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Sequential Organ Failure Assessment (SOFA) Score versus PCT and Lactate for Mortality Prediction in Sepsis: A Meta-Analysis of Comparative and Combined Prognostic Value

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

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 17 March 2025 and was last updated on 17 March 2025.

INTRODUCTION

Review question / Objective This systematic review addresses a critical gap in sepsis management by evaluating the diagnostic accuracy of established and emerging prognostic tools for mortality prediction. Sepsis, a leading cause of death globally, demands precise risk stratification to guide timely interventions. However, existing tools like SOFA and qSOFA face limitations: SOFA relies on laboratory parameters inaccessible in resource-constrained settings, while qSOFA's variable performance across populations (sensitivity 32–65%) raises concerns about its generalizability. Biomarkers like PCT and lactate show promise but lack direct comparison with established scores.Through this meta - analysis, we aim to: 1) systematically compare the independent predictive power of the Sequential Organ Failure Assessment (SOFA), the Quick Sequential Organ Failure Assessment (qSOFA), procalcitonin (PCT), and lactate; 2) quantify the value of the combination of PCT and qSOFA, as well as the combination of lactate and qSOFA, in predicting the prognosis of patients with sepsis. The research results will provide evidence - based guidance for optimizing sepsis risk stratification.

Condition being studied Sepsis, a syndrome of organ dysfunction caused by dysregulated host immune responses to infection, has become one of the leading causes of death in critically ill patients globally, accounting for over 11 million deaths annually. Early and accurate prediction of mortality risk in septic patients is critical for optimizing clinical decisions and resource allocation. Since its introduction in 1996, the Sequential Organ Failure Assessment (SOFA) score has served as the gold standard for evaluating organ dysfunction and prognosis. However, its reliance on laboratory parameters such as blood gas analysis, bilirubin, and creatinine limits its applicability in low- and

middle-income countries (LMICs) with constrained resources.

The 2016 Sepsis-3 consensus introduced the quick SOFA (qSOFA) score, simplifying assessment through three bedside criteria: systolic blood pressure (≤100 mmHg), respiratory rate (≥22 breaths/min), and altered mentation. While qSOFA offers operational convenience in non-ICU settings, its sensitivity (32%-65%) and specificity (67%-94%) demonstrate significant heterogeneity across populations, particularly in LMICs with high sepsis burdens. This limitation has spurred investigations into composite scoring systems integrating biomarkers to enhance prognostic accuracy.

Recent studies highlight procalcitonin (PCT) as a specific biomarker for bacterial infection, with levels strongly correlated with sepsis severity and mortality. Blood lactate (≥2 mmol/L), a sensitive marker of tissue hypoperfusion, independently predicts mortality. For example, Shetty et al. (2017) demonstrated in 12,555 emergency department patients that combining lactate with qSOFA (LqSOFA) improved sensitivity for adverse outcomes (death or ICU stay ≥72 hours) from 47.6% to 65.5%. Similarly, Park et al. (2023) reported in a national cohort (n=6,734) that dynamic integration of lactate with SOFA (Lac-SOFA) achieved superior predictive performance (AUROC=0.797) compared to SOFA alone (AUROC=0.781) on day 3. Additionally, combined qSOFA-PCT models improved 30-day mortality prediction sensitivity from 67% to 86.5%, while a lactate/albumin ratio (LAR>1.52) was associated with a 3.75-fold increased risk of 28-day mortality.

Despite these advancements, three major limitations persist: 1) insufficient evidence directly comparing SOFA, PCT, and lactate; 2) lack of systematic evaluation of incremental value from combined use; and 3) unclarified prediction discrepancies across healthcare resource settings (e.g., LMICs vs. high-income countries).

METHODS

Participant or population Adult patients (≥18 years) diagnosed with confirmed or suspected sepsis, across different healthcare settings (including low- and middle-income countries).

Intervention Prognostic tools for sepsis mortality prediction, including SOFA score, qSOFA score, procalcitonin (PCT) levels, blood lactate levels, and combined models (e.g., qSOFA+PCT).

Comparator Direct comparison between tools (e.g., SOFA vs. PCT) and comparison between combined models vs. single markers (e.g., qSOFA+PCT vs. qSOFA alone).

Study designs to be included Diagnostic accuracy studies (reporting sensitivity, specificity, AUROC) and cohort studies evaluating tool performance in sepsis mortality prediction.

Eligibility criteria

Inclusion criteria:

This study includes diagnostic studies. The research subjects are patients aged ≥18 years with confirmed or suspected sepsis (based on clinical symptoms, laboratory indicators, or imaging examinations). Studies must report the model performance of using SOFA, QSOFA, PCT, lactate alone, or their combined indicators (e.g., QSOFA+PCT, SOFA + lactate) to predict short-term mortality (e.g., 28-day, 30-day, or in-hospital mortality). Studies should provide true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values, or raw data enabling calculation of sensitivity (SEN), specificity (SPE), and AUC values, while clearly linking the predictive model performance (e.g., AUC, SEN, SPE) to mortality outcomes.

Exclusion criteria:

Exclude non-diagnostic accuracy studies, methodology studies, reviews, conference abstracts, case reports, or expert consensus; studies lacking fourfold table data (TP/FP/FN/TN) or unable to calculate SEN, SPE, and AUC values; studies involving pediatric patients (aged < 18 years) that may distort mortality assessment; and duplicate publications (for multi-timepoint reports of the same study population, only retain the latest data; exclude studies with overlapping data from those already included).

Information sources Electronic databases: PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI) Database.

Main outcome(s) Main outcome: Short-term mortality (28-day or in-hospital mortality). Effect measures: Sensitivity, specificity, and AUROC of prognostic tools (e.g., SOFA, qSOFA) in predicting mortality.

Quality assessment / Risk of bias analysis The QUADAS-2 tool was applied to evaluate the risk of bias and applicability of included studies, covering four domains: patient selection (consecutive inclusion/exclusion criteria), index test (preset threshold/operational independence), reference standard (accuracy of the gold standard), and flow & timing (detection interval/data completeness).

Two researchers independently determined the risk level (low/high/unclear) for each domain. Applicability assessment focused on the alignment of the first three domains with the sepsis population, indicators, and outcomes. Disagreements were resolved via third-party arbitration. Results presented the distribution of key issues using forest plots or summary tables, with emphasis on high-risk links like post-hoc adjustment of indicator thresholds.
Publication bias is tested by Deeks' funnel plot. Combined with subgroup analysis and Meta-regression, explore the sources of heterogeneity. Conduct sensitivity analysis by excluding studies to verify the robustness.

Strategy of data synthesis Extract the 2×2 tables (true positive, false negative, false positive, true negative) of each research report, as well as the area under the receiver operating characteristic curve (AUROC) values and 95% confidence intervals (CIs). Use the bivariate random-effects model to combine the sensitivity (SEN), specificity (SPE), and their correlation (ρ), calculate the pooled positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and AUROC, and fit the summary receiver operating characteristic curve (SROC) to evaluate the predictive efficacy of the Sequential Organ Failure Assessment (SOFA) score, procalcitonin (PCT), and lactate for the mortality of sepsis. If the included studies contain a direct comparison of two methods in the same patient cohort (such as reporting the AUROC of both SOFA and PCT simultaneously), based on the paired data design, combine the ΔAUROC (SOFA vs other indicators) through the random-effects model. The heterogeneity is evaluated by the I^2 statistic (>50%) and Cochrane's Q test. When there is significant heterogeneity, the random-effects model is adopted. Visualize the ΔAUROC and 95% CI using a forest plot, and mark the P value of the Z test ($P<0.05$). All analyses are completed using Stata 18.0 software, and a P value <0.05 is defined as statistically significant.

Subgroup analysis Subgroup analyses will be conducted according to healthcare settings (low- and middle-income countries vs. high-income countries), publication years (before 2020 vs. 2020 and after), regions (Asia vs. non-Asia areas), departments (emergency department vs. ICU), outcome time (28/30-day mortality vs. emergency department mortality), and study designs (prospective vs. retrospective studies). The analyses aim to explore how these factors influence the diagnostic accuracy of prognostic tools in predicting sepsis mortality.

Sensitivity analysis Conduct sensitivity analysis by excluding low-quality studies (based on QUADAS-2 scores) or studies with missing data to assess robustness of pooled results.

Country(ies) involved China.

Keywords sepsis; mortality prediction; SOFA score; qSOFA.

Contributions of each author
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