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Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score With Excess Hospital Mortality in Adults With Suspected Infection in Low- and Middle-Income Countries

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IMPORTANCE The quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score has not been well-evaluated in low- and middle-income countries (LMICs).

OBJECTIVE To assess the association of qSOFA with excess hospital death among patients with suspected infection in LMICs and to compare qSOFA with the systemic inflammatory response syndrome (SIRS) criteria.

DESIGN, SETTINGS, AND PARTICIPANTS Retrospective secondary analysis of 8 cohort studies and 1 randomized clinical trial from 2003 to 2017. This study included 6569 hospitalized adults with suspected infection in emergency departments, inpatient wards, and intensive care units of 17 hospitals in 10 LMICs across sub-Saharan Africa, Asia, and the Americas.

EXPOSURES Low (0), moderate (1), or high (≥2) qSOFA score (range, 0 [best] to 3 [worst]) or SIRS criteria (range, 0 [best] to 4 [worst]) within 24 hours of presentation to study hospital.

MAIN OUTCOMES AND MEASURES Predictive validity (measured as incremental hospital mortality beyond that predicted by baseline risk factors, as a marker of sepsis or analogous severe infectious course) of the qSOFA score (primary) and SIRS criteria (secondary).

RESULTS The cohorts were diverse in enrollment criteria, demographics (median ages, 29-54 years; males range, 36%-76%), HIV prevalence (range, 2%-43%), cause of infection, and hospital mortality (range, 1%-39%). Among 6218 patients with nonmissing outcome status in the combined cohort, 643 (10%) died. Compared with a low or moderate score, a high qSOFA score was associated with increased risk of death overall (19% vs 6%; difference, 13% [95% CI, 11%-14%]; odds ratio, 3.6 [95% CI, 3.0-4.2]) and across cohorts ($P < .05$ for 8 of 9 cohorts). Compared with a low qSOFA score, a moderate qSOFA score was also associated with increased risk of death overall (8% vs 3%; difference, 5% [95% CI, 4%-6%]; odds ratio, 2.8 [95% CI, 2.0-3.9]), but not in every cohort ($P < .05$ in 2 of 7 cohorts). High, vs low or moderate, SIRS criteria were associated with a smaller increase in risk of death overall (13% vs 8%; difference, 5% [95% CI, 3%-6%]; odds ratio, 1.7 [95% CI, 1.4-2.0]) and across cohorts ($P < .05$ for 4 of 9 cohorts). qSOFA discrimination (area under the receiver operating characteristic curve [AUROC], 0.70 [95% CI, 0.68-0.72]) was superior to that of both the baseline model (AUROC, 0.56 [95% CI, 0.53-0.58; $P < .001$) and SIRS (AUROC, 0.59 [95% CI, 0.57-0.62]; $P < .001$).

CONCLUSIONS AND RELEVANCE When assessed among hospitalized adults with suspected infection in 9 LMIC cohorts, the qSOFA score identified infected patients at risk of death beyond that explained by baseline factors. However, the predictive validity varied among cohorts and settings, and further research is needed to better understand potential generalizability.

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Annually, there are about 20 million cases of sepsis, defined as life-threatening acute organ dysfunction caused by a dysregulated host response to infection,[1] leading to more than 5 million deaths, with most of the burden in low- and middle-income countries (LMICs).[2] There is no reference standard that allows easy, accurate diagnosis of sepsis.[1,3] Although the 1991 International Consensus Definition Task Force proposed the systemic inflammatory response syndrome (SIRS) criteria to identify patients with a septic host response,[4] these criteria do not measure whether the response is injurious, and their utility is limited.[1,3] In 2016, the Sepsis-3 Task Force proposed that, for patients with suspected infection, an increase of 2 points in the Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) score could serve as clinical criteria for sepsis.[1] This approach was justified based on content validity (SOFA reflects the facets of organ dysfunction) and predictive validity (the proposed criteria predict downstream events associated with the condition of interest).[5] However, the utility of SOFA is limited outside the intensive care unit (ICU) because many SOFA variables are not measured routinely.

The Sepsis-3 Task Force also reported that, in patients outside the ICU, a combination of respiratory rate, mental status, and systolic blood pressure, named quick SOFA (qSOFA), had strong predictive validity for sepsis.[5] qSOFA requires only a clinical examination, and therefore may be particularly valuable in resource-limited settings. However, the patients, pathogens, and clinical capacity to manage sepsis differ considerably between high-income and LMIC settings.[6,7] In particular, the mechanisms that lead to life-threatening acute organ dysfunction from infections such as malaria can differ from those of classic bacterial sepsis. Therefore, the purpose of this study was to evaluate the predictive validity of the qSOFA score to identify patients with suspected infection who are likely to have sepsis (or analogous severe infectious course) across a variety of LMIC settings and to compare qSOFA with previously recommended SIRS criteria.

Key Points

Question What is the association between the quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score and excess hospital mortality, as a marker of sepsis or analogous severe infectious course, in patients with suspected infection in low- and middle-income countries (LMICs)?

Findings In this retrospective secondary analysis of 9 diverse LMIC cohorts that included 6569 hospitalized adults with suspected infection, a qSOFA score greater than or equal to 2 was significantly associated with increased likelihood of excess hospital death compared with a lower score (odds ratio, 3.6).

Meaning The qSOFA score may help identify patients at higher risk for excess hospital mortality among adults with suspected infection in LMICs.

Methods

All contributing studies received human participant approvals from appropriate regulatory bodies (eTable 1 in the Supplement) and participants provided informed consent as required by each individual cohort's institutional review board.

Study Design, Setting, and Population

We conducted a secondary analysis of 9 data sets: 8 cohort studies (5 prospective and 3 retrospective) and 1 randomized clinical trial.[8-15] Of the countries represented in this study (Bangladesh, Haiti, India, Indonesia, Myanmar, Rwanda, Sierra Leone, Sri Lanka, Thailand, and Vietnam), 3 are classified as low income, 6 as lower middle income, and 1 as upper middle income by the World Bank.[16] Patients were recruited to the cohorts from a range of hospital settings, including small community hospitals, military hospitals, rural regional hospitals, national referral hospitals, and specialty infectious disease hospitals. As the Sepsis-3 Task Force did not specify which infections should be considered as potential causes of sepsis, we sought preexisting cohorts of adult patients admitted to the hospital with a wide variety of suspected infections. Some cohorts were limited exclusively to patients with specific infections (eg, suspected Lassa fever in Sierra Leone and severe falciparum malaria in the SEAQUAMAT cohort), and others were largely composed of patients with 1 or 2 specific infections or syndromes, such as pneumonia.

Because there is controversy regarding whether sepsis is the appropriate term for life-threatening acute organ dysfunction arising from nonbacterial infections, we use the term *sepsis or analogous severe infectious course*. The lower age limit of patients included in the SAILORS Study from each cohort ranged from 15 to 19 years (eMethods in the Supplement). Cohorts included primarily medical patients enrolled from the emergency department, hospital ward, or ICU. Suspected infection was defined based on the primary admitting diagnosis in the patient medical record, assigned by the treating clinician. Most study sites did not have electronic health record data. There was significant methodological heterogeneity between the data sets, including study design and risk of bias (**Table 1**).

Data Collection

The following data were extracted for each patient: demographics; components of the SIRS criteria and qSOFA score (most abnormal value in the first 24 hours after presentation); HIV status; whether the patient was transferred to the study hospital from an emergency department or inpatient setting at another facility; primary infectious etiology as diagnosed on admission by the treating clinician; laboratory-confirmed infectious etiology (where unavailable, we recorded primary infectious etiology as diagnosed by the treating clinician on hospital discharge); and vital status at hospital discharge. Plasma lactate levels, other comorbidity data, and many components of the SOFA[17] score were unavailable in most cohorts and thus were not included in this study.

The qSOFA score includes respiratory rate of 22/min or greater, abnormal mental status, and systolic blood pressure of 100 mm Hg or less.[5] SIRS criteria include respiratory rate greater than 20/min or $PaCO_2$ less than 32 mm Hg; temperature greater than 38°C or less than 36°C; pulse greater than 90

Table 1. Summary of Cohorts

Characteristic	Kigali[8]	Gitwe	Suspected Lassa[9]	Haiti-RELIC 1[10]	Haiti-RELIC 2[11]	Ubon-Sepsis[12]	SEAQUAMAT[13]	Vietnam[14]	Sri Lanka[15]
Country	Rwanda	Rwanda	Sierra Leone	Haiti	Haiti	Thailand	Bangladesh, India, Indonesia, Myanmar	Vietnam	Sri Lanka
Dates	2013	2016-2017	2012-2016	2012	2014	2013-2014	2003-2005	2014-2016	2015-2017
No. of sites	1	1	1	1	1	1	9	1	2
Study design	Retrospective cohort	Prospective cohort[a]	Prospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Randomized, open-label trial	Prospective cohort	Prospective cohort
Major inclusion criteria[b]	Presentation to the ED, suspected infection by ED clinician, age ≥15 y	Admitted with suspected infection, age >28 d	Suspected Lassa fever, age ≥15 y	Presentation to the ED, suspected infection by ED clinician, age ≥17 y	Presentation to the ED, suspected infection by ED clinician, age ≥17 y, ≥2 modified WHO SIRS criteria[c]	Admitted with suspected community-acquired infection to medical ward for <24 h, ≥3 modified sepsis criteria,[d] age ≥18 y	Severe malaria, laboratory-confirmed parasitemia, age >2 y	Admitted to ICU, suspected infection by ICU clinician, age ≥15 y	Age ≥18 y
Major exclusion criteria	Acute trauma	Limited therapy due to terminal disease	Prisoner, institutionalized	Hemoglobin <7.0 g/dL, trauma, pregnant, peripartum, acute hemorrhage	Hemoglobin <7.0 g/dL, trauma, pregnant, peripartum, acute hemorrhage	Pregnant, suspected hospital-acquired infection	Full treatment with quinine or an artemisinin derivative or allergy to study medications	Previous admission to study hospital ICU in past 90 d	None
Setting	National referral hospital ED	District referral hospital	Lassa fever ward of national referral hospital	Community hospital ED	Community hospital ED	Regional referral hospital ED, wards, ICU	Multiple	Tertiary infectious disease regional referral hospital	National referral hospital and district referral hospital
No. of patients[e]	302	561	540	156	105	1210	1148	624	1923
Resource availability									
ICU	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Mechanical ventilators	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Vasopressors	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: ED, emergency department; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; WHO, World Health Organization.

[a] This study had a before-and-after study design, with a focused sepsis-specific training component for medical personnel that occurred halfway through study enrollment.

[b] Additional inclusion criteria for the current study include admission to the hospital and age older than the minimum for adults as defined by each contributing cohort. The minimum age of patients included in this study was 15 years for the Kigali, Suspected Lassa, and Vietnam cohorts; 18 years for the Haiti-RELIC 1, Haiti-RELIC 2, Ubon-Sepsis, SEAQUAMAT, and Sri Lanka cohorts; and 19 years for the Gitwe cohort.

[c] This study modified the WHO Integrated Management of Adult Illness District Clinician Manual SIRS criteria for resource-limited countries as any 2 of the following: heart rate ≥100/min, respiratory rate ≥24 breaths/min, or temperature <36° or ≥38°C.

[d] Enrollment criteria for this study included ≥3 of 20 modified Surviving Sepsis Campaign diagnostic criteria for sepsis documented in the medical record.

[e] Included in analysis of the current study.

beats/min; and white blood cell count greater than 12 000/μL, less than 4000/μL, or with more than 10% bands.[4] While Sepsis-3 criteria recommend the more general use of "abnormal mental status" as a qSOFA criterion,[1] many authors have operationalized this as Glasgow Coma Scale score of 14 or less.[5] We defined abnormal mental status as a Glasgow Coma Scale score of 14 or less, with the verbal score adjusted for intubated patients[18]; voice, pain, or unresponsive criteria on the alert, voice, pain, unresponsive scale[19]; or treating physician documentation of altered mental status.

SIRS criteria were chosen for comparison to qSOFA given mixed evidence on the clinical utility of qSOFA vs SIRS for the identification of patients likely to have sepsis,[20,21] because they were the recommended criteria for sepsis prior to Sepsis-3,[4] and because they continue to be used by many clinicians and researchers.[22] SIRS criteria (range, 0 [best] to 4 [worst] criteria) and qSOFA scores (range, 0 [best] to 3 [worst] points) were calculated using the most abnormal values within the first 24 hours of presentation to the study hospital, and they were categorized as low (0), moderate (1), and high (≥2) as per recommendations.[4,5] Where HIV status, hospital transfer status, and individual components of the qSOFA or SIRS scores were missing, they were assumed to be normal.

Outcomes

The primary outcome was predictive validity of the qSOFA score for sepsis (or analogous severe infectious course), as measured by the degree to which qSOFA and SIRS were associated

with subsequent hospital death, after adjusting for baseline risk factors. Predictive validity is a form of criterion validity used to assess potential diagnostic criteria for conditions, such as sepsis, that lack an unambiguous reference standard approach. Because sepsis itself cannot be identified with certainty, predictive validity instead evaluates a potential criterion's ability to identify, from among patients at risk for sepsis, those more likely to develop features associated with sepsis.

Among individuals with suspected infection, those who develop life-threatening acute organ dysfunction (defined as *sepsis* according to the Sepsis-3 criteria[1]) are, by definition, more likely to die. Consequently, a criterion measured in those with suspected infection that is associated with subsequent death, after adjusting for other obvious risk factors for death, has predictive validity for sepsis (or analogous severe infectious course). We constructed logistic regression models for hospital mortality, comparing a model using only baseline risk variables vs models with the addition of qSOFA score and SIRS criteria, and assessed both the change in risk of death and improvement in discrimination.

Statistical Analysis

All analyses were performed using Stata/SE version 15.1 (StataCorp). Group comparisons were performed using χ^2 tests for equal proportions and Wilcoxon rank sum tests.[23] We assessed the odds ratio (OR) for hospital mortality comparing infected patients with high (≥2) vs moderate or low (<2) qSOFA scores and SIRS criteria across quartiles of baseline risk of hospital mortality in the combined cohort. We used the risk ratio (RR) for hospital mortality to compare infected patients with high vs moderate or low qSOFA scores and SIRS criteria within individual cohorts. We repeated these analyses across subgroups of HIV status and type of infection (malaria, dengue, pneumonia, and tuberculosis). These specific infections were chosen a priori because they were highly prevalent in the contributing data sets and because they are among the leading communicable causes of death worldwide. For infection subgroup analyses, patients were preferentially classified according to laboratory-confirmed diagnosis. When this was unavailable or inapplicable, patients were classified according to discharge diagnosis or, last, according to admission diagnosis. Additionally, we assessed the OR for hospital mortality comparing infected patients with moderate (1) vs low (0), and high (≥2) vs low (0), qSOFA score and SIRS criteria in the combined cohort; we used the RR for hospital mortality to compare these groups within the individual cohorts.

For predictive validity analyses, we developed a baseline risk model of hospital mortality using generalized estimating equations with a panel-data model using binomial family, logit link, and robust standard errors. The baseline risk model included age (continuous), sex (female reference), HIV status (negative reference), and transfer status (negative reference), and accounted for the nonindependence of observations within cohorts. Separate models were created for each cohort or infection subgroup with sufficient patients by infection type for models to converge. The variables in each model remained the same but the coefficients were specific to each cohort or infection subgroup. Data on other chronic comorbidities or features of baseline risk of hospital mortality were not available for most cohorts and thus were not included in the baseline risk model. We calculated the discrimination of hospital mortality using the baseline risk model, baseline risk model plus qSOFA score, and baseline risk model plus SIRS criteria. We then compared area under the receiver operating characteristic (AUROC) curves for each of these 3 models.

All statistical analyses were 2-sided, and $P < .05$ was required for statistical significance. We adjusted for multiple comparisons using the Bonferroni method when comparing AUROC values for models of baseline risk, baseline plus qSOFA score, and baseline plus SIRS criteria ($P < .02$ considered significant).

Sensitivity Analyses

We performed several sensitivity analyses. We repeated models after excluding cohorts that (1) were enrolled based on positive SIRS criteria or slightly modified SIRS criteria; (2) did not record a SIRS or qSOFA component variable as part of the study design; (3) recorded the worst values (of more than 1 observation) of SIRS and qSOFA component variables in the first 24 hours after presentation vs the initial values on presentation; (4) did not record patient transfer status; or (5) did not record HIV status. We excluded patients younger than age 18 years or patients with missing SIRS or qSOFA components. We performed multiple imputation using chained regression equations to address missing data. We also assessed the performance of the qSOFA score and SIRS criteria as mortality prediction tools, calculating the discrimination of hospital mortality, using AUROC, with models that excluded baseline risk factors. As opposed to predictive validity, which evaluates a score's ability to predict excess deaths (adjusting for baseline factors), mortality prediction assesses the extent to which a tool predicts all deaths.

Results

Patient Characteristics

A total of 6569 adults admitted to 17 hospitals in 10 countries in sub-Saharan Africa, Asia, and the Americas were included in this analysis (Table 1; eMethods in the Supplement). The median cohort size was 561 (range, 105-1923 patients). There were varying levels of HIV prevalence among the cohorts (range, 2%-43%), and substantial heterogeneity in types of infection (**Table 2**). Hospital mortality (range, 1%-39%) in all but the Sri Lanka cohort exceeded that of the cohorts used in the Sepsis-3 analyses (4% hospital mortality).[5]

Overall, 1759 patients (27%) had a qSOFA score of 0, 2548 (39%) had 1, 1882 (29%) had 2, and 380 (6%) had 3 (**Figure 1**). In comparison, 1476 patients (22%) had 0 SIRS criteria, 1986 (30%) had 1, 1687 (26%) had 2, 1057 (16%) had 3, and 363 (6%) had 4. The distribution of patients by qSOFA score and SIRS criteria differed substantially between cohorts (eFigure 1 in the Supplement). Across the cohorts, qSOFA and SIRS components were variably missing (eTable 2 in the Supplement). Heart rate was not recorded in the SEAQUAMAT cohort, and white blood cell count was not recorded in either the SEAQUAMAT

Table 2. Patient Characteristics

Variable	No. (%)									
	Kigali[8] (N = 302)	Gitwe (N = 561)	Suspected Lassa[9] (N = 540)	Haiti-RELIC 1[10] (N = 156)	Haiti-RELIC 2[11] (N = 105)	Ubon-Sepsis[12] (N = 1210)	SEAQUAMAT[13] (N = 1148)	Vietnam[14] (N = 624)	Sri Lanka[15] (N = 1923)	Combined Cohort (N = 6569)
Age, median (IQR), y	36 (26-49)	39 (28-58)	30 (22-39)	42 (28-56)	38 (26-63)	54 (38-69)	29 (22-40)	41 (27-58)	40 (29-55)	38 (26-55)
Male	181 (60)	202 (36)	223 (41)	62 (40)	40 (38)	637 (53)	871 (76)	330 (53)	1203 (63)	3749 (57)
HIV infected	130 (43)	30 (5.4)	NR[a]	13 (8.3)	6 (5.7)	27 (2.2)	NR[a]	27 (4.3)	NR[a]	233 (3.6)
Infection type[b]										
Malaria	29 (9.6)	259 (46)	0 (0)	9 (5.8)	38 (36)	37 (3.1)	1088 (95)	1 (0.2)	0 (0)	1461 (24)
Dengue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	134 (11)	0 (0)	214 (34)	18 (0.9)	366 (6.1)
Pneumonia	31 (10)	59 (11)	0 (0)	17 (11)	26 (25)	280 (23)	0 (0)	118 (19)	59 (3.1)	590 (9.8)
Tuberculosis	82 (27)	4 (0.7)	0 (0)	11 (7.1)	15 (14)	37 (3.1)	0 (0)	40 (6.4)	21 (1.1)	210 (3.5)
Transferred from other hospital	216 (72)	NR[a]	NR[a]	0 (0)	0 (0)	890 (74)	NR[a]	256 (41)	NR[a]	1362 (21)
SIRS ≥2[c]	138 (46)	278 (50)	310 (57)	85 (54)	104 (99)	1095 (91)	389 (34)	321 (51)	387 (20)	3107 (47)
Temperature >38°C or <36°C	84 (28)	208 (37)	105 (19)	65 (42)	74 (70)	804 (66)	557 (49)	208 (33)	309 (16)	2414 (37)
Heart rate >90 bpm	197 (65)	318 (57)	354 (66)	83 (53)	94 (90)	1056 (87)	NR[a]	329 (53)	511 (27)	2942 (45)
White blood cell count >12 000/μL or <4000/μL or >10% immature bands	40 (13)	161 (29)	78 (14)	6 (3.9)	16 (15)	776 (64)	NR[a]	153 (25)	NR[a]	1230 (19)
Respiratory rate >20 min or $Paco_2$ <32 mm Hg	115 (38)	161 (29)	368 (68)	85 (54)	87 (83)	733 (61)	790 (69)	303 (49)	755 (39)	3397 (52)
qSOFA ≥2[c]	62 (21)	107 (19)	196 (36)	48 (31)	55 (52)	592 (49)	748 (65)	200 (32)	254 (13)	2262 (34)
Respiratory rate ≥22 min	113 (37)	145 (26)	368 (68)	85 (54)	87 (83)	733 (61)	788 (69)	303 (49)	755 (39)	3377 (51)
Altered mental status	74 (25)	57 (10)	12 (2.2)	19 (12)[d]	12 (11)[d]	163 (13)[e]	702 (61)	121 (19)	58 (3)	1218 (19)
SBP ≤100 mm Hg	72 (24)	239 (43)	240 (44)	60 (38)	55 (52)	781 (65)	567 (49)	287 (46)	556 (29)	2857 (43)
Hospital mortality	66 (22)	38 (6.8)	85 (39)	28 (19)	11 (11)	90 (7.4)	218 (19)	83 (13)	24 (1.3)	643 (10)

Abbreviations: bpm, beats per minute; IQR, interquartile range; NR, not recorded; $Paco_2$, arterial partial pressure of carbon dioxide; qSOFA, quick Sequential (Sepsis-Related) Organ Failure Assessment; SIRS, systemic inflammatory response syndrome; SBP, systolic blood pressure.

[a] Data not recorded; where HIV status, hospital transfer status, and individual components of the qSOFA score or SIRS criteria were missing, they were assumed to be normal.

[b] Infection type was preferentially classified according to laboratory-confirmed diagnosis. When this was unavailable or inapplicable, patients were classified according to discharge diagnosis or, last, according to admission diagnosis.

[c] For all components of the qSOFA score and the SIRS criteria, the most abnormal values in the first 24 hours after presentation to the study hospital were included.

[d] Mental status not explicitly recorded in the medical record. Any patient with diagnosis of encephalopathy on admission was counted as abnormal. All others were assumed normal.

[e] Glasgow Coma Scale was adjusted using the method described by Meredith et al[18] for 142 patients in the Ubon-Sepsis cohort. Glasgow Coma Scale was otherwise not adjusted.

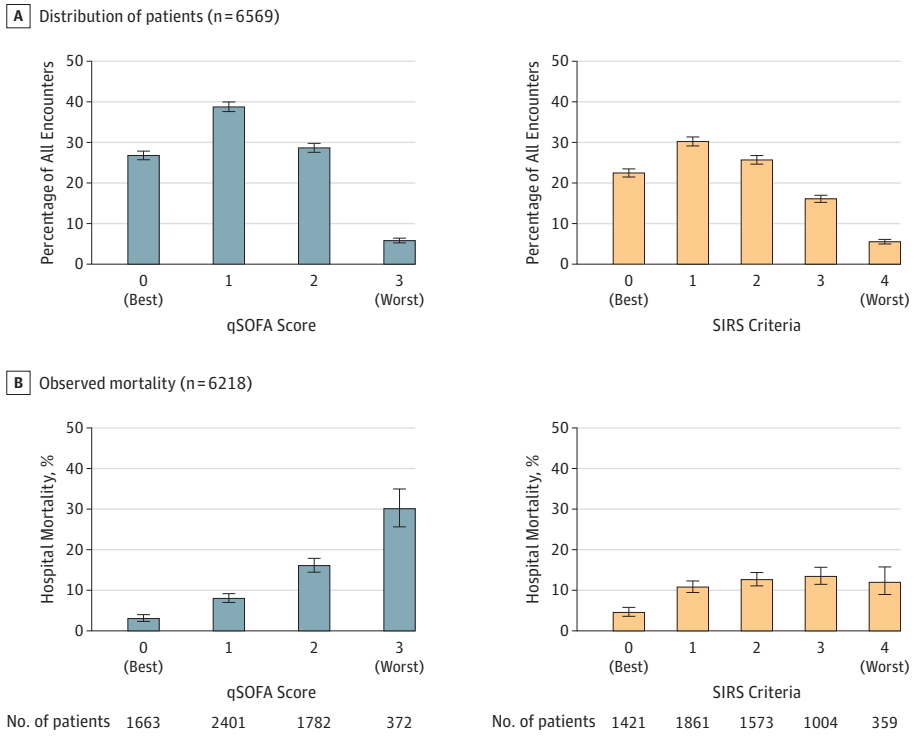
or Sri Lanka cohorts. Mental status was the most frequently missing qSOFA component, missing in up to 95% of patients in one cohort (Suspected Lassa, 512 of 540 missing). Of the SIRS components, white blood cell count was the most frequently missing, missing in up to 92% of patients in one cohort (Haiti-RELIC1, 143 of 156 missing). Overall, qSOFA score was more frequently complete than SIRS criteria in most cohorts. Outcome data were missing for 351 patients (5.3%).

The proportion of patients who died consistently increased with higher qSOFA score, but this was not the case for SIRS criteria (3%, 8%, 16%, and 30% mortality for qSOFA score of 0, 1, 2, or 3, respectively, and 5%, 11%, 13%, 13%, and 12% for 0, 1, 2, 3, or 4 SIRS criteria in the combined cohort) (Figure 1). Among those with known vital status at hospital discharge, the 2154 patients (35%) with 2 or more qSOFA points accounted for 62% of deaths (399/643), and the 2936 patients (47%) with 2 or more SIRS criteria accounted for 59% of deaths (377/643). The association with mortality remained generally stronger for qSOFA than for SIRS across the individual cohorts, but the relationship was less consistent (eFigure 2 in the Supplement).

Predictive Validity of qSOFA Score and SIRS Criteria Among Hospitalized Patients With Suspected Infection

In the individual cohorts, the range of RR for hospital mortality comparing patients with high vs low or moderate score was generally higher for qSOFA than for SIRS (qSOFA: RR range, 1.1 [95% CI, 0.7-1.9]; hospital mortality, 24% vs 21%; difference, 3% [95% CI, −9% to 15%] to 5.6 [95% CI, 2.5-12]; hospital mortality, 4% vs 1%; difference, 4% [95% CI, 1%-6%]) and SIRS: RR range, 0.9 [95% CI, 0.5-1.8]; hospital mortality,

Figure 1. Distribution of Patients (A) and Observed Mortality (B) by Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score and Systemic Inflammatory Response Syndrome (SIRS) Criteria Among Patients With Suspected Infection in the Combined Cohort



Maximum qSOFA scores and SIRS criteria were calculated based on all available information in the first 24 hours after presentation to study hospital. Error bars indicate 95% CIs. Only those patients with known outcome status were included in the analytic sample for panel B.

7% vs 8%; difference, −0.4% [95% CI, −6% to 5%] to 3.5 [95% CI, 1.4-8.6]; hospital mortality, 27% vs 8%; difference, 19% [95% CI, 8%-31%]; **Figure 2**; eTable 3 in the Supplement). In the combined cohort, the OR for hospital mortality comparing patients with high vs low or moderate score was higher for qSOFA than for SIRS overall (qSOFA: OR, 3.6 [95% CI, 3.0-4.2]; hospital mortality, 19% vs 6%; difference, 13% [95% CI, 11%-14%] vs SIRS: 1.7 [95% CI, 1.4-2.0]; hospital mortality, 13% vs 8%; difference, 5% [95% CI, 3%-6%]), and across quartiles of baseline risk (qSOFA: OR range, 2.2 [95% CI, 1.7-3.0]; hospital mortality, 20% vs 10%; difference, 10% [95% CI, 6%-14%] to 4.6 [95% CI, 3.2-6.6]; hospital mortality, 19% vs 5%; difference, 14% [95% CI, 11%-18%] vs SIRS: OR range, 1.4 [95% CI, 0.9-2.0]; hospital mortality, 10% vs 7%; difference, 2% [95% CI, −1% to 5%] to 2.0 [95% CI, 1.4-2.9]; hospital mortality, 13% vs 7%; difference, 6% [95% CI, 3%-9%]; eTable 4 in the Supplement).

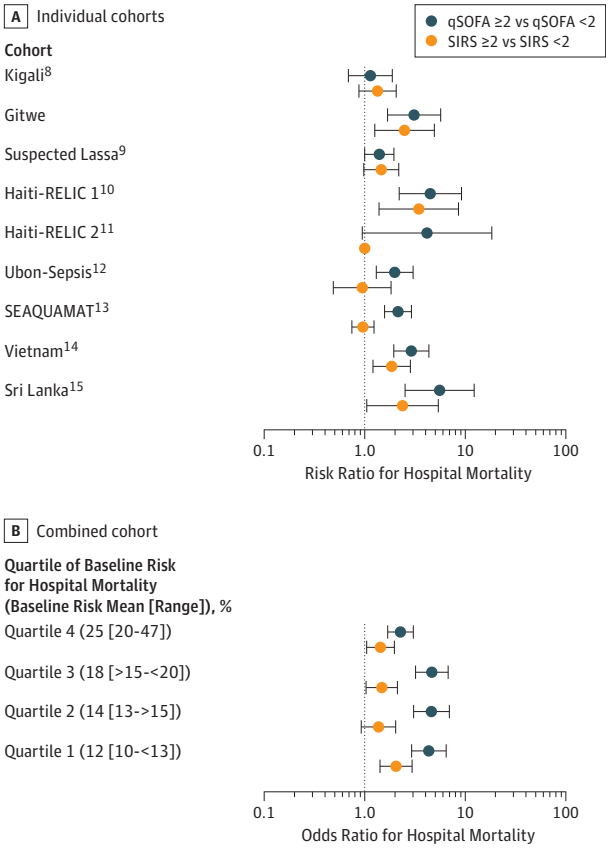
There was a stepwise increase in the odds of hospital mortality comparing moderate (1) vs low (0), and high (≥2) vs low (0), qSOFA score in the combined cohort (eFigure 3 in the Supplement). These incremental changes were less apparent for SIRS criteria. For example, the OR for hospital mortality (moderate vs low) was 2.8 for qSOFA (95% CI, 2.0-3.9; hospital mortality, 8% vs 3%; difference, 5% [95% CI, 4%-6%]) compared with 2.5 for SIRS criteria (95% CI, 1.9-3.4; hospital mortality, 11% vs 5%; difference, 6% [95% CI, 4%-8%]). For high vs low qSOFA, the OR was 7.2 (95% CI, 5.3-9.9; hospital mortality, 19% vs 3%; difference, 16% [95% CI, 14%-17%]), and ranged from 3.3 (95% CI, 2.1-5.3; hospital mortality, 20% vs 7%; difference, 13% [95% CI, 9%-17%]) to 16 (95% CI, 6.3-49; hospital mortality, 17% vs 1%; difference, 16% [95% CI, 12%-19%]) across quartiles of baseline risk. The OR for hospital mortality was 3.1 (95% CI, 2.3-4.1; hospital mortality, 13% vs 5%; difference, 8% [95% CI, 7%-10%]) comparing patients with high vs low SIRS criteria, and ranged from 2.0 (95% CI, 1.2-3.5; hospital mortality, 16% vs 8%; difference, 7% [95% CI, 3%-12%]) to 4.4 (95% CI, 2.3-9.0; hospital mortality, 13% vs 3%; difference, 10% [95% CI, 6%-13%]) across quartiles of baseline risk. These findings were similar in the individual cohorts.

The AUROC values for a model with qSOFA points plus baseline risk varied across the individual cohorts (AUROC range, 0.63 [95% CI, 0.55-0.71] to 0.92 [95% CI 0.84-0.99]), while the AUROC values for a model with SIRS criteria plus baseline risk were generally lower (AUROC range, 0.59 [95% CI 0.55-0.63] to 0.87 [95% CI 0.75-0.99]; **Figure 3**; eTable 5 and eFigure 4 in the Supplement). Discrimination for hospital mortality in the combined cohort was improved by adding qSOFA to the baseline risk model (increase in AUROC, 0.15; $P < .001$), as well as compared with the model of SIRS criteria plus baseline risk (increase in AUROC, 0.11; $P < .001$; **Figure 4**; eTable 5 in the Supplement).

Predictive Validity of qSOFA Score and SIRS Criteria Among Prespecified Subgroups

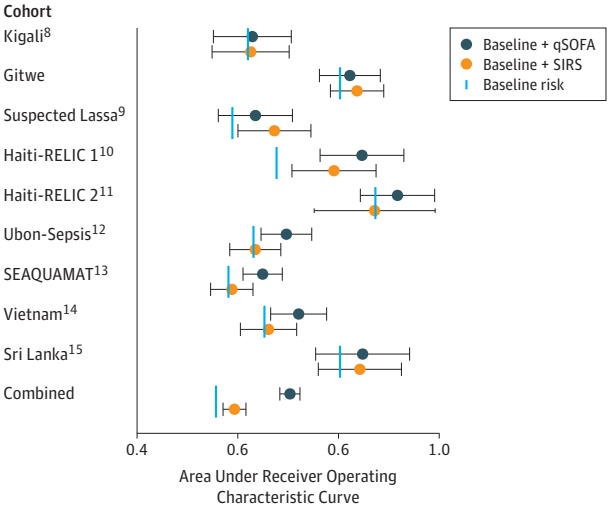
The qSOFA score and SIRS criteria were evaluated among prespecified subgroups of patients with HIV, malaria, dengue fever,

Figure 2. Risk Ratios and Odds Ratios for Hospital Mortality



A, Risk ratio for hospital mortality (log-scale) comparing encounters with ≥2 vs <2 Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) points and ≥2 vs <2 systemic inflammatory response syndrome (SIRS) criteria among patients with suspected infection by individual cohort. B, Odds ratio for hospital mortality (log-scale) comparing encounters with ≥2 vs <2 qSOFA points and ≥2 vs <2 SIRS criteria among patients with suspected infection by quartile of baseline risk for hospital mortality in the combined cohort. Only those patients with known outcome status (n = 6218) were included in the analytic sample. Overlaps in the quartile limits are due to rounding. Baseline risk determined based on age, sex, HIV status, and transfer status. Error bars indicate 95% CIs. For crude data, see eTables 3 and 4 in the Supplement for panels A and B, respectively.

Figure 3. Discrimination of Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score or Systemic Inflammatory Response Syndrome (SIRS) Criteria Added to Baseline Risk Model for Hospital Mortality Among Patients With Suspected Infection in the Individual and Combined Cohorts



Baseline risk determined based on age, sex, HIV status, and transfer status. The area under the receiver operating characteristic curve data derive from the baseline model alone, baseline model plus qSOFA score (range, 0-3), and baseline model plus SIRS criteria (range, 0-4). Error bars indicate 95% CIs. Only those patients with known outcome status (n = 6218) were included in the analytic sample.

pneumonia, and tuberculosis within individual cohorts with adequate data and within the combined cohort (eTable 6, eFigure 5, and eFigure 6 in the Supplement). The overall predictive validity patterns were similar to those for the combined cohorts.

Sensitivity Analyses

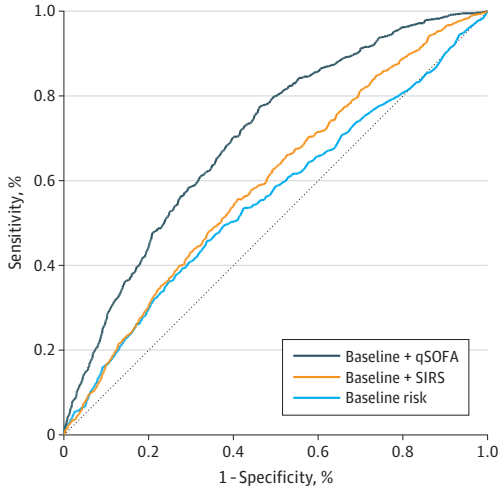
The qSOFA score and SIRS criteria were evaluated across a range of sensitivity analyses, and the results of these analyses were consistent with the main study findings (eTable 7 in the Supplement). The qSOFA score was a superior mortality prediction tool relative to SIRS (AUROC for qSOFA, 0.69 [95% CI 0.67-0.71] vs AUROC for SIRS, 0.59 [95% CI 0.57-0.61]; $P < .001$; eTable 8 in the Supplement).

Discussion

This secondary analysis of 9 cohorts of adult patients hospitalized with suspected infection in LMICs found that the qSOFA score had good predictive validity for the identification of sepsis or analogous severe infectious course across a wide variety of clinical settings in sub-Saharan Africa, Asia, and the Americas, ranging from community hospitals to academic referral centers, both within and outside of the ICU, and among patients with variable prevalence of HIV infection, illness severity, and baseline risk of death. Additionally, a moderate qSOFA score was associated with increased risk of death above and beyond baseline risk. The qSOFA score had greater predictive validity compared with the SIRS criteria.

The patients included in this study were distinct from those included in the derivation and validation cohorts used for the development of qSOFA, as well as in subsequent external validations in high-income settings. The patients in this study were substantially younger and had very different comorbidities, including high prevalence of HIV,[5,24] and many were treated in hospitals with no or limited access to organ support resources such as mechanical ventilators and vasopressors. These findings are consistent with those of 2 single-center studies of adult inpatients in Gabon and Malawi,[6,7] but add to them by substantially increasing sample size and breadth of settings, infections, and severity of illness.

Figure 4. Receiver Operating Characteristic Curves for Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score or Systemic Inflammatory Response Syndrome (SIRS) Criteria Added to Baseline Risk Model for Hospital Mortality Among Patients With Suspected Infection in the Combined Cohort



Baseline risk determined based on age, sex, HIV status, and transfer status. The area under the receiver operating characteristic curve (AUROC) data derive from the baseline model alone, baseline model plus qSOFA score (range, 0-3), and baseline model plus SIRS criteria (range, 0-4). AUROCs: baseline risk model, 0.56 (95% CI, 0.53-0.58); baseline risk plus qSOFA, 0.70 (95% CI, 0.68-0.72); and baseline risk plus SIRS, 0.59 (95% CI, 0.57-0.62).

These findings may have important clinical implications. First, while qSOFA has been endorsed by more than 30 professional societies worldwide, clinicians and researchers now have data to support its use as part of clinical decision-making tools to be tested among hospitalized patients with suspected infection in LMICs. Second, the findings of this study support the use of qSOFA, which is comprised entirely of data that can be assessed at the bedside without additional resources, over SIRS, which necessitates laboratory testing. This is important for hospitals in resource-limited settings, which often do not have the laboratory capacity or financial resources to routinely perform a complete blood count test and blood chemistry among all patients with suspected infection. Third, these data demonstrate that qSOFA performed well among patients with infections such as malaria, dengue fever, and viral hemorrhagic infection, a novel finding that expands on previous research from high-income countries that included primarily patients with bacterial, fungal, and other viral infections.[5]

Fourth, these findings demonstrate that, while a low qSOFA score (0) may be associated with low risk of hospital death, a moderate qSOFA score (1) was associated with increased risk of death and may have important and previously undescribed implications for triage and resource allocation in low-resource settings. Patients with a low qSOFA score may not require hospitalization in the setting of an otherwise reassuring clinical assessment, whereas those with a moderate qSOFA score may require careful observation for clinical deterioration, or early medical intervention. Those with a high qSOFA score (≥2) may merit immediate deployment of scarce critical care resources.[22] These findings are consistent with previous work in Tanzania that demonstrated increasing risk of death among adult ICU patients with no, single, or multiple vital sign derangement.[25]

Limitations

This study has several limitations. First, the study was retrospective, with important consequences such as missing data, varied definitions of *suspected infection* in each cohort, and lack of uniformity in the assessment of qSOFA and SIRS component variables (eg, mental status) or baseline risk factors. Additionally, the retrospective design limits the ability to draw definitive conclusions about the clinical utility of the qSOFA score when deployed prospectively. The findings of the importance of a moderate qSOFA score underscore the need for formal prospective evaluation of any decision rule incorporating the qSOFA score, potentially exploring the merits of different cut points or time windows for score assessment, in a randomized clinical trial. Second, several qSOFA and SIRS component variables were inconsistently missing across the individual data sets. It is possible that the performance of the scores could have been affected by these missing values, although some of this missingness reflects the likely conditions in clinical practice.

Third, this study did not compare the predictive validity of qSOFA with the SOFA score, which some studies have found to have superior predictive validity for the identification of patients likely to be septic.[24] The SOFA score was not assessed because of the unavailability of requisite laboratory and other variables in the data. Fourth, while heterogeneity between the cohorts was a strength of this study, and the analytic approach for the combined cohort accounted for nonindependence within each individual data set, it is possible that results in the combined cohort were skewed by clinical, methodological, or statistical heterogeneity. Fifth, this study focused on adult patients only and did not evaluate children at risk for sepsis. Sixth, this study tested only whether qSOFA was associated with excess death: this is a test of predictive validity related to the concept that sepsis increases the odds of death. We did not test whether qSOFA offered any information that might distinguish between different types of infection or infection-associated organ dysfunction.

Conclusions

When assessed among hospitalized adults with suspected infection in 9 LMIC cohorts, the qSOFA score identified infected patients at risk of death beyond that explained by baseline factors. However, the predictive validity varied among cohorts and settings, and further research is needed to better understand potential generalizability.

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