e-ISSN: 3025-6224

Scientific Journal of Pediatrics (SJPed)

Journal website: https://phlox.or.id/index.php/sjped

Maternal and Perinatal Determinants of Neonatal Sepsis in Asia: An Exploratory Meta-Analysis

I Kadek Putra Dwipayana[1*], Romy Windiyanto[1]

[1]Department of Paediatrics, Sanjiwani Gianyar Hospital, Gianyar, Indonesia

ARTICLE INFO

Keywords:
Asia
Meta-analysis
Neonatal sepsis
Premature rupture of membranes
Urinary tract infection

***Corresponding author:**
I Kadek Putra Dwipayana

E-mail address:
putradwipayana1@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjped.v3i2.270

ABSTRACT

Introduction: Neonatal sepsis is a leading cause of newborn death in Asia, but the pooled evidence on its maternal and perinatal determinants is dominated by African cohorts. This study synthesised Asian observational evidence on these determinants.

Methods: PubMed/MEDLINE was searched for case-control, cohort, and cross-sectional studies reporting odds ratios for maternal or perinatal determinants of clinically or culture-diagnosed neonatal sepsis in Asian populations. Ten studies from six countries were included. Because the outcome was dichotomous, effects were pooled as odds ratios using a DerSimonian-Laird random-effects model; risk of bias was appraised with ROBINS-I.

Results: Premature rupture of membranes (odds ratio 2.47, 95% CI 1.63-3.73; I-squared 0%) and maternal urinary tract infection (odds ratio 4.33, 95% CI 2.38-7.86; I-squared 5%) were significantly and consistently associated with neonatal sepsis. Maternal or intrapartum fever (odds ratio 1.98, 95% CI 0.75-5.24) and caesarean delivery (odds ratio 1.44, 95% CI 0.74-2.83) were not significant and were heterogeneous. The direction of every pooled effect matched an independent Ethiopian meta-analysis.

Conclusion: In Asian settings, premature rupture of membranes and maternal urinary tract infection were the most credible and consistent maternal determinants of neonatal sepsis, supporting antenatal screening and timely intrapartum management.

1. Introduction

Neonatal sepsis is a systemic infection occurring within the first 28 days of life and remains one of the principal contributors to neonatal morbidity and mortality worldwide. A pooled global estimate placed the population-level incidence at approximately 2,824 cases per 100,000 live births, with a case-fatality of around 17.6%, equivalent to roughly three million episodes each year.[1] The burden falls disproportionately on low-income and middle-income countries, including much of South and South-East Asia, where constrained antenatal services, high rates of home or unbooked delivery, and limited microbiological capacity for timely diagnosis increase both the incidence and the lethality of the condition.[1,2] In the authors' own setting, Indonesia, neonatal sepsis is among the most frequent reasons for neonatal intensive care admission, with contemporaneous hospital data reporting a neonatal sepsis frequency of the order of 13% among admitted neonates, against a national infant mortality rate that has historically approached 32 per 1,000 live births.[3] These figures locate the present work firmly within a high-burden regional context.

Clinically, neonatal sepsis is divided into early-onset disease, presenting within the first 72 hours of life and largely attributable to vertically transmitted organisms, and late-onset disease, presenting thereafter and more frequently associated with nosocomial and device-related exposures. Because the early-onset form is

driven by maternal and intrapartum factors, identification of these factors offers a direct route to prevention through antenatal screening, intrapartum antibiotic prophylaxis, and rationalised obstetric decision-making.[4] It should be emphasised that, in observational data, the factors examined here are statistical associations rather than proven causes; causal language is therefore used cautiously throughout.

Several maternal and perinatal factors have been repeatedly implicated, including premature rupture of membranes, prolonged rupture of membranes, maternal urinary or reproductive-tract infection, chorioamnionitis, intrapartum fever, meconium-stained amniotic fluid, multiple vaginal examinations, low birth weight, prematurity, and low Apgar scores. Each of these plausibly contributes to either the maternal-to-fetal transmission of organisms or to the neonate's vulnerability to infection, and several are amenable to antenatal or intrapartum intervention, which is precisely why a clear, regionally relevant ranking of their associations would be useful at the bedside. The present quantitative synthesis was able to pool four maternal and perinatal factors, namely premature rupture of membranes, maternal urinary tract infection, maternal or intrapartum fever, and caesarean delivery; the remaining factors, although clinically important and discussed below, could not be pooled because too few Asian studies reported them with extractable effect estimates, and they are therefore considered narratively rather than quantitatively.

The strongest existing syntheses are concentrated in particular regions. Comprehensive meta-analyses have characterised the determinants of neonatal sepsis in Sub-Saharan Africa, pooling thirty-six studies,[5] and across Africa as a whole, pooling forty-nine studies,[2] while a separate meta-analysis pooled seventeen studies of perinatal risk factors for early-onset disease using predominantly Chinese-language databases.[4] Country-specific syntheses exist for India, pooling fifteen studies,[6] and China, pooling twenty-nine studies,[7] and a national Ethiopian meta-analysis of nineteen studies provides a robust external benchmark.[8] These efforts share two limitations for Asian practice: the comprehensive regional syntheses are African, and the only large Asian efforts are confined to a single country. No synthesis has drawn together the heterogeneous primary literature from across Asia, even though the continent bears an enormous share of the global burden and its care contexts differ materially from those of Africa.

The novelty of this study lies in being, to our knowledge, the first meta-analysis to focus specifically on the maternal and perinatal determinants of neonatal sepsis within Asian populations, deliberately separating them from the African-dominated literature and going beyond existing single-country Indian and Chinese syntheses to provide a regional, determinant-stratified view, and in transparently using the odds ratio rather than a standardised mean difference because the outcome is dichotomous. The aim of this study was to identify and quantitatively pool the maternal and perinatal determinants of neonatal sepsis reported by Asian observational studies, to assess the consistency and robustness of these associations, and to benchmark them against the wider international evidence so as to inform preventive pediatric and neonatal practice.

2. Methods

Design and reporting

This study was conducted and reported as a systematic review with an exploratory meta-analysis, following the principles of the PRISMA 2020 statement.[9] Because every included study used a dichotomous outcome, the effect measure throughout was the odds ratio. The standardised mean difference and Hedges g were not used, as they are defined for continuous outcomes and are invalid for binary data; the pooled odds ratio was substituted. The review was not registered in a prospective registry and is framed as exploratory and hypothesis-generating.

Search strategy

PubMed/MEDLINE was searched as the primary database, supplemented by manual screening of the reference lists of relevant reviews, with indexing cross-checked in Scopus and Web of Science. The search combined disease, exposure, design and region

concepts using the following Boolean structure: ("neonatal sepsis"[MeSH] OR "neonatal sepsis"[tiab] OR "early onset neonatal sepsis"[tiab] OR "late onset neonatal sepsis"[tiab]) AND ("risk factors"[MeSH] OR "risk factor*"[tiab] OR determinant*[tiab] OR "premature rupture of membranes"[tiab] OR "urinary tract infection"[tiab] OR chorioamnionitis[tiab] OR fever[tiab] OR meconium[tiab] OR caesarean[tiab]) AND (cohort[tiab] OR "case-control"[tiab] OR "cross-sectional"[tiab]) AND (India OR Indonesia OR China OR Taiwan OR Pakistan OR Nepal OR Bangladesh OR Iran OR "Saudi Arabia" OR "United Arab Emirates" OR Thailand OR Vietnam OR Asia). The search was confined to a single bibliographic database and was performed by a single reviewer, with a deliberate cap of ten included studies. The synthesis therefore makes no claim to exhaustive comprehensiveness; this constraint is revisited among the limitations.

Eligibility criteria

Studies were eligible if they were primary observational research (case-control, cohort or analytical cross-sectional) conducted in an Asian population; enrolled neonates aged 0 to 28 days; assessed at least one maternal or perinatal determinant; and reported an odds ratio with a 95% confidence interval, or a two-by-two table from which one could be reconstructed, for clinically and/or culture-diagnosed neonatal sepsis. Systematic reviews, meta-analyses, Global Burden of Disease modelling studies, narrative reviews, editorials, case reports and animal studies were excluded, as were studies whose outcome was a condition other than sepsis (for example necrotising enterocolitis,[10] intraventricular haemorrhage, acute kidney injury, candidaemia or bronchopulmonary dysplasia).

Study selection and data extraction

Records were screened on title and abstract and then at full-text level. For each study the following were extracted: first author and year, country and setting, design, sepsis onset, sepsis definition, number of cases and controls, the determinant assessed, whether the estimate was crude or adjusted, and the effect estimate with its confidence interval. The standard error of each log-odds-ratio was derived from the reported confidence interval as the difference between the natural logarithms of the upper and lower limits divided by twice the 0.975 quantile of the standard normal distribution.

Where confidence intervals were missing, unclear or internally inconsistent, the open-access full text was retrieved and the estimate re-derived from the published counts. Two consequential corrections were made and are documented in the Results: in one Indian case-control study the printed confidence interval for premature rupture of membranes was internally inconsistent, and the two-by-two counts (27 of 78 cases versus 12 of 78 controls) yielded an odds ratio of 2.91 (95% CI 1.35-6.30); in one Chinese cohort the headline adjusted odds ratio for premature rupture of membranes was a direction-flipped artefact, and the crude reconstruction (32 of 84 versus 102 of 484) gave 2.31 (95% CI 1.41-3.77). The dataset and analysis code are available from the corresponding author on reasonable request.

Risk-of-bias assessment

Cochrane Risk of Bias 2.0 applies only to randomized trials and was not appropriate here. As all ten studies were non-randomized observational designs, risk of bias was appraised with the ROBINS-I tool[11] across the domains of confounding, participant selection, exposure classification, departures from intended exposure, missing data, outcome measurement, and selection of the reported result, with an overall judgement of low, moderate, serious or no information.

Statistical analysis

Odds ratios were combined on the natural-log scale and pooled with a DerSimonian-Laird random-effects model,[12] chosen a priori because heterogeneity was expected. Heterogeneity was quantified with the I-squared statistic and the Cochran Q test, reported with its degrees of freedom.[13] With only two studies per determinant pool, the estimator of the between-study variance is imprecise and the confidence intervals are likely to be optimistically narrow; a small-sample adjustment such as the Hartung-Knapp method would widen them, and the significance of the rupture-of-

membranes and urinary-tract-infection findings should be read with that caveat. Determinant-stratified pooling was the primary analysis. A single naive estimate across all determinants was computed only as an exploratory, descriptive quantity and is reported solely in the Results, not in the abstract, because the contributing estimates are non-independent and clinically distinct. Pre-specified subgroup analyses examined study design and outcome definition. Robustness was tested by leave-one-out sensitivity analysis. Egger's test was planned only if at least ten independent estimates were available, a threshold not met, so the funnel plot is descriptive only. Analyses used R with the metafor package, and figures were produced at 300 dpi. All estimates are reported to two decimal places.

3. Results

Study selection

The search identified 81 records; 29 duplicates were removed, 52 records were screened, and 22 full-text reports were assessed. Twelve were excluded, most commonly because the outcome was not sepsis, because the study was non-Asian or was a review, or because no extractable odds ratio with a confidence interval was available. Ten Asian primary studies were included, of which seven contributed to the quantitative pools and three to subgroup or sensitivity analyses. The full selection process is shown in Figure 1.

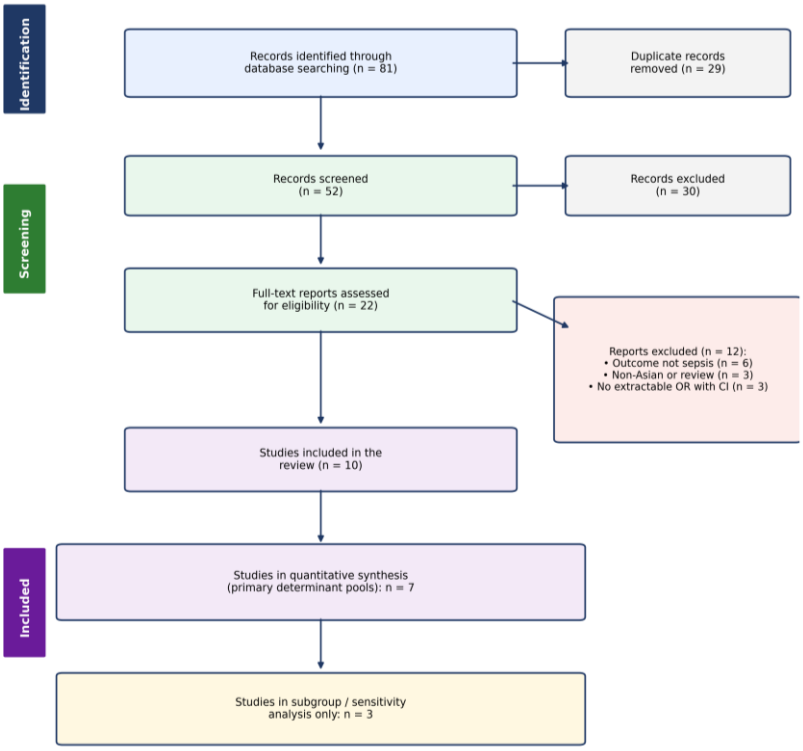

Figure 1. PRISMA 2020 flow diagram of study identification, screening, and inclusion.

Characteristics of included studies

As summarised in Table 1, the ten studies were conducted in six Asian countries: India (four studies),[14-17] Indonesia (two studies),[3,18] China,[19] Taiwan,[20] Saudi Arabia,[21] and the United Arab Emirates.[22] Designs comprised case-control, prospective and retrospective cohort, and analytical cross-sectional studies; six addressed early-onset disease, two addressed late-onset disease, and two covered both. Table 1 also records, for each study, whether the reported estimate was crude or adjusted, a distinction that bears directly on how much weight it should carry.

Table 1. Characteristics of the ten included Asian studies, including whether the reported effect estimate was crude or adjusted.

Study	Author (Year), Country	Design	Onset	Cases / controls	Estimate	Key determinants
S1	Kumar et al. (2024), India	Case-control	Early	78 / 78	Crude	Maternal UTI, age, PROM
S2	Gandra et al. (2021), India	Prospective cohort	Early	32 / 204	Adjusted	Clinical indicators, intrapartum factors
S3	Zakariya et al. (2011), India	Prospective cohort	Both	50 / 70	Adjusted	PROM, Apgar, birth weight, ventilation
S4	Santhanam et al. (2018), India	Case-control 1:4	Early	Not reported (1:4 ratio)	Crude	Vaginal exams, fever, UTI, meconium
S5	Ocviyanti & Wahono (2018), Indonesia	Cross-sectional	Both	21 / 384	Crude	Prolonged ROM, preterm gestation
S6	Miranda et al. (2024), Indonesia	Cross-sectional	Both	113 total	Adjusted	PROM, meconium, Apgar (MDRO)
S7	An et al. (2022), China	Retrospective cohort	Early	84 / 484	Crude	Chorioamnionitis, maternal WBC, PROM
S8	Kung et al. (2013), Taiwan	Matched case-control	Late	164 matched	Adjusted	Parenteral nutrition, IVH
S9	Almudeer et al. (2020), Saudi Arabia	Retrospective review	Early	series	Descriptive	Prematurity, birth weight
S10	Dawoud et al. (2025), UAE	Case-control	Late	29 / 143	Adjusted	Sex, NEC, catheter (MDRO)

Notes: PROM, premature rupture of membranes; ROM, rupture of membranes; UTI, urinary tract infection; WBC, white-blood-cell count; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; MDRO, multidrug-resistant organism.

The sepsis case definition varied across the included studies, from strictly culture-confirmed to purely clinical to a combination of the two, as detailed in Table 2. Because culture-confirmed and clinically diagnosed sepsis are not interchangeable, and because the sensitivity of blood culture in neonates is limited, this variation is itself a recognized source of between-study heterogeneity and is considered further in the Discussion.

Table 2. Sepsis case definitions across the ten included studies, a recognized source of between-study heterogeneity.

Study	Author (Year)	Onset	Sepsis case definition
S1	Kumar et al. (2024)	Early	Clinical plus laboratory parameters
S2	Gandra et al. (2021)	Early	Culture-confirmed (NICE-criteria screened)
S3	Zakariya et al. (2011)	Both	Culture-proven (blood culture)
S4	Santhanam et al. (2018)	Early	Culture-proven group B streptococcal sepsis
S5	Ocviyanti & Wahono (2018)	Both	Culture-proven (blood culture)
S6	Miranda et al. (2024)	Both	Culture-positive sepsis
S7	An et al. (2022)	Early	Clinical diagnostic criteria for early-onset sepsis
S8	Kung et al. (2013)	Late	Culture-proven bloodstream infection
S9	Almudeer et al. (2020)	Early	Clinical plus culture
S10	Dawoud et al. (2025)	Late	Culture-positive late-onset sepsis

Risk of bias

As displayed in Figure 2, the principal concerns were unadjusted or crude effect estimates, restricted source populations (one study enrolling only mothers with premature rupture of membranes and another only febrile mothers), non-extractable data in three studies, and the use of a multidrug-resistant or bloodstream-infection comparator rather than a sepsis-versus-no-sepsis comparison in three studies. Two retrospective record-based studies were judged at serious overall risk of bias. Crucially, these two serious-risk studies did not contribute to any of the four primary determinant pools, which drew only on studies judged at low-to-moderate risk; a narrative sensitivity consideration that excludes the serious-risk studies therefore leaves the determinant-stratified estimates unchanged and affects only the exploratory descriptive overall figure.

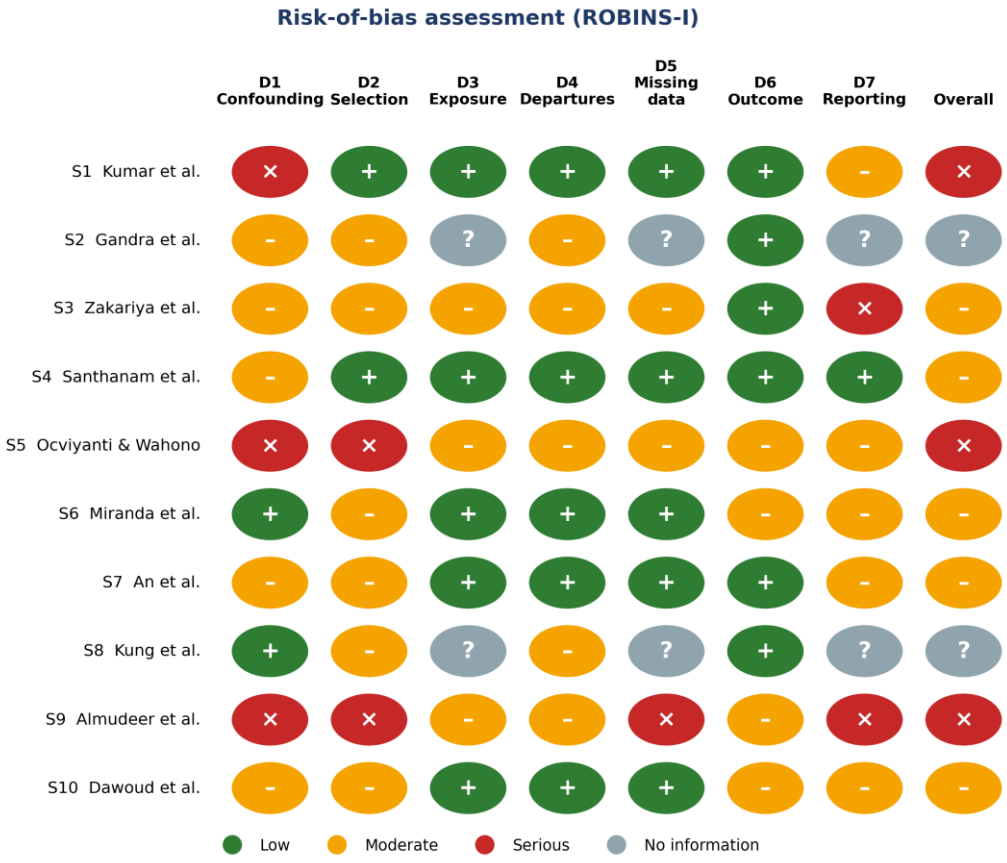

Figure 2. ROBINS-I risk-of-bias summary for the ten included observational studies (substituted for Cochrane RoB 2.0, which applies only to randomized trials).

Individual and pooled determinant effects

To make the contribution of each study explicit, the individual study estimates that entered each pool are listed alongside the pooled value in Table 3. All four primary determinant pools rest on crude estimates, because the two contributing studies for every determinant reported crude rather than adjusted odds ratios; adjusted estimates entered only the multidrug-resistant subgroup. This is an important qualifier, because most maternal determinants are correlated with prematurity and low birth weight, so the crude pooled estimates are likely to overstate the true adjusted associations to some degree.

Table 3. Individual study odds ratios and determinant-stratified pooled random-effects estimates (shaded rows). All primary pools are based on crude estimates.

Determinant/studies	Type	Study OR (95% CI)	Pooled OR (95% CI)	I-squared
Premature rupture of membranes			**2.47 (1.63-3.73)**	**0%**
Kumar et al. (2024)	Crude	2.91 (1.35-6.30)		
An et al. (2022)	Crude	2.31 (1.41-3.77)		
Maternal urinary tract infection			**4.33 (2.38-7.86)**	**5%**
Kumar et al. (2024)	Crude	5.44 (2.65-11.16)		
Santhanam et al. (2018)	Crude	2.88 (1.08-7.63)		
Maternal or intrapartum fever			**1.98 (0.75-5.24)**	**64%**
Kumar et al. (2024)	Crude	1.30 (0.69-2.44)		
Santhanam et al. (2018)	Crude	3.54 (1.30-9.67)		
Caesarean section			**1.44 (0.74-2.83)**	**61%**
Kumar et al. (2024)	Crude	1.00 (0.52-1.91)		
Santhanam et al. (2018)	Crude	1.99 (1.16-3.43)		

The determinant-stratified forest plot is presented in Figure 3. Premature rupture of membranes was significantly associated with neonatal sepsis (pooled OR 2.47, 95% CI 1.63-3.73) with no detectable heterogeneity (I-squared 0%; Cochran Q = 0.25 on 1 degree of freedom, p = 0.62). Maternal urinary tract infection carried the largest effect (pooled OR 4.33, 95% CI 2.38-7.86; I-squared 5%; Q = 1.05 on 1 degree of freedom, p = 0.31). Maternal or intrapartum fever (pooled OR 1.98, 95% CI 0.75-5.24; I-squared 64%) and caesarean section (pooled OR 1.44, 95% CI 0.74-2.83; I-squared 61%) were not statistically significant and showed substantial heterogeneity. The exploratory descriptive estimate across all determinants was OR 2.26 (95% CI 1.63-3.15; I-squared 51%); this quantity characterises only the overall direction of association and is deliberately omitted from the abstract because it is non-independent and does not constitute a valid single effect.

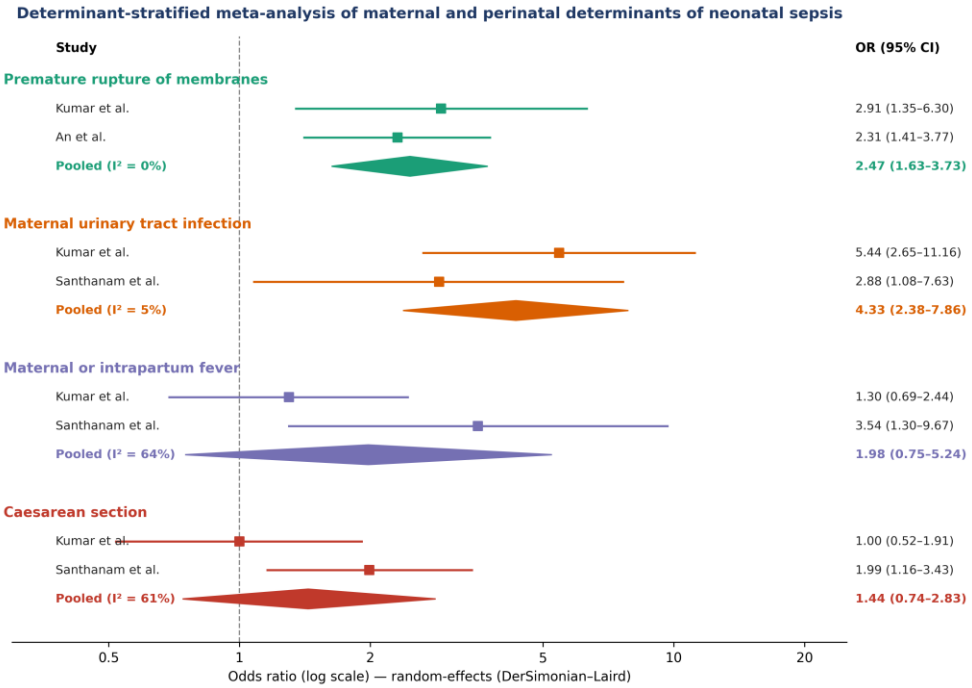

Figure 3. Forest plot of determinant-stratified random-effects pooling (DerSimonian-Laird; two studies per determinant). Effects are odds ratios on a logarithmic scale, with the reference value at unity.

Audit of reconstructed estimates

Because two corrected estimates bear directly on the headline findings, their derivation is set out in Table 4 so that readers may audit them. Both reconstructions used only the published two-by-two counts, and neither altered the qualitative conclusion. Confirmation from the original study authors was not obtained, and the corrections rest solely on the published counts; this is noted among the limitations.

Table 4. Audit trail for the two reconstructed estimates. Both reconstructions used the published two-by-two counts; neither altered the qualitative conclusion.

Study/determinant	Reported value	Issue identified	Counts used	Reconstructed value
Kumar et al. (2024), PROM	OR 2.91 (CI 4.61-33.73)	Printed CI internally inconsistent	27/78 vs 12/78	OR 2.91 (1.35-6.30)
An et al. (2022), PROM	Adjusted OR 0.34 (0.11-1.04)	Direction-flipped adjusted artefact	32/84 vs 102/484	Crude OR 2.31 (1.41-3.77)

Subgroup analyses

When premature rupture of membranes and meconium-stained amniotic fluid were grouped by outcome definition, the estimates were similar for the sepsis-versus-no-sepsis comparator (OR 2.48, 95% CI 1.72-3.56; I-squared 0%) and the multidrug-resistant-sepsis comparator (OR 2.77, 95% CI 1.99-3.86). These two comparators answer different clinical questions: the former asks what raises the risk of sepsis at all, the latter what raises the risk that a sepsis episode is drug-resistant. The subgroup analysis is therefore presented only to demonstrate directional consistency, not equivalence. Pooling restricted to case-control designs yielded OR 2.28 (95% CI 1.53-3.38).

Sensitivity analysis

Because each determinant pool contained only two studies, leave-one-out analysis necessarily reduced each pool to a single study; these single-study estimates remained directionally consistent. The exploratory overall estimate was robust to the omission of any single contributing estimate, with the pooled odds ratio ranging narrowly from 2.00 to 2.49 and I-squared between 27% and 57%.

Publication bias

Formal small-study testing was not performed because fewer than ten independent estimates were available for any determinant, a threshold below which Egger's test is unreliable. The funnel plot in Figure 4 is therefore descriptive only and should not be read as evidence for or against publication bias.

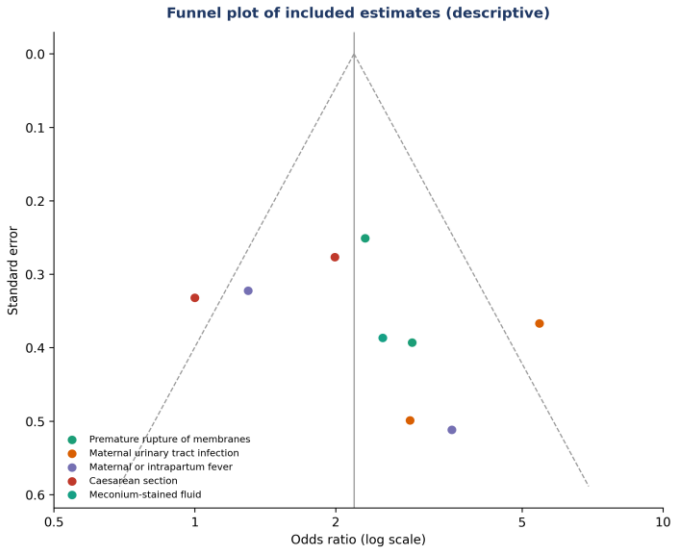

Figure 4. Funnel plot of the included estimates (descriptive only; formal small-study testing was not performed because fewer than ten independent estimates were available).

4. Discussion

This exploratory meta-analysis synthesised the maternal and perinatal determinants of neonatal sepsis reported by Asian observational studies, drawing together ten primary studies from six countries that had not previously been considered as a regional whole. As shown in Table 3 and Figure 3, two determinants emerged as both statistically significant and internally consistent: premature rupture of membranes, with a pooled odds ratio of 2.47 and no detectable heterogeneity, and maternal urinary tract infection, with the largest pooled odds ratio of 4.33 and minimal heterogeneity. Maternal or intrapartum fever and caesarean delivery, by contrast, were not statistically significant and were substantially heterogeneous. These last two results must be interpreted correctly: a non-significant pooled estimate derived from only two heterogeneous studies represents an absence of evidence, not evidence of absence, and it would be a serious error to conclude from these data that maternal fever or caesarean delivery is unrelated to neonatal sepsis; the data are simply too few and too inconsistent to estimate those associations reliably. The remainder of this discussion interprets each significant determinant, situates the findings within the international literature, and sets out the practical and research implications.

Interpretation of the rupture-of-membranes finding

The association between premature rupture of membranes and neonatal sepsis is biologically coherent, because rupture removes the mechanical and immunological barrier that protects the fetus from ascending genital-tract organisms, exposing the amniotic cavity to colonisation. Critically, it is the duration of rupture, more than its mere presence, that governs the opportunity for colonisation and invasion: the longer the latency, the greater the microbial load to which the fetus is exposed. The Indonesian study reported a clear time-dependent gradient, with progressively higher odds as the rupture interval lengthened and the odds being highest when rupture persisted to delivery.[3] This dose-response pattern has a direct and practical corollary: documenting the latency interval between rupture and birth is not a clerical formality but a clinically meaningful act that should inform the intensity of neonatal observation and the threshold for investigation. Obstetric trial evidence that planned early birth after term prelabour rupture of membranes reduces early-onset neonatal sepsis reinforces the causal plausibility of this pathway and links the determinant identified here to an established preventive intervention.[23]

Interpretation of the urinary tract infection finding

Maternal urinary tract infection carried the largest pooled odds ratio, as Table 3 shows, and because it is both screenable and treatable, it is arguably the most clinically actionable result of this synthesis. It reflects a reservoir of uropathogens, frequently Escherichia coli and group B streptococcus, that may be transmitted vertically to the neonate and that also serves as a marker of subclinical chorioamnionitis and ascending genital-tract infection. The two contributing studies were internally consistent, and the negligible heterogeneity strengthens confidence in the direction of the effect even though only two studies were available. Its prominence in the Asian data mirrors its identification as a determinant in both the Indian and the Ethiopian syntheses,[6,8] suggesting a robust and generalisable signal rather than a chance finding. The practical implication is substantial: structured antenatal screening for and treatment of asymptomatic bacteriuria and symptomatic urinary tract infection, which is already feasible and inexpensive at the primary-care level in most Asian settings, may represent one of the more attainable routes to reducing the incidence of early-onset neonatal sepsis, and it deserves prospective evaluation as a preventive target in its own right.

A cautious, illustrative risk-stratification pathway

Although the data cannot support a validated scoring system, the consistent determinants can be assembled, for illustration only, into the reasoning a neonatal team already performs. A term neonate born after prolonged rupture of membranes to a mother with a treated urinary tract infection, who is clinically well,

might reasonably be observed closely; the same exposure history with any clinical instability would lower the threshold for sepsis screening and empirical antibiotics; and where blood culture is slow or unavailable, this maternal-determinant reasoning can shorten the interval to treatment for the highest-risk neonates.[14,15] Such a pathway is illustrative rather than prescriptive, but it shows how the two robust determinants translate into practice.

Antimicrobial stewardship

Better identification of genuinely high-risk neonates is itself an antimicrobial stewardship intervention. Several included studies addressed multidrug-resistant organisms,[18,22] and the tension they expose is real: prompt empirical treatment of at-risk neonates must be balanced against the avoidance of unnecessary antibiotic exposure that drives resistance. Using maternal and perinatal determinants to concentrate empirical therapy where risk is highest, and to withhold it where risk is low, allows that balance to be struck more rationally, a linkage of growing importance in Asian neonatal units where drug resistance is escalating.[7]

Maternal and neonatal determinants are intertwined

Although this synthesis focused on maternal and perinatal determinants, several included studies also reported neonatal determinants such as low birth weight, prematurity, low Apgar score, and the need for ventilation, which are among the most consistently reported risk factors in the wider literature.[6,16] These were not pooled because too few Asian studies reported them comparably, but they cannot be considered in isolation: maternal infection and prolonged rupture of membranes themselves contribute to prematurity and low birth weight, which in turn predispose to sepsis. The maternal determinants therefore act partly through neonatal intermediates, which is one reason the crude pooled estimates should be read as upper bounds.

Comparison with other meta-analyses

The direction and magnitude of the present estimates align with the wider literature. The Ethiopian national meta-analysis of nineteen studies reported odds ratios of 3.85 for prolonged rupture of membranes and 3.17 for maternal urinary tract infection,[8] the Sub-Saharan African synthesis of thirty-six studies reported a rupture-of-membranes odds ratio of about 2.15,[5] and the early-onset perinatal meta-analysis of seventeen studies reported 2.63.[4] The Indian synthesis of fifteen studies likewise identified premature rupture of membranes and prematurity as leading factors.[6] That our independently assembled Asian estimates fall within the same range as these much larger syntheses provides reassuring face validity. The consistency across continents suggests the obstetric pathway to early-onset sepsis is biologically conserved, even as the absolute burden differs by health-system context. The distinctive contribution here is regional specificity: a pan-Asian, determinant-stratified view of direct relevance to Indonesian and comparable services.

Heterogeneity and generalisability

Heterogeneity was determinant-specific, as the I-squared values in Table 3 show: absent for rupture of membranes, negligible for urinary tract infection, but substantial for fever (I-squared 64%) and caesarean section (I-squared 61%). This pattern is biologically plausible. Rupture of membranes and urinary tract infection are relatively well-defined exposures with comparable ascertainment across studies, whereas intrapartum fever conflates infectious and non-infectious causes, including epidural-associated and dehydration-related temperature rises, and caesarean section is performed for widely varying indications, some of which, such as fetal distress or obstructed labor, are themselves markers of an already compromised fetus. The high heterogeneity for these two determinants is the principal reason they are reported as non-significant exploratory signals rather than established associations, and it cautions strongly against pooling them without attention to indication and definition. More broadly, Asia is not a single epidemiological entity; the included studies span a remote Indian district hospital, a Chinese women's hospital, and tertiary units in the Arabian Peninsula, settings that differ markedly in antenatal-care access, delivery environment, and microbial ecology. A pooled

Asian estimate therefore necessarily masks real variation, and the findings most likely to transfer to the authors' own Indonesian setting are the biologically robust and homogeneous rupture-of-membranes and urinary-tract-infection associations; setting-specific findings such as the caesarean association should not be assumed to generalise.

Strengths and limitations

The principal strengths of this work are its explicit regional focus, its transparent correction and full documentation of two source-level data errors (Table 4), its methodologically appropriate use of the odds ratio in place of a standardised mean difference, the labelling of crude versus adjusted estimates (Table 1), the tabulation of sepsis case definitions (Table 2), and its honest framing of the single overall estimate as descriptive rather than inferential. These features make the synthesis auditable and reduce the risk that its preliminary nature is misread. Several material limitations must nonetheless be acknowledged, and they are consequential rather than cosmetic.

First, each primary determinant was pooled from only two studies. Such estimates are exploratory and statistically underpowered, the heterogeneity statistic is unstable when computed from two studies, and the confidence intervals are likely to be optimistically narrow because the DerSimonian-Laird estimator performs poorly with very few studies; the findings are therefore hypothesis-generating rather than definitive.

Second, all four primary pools rest on crude estimates reconstructed or reported without adjustment, and because most maternal determinants are correlated with prematurity and low birth weight, residual confounding is likely and the crude pooled odds ratios probably overstate the independent maternal effects.

Third, screening relied on a single database with a single reviewer and a deliberate cap on the number of included studies, so this is not a fully dual-reviewer systematic review and was not prospectively registered; relevant studies indexed only in regional databases or published in languages other than English will have been missed, and selection bias cannot be excluded.

Fourth, the sepsis case definition varied from strictly culture-confirmed to purely clinical across studies (Table 2), and because culture-confirmed and clinically diagnosed sepsis are not interchangeable, this is a recognized source of heterogeneity that could not be formally explored with so few studies. Fifth, three studies used a multidrug-resistant or bloodstream-infection comparator rather than a sepsis-versus-no-sepsis comparison and were therefore restricted to subgroup or sensitivity roles; their inclusion in any pooled view must be interpreted cautiously, since they answer a different clinical question. Sixth, formal publication-bias testing was not feasible given the small number of estimates, and the two reconstructed estimates, although transparently documented in Table 4, were not independently confirmed with the original study authors and rest solely on the published counts.

Taken together, these limitations mean that premature rupture of membranes and maternal urinary tract infection should be read as the most credible signals in the current Asian evidence, while the remaining determinants await confirmation. The findings make a clear and specific case for the kind of primary research that is now needed: larger, prospectively designed, and fully reported Asian cohorts that use harmonised, internationally accepted sepsis definitions, that report both crude and adjusted estimates, and that adjust for the major neonatal confounders of gestational age and birth weight. Multi-country collaborative networks would be particularly valuable, because they could accumulate enough events per determinant to move beyond the two-study pools that constrain the present synthesis. There is also an important equity dimension: because these determinants cluster among women with limited antenatal access, strengthening primary maternal care, antenatal screening, and skilled intrapartum monitoring is itself a route to reducing neonatal sepsis, a message of particular relevance to the low-resource settings that carry the greatest share of the global burden.

5. Conclusion

This exploratory pan-Asian meta-analysis of ten observational studies from six countries identified premature rupture of membranes (pooled OR 2.47) and maternal urinary tract infection (pooled OR 4.33) as the most consistent and statistically robust maternal determinants of neonatal sepsis, with little or no between-study heterogeneity, whereas maternal or intrapartum fever and caesarean delivery were not significantly associated and were heterogeneous. For pediatric and neonatal practice in Asian settings, these findings support antenatal screening and treatment of maternal urinary tract infection, documentation of the duration of membrane rupture, and structured risk stratification of neonates exposed to prolonged rupture, particularly where microbiological confirmation is delayed; the same measures double as antimicrobial stewardship by concentrating empirical therapy where the risk of sepsis is genuinely high. The results should be interpreted as hypothesis-generating rather than definitive, given that each determinant was pooled from only two crude estimates and that the review was single-database, single-reviewer and unregistered. They nonetheless make a clear case for larger, prospectively designed, and fully reported Asian cohorts, so that these preliminary but promising signals can be confirmed and translated into regionally tailored, equitable prevention strategies for one of the most consequential conditions in newborn medicine.

Data availability and conflicts of interest

The extracted dataset, the corrected-estimate audit trail (Table 4), and the analysis code are available from the corresponding author on reasonable request. The study is reported in accordance with the PRISMA 2020 guideline. The authors declare no conflicts of interest and received no specific funding for this work.

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