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Original article

Validation of the new Sepsis-3 definitions: proposal for improvement in early risk identification

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ABSTRACT

Objectives: Sepsis-3 definitions generated controversies regarding their general applicability. The Sepsis-3 Task Force outlined the need for validation with emphasis on the quick Sequential Organ Failure Assessment (qSOFA) score. This was done in a prospective cohort from a different healthcare setting.
Methods: Patients with infections and at least two signs of systemic inflammatory response syndrome (SIRS) were analysed. Sepsis was defined as total SOFA ≥2 outside the intensive care unit (ICU) or as an increase of ICU admission SOFA ≥2. The primary endpoints were the sensitivity of qSOFA outside the ICU and sepsis definition both outside and within the ICU to predict mortality.
Results: In all, 3346 infections outside the ICU and 1058 infections in the ICU were analysed. Outside the ICU, respective mortality with ≥2 SIRS and qSOFA ≥2 was 25.3% and 41.2% ($p < 0.0001$); the sensitivities of qSOFA and of sepsis definition to predict death were 60.8% and 87.2%, respectively. This was 95.9% for sepsis definition in the ICU. The sensitivity of qSOFA and of ≥3 SIRS criteria for organ dysfunction outside

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Mortality
Sepsis
Septic shock

the ICU was 48.7% and 72.5%, respectively (p <0.0001). Misclassification outside the ICU with the 1991 and Sepsis-3 definitions into stages of lower severity was 21.4% and 3.7%, respectively (p <0.0001) and 14.9% and 3.7%, respectively, in the ICU (p <0.0001). Adding arterial pH ≤7.30 to qSOFA increased sensitivity for prediction of death to 67.5% (p 0.004).
Conclusions: Our analysis positively validated the use of SOFA score to predict unfavourable outcome and to limit misclassification into lower severity. However, qSOFA score had inadequate sensitivity for early risk assessment. **E.J. Giamarellos-Bourboulis, CMI 2017;23:104**

Introduction

Sepsis is the main pathway to death from infection. The global incidence of hospital-treated sepsis and hospital-treated severe sepsis is 437 and 270 cases per 100 000 person-years with 17% and 26% mortality, respectively [1]. Prompt and early recognition of sepsis may lead to earlier and more efficient management, possibly with improved survival. This mandates a simple and clear definition of sepsis. The first definition was framed in 1991 and published in 1992. The backbone of this definition was that sepsis was the systemic response to an infection where the systemic response was defined as the presence of at least two signs of the systemic inflammatory response syndrome (SIRS) [2]. However, this definition was not helpful to differentiate sepsis from uncomplicated infection and it did not conform to our current understanding of sepsis pathobiology. The need for improvement led to a second definition in 2003 [3], but this did not materially change the traditional classification.

In 2016, an international consensus task force framed the Sepsis-3 definitions [4]. Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. These definitions were developed using a broad analysis of clinical and laboratory parameters of patients from five large independent cohorts [5,6]. The Sequential Organ Failure Assessment (SOFA) score is now critical for the definition of sepsis. However, to provide early bedside evaluation of a patient for the likelihood of sepsis, the quick SOFA (qSOFA) score was introduced.

Sepsis-3 definitions are not universally accepted and are becoming a matter of controversy [7,8]. Clinical data used for the development of the Sepsis-3 definitions were derived mainly from patients hospitalized in US Intensive Care Units (ICU). Analysis was driven by mortality as the main outcome measure. However, the presence of organ dysfunction should also be part of this analysis.

The Hellenic Sepsis Study Group (HSSG) is a continuing collaboration of 65 departments in Greece (departments of Internal Medicine, Surgery and ICUs) registering clinical and laboratory data of patients with severe infection since 2006 (www.sepsis.gr). Participating study sites cover the entire country including both rural and urban areas. Information framing Sepsis-3 definitions are available in this registry, so we decided to retrospectively analyse the performance of the new Sepsis-3 definitions for early assessment of mortality and organ dysfunction.

Patients and methods

Study cohort

The study protocol was approved by the ethics committees of the participating hospitals and patients were prospectively enrolled between May 2006 and December 2015 after written consent from themselves, or from first-degree relatives for patients unable to consent. Consenting comprised the analysis of clinical, laboratory and therapeutic variables associated with patient's outcomes. This allowed retrospective classification of patients using the Sepsis-3 definitions.

Inclusion criteria were: (a) age ≥18 years; (b) onset of signs of infection within the last 24 h; (c) one of the following infections: acute pyelonephritis, community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, primary bacteraemia, intra-abdominal infections, acute bacterial skin and skin structure infections and central nervous system infections; and (d) at least two signs of SIRS. The only exclusion criteria were infection by human immunodeficiency virus and neutropenia caused by medical conditions other than SIRS. Diagnosis of acute pyelonephritis, community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, primary bacteraemia, intra-abdominal infections, acute bacterial skin and skin structure infections and central nervous system infections used internationally accepted definitions [9].

Studied patients were divided into two populations: (a) patients outside the ICU; this population comprised either patients admitted in the emergency department for suspected infection or patients already hospitalized in the general ward who developed an infection at least 48 h after hospital admission; and (b) patients already in the ICU who developed an infection at least 48 h after ICU admission.

On the first day fulfilling SIRS criteria, a complete diagnostic work-up was performed comprising present and past medical history, physical examination, vital signs, laboratory tests for haematology, biochemistry and coagulation, arterial blood gases, microbiological cultures for blood, urine, sputum and tracheobronchial secretions, and calculation of APACHE II (Acute Physiology and Chronic Health Evaluation II) and SOFA scores. For patients outside the ICU, vital signs and the Glasgow Coma score were recorded on admission at the emergency department, or at the bedside for patients already hospitalized at the general ward. For patients in the ICU the admission SOFA scores were collected. Chest X-ray and urinalysis were performed. If necessary, renal and abdominal ultrasound and chest and abdominal computed tomography were also carried out. All patients were followed up for 28 days and survival was recorded. On each day of follow up, need for vasopressors, organ failures and administered antimicrobials were recorded. All data were recorded in a case-report form. All case-report forms were monitored by an independent monitor.

Classification of patients

In the original case-report forms, the investigators were asked to classify patients as sepsis, severe sepsis and septic shock using the 1991 definitions [2]. Based on the available information, patients were re-classified in June 2016 using the Sepsis-3 2016 Task Force criteria [6]. The qSOFA score was calculated for all patients

outside the ICU using available information on blood pressure, respiratory rate and Glasgow Coma score. Patients with Glasgow Coma score <13 were considered to have altered mental activity. The qSOFA score was not calculated for ICU patients. In these patients, mental alteration and respiratory rate could not be assessed as they were under mechanical ventilation. Using the Sepsis-3 criteria, sepsis was diagnosed outside the ICU as any total SOFA score ≥2 points and in the ICU as any ≥2-point increase of the ICU admission SOFA score attributable to an infection.

Study endpoints

The primary study endpoint was the sensitivity of qSOFA and of the new sepsis definition to predict 28-day mortality. Sensitivities for mortality were calculated for both qSOFA and sepsis definition for non-ICU patients and only for the sepsis definition for ICU patients.

The secondary study endpoints were (a) to compare the performance of qSOFA and SIRS criteria for the early prediction of organ dysfunction outside the ICU (by the new definitions [4], organ dysfunction was considered as any total SOFA score ≥2); and (b) to compare misclassification of severe cases by the 1991 definitions and by Sepsis-3 definitions separately for non-ICU and ICU patients.

The exploratory study endpoint was how the introduction of more criteria could improve the ability of the qSOFA score to predict 28-day mortality outside the ICU. Candidate criteria were rapid and cheap bedside measurements.

Statistical analysis

Qualitative variables were expressed as frequencies and 95% CI. One element of the primary endpoint was the validity of qSOFA as a predictor of 28-day outcome compared with the presence of at least two SIRS criteria. Since all enrolled patients had at least two SIRS criteria, overall mortality was compared with the mortality of patients with qSOFA ≥2. Patients were sub-grouped for the number of SIRS criteria and of qSOFA criteria and mortalities were compared. Sensitivities, specificities, and positive and negative predictive values of qSOFA and SIRS for prediction of mortality and organ dysfunction and of sepsis defined according to Sepsis-3 were calculated and compared. All above comparisons were made using the chi-squared test. Odds ratios (OR) and 95% CIs were calculated by Mantel and Haenzel's statistics. For definition of misclassification, either outside or in the ICU, patients defined as either sepsis according to Sepsis-3 and/or severe sepsis by the 1991 definitions, were considered together as severe cases. Among these severe cases, those defined as sepsis by the Sepsis-3 definitions and as uncomplicated sepsis by the 1991 definitions were considered misclassified by the 1991 definitions; those defined as infection by the Sepsis-3 definitions and as severe sepsis by the 1991 definitions were considered misclassified by the Sepsis-3 definitions. Misclassification rates were compared by the Fisher exact test.

For the exploratory endpoint, receiver operator characteristics curves were designed to identify rapid bedside tools aiming to identify unfavourable outcome after 28 days. Areas under the curves were compared by Vassar statistics. The coordinate point of the curve with more than 90% specificity for unfavourable outcome was selected; patients were dichotomized using this cut-off. This cut-off was validated after logistic regression analysis; mortality after 28 days was the dependent variable; qSOFA, sepsis defined by the Sepsis-3 definitions and the new tool entered the equation as independent variables. Any value of p below 0.05 was considered statistically significant.

Results

The study flow chart is shown in Fig. 1. Complete data sets were available for 3436 patients with infection presenting outside the ICU and for 1058 patients with infection presenting after ICU admission.

Performance of qSOFA, SIRS criteria and Sepsis-3 definitions outside the ICU

Mortality outside the ICU for patients with ≥2 SIRS criteria was 25.3% (868 of 3436 patients). A total of 1283 patients had qSOFA ≥2; 542 died (mortality 41.2%, p <0.0001 compared with ≥2 SIRS criteria). Mortality of patients with three SIRS criteria was greater

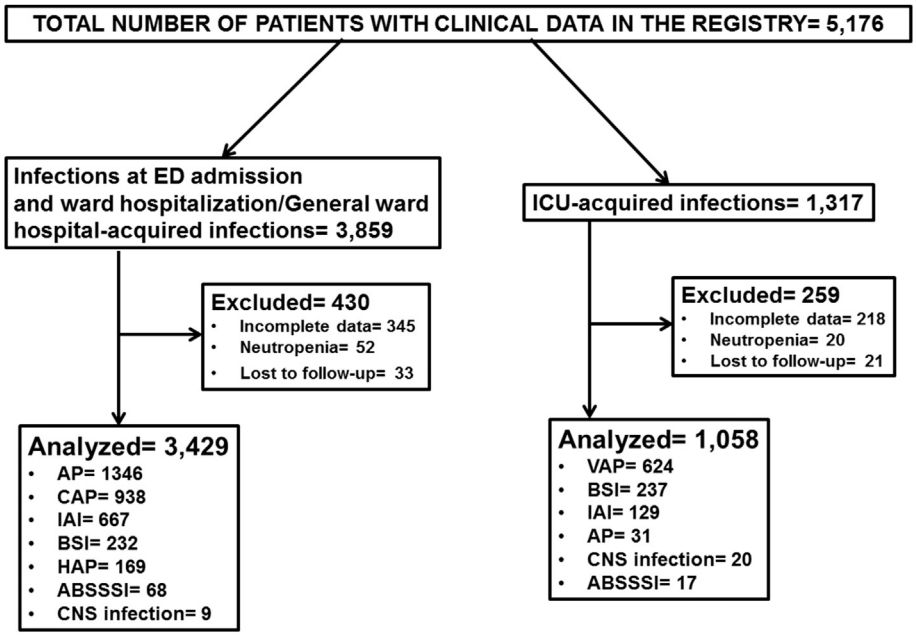


Fig. 1. Study flow chart. Abbreviations: AP, acute pyelonephritis; ABSSSI, acute bacterial skin and soft-tissue infection; BSI, primary bacteraemia; CAP, community-acquired pneumonia; CNS, central nervous system; ED, emergency department; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; ICU, intensive care unit; VAP, ventilator-associated pneumonia.

than of patients with two SIRS criteria and of patients with three SIRS criteria similar to patients with four SIRS criteria (Fig. 2a). Mortality increased steadily with each point of increase of qSOFA (Fig. 2b). The sensitivity of qSOFA ≥2 to predict 28-day death outside the ICU was 60.8% (Fig. 2c).

Mortality in relation to SOFA score is shown in the Supplementary material (Fig. S1). The sensitivity, specificity, and positive and negative predictive values of the Sepsis-3 definitions to predict 28-day mortality were 87.5%, 50.4%, 37.3% and 92.1%, respectively (see Supplementary material, Table S1).

Performance of Sepsis-3 definitions in the ICU

Mortality in relation to the change of SOFA score from admission is shown in Fig. 3a. Sensitivity of the Sepsis-3 definition to predict 28-day mortality was 95.9% (Fig. 3b).

qSOFA versus SIRS for organ dysfunction outside the ICU

Following the analysis showing that mortality with ≥3 SIRS criteria was greater than mortality with only 2 SIRS criteria (Fig. 2a) the presence of ≥3 SIRS criteria was compared with qSOFA as an early indicator of organ dysfunction (Fig. 4). The sensitivity of qSOFA to diagnose organ dysfunction was 48.7% compared with 72.5% of ≥3 SIRS criteria (p <0.0001).

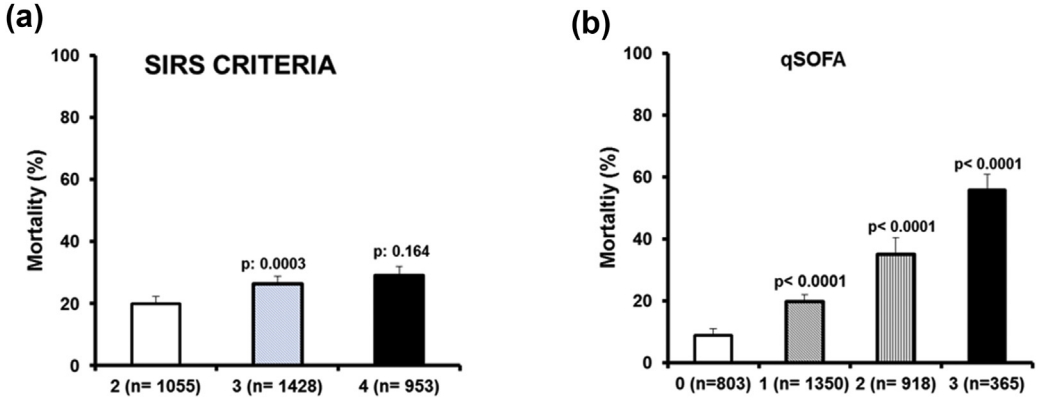
Misclassification of severe cases by the 1991 definitions and Sepsis-3 definitions

When the new Sepsis-3 definitions were used for patients outside the ICU, all patients defined by the 1991 definitions as septic shock were also classified by the Sepsis-3 definitions as septic shock (see Supplementary material, Fig. S2a). Misclassification of severe cases by the 1991 definition occurred in 734 out of 2172 severe cases (33.8%). Using the Sepsis-3 definitions, this occurred in 128 out of 2172 severe cases (5.9%) (p <0.0001 between the 1991 and Sepsis-3 definitions) (see Supplementary material, Fig. 2b).

When the new Sepsis-3 definitions were used for patients in the ICU, all patients defined by the 1991 definitions with septic shock were also classified by the Sepsis-3 definitions as septic shock (see Supplementary material, Fig. 3a). Misclassification of severe cases by the 1991 definition occurred in 158 of 1001 severe cases (15.8%). Using the Sepsis-3 definitions, this occurred in 37 of 1001 severe cases (3.7%) (p <0.0001 between the 1991 and Sepsis-3 definitions) (see Supplementary material, Fig. 3b).

Exploratory endpoint

Based on the concept of the Task Force of Sepsis-3 definitions to seek for variables predicting mortality, two tests, namely arterial blood pH and arterial lactate, showed better performance than the other quick point-of-care tests. The area under the receiver operator characteristics curve for pH for 28-day mortality was greater than for lactate (see Supplementary material, Fig. S4). Conditional forward logistic regression analysis showed that pH ≤7.30 was an independent predictor of unfavourable outcome (see Supplementary material, Table S2). We added this criterion to qSOFA and the area under the curve of qSOFA for 28-day mortality was significantly increased (see Supplementary material, Fig. S5). The sensitivity of this new qSOFA score for 28-day mortality was

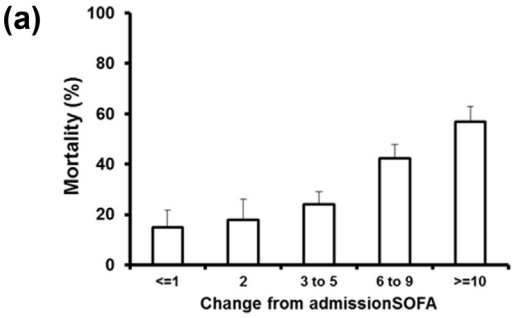


(c)

	Death	Survival	Total
qSOFA ≥2	528 Sens 60.8% (57.5-61.1%) PPV 41.2% (38.5-42.9%)	755	1283
qSOFA <2	340	1813 Spec= 70·6% (68.9-72.3%) NPV= 84·2% (82.7-85.7%)	2153
	868	2568	3436

$OR_{qSOFA \geq 2}$ (95%CIs)= 3.73 (3.16-4.37); p< 0·0001

Fig. 2. Quick Sequential Organ Failure Assessment (qSOFA) as predictor of final outcome for patients with infections outside the ICU. Mortality according to (a) the number of SIRS criteria and (b) the number of qSOFA score; error bars represent the upper 95% limit of confidence and p values comparisons with the previous bar. (c) Performance of qSOFA ≥2 for mortality. Abbreviations: ICU, intensive care unit; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Sens, sensitivity; SIRS, systemic inflammatory response syndrome; Spec, specificity.



(b)

	Death (n of patients)	Survival (n of patients)	Total
SOFA increase ≥2	370 Sens 95.8% (93.8-97.8%) PPV 38.9% (35.8-42.0%)	582	952
SOFA increase <2	16	90 Spec= 13.4% (10.8-16.0%) NPV= 84.9% (78.1-91.7%)	1404
	386	672	1058

$OR_{SOFA\ increase\ \geq 2}$ (95%CIs)= 3.57 (2.06-6.19); p< 0.0001

Fig. 3. The new Sepsis-3 definitions as predictors of final outcome in the ICU. (a) Mortality according to the change of SOFA score from admission in the ICU; error bars represent the upper 95% limit of confidence. (b) Performance of the new Sepsis-3 definitions for mortality in the ICU. Abbreviations: ICU, intensive care unit; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Sens, sensitivity; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; Spec, specificity.

67.5% (p 0.004 compared with the sensitivity of qSOFA score) (Fig. 5 and see Supplementary material, Table S3).

Discussion

In a retrospective validation of the Sepsis-3 definitions using the prospective cohort of the HSSG, the sensitivity of the new definitions using SOFA score to predict 28-day mortality was 87.5% outside the ICU and 95.8% in the ICU. The introduction of Sepsis-3 definitions limited misclassification of severe cases. In contrast, the performance of qSOFA was rather poor. The sensitivity of qSOFA ≥2 for the early prediction of mortality was only 60.8% whereas sensitivity of qSOFA ≥2 for the early diagnosis of organ dysfunction was lower than ≥3 SIRS criteria.

The Task Force of the Sepsis-3 definitions is explicitly stating the need for a validation of the new proposed definitions using non-US databases of patients. The authors particularly underline the need to validate the utility of the qSOFA score [4]. The new Sepsis-3 definitions were developed to indicate patients with a risk of death of at least 10%. To this end, the goals of the Sepsis-3 definition using the SOFA score were achieved. The Sepsis-3 definitions introduce qSOFA as a clinical tool that can be used at bedside for the early detection of sepsis. The OR for death with qSOFA ≥2 of the

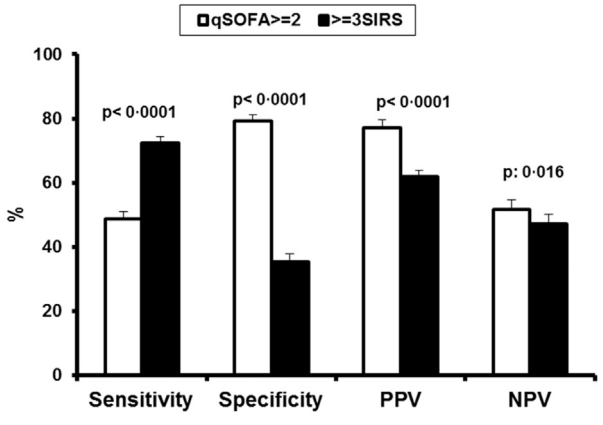


Fig. 4. Comparative performance of qSOFA and SIRS criteria as predictors of organ dysfunction among patients with infections outside the ICU. Error bars indicate the respective upper 95% confidence interval and p values indicate statistical comparisons between qSOFA score and the presence of at least three SIRS criteria. Organ dysfunction is defined as SOFA ≥2. Abbreviations: ICU, intensive care unit; NPV, negative predictive value; PPV, positive predictive value; qSOFA, quick Sequential Organ Failure Assessment; SIRS, systemic inflammatory response syndrome.

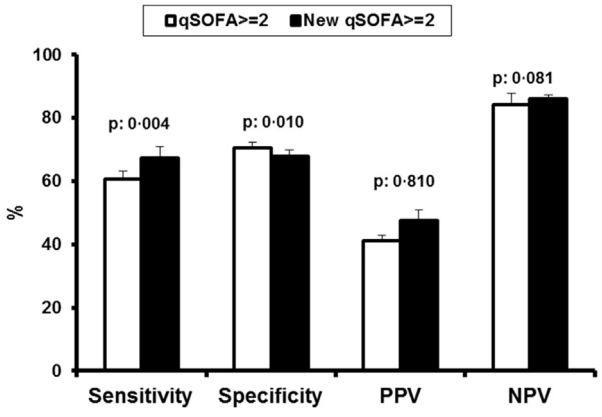


Fig. 5. Comparative performance of qSOFA and of the proposed new qSOFA as predictors of unfavourable outcome among patients with infections outside the ICU. Error bars indicate the respective upper 95% confidence interval and p values indicate statistical comparisons between qSOFA score ≥2 and new qSOFA score ≥2. Abbreviations: ICU, intensive care unit; NPV, negative predictive value; PPV, positive predictive value; qSOFA, quick Sequential Organ Failure Assessment.

HSSG cohort was 3.73, corroborating the OR of the analysis of the US databases [6].

All biomarkers that can effectively prognosticate unfavourable outcome should have sensitivity and NPV >80% [10,11]. To this end, the 60.8% sensitivity of qSOFA to predict 28-day mortality outside the ICU raises concerns. The addition of arterial pH to qSOFA significantly increases the sensitivity of qSOFA for early prediction of death to 67.5%. Based on our findings, we propose the measurement of arterial pH in any patient with suspected infection who scores qSOFA <2. In that case, arterial pH $\leq$7.30 can help to detect patients with high likelihood for sepsis.

Two major concerns led to the development of new sepsis definitions: the first concern was lack of insight into the pathophysiology of sepsis [12]. The second concern was the need to differentiate between organ dysfunction and uncomplicated infection as many patients considered as having uncomplicated sepsis by the old definition have a considerable risk for death [13,14]. Two important findings from the analysis of the database of the HSSG should be emphasized: (a) the new definitions do not miss patients with septic shock; and (b) the rate of misclassification of severe patients is lower using the Sepsis-3 definitions than the 1991 definitions.

The advent of Sepsis-3 definitions raised several concerns about the global applicability of these definitions, mainly among healthcare professionals [8,15]. The Global Sepsis Alliance recommended the validation of these definitions in other healthcare systems and expressed concerns on how to identify septic patients who do not score qSOFA $\geq$2 [16]. The HSSG cohort is a prospectively collected cohort that was used for the external validation of Sepsis-3 definitions. This cohort is based on well-characterized infections for research purposes. Our analysis has positively validated the use of SOFA score to demonstrate patients with a high likelihood of death. However, qSOFA score possessed inadequate sensitivity for early prediction of death. This strengthens the limitation recognized by the Task Force of Sepsis-3 that failure of a patient to meet two or more qSOFA criteria should not lead to any delay of care [4].

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Transparency declaration

EJGB has received honoraria for providing scientific advice to AbbVie, Chicago IL, USA; Astellas, Athens, Greece; Biotest AG, Dreieich, Germany; and ThermoFisher Scientific GmbH, Henningdorf, Germany. He has received unrestricted educational funding by Biotest AG, Dreieich, Germany (grant number 13067 to the National and Kapodistrian University of Athens); and ThermoFisher Scientific GmbH, Henningdorf, Germany (grant number 13007 to the National and Kapodistrian University of Athens); Sanofi SA, Athens, Greece (grant number 12309 to the National and Kapodistrian University of Athens); and by the Seventh Framework European Program (grant HemoSpec 611682). The other authors do not have any conflict of interest to declare.

Appendix A. Supporting information

Additional Supporting Information may be found in the online version of this article at http://dx.doi.org/10.1016/j.cmi.2016.11.003.

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