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Validation of prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among cardiac-, thoracic-, and vascular-surgery patients admitted to a cardiothoracic intensive care unit

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Abstract

Sepsis-3 Definition: Sepsis is defined as life-threatening organ dysfunction due to a dysregulated host response to infection. The clinical criteria of sepsis include organ dysfunction, which is defined as an increase of two points or more on the sequential organ failure assessment (SOFA). For patients with infection, an increase of 2 SOFA points yields an overall mortality rate of 10%. Patients with suspected infection who are likely to have a prolonged intensive care unit (ICU) stay or to have in-hospital mortality can be promptly identified at the bedside with a quick SOFA (qSOFA) score of 2 or higher.

Importance: The sepsis-3 criteria have emphasized the value of a change of two or more points on the SOFA, introduced the qSOFA, and removed the systemic inflammatory response syndrome (SIRS) criteria from the sepsis definition.

Objective: To externally validate and assess the discriminatory capacities of an increase in the SOFA score by two or more points, the presence of two or more SIRS criteria, or a qSOFA score of 2 or more points for outcomes in 5109 patients, the vast majority of whom were postcardiac surgery patients who were admitted to a Cardiothoracic Surgical ICU in Singapore.

Design, Setting, and Participants: A retrospective cohort analysis of 5109 patients with an infection-related primary admission diagnosis in the cardiothoracic intensive care unit (CTICU) at the National University Hospital (NUH) in Singapore from 2010 to 2016.

Exposures: The SOFA, qSOFA, and SIRS criteria were applied to the data representing the worst condition within 24 hours of ICU admission.

Main Outcomes and Measures: The primary outcome was in-hospital mortality. Discrimination was assessed using the area under the receiver operating characteristic curve (AUROC).

Results: In 5109 patients, the average mortality of patients with an increase in the SOFA scores of less than 2 points was 3.5% (n = 64), and it was 6% (n = 199) for those

with an increase in the SOFA scores of 2 or more points. The mortality of patients with an increase in the qSOFA scores of less than 2 points was 2.6% (n = 7), and it was 5.3% (n = 256) for those with an increase in the qSOFA scores of 2 or more points. The mortality of patients with an increase in the SIRS criteria of less than 2 points was 3.6% (n = 30), and it was 5.4% (n = 233) for those with an increase in the SIRS criteria of 2 or more points. The AUROC of in-hospital mortality of patients with an increase in the SOFA, qSOFA, and SIRS criteria of 2 or more points was 0.96, 0.95, and 0.95, respectively.

Conclusions and Relevance: In adults with suspected infection admitted to the CTICU in NUH, the change in in-hospital mortality between patients with an increase in SOFA scores of less than 2 and those with an increase of 2 or more was 2.5 percentage points. In contrast to other studies, the absolute change in mortality was nearly the same compared to the qSOFA and SIRS criteria, and the qSOFA score had the greatest percentage increase of 104%, compared to 71% for the SOFA score and 50% for the SIRS criteria. Besides, from the perspective of discriminatory capacities, an increase in SOFA scores of 2 or more did not demonstrate significantly greater prognostic accuracy for in-hospital mortality than equivalent increases in qSOFA scores or SIRS criteria. These findings suggest distinctive characteristics of the study population in the CTICU that are different from the general population.

KEYWORDS

quick sequential organ failure assessment, sepsis, sepsis definition, Sepsis-3, sequential organ failure assessment, systemic inflammatory response syndrome

1 | INTRODUCTION

1.1 | About sepsis

Sepsis, which is a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, is a leading cause of mortality and critical illness worldwide.[1] A 1992 consensus conference developed an initial definition of sepsis, and the definitions of sepsis and septic shock were revised in 2001. The most recent definition, Sepsis-3, was introduced to replace previous definitions and offers greater consistency for epidemiological studies and clinical trials.

Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, with an emphasis on acute changes in total sequential organ failure assessment (SOFA) scores equal to or larger than 2 points. At the same time, the quick sofa (qSOFA) was introduced to identify patients with suspected infection who are likely to have a prolonged ICU stay or to experience in-hospital mortality. By contrast, the previous definition was based on the systemic inflammatory response syndrome (SIRS) criteria. Due to the worldwide significance of the new definition, public awareness has risen rapidly with its introduction. Numerous researchers have conducted related studies to compare the new definition with the previous version, with a wide variety of results.

Ho et al[2] found that the qSOFA had a modest ability to predict the mortality of both septic and nonseptic patients while combining qSOFA with plasma lactate had a predictive potential comparable to the standard SOFA score. For contrast, Askim et al[3] found that the qSOFA did not perform reliably in predicting severe sepsis and mortality for those patients admitted to the emergency department. In 2016, Seymour et al[4] conducted a verification trial based on the new definition and demonstrated that SOFA's predictive validity for in-hospital mortality was not significantly different from that of the more complex Logistic Organ Dysfunction System, but it was statistically greater than those for the SIRS and qSOFA, thereby supporting its use for capturing clinical criteria related to Sepsis-3. Matics et al[5] focused on critically ill children using the SOFA and determined that the Sepsis-3 definition was feasible and yielded promising results. In contrast to studies conducted in developed countries, Besen et al[6] analyzed data from a Brazilian intensive care unit (ICU) and concluded that the new Sepsis-3 definition was accurate for stratifying mortality and superior to previous definitions. In 2017, Giamarellos-Bourboulis et al[7] conducted a review to evaluate the new Sepsis-3 definition. That analysis positively validated the use of the SOFA to predict unfavorable outcomes and to limit misclassification into lower severity classes. These authors also found that the SOFA performed better than the qSOFA. Both scores were superior to the SIRS criteria.

Accurate diagnostic criteria and consensus definitions play an important role in intensive care medicine by providing tools for research, benchmarking, performance monitoring, and accreditation. Seymour et al[4] published data regarding the validity of a 2-point-or-

more change in SOFA scores as a means of identifying sepsis in patients who were critically ill with suspected infection, assuming a SOFA of 0 for patients not known to have pre-existing organ dysfunction. Besides, the qSOFA was introduced as a possible predictive tool for patients with suspected infection outside of the ICU. Recently, Raith et al[8] observed that, in adults with suspected infection admitted to an ICU, an increase in SOFA scores of 2 or more had greater prognostic accuracy for in-hospital mortality than comparable increases in SIRS criteria or qSOFA scores.

1.2 | The goal of the study

The primary aims of this study were to (a) compare the functionality of an increase in SOFA scores by 2 or more points, an increase in SIRS criteria of 2 or more, and an increase in qSOFA scores by 2 or more points, all measured within the first 24 hours of admission, to categorize in-hospital mortality using external data from the cardiothoracic intensive care unit (CTICU) at the National University Hospital (NUH) in Singapore and (b) compare their effectiveness invalidating the latest definition of sepsis.[9]

2 | METHODS

2.1 | Study design and data extraction

A total of 5593 patient records were collected from the CTICU of the National University Hospital, Singapore, from March 2010 to October 2016. The CTICU uses the IntelliSpace Critical Care and Anesthesia (ICCA; Philips Medical Systems) system, which is a digital tracking system that automatically collects patients' clinical records in real-time. We also collected a set of patients' demographic and clinical records (including vital signs, laboratory tests, and nursing assessments) from ICU admission to ICU discharge. This study was approved by the National Healthcare Group (NHG) Domain Specific Review Board (DSRB) (Reference number: 2016/00062).

Of the 5593 patients who were admitted to the CTICU, 484 were excluded due to incomplete data, leaving 5109 patients in our analysis. Our study population included patients who were admitted to the CTICU after cardiac surgery (vast majority), thoracic surgery, and vascular surgery, patients who presented with critical cardiac, thoracic and vascular surgical diagnoses (eg, Stanford type A aortic dissection and critical coronary artery stenosis with intra-aortic balloon pump), and patients who developed severe postoperative complications requiring ICU management.

The following data were extracted: length of stay, urea, respiratory rate, sodium, urine, systolic, white blood cell, creatinine, diastolic, platelets, mean arterial pressure, total brand, Glasgow Coma Scale, chloride, arterial pO_2, lactate, and central venous pressure. SOFA scores (range, 0 [best] to 24 [worst] points), qSOFA scores (range, 0 [best] to 3 [worst] points), and SIRS criteria (range, 0 [best] to 4 [worst] points) were calculated using physiological and laboratory parameters recorded over the first 24 hours of ICU admission. Standard criteria were applied, with a threshold of 2 or more points for each scoring system. In the primary analysis, a baseline score of 0 was assumed for all patients for the SOFA score, qSOFA score, and SIRS criteria.

2.2 | Outcome and statistical analysis

The primary study outcome was in-hospital mortality. For statistical analysis of evaluation, discriminatory capacities were determined by individually comparing the area under the receiver operating characteristic curves (AUROC) for each score. Furthermore, we conducted another baseline model, which was regarded as an improvement in the statistical analysis of evaluation.

3 | RESULTS

3.1 | Study population

Among the 5109 patients in our sample, the mean age was 59 years, 74% (n = 3781) were male, and 26% (n = 1328) were female. Of these patients, 263 (5.15%) died in the hospital. Of the study cohort, 3329 patients (65.2%) had an increase in SOFA scores from baseline of 2 or more, 4837 patients (94.7%) had a qSOFA score of 2 or more, and 4313 patients (84.4%) manifested two or more SIRS criteria. Demographic data are displayed in Table 1 and Figure 1. It is worth noting that those who had SOFA scores of 2 or more accounted for a smaller proportion than patients who had qSOFA scores or SIRS criteria of 2 or more. The distribution of criteria concerning the number of patients and their relationship with in-hospital mortality are presented in Figures 2 and 3, respectively.

TABLE 1 Demographic data for 5109 patients admitted to the intensive care unit

	All (N = 5109)	Survivors (n = 4846)	Nonsurvivors (n = 263)	Post-cardiac (n = 4478)	Post-thoracic (n = 631)
Age (mean), y	59.0	58.6	65.9	59.9	58.4
Male, n (%)	3781 (74)	3599 (95.2)	182 (4.8)	3359 (75.01)	420 (66.56)
Female, n (%)	1328 (26)	1247 (93.9)	81 (6.1)	1119 (24.99)	211 (33.44)
SOFA ≥2, n (%)	3329	3130 (94)	199 (6)	2825 (63.09)	504 (79.9)
qSOFA ≥2, n (%)	4837	4581 (94.7)	256 (5.3)	4321 (96.49)	516 (81.77)
SIRS ≥2, n (%)	4313	4080 (94.6)	233 (5.4)	3885 (86.76)	428 (67.83)

Abbreviations: qSOFA, quick SOFA; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

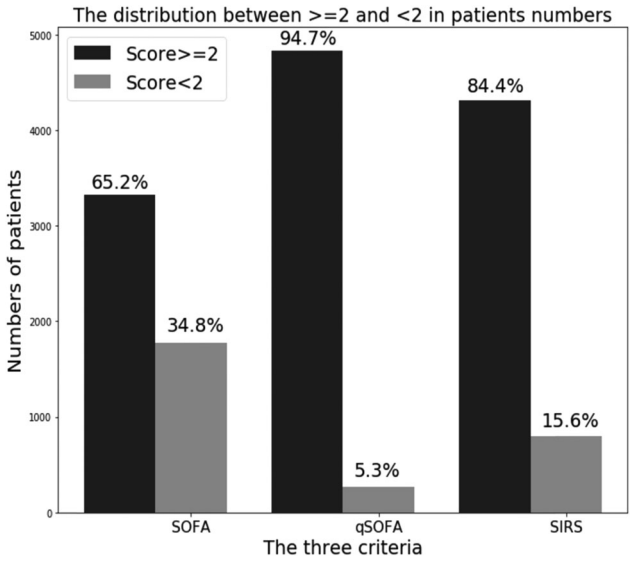

FIGURE 1 Distribution of patients by sequential organ failure assessment (SOFA) score, quick SOFA (qSOFA) score, and systemic inflammatory response syndrome (SIRS) criteria

3.2 | SOFA, SIRS, qSOFA, and study outcomes

The in-hospital mortality rate for patients whose SOFA scores increased by 2 or more from baseline was 6% vs 3.5% for those whose SOFA scores increased by less than 2, yielding a difference in mortality of 2.5%. Mortality was 5.3% for those whose qSOFA score was 2 or more vs 2.6% for patients with a qSOFA score of less than 2, yielding a difference in mortality of 2.7%. For those who had SIRS criteria of two or more, mortality was 5.4% vs 3.6% for those whose SIRS score was less than 2 points, yielding a difference of approximately 3%. Values are shown in Table 2.

3.3 | Score discrimination

In terms of discrimination of in-hospital mortality, the AUROC was 0.96 for SOFA scores, 0.95 for qSOFA scores, and 0.95 for SIRS criteria, as shown in Figure 4. Therefore, patients with an increase in SOFA scores from baseline of 2 or more points did not have a greater incremental increase in mortality across all deciles of baseline risk

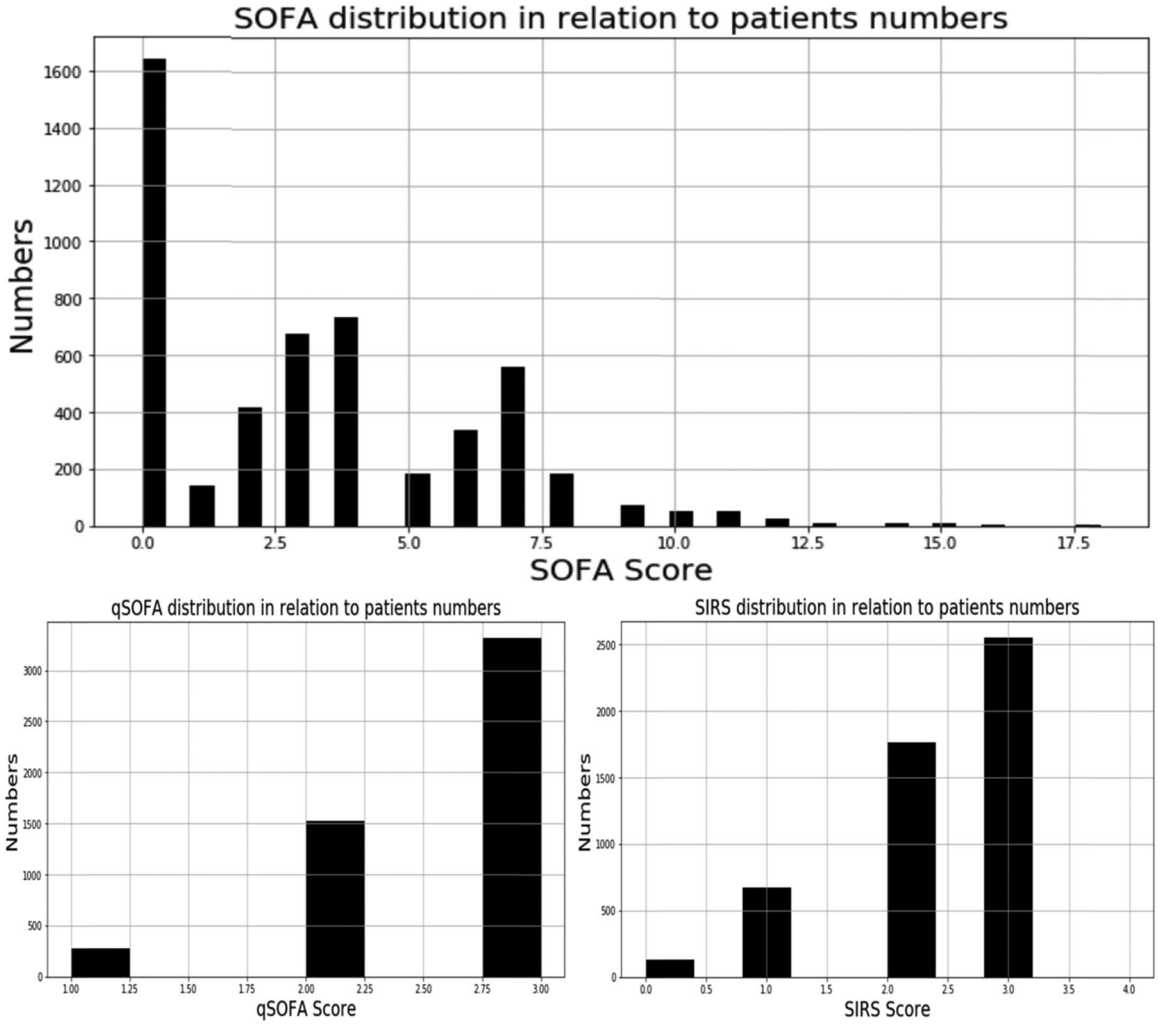

FIGURE 2 Distribution of patients admitted to intensive care unit with suspected infection (N = 5109) by sequential organ failure assessment (SOFA) score, quick SOFA (qSOFA) score, and systemic inflammatory response syndrome (SIRS) criteria

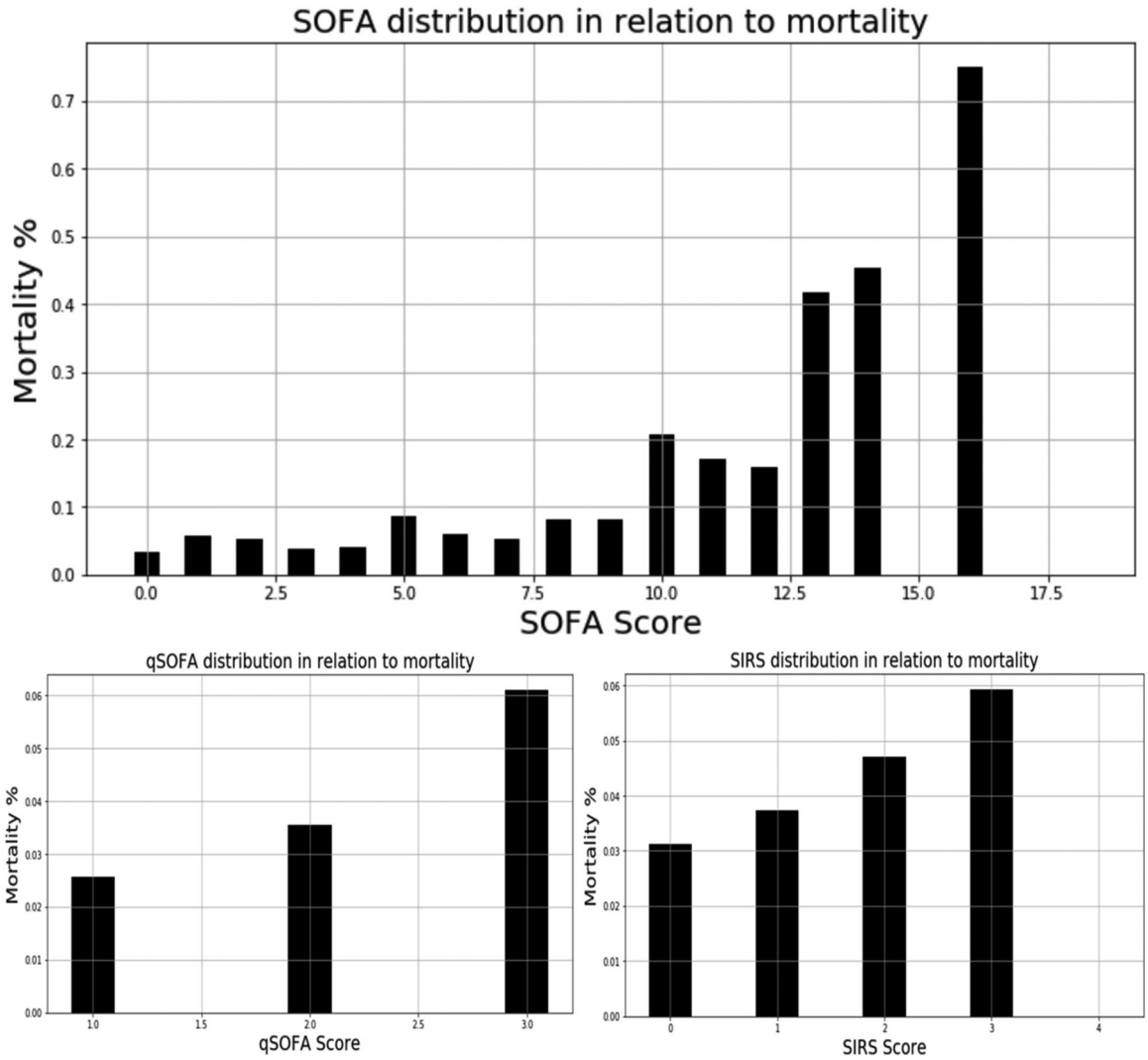

FIGURE 3 Mortality by sequential organ failure assessment (SOFA) score, quick SOFA (qSOFA) score, and systemic inflammatory response syndrome (SIRS) criteria among patients admitted to intensive care unit with suspected infection (N = 5109)

than patients with an increase of 2 or more in qSOFA scores or those with SIRS criteria of 2 or more.

4 | DISCUSSION

4.1 | Comparison of previous sepsis definition and Sepsis-3

Concerning the 1992 sepsis definition, the American College of Chest Physicians and the Society of Critical Care Medicine convened an international consensus conference to clarify the definitions of sepsis, severe sepsis, and septic shock, standardize research principles, and improve clinical detection. The resulting consensus report described SIRS criteria as the clinical response to an inflammatory process, with the presence of at least two SIRS criteria required to diagnose severe sepsis in critically ill patients.[1,10,11]

TABLE 2 Mortality between scores 2 or more and less than 2 for SOFA scores, qSOFA scores, and SIRS criteria

Criteria	SOFA	qSOFA	SIRS
Mortality (≥2)	6%	5.3%	5.4%
Mortality (<2)	3.5%	2.6%	3.6%

Abbreviations: qSOFA, quick SOFA; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

Of the 5109 patients included in this study, 4313 met the 1992 sepsis definition, while 3329 met the Sepsis-3 criteria. The primary outcome of mortality in patients meeting the Sepsis-3 criteria was 200 out of 3329 (6.0%). This mortality rate is slightly higher than that of 234 out of 4313 (5.4%) for patients who satisfied the 1992 definition. Similarly, the SOFA scores of patients meeting the Sepsis-3 criteria for septic shock were modestly higher (mean 5.03 vs 3.34) than those meeting the 1992 definition (Table 3).

In patients with qSOFA scores less than 2, those meeting the Sepsis-3 criteria had approximately double the mortality rate of those meeting the 1992 definition (4 of 169 (2.37%) vs 1 of 80 (1.25%), $P < .001$). Similarly, in patients with qSOFA score of 2 or more, those meeting the Sepsis-3 criteria had a higher mortality rate

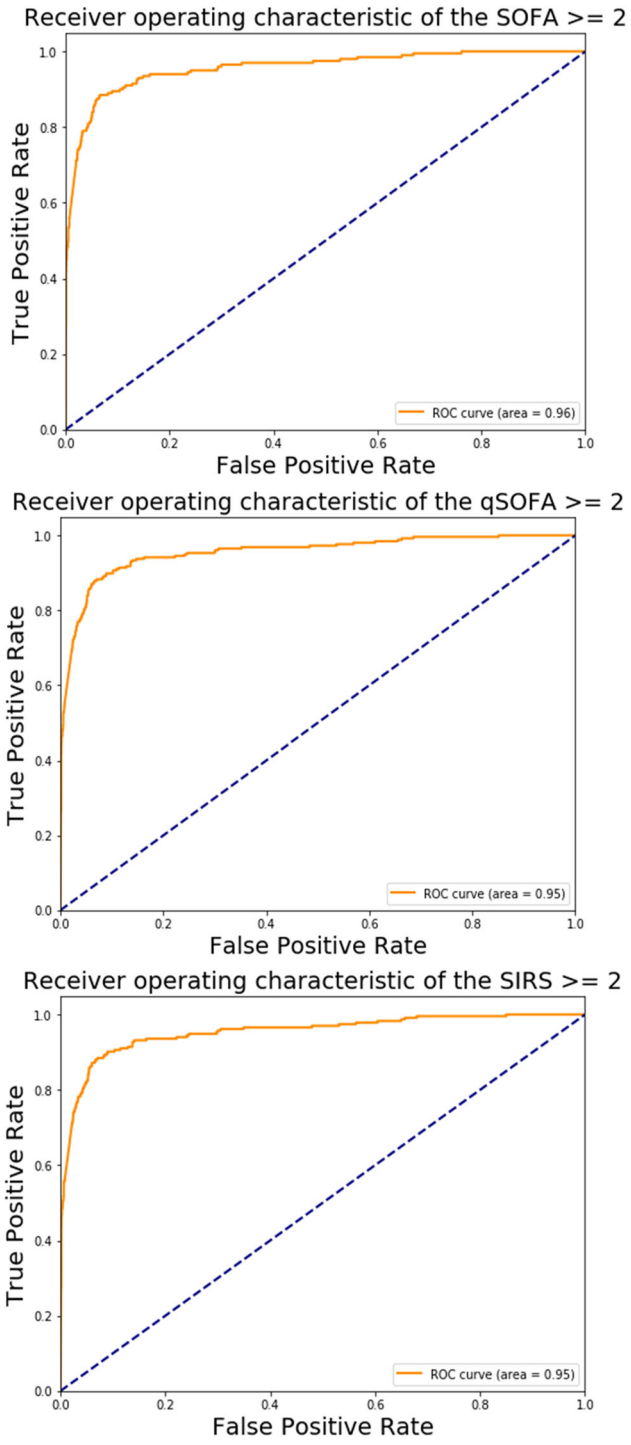

FIGURE 4 AUROCs (area under the receiver operating characteristic curves) for discriminatory capacity for in-hospital mortality for sequential organ failure assessment (SOFA) score, quick SOFA (qSOFA) score, and systemic inflammatory response syndrome (SIRS) criteria (increase in score) on intensive care unit admission

than those meeting the 1992 definition (196 of 3160 [6.2%] vs 233 of 4233 [5.5%], $P < .001$) (Table 4).

Thus, we can conclude that the new Sepsis-3 criteria identify patients with more organ failure, and they more accurately predict mortality compared to the 1992 sepsis definition. Nevertheless, it is fair to note that the 1992 definition is also effective for capturing mortality risk.

TABLE 3 Mortality and systemic inflammatory response syndrome (SOFA) score: Comparison between 1992 Sepsis definition and Sepsis-3 criteria

Variable	New Sepsis criteria (Sepsis-3) (N = 3329)	1992 Sepsis definition (N = 4313)
Mortality, n (%)	200 (6.0)	234 (5.4)
SOFA Mean	5.03	3.34

4.2 | Validation of the baseline model

Raith et al[8] concluded that defining sepsis by an increase in SOFA score provides greater prognostic accuracy for in-hospital mortality than either SIRS criteria or qSOFA score. However, our study found that the prognostic accuracies of the SOFA score, qSOFA score, and SIRS criteria are almost the same.

To further validate our results, we leveraged another baseline risk model (adjusted analysis). This baseline risk model for in-hospital mortality uses the same model for predicting mortality for all 5109 patients. It is constructed using some likely uncorrelated information at time of ICU admission, including factors relating to admission time (year, month, day, hour, minute, and second) and patient demographics (age, sex, IC, and race), in addition to the 17 attributes described previously, as shown in Table 5. Similarly, for the statistical analysis of the evaluation of the updated baseline risk model, we simultaneously compared the adjusted AUROCs derived from the baseline risk model for each score individually, as illustrated in Figure 5. The comparison of crude AUROC and adjusted AUROC (baseline risk model) is presented in Table 6.

Moreover, we divided our baseline risk into five ordered partitions, with approximately 1000 patients in each partition. The cutoff points corresponding to the partitions were the 20th, 40th, 60th, and 80th percentiles of the baseline risk. The results showed that patients with an increase from baseline in SOFA scores of 2 or more did not have a greater incremental increase in mortality across all deciles of baseline risk than patients with two or more SIRS criteria or those with a qSOFA score of 2 or more (Figure 6). These results coincide with the previous conclusions we obtained. It is worth mentioning that the SOFA even had inferior prognostic accuracy for in-hospital mortality than the qSOFA and SIRS in the first and last decile.

TABLE 4 Mortality and quick systemic inflammatory response syndrome (qSOFA) score: Comparison between 1992 Sepsis definition and Sepsis-3 criteria

Variable	New Sepsis criteria (Sepsis-3) (N = 3329)	1992 Sepsis definition (N = 4313)
qSOFA <2; mortality, n (%)	169; 4 (2.37)	80; 1 (1.25)
qSOFA ≥2; mortality, n (%)	3160; 196 (6.2)	4233; 233 (5.5)

TABLE 5 The attributes used in baseline risk model

Attributes	Explanations/Definitions
Sex	Patient's sex.
Race	Seven categories of race, disguised as "R1" to "R7".
IC	The numbers assigned to each patient by NUH, Singapore.
Admission year	The admission year of the patient.
Admission month	The admission month of the patient.
Admission day	The admission day of the patient.
Admission hour	The admission hour of the patient.
Admission minute	The admission minute of the patient.
Admission second	The admission second of the patient.
Length of stay (LOS)	The time length of the patient staying in ICU.
Age	Patient's age at the ICU admission.
Mortality	Indicator variable, =1 if the patient died in the hospital, =0 otherwise.
Respiratory rate (RR)	Frequency of breath (unit: times/min).
SpO_2	Peripheral capillary oxygen saturation; the amount of oxygen carried by the red blood cells in the body's arteries.
Urea	Amount of urea nitrogen in blood (unit: mmol/L).
Urine	Liquid waste produced by the kidneys.
Sodium	The major positive ion (cation) in the fluid surrounding the cells in the body.
Heart rate (HR)	Heart rate (unit: beats/min).
White blood cells (WBCs)	Amount of white blood cell in the blood (unit: number $\times 10^9$/L).
Hemoglobin	Iron-containing oxygen-transport metalloprotein in the red blood cells (unit: g/dL).
Systolic blood pressure	Systolic blood pressure; maximum pressure in blood vessels during a heartbeat (unit: mm Hg).
Potassium	The major positive ion (cation) found inside cells.
Temperature	Body temperature (unit: Celsius).
Creatinine	A byproduct of muscle metabolism that is excreted unchanged by the kidneys, an important indicator of renal health (unit: μmol/L).
Prothrombin time (PT)	A blood test measuring the time taken for the liquid portion (plasma) of blood to clot.
Diastolic blood pressure	Diastolic blood pressure; minimum pressure in blood vessels between two heartbeats (unit: mm Hg).
Platelets	An irregular, disc-shaped element in blood that assists blood clotting.
Glasgow Coma Scale (GCS)	Glasgow Coma Scale/Score; a neurological scale that records the conscious state of a person for initial as well as subsequent assessment (unit: point score from 3 [worst] to 15 [best]).
Mean arterial pressure (MAP)	Average pressure in arteries during one cardiac cycle.
Arterial pO_2	The partial pressure of oxygen in arterial blood (unit: mm Hg).
Arterial pCO_2	The partial pressure of carbon dioxide in arterial blood (unit: mm Hg).
Chloride	The major anion in the blood and extracellular fluid.
Lactate	A test that measures the amount of lactate in the blood.
Central venous pressure (CVP)	Blood pressure in the venae cavae, near the right atrium of the ability of the heart to pump the blood back into the arterial system.
Arterial pH	The acidity of arterial blood.
Hematocrit	The proportion of the blood that consists of packed red blood cells.
Albumin	A protein made by your liver.

4.3 | Relationship with previous studies

The relationship between SOFA scores and the risk of death has been confirmed in a variety of subgroups of patients,[1,12,13] including sepsis.[3,11] Raith et al[8] found that the qSOFA and SIRS criteria are suboptimal predictors of an adverse course of sepsis.

After external validation using the data from 5109 patients at NUH, the phenomenon by which the SOFA score has superior discriminatory performance over both the qSOFA score and SIRS criteria was not supported by our study. On the one hand, patients with an increase from baseline in SOFA scores of 2 or more did not have a greater incremental increase in mortality than patients with

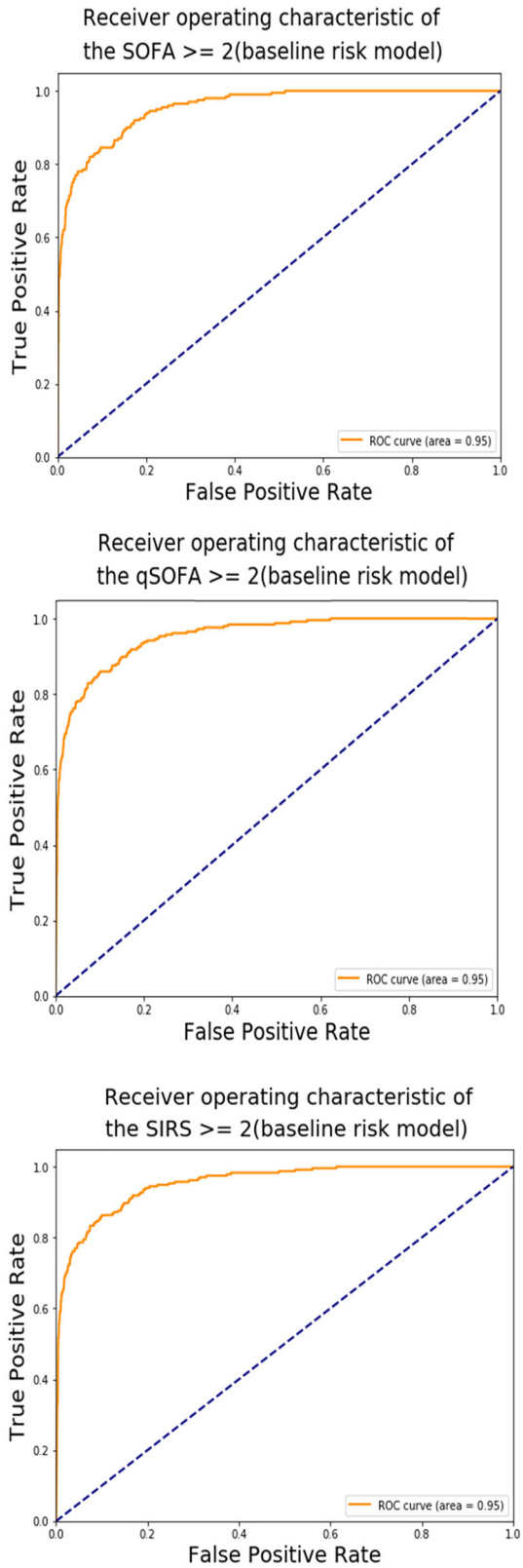

FIGURE 5 AUROCs (area under the receiver operating characteristic curves) for discriminatory capacity for in-hospital mortality using the baseline risk model for sequential organ failure assessment (SOFA) score, quick SOFA (qSOFA) score, and systemic inflammatory response syndrome (SIRS) criteria (increase in score) on intensive care unit admission

TABLE 6 Crude and Adjusted AUROCs (baseline risk model) for Discrimination of SOFA, qSOFA, and SIRS

In-hospital Mortality	SOFA Score	qSOFA Score	SIRS criteria
Crude AUROC	0.96	0.95	0.95
Adjusted AUROC (baseline risk model)	0.95	0.95	0.95

Abbreviations: AUROC; area under the receiver operating characteristic curves; qSOFA, quick SOFA SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

qSOFA scores of 2 or more or those with SIRS criteria of 2 or more. Besides, the incremental range was not as substantial as that reported by Raith et al.[8] On the other hand, the prognostic accuracy of an increase in SOFA scores by 2 or more for in-hospital mortality was similar to that of similar increases in the qSOFA score and SIRS criteria, based on our study.

It is worth noting that our accuracy in terms of AUROC is significantly higher than what has been reported in previous studies.[3,8] Most previous studies adopted logistic regression to predict the in-hospital mortality, which resulted in AUROC varying in the range between 0.6 and 0.8. In our analysis, we developed deep neural network models, which have demonstrated much higher accuracy than logistic regression models in many applications. We believe that the high accuracy (AUROC >0.9) in our study could be attributed to the adoption of advanced prediction models and the availability of a comprehensive data set.

4.4 | Study implications

To the best of our knowledge, validation of the new Sepsis-3 definition has not been performed in thoracic, cardiac, or vascular surgical populations in Asia. This serves as a basis for future comparison with other cardiothoracic surgical cohorts.

Our study shows that findings in individual study populations may differ significantly from one another. It is, therefore, prudent for individual ICUs to analyze their data to evaluate the prognostic accuracy of each of the three scores.

4.5 | Strengths

Health care quality in Singapore is on par with that of Western countries, thus eliminating any potential bias in the data set arising from the provision of substandard medical therapy.[13] Additionally, the mean age and sex distribution of our cohort are comparable with those of other studies. These factors establish a fair comparison with previous studies.

4.6 | Limitations

As this is an observational study, it was not possible to examine the efficacy of treatment once early warning of sepsis had been

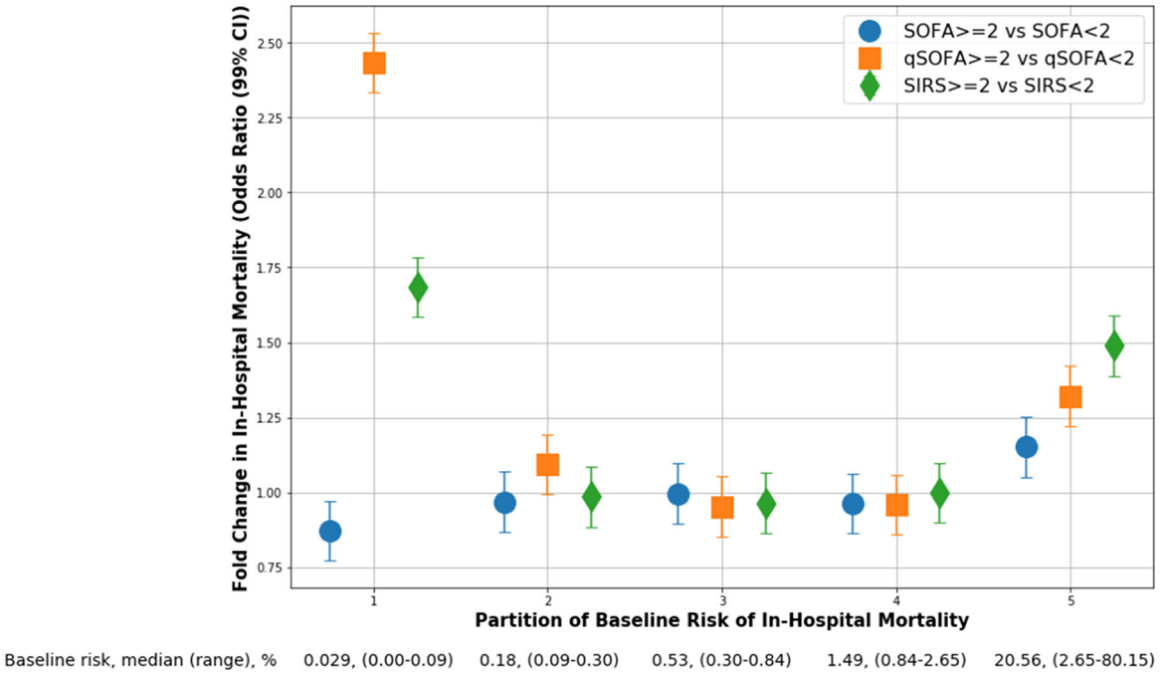

FIGURE 6 Odds ratios for in-hospital mortality comparing encounters with 2 or more vs less than 2 on sequential organ failure assessment (SOFA) score, quick SOFA (qSOFA) score, and systemic inflammatory response syndrome (SIRS) criteria for each partition of baseline risk in intensive care unit patients with suspected infection (N = 5109)

observed, particularly if prompt intervention altered the course of the disease process.

Furthermore, the study population was limited to patients admitted to a specialty ICU (the cardiothoracic ICU in the NUH, Singapore). However, our findings are important in terms of raising concerns regarding studies based on aggregated data, which fail to capture the individual characteristics of different clinical units and patient populations.

5 | CONCLUSIONS

In adults with suspected infection admitted to the cardiothoracic intensive care unit, an increase in the SOFA score of 2 or more did not have significantly greater prognostic accuracy or discriminative power for in-hospital mortality than comparable increases in the qSOFA score or SIRS criteria. In contrast with most prior studies,[8,9,14] those three criteria were equally effective, with the qSOFA yielding the greatest percentage increase in in-hospital mortality in our studies. Given its simple computation, the qSOFA is valid for identifying patients at risk of sepsis before the availability of laboratory parameters. Our study supports Vincent et al's[15] and Seymour et al's[4] recommendation to use the qSOFA as a bedside tool to identify sepsis and initiate prompt intervention. Notwithstanding, it is prudent for individual ICUs to analyze their data and validate the adoption of the qSOFA in conjunction with the Sepsis-3 definition.

CONFLICT OF INTERESTS

Dr Zheng's institution received funding from the Ministry of Education (MOE) of Singapore Tier 1 Academic Research Fund, grant 16-C207-SMU-029. The remaining authors have declared that there are no conflict of interests.

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