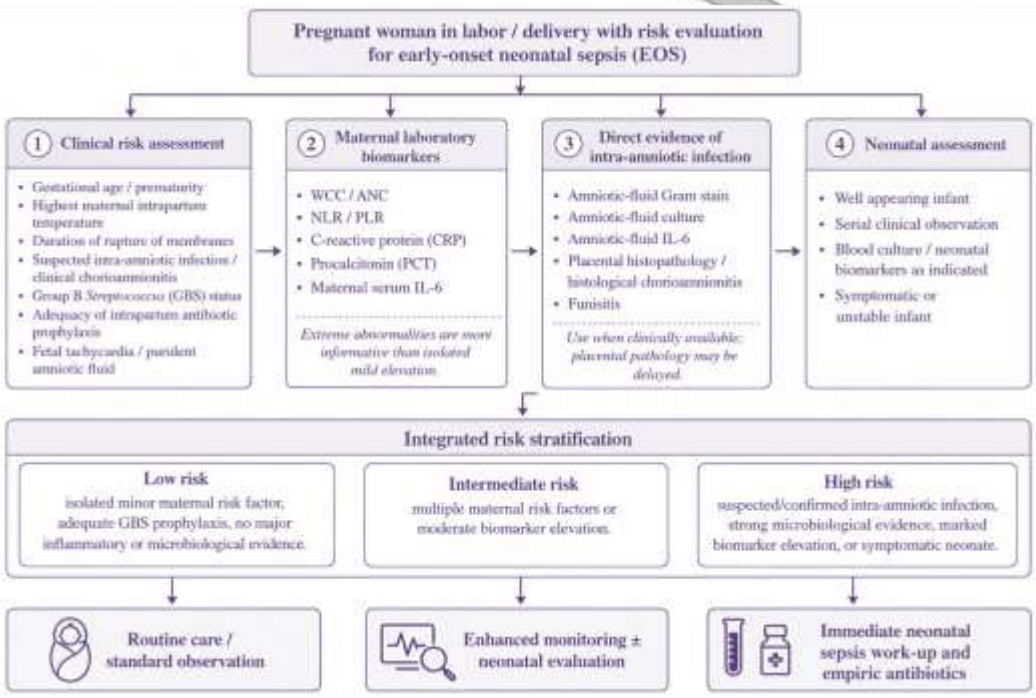
Maternal clinical, microbiological, and inflammatory characteristics provide meaningful information for predicting early-onset neonatal sepsis. Clinical chorioamnionitis, histological placental inflammation, funisitis, extreme maternal leukocytosis, preterm delivery, maternal fever, and prolonged rupture of membranes are associated with increased risk. Maternal GBS colonization is most informative when intrapartum prophylaxis is absent or inadequate.

Maternal leukocyte count and CRP alone have insufficient accuracy for neonatal treatment decisions. Maternal IL-6 and procalcitonin offer moderate discrimination, while amniotic-fluid Gram stain and IL-6 provide stronger predictive performance in selected high-risk pregnancies. The most reliable strategy is a multivariable approach combining maternal clinical findings, gestational age, microbiological evidence, inflammatory markers, intrapartum antibiotic exposure, and the newborn's clinical condition.

Declarations

Ethics Approval: Not applicable because this study is a systematic review and meta-analysis of published data.
Funding: No specific funding was received for this study.
Conflicts of Interest: The authors declare no conflicts of interest.
Data Availability: A verified study-level extraction sheet and statistical-analysis dataset must be prepared before submission.
PROSPERO Registration: The review was not prospectively registered.

Figure 6. Integrated maternal risk-assessment pathway for early-onset neonatal sepsis.



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