Age-adjusted quick Sequential Organ Failure Assessment score for predicting mortality and disease severity in children with infection: a systematic review and meta-analysis

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We assessed the diagnostic accuracy of the age-adjusted quick Sequential Organ Failure Assessment score (qSOFA) for predicting mortality and disease severity in pediatric patients with suspected or confirmed infection. We conducted a systematic search of PubMed, EMBASE, the Cochrane Library, and Web of Science. Eleven studies with a total of 172,569 patients were included in the meta-analysis. The pooled sensitivity, specificity, and diagnostic odds ratio of the age-adjusted qSOFA for predicting mortality and disease severity were 0.69 (95% confidence interval [CI] 0.53–0.81), 0.71 (95% CI 0.36–0.91), and 6.57 (95% CI 4.46–9.67), respectively. The area under the summary receiver-operating characteristic curve was 0.733. The pooled sensitivity and specificity for predicting mortality were 0.73 (95% CI 0.66–0.79) and 0.63 (95% CI 0.21–0.92), respectively. The pooled sensitivity and specificity for predicting disease severity were 0.73 (95% CI 0.21–0.97) and 0.72 (95% CI 0.11–0.98), respectively. The performance of the age-adjusted qSOFA for predicting mortality and disease severity was better in emergency department patients than in intensive care unit patients. The age-adjusted qSOFA has moderate predictive power and can help in rapidly identifying at-risk children, but its utility may be limited by its insufficient sensitivity.

Recently, remarkable progress has been achieved in reducing overall incidence of infectious diseases1,2. However, infectious diseases remain a leading cause of childhood morbidity and mortality globally3,4. Specifically, mortality of up to 20% has been reported in children with sepsis5, largely because the lack of specific signs and symptoms in children makes early diagnosis and treatment challenging6. In addition, rapid deterioration can occur when compensation fails in pediatric patients7,8. Thus, early recognition of sepsis is crucial to ensure timely management and to reduce mortality9,10.

Pediatric sepsis has been defined by the International Pediatric Sepsis Consensus Conference (IPSCC) as the presence of systemic inflammatory response syndrome (SIRS) with suspected or proven infection in a child11. However, the SIRS criteria lack specificity for identifying infected patients at high risk of mortality because children with non-infectious conditions can also meet the SIRS criteria; moreover, children who meet the SIRS criteria for sepsis often do not have organ dysfunction12,13.

In the case of adults, the Sepsis-1 and Sepsis-2 consensus definitions also adopted the SIRS criteria14,15. However, the Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3) task force revised the sepsis definition as the presence of a dysregulated host response that manifests as detrimental organ dysfunction, thus enabling the differentiation of sepsis from uncomplicated infections or non-infectious conditions16,17.
Organ dysfunction is specifically defined by acute changes in the Sequential Organ Failure Assessment score (SOFA) with ≥ 2 points16,17.

The SEPSIS-3 task force also recommended the bedside tool, the quick SOFA (qSOFA), for the early recognition of adult patients with suspected infection at risk for poor outcomes. The qSOFA is a simplified version of the SOFA, comprising only three components: low systolic blood pressure (≤ 100 mmHg), high respiratory rate (≥ 22 breaths/min), and altered mental status (Glasgow Coma Scale [GCS] < 15)16,17. The SOFA and qSOFA showed better prognostic performance than the former sepsis criteria among adult patients in various clinical settings17–20. However, the SEPSIS-3 criteria were developed and validated for adult patients and did not consider age-dependent physiologic variables16.

Recently, there have been attempts to adapt the SEPSIS-3 criteria for pediatric patients21,22. The age-adjusted or age-adapted qSOFA, which is adjusted according to age-specific cutoffs, has shown promising results among pediatric patients in emergency department (ED)23,24 and intensive care unit (ICU) settings25,26. However, there is no systematic review and meta-analysis reporting the predictive value of the age-adjusted qSOFA in children. Therefore, we aimed to evaluate the performance of the age-adjusted qSOFA in predicting outcomes, including mortality and disease severity, among pediatric patients with suspected or confirmed infection.

Materials and methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA)26 and is registered with PROSPERO (CRD42021232257).

Study selection, eligibility, and data extraction.

Two authors (SHY and HK) independently conducted literature searches of PubMed, EMBASE, the Cochrane Library, and Web of Science, without language or time restrictions, on January 6, 2021, with the aim of finding eligible studies assessing the performance of age-adjusted qSOFA in predicting mortality and/or disease severity in pediatric patients with suspected or confirmed infection. Various combinations of the following key words were used in the systematic search: “Quick Sequential Organ Failure Assessment,” “qSOFA,” “quick SOFA,” “q-SOFA,” “quick-SOFA,” and “pediatric,” “child,” “adolescent,” “infant,” and “neonate.”

Studies were eligible if they aimed to assess the performance of age-adjusted qSOFA to predict mortality or disease severity in pediatric patients (aged < 18 years) with suspected or confirmed infection. We used the following as indicators reflecting disease severity: admission or transfer to an ICU (including a critical care unit), development of severe sepsis13, or prolonged hospital stay (dependent on the authors’ definition, regardless of duration). If enrolled patients received a diagnostic code (e.g., International Classification of Diseases code) indicative of an infection or were diagnosed with sepsis/septic shock via consensus definition, we accepted them as patients with confirmed infection. In addition, if enrolled patients had signs or symptoms of infection (e.g., fever), or were treated for a bacterial infection (e.g., treated with therapeutic antibiotics), we inferred suspected infection. Studies were included if they reported sufficient data to construct a 2 × 2 contingency tables. Reviews, editorials, expert opinions, animal experiments, or studies presenting duplicate data were excluded.

The following information was retrieved from each study: first author, publication year, sample size, patient source (e.g., ED or ICU), time of age-adjusted qSOFA assessment, cutoff criteria of age-adjusted qSOFA, true positives, false positives, true negatives, and false negatives derived from the sensitivity and specificity of the age-adjusted qSOFA in predicting mortality and disease severity. When studies comprised multiple groups, each group was considered as an individual study.

Quality assessment.

Currently, there is no widely used assessment tool for assessing the quality of studies of predictive risk scores. This study used a revised seven-item quality assessment scale27,28, which was derived from the Quality Assessment of Diagnostic Accuracy Studies tool29 and Newcastle–Ottawa Scale30. It comprises seven criteria: unbiased patient selection; representative of a wide spectrum of disease severity; predictor variables assessed blinded to outcome; outcome assessed blinded to the predictor variables; accurate definition of outcomes; availability of the same clinical data; and adequate follow-up31,32. We defined adequate follow-up as a follow-up of > 90%. Two reviewers (SE and SHY) independently performed the methodological quality assessment. Any disagreements were resolved by discussion.

Statistical analyses.

Summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR−), and pooled diagnostic odds ratio (DOR) were calculated using a bivariate random-effects model31. The DOR of a test (or score) is the ratio of the odds of positivity among patients versus the odds among healthy individuals or a control group32,33. When the DOR increases to greater than 1, the discriminative power of the outcome becomes greater35. We used summary receiver-operating characteristic (SROC) curves to calculate the area under the curve (AUC), which assisted in estimating the discriminative power of a test or score35. The AUC takes values between 0 and 1, with higher values indicating better test (or score) performance35. Heterogeneity of sensitivity and specificity were evaluated from the forest plots of the studies’ estimates and using a χ² test (P < 0.1, significant). In the presence of significant heterogeneity, we conducted meta-regression analysis and a priori planned subgroup analysis to explore the sources of heterogeneity using the following as covariates with 95% confidence interval (CI): patient source (ED vs. ICU); sample size (< 10,000 vs. ≥ 10,000); outcome (mortality vs. disease severity); scales for assessing mental status in age-adjusted qSOFA (GCS vs. Alert, Voice, Pain, Unresponsive [AVPU] scale); age-specific vital signs criteria (2005 IPSSC definition vs. others); center (single center vs. multicenter); and cut-off value (≥ 2 vs. ≥ 1). We excluded studies in the meta-regression analysis if they used both the GCS and AVPU scale for mental status checks, or if their primary outcome was both in-hospital mortality and disease severity concomitantly. In addition, we also performed pooled analysis using
one study population per study to examine whether the results were biased by including the same populations multiple times. As the reason for separation into different datasets from a study varies (e.g., outcomes, cutoff, age-specific vital signs criteria), we selected the data using the cutoff value of ≥ 2 and 2005 IPSCC definition as age-specific vital sign criteria. We measured publication bias with visualization of funnel plots and Egger’s test.

Statistical analyses and meta-analyses were conducted using R program, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria); P-values < 0.05 were considered statistically significant.

Results
PubMed, EMBASE, Web of Science and Cochrane database searches as per the predefined search words revealed 81 articles. After removing duplicates and screening abstracts, 20 full-text articles were read, resulting in 11 articles that met the inclusion criteria for the systematic review and meta-analysis. Reasons for exclusion are shown in the flow diagram (Fig. 1). Data from 172,569 patients of 11 observational studies were finally included. The general characteristics of the included studies are presented in Table 1 and Supplementary Table S1.

Study characteristics. The majority of studies were retrospective, and only one study was prospective. Six studies were designed to evaluate the value of the age-adjusted qSOFA in predicting mortality. Four studies evaluated the performance of the age-adjusted qSOFA in predicting disease severity; three studies adopted the 2005 IPSCC definition for age-specific vital signs criteria. Six studies used GCS, four studies used AVPU, and one study used either GCS or AVPU to assess mental status. All of the studies were published between 2018 and 2020 (Table 1 and Supplementary Table S1).

Quality assessment of the included studies. Three studies enrolled patients consecutively, and one single-center study defined suspected bacterial infection as the commencement of antibiotics within 24 h after ED arrival at the non-academic facility and excluded surgical diagnoses; thus, the study was deemed not representative of a wide spectrum of disease severity. Although all studies assessed the predictor variables that constituted the age-adjusted qSOFA blinded to outcomes, no studies clearly reported that the outcomes
were assessed blindly to the age-adjusted qSOFA. Overall, outcomes were clearly defined and the same clinical data was available in all studies. All included studies showed adequate follow-up of patients (Supplementary Table S2).

**Age-adjusted qSOFA for predicting mortality and disease severity.** Included studies showed a wide range of sensitivities (0.29–1.00) and specificities (0.05–0.99) (Fig. 2 and Supplementary Table S3). Pooled sensitivity and specificity of qSOFA for predicting mortality and disease severity are 0.685 (95% CI 0.527–0.809) and 0.706 (95% CI 0.362–0.911), respectively. Pooled LR+, LR−, and DOR were 2.919 (95% CI 2.186–3.898), 0.452 (95% CI 0.381–0.535), and 4.433 (95% CI 3.223–6.097), respectively. AUC was 0.733 (95% CI 0.683–0.792) and 0.626 (95% CI 0.206–0.915), respectively. Pooled LR+, LR− and DOR were significantly higher for patients with suspected sepsis, which led to in-hospital death within 28 days of admission.

**Heterogeneity exploration and subgroup analysis.** A meta-regression analysis revealed that patient source, sample size, outcome, center, and scales for assessing mental status were significant factors affecting heterogeneity (Supplementary Table S6). When comparing summary estimates of the DOR between subgroups, significant differences were only found in relation to patient source and scales for assessing mental status (Table 2). Age-adjusted qSOFA showed a significantly higher pooled DOR in the studies including ED patients than in the studies including ICU patients [22.214 (95% CI 7.115–69.360) vs. 4.092 (95% CI 3.058–5.474), \( P = 0.005 \)]; Studies that used the APVU to assess mental status also showed a significantly higher pooled DOR compared with studies including ICU patients [23.009 (95% CI 4.559–116.123) vs. 3.968 (95% CI 3.015–5.224), \( P = 0.036 \)].

**Age-adjusted qSOFA for mortality.** Six studies assessed the performance of age-adjusted qSOFA for predicting mortality. Pooled sensitivity and specificity of age-adjusted qSOFA for predicting mortality were 0.729 (95% CI 0.655–0.792) and 0.626 (95% CI 0.206–0.915), respectively. Pooled LR+, LR− and DOR were 1.925 (95% CI 1.629–2.275), 0.452 (95% CI 0.381–0.535), and 4.433 (95% CI 3.223–6.097), respectively. AUC was found to be 0.735 (95% CI 0.677–0.780) (Table 3). Further detailed accuracy estimates, coupled forest plots,
SROC curves, and heterogeneity test results of studies evaluating predictive accuracy of the age-adjusted qSOFA for mortality are provided in the Supplementary Tables S7 and S8 and Supplementary Figs. S5–S7.

**Age-adjusted qSOFA for disease severity.** Four studies reported the performance of age-adjusted qSOFA for predicting disease severity. Pooled sensitivity and specificity of age-adjusted qSOFA for predicting disease severity was 0.731 (95% CI 0.207–0.966) and 0.724 (95% CI 0.113–0.982). Pooled LR+, LR–, and DOR were 3.341 (95% CI 0.498–22.416), 0.708 (95% CI 0.618–0.811), and 8.866 (95% CI 1.355–58.035), respectively. The AUC was 0.786 (95% CI 0.518–0.905) (Table 3). Detailed accuracy estimates, coupled forest plots, SROC

Figure 2. Coupled forest plots of the sensitivity and specificity of the age-adjusted quick Sequential Organ Failure Assessment score for predicting mortality and disease severity in pediatric patients with suspected or confirmed infection.

Figure 3. Summary receiver-operating characteristic (SROC) curve of the predictive performance of age-adjusted quick Sequential Organ Failure Assessment score for mortality and disease severity in pediatric patients with suspected or confirmed infection. The area under the curve of the SROC was 0.733 (95% CI 0.683–0.768). conf.region, 95% confidence region for SROC curve.
curves, and heterogeneity test results of studies evaluating the predictive accuracy of the age-adjusted qSOFA for
disease severity are provided in the Supplementary Tables S9 and S10 and Supplementary Figs. S8–S10.

Discussion
In this review, we assessed the performance of the age-adjusted qSOFA in predicting mortality and disease
severity in pediatric patients with suspected or confirmed infection. We identified 11 studies, including 172,569
patients from the ED, pediatric tertiary referral center, and ICU. We found that the age-adjusted qSOFA had
a moderate performance for predicting in-hospital mortality and disease severity in pediatric patients.

The qSOFA was initially recommended by the SEPSIS-3 task force as a readily available bedside tool16,36, and
the age-adjusted qSOFA has the same advantages: it does not require laboratory tests and enables prompt and
repeatable assessment of patients. However, as a screening tool to identify ‘at-risk patients’, the age-adjusted
qSOFA satisfies the requirements for convenience and feasibility, but does not satisfy the requirement for high
sensitivity37. In clinical practice, screening tools typically require high sensitivity to safely rule out those at low
risk of adverse outcomes38.

Determining which patients are at high risk of severe illness or mortality is essential for appropriate clinical
decision making. When clinicians initially encounter pediatric patients with suspected infection, the specific
outcomes (e.g. mortality, ICU admission or prolonged hospital admission itself) would be not matter at that
moment, only whether this patient has a potential to become a severe, critical patient requiring close observa-
tion, and intensive treatment will be of more interest to clinicians. Thus, we intended to assess the predictive
performance of age-adjusted qSOFA as a quick, easy, bedside screening tool for identifying these ‘at risk patients’.

Table 2. Subgroup analysis. Bold values denote statistical significance at the P < 0.05 level. AVPU, Alert, Voice,

Pain, Unresponsive scale; CI, confidence interval; DOR, diagnostic odds ratio; ED, Emergency Department;
GCS, Glasgow Coma Scale; ICU, Intensive Care Unit; IPSSC, International Pediatric Sepsis Consensus
Conference.

| Covariates                      | Subgroup   | Number of studies | DOR    | 95% CI          | P-value |
|---------------------------------|------------|------------------|--------|-----------------|---------|
| Patient source                  | ICU        | 4                | 4.092  | 3.058–5.474     | 0.005   |
|                                 | ED         | 5                | 22.214 | 7.115–69.360    |         |
| Sample size                     | ≥ 10,000   | 7                | 8.628  | 5.422–13.730    | 0.123   |
|                                 | < 10,000   | 4                | 3.949  | 1.642–9.499     |         |
| Outcome                         | Mortality  | 6                | 4.372  | 3.192–5.989     | 0.448   |
|                                 | Severity   | 4                | 9.099  | 1.409–58.743    |         |
| Scales for assessing mental status | GCS       | 6                | 3.968  | 3.015–5.224     | 0.036   |
|                                 | AVPU       | 4                | 23.009 | 4.559–116.123   |         |
| Center                          | Multicenter| 4                | 4.092  | 3.058–5.474     | 0.132   |
|                                 | Single center| 7            | 10.925 | 3.145–7.958     |         |
| Age-specific vital signs criteria | 2005 IPSSC definition   | 9          | 7.717  | 3.233–18.422    | 0.388   |
|                                 | Others     | 2                | 4.999  | 3.147–7.941     |         |
| Cut off value                   | ≥ 2        | 9                | 6.676  | 4.508–9.888     | 0.694   |
|                                 | ≥ 1        | 2                | 3.229  | 0.138–75.410    |         |

Table 3. Summary estimates of the predictive accuracy of the age-adjusted quick Sequential Organ Failure
Assessment score according to the outcome. AUC, area under the curve; CI, confidence interval; SROC,
summary receiver-operating characteristic.

| Predictive performance                  | Mortality               | Disease severity          |
|-----------------------------------------|-------------------------|---------------------------|
| Sensitivity (95% CI)                    | 0.729 (0.655–0.792)     | 0.731 (0.207–0.966)       |
| Specificity (95% CI)                    | 0.626 (0.206–0.915)     | 0.724 (0.113–0.982)       |
| Positive likelihood ratio (95% CI)      | 1.925 (1.629–2.275)     | 3.341 (0.498–22.416)      |
| Negative likelihood ratio (95% CI)      | 0.452 (0.381–0.535)     | 0.708 (0.618–0.811)       |
| Diagnostic odds ratio (95% CI)          | 4.433 (3.223–6.097)     | 8.866 (1.355–58.035)      |
| AUC of SROC curve (95% CI)              | 0.735 (0.677–0.780)     | 0.786 (0.518–0.905)       |
Likewise, the DOR was also calculated as another single indicator of age-adjusted qSOFA performance for discrimination of at-risk patients\(^5\). DOR of 6.57 in our result means that the odds of positivity (above cutoff value of age-adjusted qSOFA) in at risk patients is about six times higher than the odds of positivity in non-risk patients. DOR does not depend on disease prevalence\(^6\). However, it depends on what criteria are used to define disease or pathological conditions of the study population (e.g., comorbidity, disease severity are used to define the age-adjusted qSOFA in adults uses the GCS\(^16\). In our analysis, studies using the AVPU to assess mental status showed higher overall predictive power of the age-adjusted qSOFA for mortality and morbidity can be considered similar in both analyses. This also indicates that the results would not to be strongly biased by including the same populations multiple times. Nevertheless, our results still need to be interpreted and applied cautiously because the same study population was pooled. Third, most of the included studies are retrospective studies, which were not conducted in western countries. Fourth, most of the studies were conducted in western countries.

Further studies are required to ensure the applicability of the results of studies of the age-adjusted qSOFA to other countries. Fifth, we did not search gray literature, as we aimed to review the characteristics of published literature. Incorporating a gray literature search may help to minimize the effects of publication bias\(^5\), however, we found no significant publication bias in this analysis. Sixth, long-term outcomes or healthcare costs were not available in the literature that was included; thus we could not evaluate these in this analysis. Finally, we could not compare the overall predictive performance of the age-adjusted qSOFA with other predictive biomarkers, due to the limited number of clinical studies.
Conclusions
Current evidence suggests that the age-adjusted qSOFA has a moderate predictive value for mortality and disease severity in pediatric patients with suspected or confirmed infection. The age-adjusted qSOFA is a simple and feasible tool to use in settings outside the ICU such as ED, and in resource-limited settings. However, a screening tool with higher sensitivity for pediatric patients is needed.

Data availability
All data generated or analyzed during this systematic review are included in this manuscript (and its Supplementary Materials).

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