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Prediction of 28-days mortality with sequential organ failure assessment (SOFA), quick SOFA (qSOFA) and systemic inflammatory response syndrome (SIRS) — A retrospective study of medical patients with acute infectious disease

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ABSTRACT

Aims: Evaluating the use of sequential organ failure assessment (SOFA) ≥ 2 compared to quick SOFA (qSOFA) and to systemic inflammatory response syndrome (SIRS) in assessing 28-days mortality in medical patients with acute infection.
Methods: In total, 323 patients with verified infection were stratified in accordance to Sepsis-3. SOFA, qSOFA and SIRS were calculated using registered variables. Adverse outcome was death within 28-days of admission.
Results: In total, 190 (59%) patients had a SOFA score ≥ 2 and the overall in-hospital mortality was 21 (6%). Scores of SOFA and qSOFA were both significantly elevated in non-survivors. SOFA showed good accuracy (Area under the receiver operating characteristic (AUROC) = 0.83, 95% CI, 0.76 - 0.90) for 28-days mortality compared with qSOFA (AUROC = 0.67, 95% CI, 0.54 - 0.80) and SIRS (AUROC = 0.62, 95% CI 0.49 - 0.74). SOFA was ≥ 2 in all patients who died, while qSOFA and SIRS was ≥ 2 in 8 (38%) and 17 (81%) of the patients who died, respectively.
Conclusion: SOFA score ≥ 2 was better than SIRS and qSOFA to predict mortality within 28-days of admission among patients with acute infectious disease.

Introduction

Sepsis is a life-threatening and complex disease with a pathobiology formed by factors relating to both the pathogen involved and the host (Angus and van der Poll, 2013; Deutschman and Tracey, 2014; Mayr et al., 2014; Wiersinga et al., 2014). For more than two decades, characterization of sepsis has focused on inflammatory excess and been defined as an infection with at least two of four systemic inflammatory response syndrome (SIRS) criteria (Bone et al., 1992). Yet, the current use of SIRS might not necessarily identify patients with severe disease (Churpek et al., 2015).

New international definitions termed Sepsis-3, defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection, and septic shock as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality (Shankar-Hari et al., 2016; Singer et al., 2016). Along with the definitions, clinical guidelines proposed by Sepsis-3 recommend the use of a total sequential organ failure assessment (SOFA) score above or equal to two in patients with verified infection to identify a patient with sepsis. Acknowledging the need to identify patient with sepsis prior to available laboratory test results required for calculation of SOFA, a new readily and inexpensively assessed

Abbreviations: ALAT, alaninaminotransferase; AUROC, area under the receiver operating characteristic; BP, blood pressure; CI, confidence level; CRP, C-reactive protein; ED, emergence department; GCS, Glasgow coma scale; HW, hospital wards; ICU, intensive care unit; IQR, inter quartile range; n, number of patients; ND, not determined; ns, not significant; OD, organ dysfunction; P, prospective; PCT, procalcitonin; qSOFA, quick SOFA; R, retrospective; RR, respiratory rate; $SatO_2$, oxygen saturation; SEN, sensitivity; SI, suspected infection; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; SPE, specificity; VI, verified infection.

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bedside clinical score, termed quick SOFA (qSOFA), was presented in the Sepsis-3. The qSOFA score ranges from zero to three points given for each of the clinical variables, respiratory rate (RR) ≥ 22 breaths/min, Glasgow Coma Scale (GCS) < 15 and systolic blood pressure ≤ 100 mm Hg (Shankar-Hari et al., 2016; Singer et al., 2016; Seymour et al., 2016).

The initial and large retrospective study, which correlated patients hospitalized with suspicion of infection and a SOFA score ≥ 2, found a 2- to 25-fold increased risk of in-hospital mortality for patients outside the ICU, depending on the patients' baseline level of risk, for SOFA ≥ 2 compared with SOFA < 2 (Seymour et al., 2016). For patients in the ICU, in-hospital mortality increased with 3- to 11-fold for SOFA ≥ 2 compared with SOFA < 2.

Moreover, the study showed that qSOFA ≥ 2 was related to in-hospital mortality, but was unable to predict mortality of patients in ICU (Seymour et al., 2016). Because qSOFA seems less robust than SOFA in ICU, Sepsis-3 recommends the use of the qSOFA outside the ICU as an early score to initiate investigation for organ dysfunction and to direct appropriate clinical management (Singer et al., 2016; Seymour et al., 2016).

The objective of the present study was to retrospectively evaluate the Sepsis-3 recommended use of SOFA ≥ 2 to evaluate risk of mortality within 28-days of admission in a broad spectrum of prospectively included patients with verified infection from a medical non-ICU ward after initial assessment between 24 and 48 h after admission.

Patients and methods

Study population

The present study was based on a post hoc retrospective analysis of patient data (n = 323) from three previously conducted prospective studies regarding patients with varying degrees of infection ranging from infection without sepsis, sepsis, severe sepsis and septic shock according to the SIRS criteria (Figure 1) (Gaini et al., 2007; Gaini et al., 2006; Gaini et al., 2008).

In short, patients were included at the Department of Internal Medicine at Odense University Hospital, a large tertiary Danish University Hospital, by referral either from a general practitioner or from the emergency ward. Enrolment criteria for two of the studies were: suspicion of infection by the doctor in charge and initiation of empirical treatment with antibiotics (Gaini et al., 2007; Gaini et al., 2006). In the third study, patients with bacteremia were enrolled after verified positive blood cultures (Gaini et al., 2008). For all three studies, the main exclusion criteria were age <18 years, earlier participation in the study and prior hospitalization within seven days of admission. The patients received a standard of care in agreement with the departmental guidelines.

Ethics

Data and blood sample collection in the three original studies were done in accordance with the Declaration of Helsinki and ethical allowances were obtained from the Scientific Ethical Committee of Southern Denmark (Funen and Vejle Counties, file number 20010076) and from the Danish Data Security Board (2003). Written informed consent was obtained from the patients or closest relatives in each case.

After completion of the original studies, all data and samples were completely and irrevocably anonymized. According to Danish law, research on anonymized data can be done without obtaining new approval from the Ethical Committee and data Protection Agency if the original data collection was done in accordance with all rules.

Stratification and characterization of study population

Patients with verified infection (Gaini et al., 2007; Gaini et al., 2006; Gaini et al., 2008), were stratified in accordance with the Sepsis-3 guidelines (Shankar-Hari et al., 2016; Singer et al., 2016; Seymour et al., 2016) in two subgroups: 1) patients with a SOFA score <2 (no sepsis) and 2) patients with a SOFA score ≥ 2 (sepsis). Information on demography, biochemical parameters, comorbidity, disease severity, hematology and outcome were available (Gaini et al., 2007; Gaini et al., 2006; Gaini et al., 2008). Primary outcome was mortality within 28-days of admission. Comorbidity was evaluated with the Charlson index (Gaini et al., 2007; Gaini et al., 2006; Gaini et al., 2008). Disease severity was classified according to SOFA scores (<2 and ≥2) (Shankar-Hari et al., 2016; Singer et al., 2016; Seymour et al., 2016), qSOFA scores (<2 and ≥2) (Shankar-Hari et al., 2016; Singer et al., 2016; Seymour et al., 2016) and SIRS criteria (<2 and ≥2) (Bone, 1992). Severe sepsis was defined as

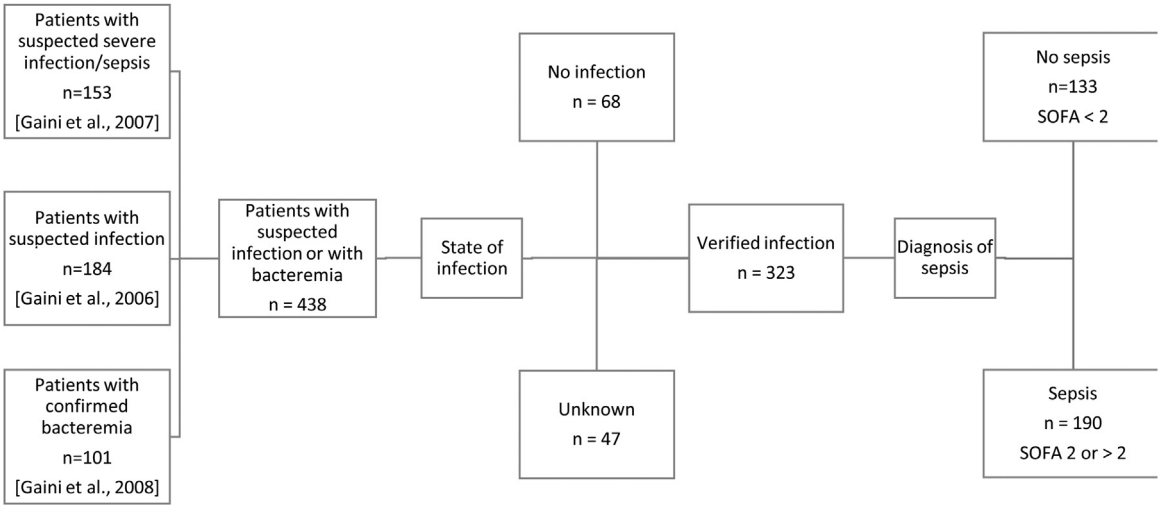

Figure 1. Flowchart of the clinical criteria for identification and stratification of the study population according to Sepsis-3 guidelines. The diagnosis of infection was made by only one physician, who was blinded to all biochemical results. The state of infection was assessed by the clinical and para-clinical results and was categorized (1) no infection, (2) verified infection or (3) unknown. n: number of patients, SOFA: Sequential organ failure assessment.

SIRS ≥ 2 in addition to one or several indices of organ dysfunction as described previously (Gaini et al., 2008).

Statistical analysis

Data were analyzed with Graphpad Prism 5.01 (GraphPad software Inc., La Jolla, CA, USA). Distributions of datasets were determined by D'Agostino & Pearson omnibus normality test. Continuous variables for the stratified subgroups of patients were compared with non-parametric tests and described as medians with interquartile ranges (IQR). For multi-group comparisons, we used Kruskal-Wallis One-way analysis of variance and for two-group comparisons, Mann-Whitney U test were used. Categorical variables for stratified groups were described as percentages. The prognostic performance was assessed using area under the receiver operating characteristic (AUROC) analysis. We considered AUROCs to be poor at 0.6 to 0.70, adequate at 0.7 to 0.8, good at 0.8 to 0.9, and excellent for AUROCs ≥ 0.9. P-values less than 0.05 were considered statistically significant.

Results

Clinical characteristics of the study population

A total of 190 (59%) patients were classified with sepsis (Figure 1). From patient characteristics, patients diagnosed with sepsis were significantly older, and showed increased comorbidity and numbers of prescribed drugs compared to those without sepsis (Table 1). Severity defined as SOFA scores ≥ 2 was significantly correlated with increasing percent of patients with qSOFA scores ≥ 2 ($p < .0001$) and SIRS criteria ≥ 2 ($p < .01$). Diagnosis of sepsis was associated with mortality within 28-days of admission, in addition to deterioration of both physiological, hematological, and biochemical parameters (Table 1).

Data for RR and GCS was missing for 120 (37%) and 30 (9%) of the patients, respectively. 35%, 27% and 51% of patients included for this study from the three original studies had missing RR values. 9%, 14% and 4% of patients included for this study from the three original studies had missing GCS values. We found that 46 (14%) of the patients might have been misclassified as having qSOFA <2 based on either 1) missing values for both RR and GCS or 2) one missing value and a qSOFA score = 1. For SIRS criteria, 38 (12%) of the patients might have been misclassified as having SIRS < 2 based missing values for RR. The effect of misclassified values was evaluated by repetition of all analyses after exclusion of potentially misclassified patients (Supplementary File S1). In total, 66 (20%) patients were excluded, but the results did not change significantly. Except that the difference in SIRS between non-survivors and survivors only just reached significance with a p-value of 0.04, probably reflecting the lower power of the estimate.

Comparison of the Sepsis-1 and Sepsis-3 definitions for classification of patients with verified infection.

Forty-five (14%) of the entire study population met none of the criteria for sepsis, while 146 (45%) patients met the criteria in accordance with both Sepsis-1 and Sepsis-3. A total of 44 (14%) patients met only the Sepsis-3 criteria, and 88 (27%) met only the

Table 1
Patient Characteristics.

	Verified Infection (n = 323)	No Sepsis SOFA < 2 (n = 133)	Sepsis SOFA ≥ 2 (n = 190)	P-value
Demography and comorbidity				
Age [year]	66 (50; 78)	57 (42; 67)	73 (59; 82)	<0.0001
Female, n [%]	158 (49)	74 (55)	84 (44)	<0.01
Glasgow coma scale	15 (15; 15)[d]	15 (15; 15)[d]	15 (15; 15)[e]	ns
Charlson index score	1 (0; 2)	0 (0; 2)	1 (0; 3)	<0.0001
Prescribed drugs*	3 (0; 6)	2 (0; 5)	4 (1; 7)	<0.0001
Disease severity and Physiology				
SOFA ≥ 2 n [%]	190 (59)	–	–	
Quick SOFA ≥ 2 n [%]	41 (13)	2 (2)	39 (21)	<0.0001
SIRS ≥ 2 n [%]	234 (72)	88 (66)	146 (77)	<0.01
Systolic BP, [mm Hg]	130 (110; 140)[a]	130 (120; 145)[b]	121 (105; 140)[a]	<0.01
Diastolic BP, [mm Hg]	70 (60; 80)[b]	80 (70; 80)[b]	70 (60; 80)[b]	<0.01
Respiratory rate, [beats/min]	24 (20; 30)[f]	22 (19; 28)[f]	28 (20; 32)[f]	ns
Temperature, [°C]	39 (38; 39)[a]	38 (38; 39)[a]	38.6 (38; 39)	ns
Hematology and biochemistry				
Hemoglobin, [mmol/L]	8 (7; 9)[b]	8 (7; 9)[c]	8 (7; 9)[b]	
Hematocrit, [%]	0.4 (0.4; 0.4)[e]	0.4 (0.4; 0.4)[e]	0.4 (0.4; 0.4)[e]	
White blood cells, [x10^9/]	12 (8; 16)[a]	11 (8; 14)[a]	13 (8; 17)	<0.01
Neutrophils, [x10^9/L]	10 (7; 14)[c]	8 (6; 13)[c]	11 (7; 15)[b]	<0.0001
PCT, [mg/L]	1 (0.2; 7)[c]	0.2 (0.09; 2)[c]	3 (0.5; 12)[c]	<0.0001
CRP, [mg/L]	181 (99; 277)[b]	142 (77; 230)[c]	201 (107; 310)[a]	<0.01
Platelets, [x10^9/L]	226 (169; 316)[c]	269 (207; 367)[d]	195 (140; 293)[c]	<0.0001
Factors II − VII − X, [Ux10^3/L]	0.8 (0.6; 1.0)[d]	0.9 (0.8; 1)[d]	0.8 (0.6; 1)[d]	<0.01
ALAT, [U/L]	26 (16; 44)[c]	25 (14; 43)[c]	26 (16; 49)[c]	ns
Bilirubin, [μmol/L]	11 (8; 16)[d]	10 (7; 13)[d]	13 (9; 20)[d]	<0.0001
Creatinine, [μmol/L]	102 (87; 131)[b]	88 (78; 96)[c]	125 (103; 180)[a]	<0.0001
Outcome				
ICU admission, n [%]	36 (11)	6 (4.5)	30 (16)	<0.01
28 – day mortality, n [%]	21 (7)	0 (0)	21 (11)	<0.0001

Demography, comorbidity, disease severity, hematology, biomarker levels and outcome in 323 patients stratified according to Sepsis-3 guidelines. Data are presented as medians with 25th and 75th percentiles in parentheses and units in square brackets, unless otherwise stated. Missing values are indicated by roman numbers: a) <1%, b) <2%, c) <4%, d) <10%, e) <15% and f) >15%. Mann-Whitney test for equality: Sepsis – No sepsis. *: Number of prescribed drugs for chronic diseases prior to admission. n: number of patients, ns: not significant, SOFA: Sequential organ failure assessment, SIRS: Systemic inflammatory response syndrome, BP: Blood pressure, $SatO_2$: Oxygen saturation, PCT: Procalcitonin, CRP: C-reactive protein, ALAT: Alaninaminotransferase, ICU: Intensive care unit.

Sepsis-1 criteria. Among the 124 patients classified as having severe sepsis according to Sepsis-1 definition, the majority also met the criteria for Sepsis-3 (30%).

Prognostic values of the SOFA, qSOFA and SIRS criteria for 28-days mortality among patients with verified infection

The SOFA score and the qSOFA score were both significantly elevated in non-survivors, while there was no significant difference in SIRS criteria between non-survivors and survivors (Table 2). The predictive value for 28-days mortality of SOFA was good compared to both SIRS and qSOFA (Table 2). The sensitivity and specificity for predicting 28-days mortality showed that SOFA ≥ 2 had 100% sensitivity and 44% specificity, while qSOFA ≥ 2 had 38% sensitivity and 89% specificity, and SIRS ≥ 2 had 81% sensitivity and 28% specificity.

The assessment of SOFA score ≥ 2, qSOFA score ≥ 2 and SIRS criteria ≥ 2 in relation to 28-days mortality are illustrated in Figure 2. The SOFA score was ≥ 2 in all 21 patients who died within 28-days of admission and in 169 (56%) of the survivors (Figure 2A), while the qSOFA score was ≥ 2 in 8 (38%) of the patients who died (Figure 2B). The distribution of patients with a SIRS criterion ≥ 2 included 17 (81%) non-survivors and 217 (72%) of the survivors (Figure 2C).

Discussion

Our results support the use of SOFA score ≥ 2 to identify patients with verified infection who have increased risk of mortality within 28-days of admission. We found that a SOFA score ≥ 2 measured after initial assessment was superior compared to both SIRS and qSOFA to classify patients according to risk of 28-days mortality.

In our study, the predictive value of SOFA ≥ 2 expressed as AUROC was slightly higher than in retrospective studies including ICU patients. The studies are summarized in Table 3 (Seymour et al., 2016; April et al., 2017; Raith et al., 2017; Giamarellos-Bourboulis et al., 2017; Cheng et al., 2017; Finkelsztein et al., 2017). Despite that our analyses were done retrospectively, to our knowledge, our study is among the first to evaluate the use of SOFA score ≥ 2 to assess risk of 28-days mortality in a population of patients prospectively included in a non-ICU setting. Only two retrospective studies by Seymour et al. and Donnelly et al., respectively, have evaluated the prognostic value of SOFA in a non-ICU setting. Both studies showed AUROC values of SOFA comparable to our results (Seymour et al., 2016; Donnelly et al., 2017). The sensitivity and specificity of SOFA ≥ 2 for mortality within 28-days have, to our knowledge, not been published previously. The high sensitivity for identifying patients who died within 28 days (100% in our study population) emphasizes the potential clinical value of SOFA ≥ 2 or SOFA < 2 to guide management of patients with supposed infection.

The AUROC of SIRS criteria in our non-ICU setting was comparable to the previous published results in both prospectively and retrospectively included patients primarily from ICU settings (Table 3) (Seymour et al., 2016; April et al., 2017; Raith et al., 2017; Cheng et al., 2017; Finkelsztein et al., 2017; Donnelly et al., 2017; Freund et al., 2017), while Donnelly et al. (2017) in their retrospective study including 30239 non-ICU patients and Williams et al. (2017) in their prospective study including 8871 non-ICU patients, both reported a slightly higher AUROC of SIRS criteria for mortality (0.72 and 0.71 respectively) (Donnelly et al., 2017; Williams et al., 2017). Only, Williams et al. (2017) have evaluated the sensitivity and specificity of SIRS ≥ 2 in non-ICU patients and showed a sensitivity of 77% and a specificity of 54% compared with 81% and 28%, respectively, in our population. In contrast, April et al. (2017) and Finkelsztein et al. (2017) in their study populations from ICU settings both reported sensitivities above 90% and very low specificities (2.3% and 12%, respectively). The predictive values of qSOFA scores have been more inconsistent (Table 3) (Seymour et al., 2016; April et al., 2017; Raith et al., 2017; Finkelsztein et al., 2017; Donnelly et al., 2017; Freund et al., 2017; Williams et al., 2017). The studies analyzing the predictive value of qSOFA score for in-hospital mortality in patients admitted to ICU for suspected infection found AUROC values ranging from 0.61 to 0.74 comparable to our results (Seymour et al., 2016; April et al., 2017; Raith et al., 2017; Finkelsztein et al., 2017), while the previous studies in a non-ICU setting have shown better predictive accuracy of qSOFA ranging from 0.76 to 0.81. Only, a few of the previous studies have provided data on sensitivity and specificity of qSOFA ≥ 2 (April et al., 2017; Giamarellos-Bourboulis et al., 2017; Finkelsztein et al., 2017; Williams et al., 2017; Henning et al., 2017). Interestingly, the results in ICU patients consistently report high sensitivity and low specificity (April et al., 2017; Giamarellos-Bourboulis et al., 2017; Finkelsztein et al., 2017), while the findings in previous non-ICU settings and in our study consistently and oppositely report lower sensitivity and high specificity (Williams et al., 2017; Henning et al., 2017). A large recently published meta-analysis pooling 406802 patients with suspected infection concluded that qSOFA was a poorly sensitive marker for in-hospital mortality in hospitalized patients not in intensive care units (sensitivity 48% and specificity 83%) (Maitra et al., 2018). The same study showed a sensitivity of 56% and specificity of 78% for in-hospital mortality among all patients including those treated at ICU units (Maitra et al., 2018). The poor accuracy for mortality of qSOFA score compared with the superior accuracy of SOFA score reported in our study were supported by previous studies

Table 2
Comparison of SOFA, qSOFA and SIRS, respectively, in patients with verified infection in relation to in-hospital mortality at the 28-day follow-up.

		Survivors n = 302	Non-survivors n = 21
SOFA score (1–24)	Median with IQR	2 (1; 3)	4 (1; 6)
	p - value	<0.0001	
	AUROC	0.83; 0.76–0.90	
	95% (Cl)		
	Sensitivity (SOFA ≥ 2) [%] (95% Cl)	100.0 (83.9–100)	
	Specificity (SOFA ≥ 2) [%] (95% Cl)	44.0 (38.4–49.8)	
qSOFA score (1–3)	Median with IQR	0 (0; 1)	1 (0; 2)
	p – value	0.004	
	AUROC	0.67; 0.54–0.80	
	95% Cl		
	Sensitivity (qSOFA ≥ 2) [%] (95% Cl)	38.1 (18.1–61.6)	
	Specificity (qSOFA ≥ 2) [%] (95% Cl)	89.1 (85.0–92.4)	
SIRS criteria (0–4)	Median with IQR	2 (1; 3)	3 (2; 4)
	p – value	ns	
	AUROC	0.61; 0.49–0.74	
	95% (Cl)		
	Sensitivity (SIRS ≥ 2) [%] (95% Cl)	80.9 (58.1–94.6)	
	Specificity (SIRS ≥ 2) [%] (95% Cl)	28.1 (23.1–33.6)	

Data are presented as median with 25th and 75th percentiles in parentheses, p values and AUROC with 95% confidence interval (Cl). Sensitivity and specificity of SOFA, qSOFA and SIRS at the Sepsis-3 and sepsis-2 thresholds are presented with 95% Cl. Mann-Whitney test was used for equality. n: number of patients, IQR: Inter quartile range, SOFA: Sequential organ failure assessment, AUROC: Area under the receiver operating characteristic, qSOFA: quick SOFA, ns: not significant and SIRS: Systemic inflammatory response syndrome.

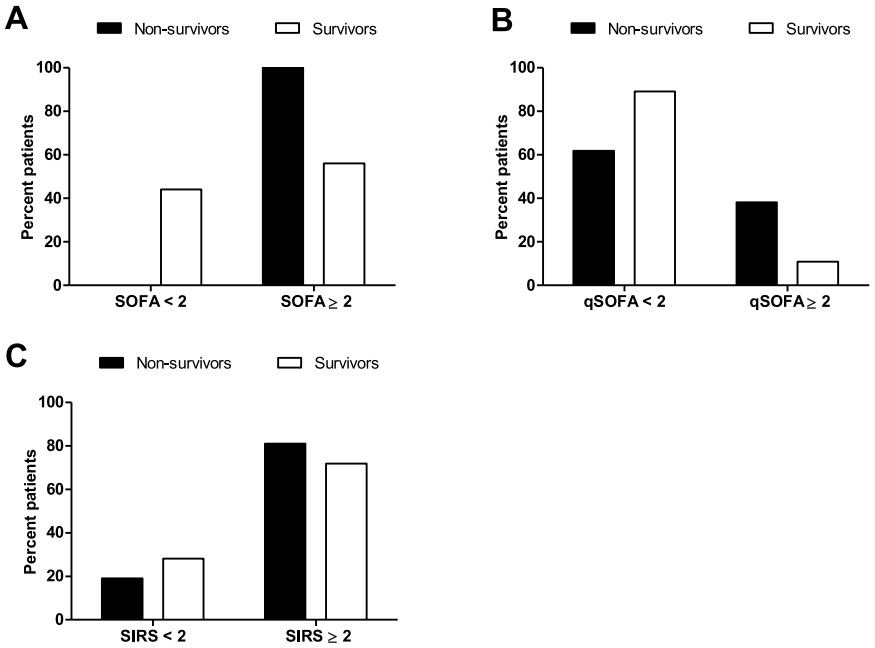

Figure 2. Validation of the Sepsis-3 definitions of sepsis to predict outcome. (A) Percent of patients deceased at the 28-day follow-up classified with SOFA score < 2 and SOFA score ≥ 2, respectively. (B) Percent of patients deceased at the 28-day follow-up classified with qSOFA score < 2 and qSOFA score ≥ 2, respectively (C) Percent of patients deceased at the 28-day follow-up classified with SIRS score < 2 and SIRS score ≥ 2, respectively. Boxes represent percent of patients. SOFA: Sequential organ failure assessment, qSOFA: quick SOFA and SIRS: Systemic inflammatory response syndrome.

demonstrating that expanding of the qSOFA score with measures of either arterial pH, heart rate, age or fever increased the sensitivity for severe sepsis and septic shock, at the expense of specificity (Giamarellos-Bourboulis et al., 2017; Dorsett et al., 2017). Although neither of the studies included AUROC analysis of SOFA score, the results are supportive of the use of SOFA, as expansion of the qSOFA score with new parameters approaches the SOFA score.

Our main finding, that a SOFA ≥ 2 predicts mortality better than qSOFA, combined with previous observations by others support the proposed guideline in Sepsis-3; that qSOFA are less robust than SOFA in ICU. Moreover, our main results complement the idea that the use of SIRS criteria does not necessarily identify patients with elevated risk of in-hospital mortality (Churpek et al., 2015).

Thus, our findings support the clinical use of Sepsis-3 in initial assessment of patients hospitalized with infection, to discriminate between patients with high and low risk of in-hospital mortality. The strength of this support must however be interpreted considering the limitations of our study.

Firstly, our study was done retrospectively and included a limited number of patients. This means that some of the subgroups were small with increased risk of false-negative results due to low statistical power. Therefore, our results should preferably be confirmed in larger, prospective studies. Secondly, serum lactate level was unavailable for many patients, and consequently we were unable to identify patients with septic shock according to Sepsis-3. Thirdly, missing values for RR and GCS might have led to an underestimation of both qSOFA and SIRS leading to underestimation of their predictive power. Yet reiteration of all the analyses with exclusion of potentially misclassified patients did not change the obtained results significantly (see web-only Supplementary File S1), and the missing values did not affect the main conclusion that SOFA ≥ 2 seems to be a valid predictor of increased in-hospital mortality. However, it may have underestimated the predictive power of qSOFA ≥ 2.

Our study supports the use of SOFA score ≥ 2 as an aid to identify patients with increased risk of in-hospital mortality among non-ICU patients hospitalized with infection, but neither SOFA nor qSOFA scores ≥ 2 should be used as a single indicator to guide clinical management.

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Region of Southern Denmark's Research foundation supported the study.

Conflict of interest

The authors declare no potential conflict of interest.

Ethics

Data and blood sample collection in the three original studies were done in accordance with the Declaration of Helsinki and ethical allowances were obtained from the Scientific Ethical Committee of Southern Denmark (Funen and Vejle Counties, file number 20010076) and from the Danish Data Security Board (2003). Written informed consent was obtained from the patients or closest relatives in each case.

After completion of the original studies, all data and samples were completely and irrevocably anonymized, so that the material cannot be directly or indirectly attributed to the donor with the means that may reasonably be used to identify the person concerned. According to Danish law, research on anonymized data

Table 3
Comparison of AUROC and sensitivity and specificity of different selected studies for validation of sepsis-3.

Patients	Setting	Inclusion severity	Design	Primary outcome	SOFA AUROC SEN SPE	qSOFA AUROC SEN SPE	SIRS AUROC SEN SPE	Reference
214	ICU	SI or VI	R	In-hospital mortality	0.70 ND ND	0.66 qSOFA ≥ 2: 89.7% (SEN) 27.4% (SPE)	0.65 SIRS ≥ 2: 97.4% (SEN) 2.3% (SPE)	April et al. (2017)
–	3346 (ED) 1058 (ICU)	VI + Sepsis-2	P	In-hospital mortality	ND	ND qSOFA ≥ 2 (ICU): 87.5% (SEN) ND	ND	Giamarellos-Bourboulis et al. (2017)
148907	ED (66617) ICU (7836)	SI	R	In-hospital mortality	0.74 (ICU) 0.79 (no ICU) ND ND	0.66 (ICU) 0.81 (no ICU) ND ND	0.64 (ICU) 0.76 (no ICU) ND ND	Seymour et al. (2016)
496	ICU	SI	R	28-day mortality	0.69 ND ND	ND	0.55 ND ND	Cheng et al. (2017)
30239	ED	SI	R	In-hospital mortality	0.77 (SOFA ≥ 2) ND ND	0.76 (qSOFA ≥ 2) ND ND	0.72 (SIRS ≥ 2) ND ND	Donnelly et al. (2017)
152	ICU (102) HW (50)	SI	P	In-hospital mortality	ND	0.74 qSOFA ≥ 2: 90% (SEN) 42% (SPE)	0.59 SIRS ≥ 2: 93% (SEN) 12% (SPE)	Finkelsztein et al. (2017)
879	ED	SI	P	In-hospital mortality	ND	0.80 ND ND	0.65 ND ND	Freund et al. (2017)
7637	ED	SI	P	In-hospital mortality	ND	ND qSOFA ≥ 2: 52% (SEN) 86% (SPE)	ND SIRS ≥ 2: 83% (SEN) 50% (SPE)	Henning et al. (2017)
184875	ICU	SI	R	In-hospital mortality	0.753 ND ND	0.61 ND ND	0,59 ND ND	Raith et al. (2017)
8871	ED	SI	P	30-day mortality	ND	0.78 qSOFA ≥ 2: 50% (SEN) 91.3% (SPE)	0.71 SIRS ≥ 2: 77% (SEN) 54% (SPE)	Williams et al. (2017)
323	HW	VI	P	In-hospital mortality	0.83 SOFA ≥ 2: 100% (SEN) 44% (SPE)	0.67 qSOFA ≥ 2: 38% (SEN) 89% (SPE)	0.61 SIRS ≥ 2: 81% (SEN) 28% (SPE)	Gaini et al. (2018 present study)

SIRS: Systemic inflammatory response syndrome, SOFA: Sequential organ failure assessment, qSOFA: quick SOFA, AUROC: Area under the receiver operating characteristic, SEN: Sensitivity, SPE: Specificity, ICU: Intensive care unit, SI: Suspected infection, VI: Verified infection, R: retrospective, ND: not determined, ED: Emergence department, P: prospective, HW: Hospital wards.

can be done without obtaining new approval from the Ethical Committee and data Protection Agency if the original data collection was done in accordance with all rules.

Availability of data and material

The datasets used are available from the corresponding author on reasonable request.

Authors' contributions

SG: Collected the original data, participated in the design of the study and helped to write and revise the manuscript.

MMR: Participated in the design of the study, carried out the analyses, performed the statistical analysis, interpreted the patient data and wrote the manuscript.

CP: Participated in the design of the study, gave valuable suggestions and helped to revise the manuscript.

ISJ: Participated in the design of the study, gave valuable suggestions and helped to revise the manuscript.

All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.09.020.

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