INPLASY

Time-dependent Prognostic Accuracy of nSOFA scores for mortality in neonates with Late-Onset Infection: A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 September 2026 and was last updated on 6 September 2026.

INTRODUCTION

Review question / Objective To determine the time-stratified prognostic accuracy of the nSOFA score for predicting in-hospital mortality in preterm infants with suspected or confirmed late-onset infection, including culture-proven LOS, suspected late-onset infection (LOI), and NEC, at four predefined time points: T0 (at infection suspicion), T6 (6 h), T12 (12 h), and T24 (24 h).

Rationale Late-onset sepsis (LOS) and necrotizing enterocolitis (NEC) remain leading causes of mortality and morbidity in neonates, especially for preterm infants. The neonatal Sequential Organ Failure Assessment (nSOFA) score has been proposed as a dynamic, bedside tool to quantify organ dysfunction and predict mortality, but its prognostic accuracy across early time points has not been systematically synthesized.

Condition being studied Late-onset infection in neonates, mainly late-onset sepsis (LOS) and necrotizing enterocolitis (NEC), accounts for substantial proportions of neonatal mortality and long-term morbidity worldwide. Early identification and intervention of LOS and NEC are of great significance, especially in infants with severe infection and organ dysfunction. Organ dysfunction-based scoring systems have emerged as a potentially superior framework for sepsis risk stratification. In adult critical care, the Sequential Organ Failure Assessment (SOFA) score was revised under the Sepsis-3 consensus. In neonatology, the neonatal Sequential Organ Failure Assessment (nSOFA) score quantifies organ dysfunction. These investigations have demonstrated that nSOFA scores obtained within the first 24 hours of suspected infection are associated with in-hospital mortality in preterm neonates. However, the optimal timing of nSOFA assessment and the degree to which diagnostic accuracy changes across the early hours after infection suspicion have not been systematically

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evaluated. Therefore, we conducted a preregistered systematic review and meta-analysis to estimate the pooled time-stratified prognostic accuracy of the nSOFA score for in-hospital mortality prediction in preterm neonates with late-onset infection.

METHODS

Search strategy The literature search was conducted on March 30, 2026, using the following databases: PubMed, Ovid Medline, Cochrane Library, and Web of Science. The following search terms were combined synonym as follows: ([Infant, Premature*] or [Infant, Newborn*]) and ([Sepsis*]) and ([Organ Dysfunction Scores*]). ([Infant, Premature*] or [Infant, Newborn*]) and ([Enterocolitis, Necrotizing*]) and ([Organ Dysfunction Scores*]). ([Infant, Premature*] or [Infant, Newborn*]) and ([infection*]) and ([Organ Dysfunction Scores*]). No publication date restrictions were applied. The literature search was limited to English-language publications. Articles were checked for duplication.

Participant or population Newborn infants with suspected or confirmed late-onset infection would be enrolled, including culture-proven LOS, clinically suspected late-onset infection, or NEC.

Intervention Conduct the nSOFA score to predict in-hospital mortality at four time points: T0, T6, T12, and T24. T0 was the moment when the blood sample was drawn from the infant with suspected infection. T6, T12, and T24 were 6 hours, 12 hours, and 24 hours after suspected infection, respectively.

Comparator No comparative intervention is applicable for this diagnostic test accuracy meta-analysis. This study evaluates the diagnostic performance of index test(s) against reference standard, rather than comparing therapeutic interventions.

Study designs to be included Retrospective cohort study.

Eligibility criteria Studies were eligible if they: (1) enrolled newborn infants with suspected or confirmed late-onset infection, including culture-proven LOS, clinically suspected late-onset infection, or NEC; (2) evaluated the prognostic accuracy of the nSOFA score for predicting in-hospital mortality; and (3) reported sufficient data to construct a 2×2 contingency table (true positives [TP], false positives [FP], true negatives [TN], false negatives [FN]) or reported paired sensitivity and specificity values.

Information sources Electronic databases including PubMed, Ovid Medline, Cochrane Library, and Web of Science will be searched. Grey literature will be retrieved from conference abstracts. Reference lists of included studies and relevant systematic reviews will be manually screened for additional eligible records. We will contact original study authors to request missing diagnostic raw data when necessary. No trial registers will be searched for this diagnostic test-accuracy meta-analysis.

Main outcome(s) The main outcome of this meta-analysis is in-hospital mortality.

Additional outcome(s) There is no other additional outcome.

Data management Data extraction and quality assessment were performed independently by 2 of us (R.L.and S.H.). The quality assessment of the studies was conducted using Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)21, which was implemented in Review Manager (RevMan, Version 5.4, The Cochrane Collaboration, Copenhagen, Denmark). QUADAS-2 evaluates studies across four domains of risk of bias: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. Applicability concerns were assessed for three domains: (1) patient selection, (2) index test, and (3) reference standard. For each domain, studies were rated as having low risk of bias/concern, high risk of bias/concern, or unclear risk of bias/concern.

Strategy of data synthesis Bivariate random-effects models were used to calculate pooled sensitivity, specificity, diagnostic odds ratio (DOR), positive and negative likelihood ratios (LR+ and LR−), and summary receiver operating characteristic (SROC) curves with 95% confidence intervals (CIs). Forest plots and SROC curves were generated to visualize results. Heterogeneity was assessed using the inconsistency index (I^2), with $I^2 < 50\%$ indicating low heterogeneity and $I^2 \geq 50\%$ substantial heterogeneity. Between-study variance (τ^2) was reported where applicable.

Subgroup analysis Subgroup analyses were prespecified and performed at T0, T6, and T12 to explore potential sources of heterogeneity:
Study sample size: small (≤200 participants) vs. large (>200 participants)
Gestational age (GA): <32 weeks vs. other GA groups

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Diagnosis: culture-proven late-onset sepsis (LOS) vs. other late-onset infections/NEC
Country: USA vs. Non-USA
Between-subgroup differences in sensitivity and specificity were evaluated using univariate meta-regression under the bivariate random effects framework. A two-sided $P < 0.05$ was considered statistically significant. Stable pooled estimates were not reported for subgroups with fewer than four studies.

Sensitivity analysis Sensitivity analysis was performed to assess the robustness of the pooled results. First, leave one out analysis was conducted by sequentially removing one study at a time and recalculating pooled sensitivity, specificity, and AUC at T0, T6, and T12. Second, analyses were repeated after excluding studies with high risk of bias in the QUADAS 2 patient selection domain. Changes in pooled estimates and 95% CIs were examined to identify influential studies or potential bias.

Language restriction The literature search was limited to English-language publications.Only English.

Country(ies) involved China.

Keywords nSOFA; neonatal sepsis; late-onset infection; NEC； systematic review; mortality.

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