# Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department

Yonathan Freund, Najla Lemachatti, Evguenia Krastinova, Mar van Laer, Yann-Erick Claessens, Aurélie Avondo, Céline Occelli, Anne-Laure Feral-Pierssens, Jennifer Truchot, Mar Ortega, et al.

# Prognostic accuracy of Sepsis-3 criteria among patients presenting to the emergency department

Freund Yonathan, MD, PhD,1,2; Lemachatti Najla, MD, 2; Krastinova Evguenia, MD,PhD, 3; Van Laer Marie, MD, 4; Claessens Yann-Erick, MD, PhD, 5; Avondo Aurélie, MD, 6; Occelli Céline, MD, 7; Feral-Pierssens Anne-Laure, MD, 8; Truchot Jennifer, MD, 9; Ortega Mar, MD, 10; Carneiro Bruno, MD, 11; Pernet Julie, MD, 12; Claret Pierre-Géraud, MD, PhD, 13; Dami Fabrice, MD, 14; Bloom Ben, MD, 15; Riou Bruno, MD, PhD, 1,2; Beaune Sébastien, MD, PhD, 16. For the French society of emergency medicine collaborators group.

1) Paris Sorbonne Universités, UPMC Paris Univ-06, Paris, France.
2) Emergency Department, Hôpital Pitie-Salpêtrière, Assistance Publique – Hôpitaux de Paris (APHP), Paris, France
3) Plateforme de recherche clinique de l'est parisien (URCEST-CRCEST), Hôpital St Antoine, APHP, Paris, France.
4) Emergency Department, Cliniques Universitaires St Luc, Bruxelles, Belgium
5) Emergency Department, Princess Grace Hospital, Monte-Carlo, Monaco
6) Emergency Department, Centre hospitalo-universitaire, Dijon, France
7) Emergency Department, Hôpital Pasteur, Nice, France
8) Emergency Department, Hôpital Européen Georges Pompidou, Paris, France
9) Emergency Department, Hôpital Lariboisière, APHP, Paris, France
10) Emergency Department, Hospital Clinic, Barcelona, Spain
11) Emergency Department, Centre hospitalo-universitaire, Angers, France
12) Emergency Department, Hôpital Tenon, APHP, Paris, France
13) Emergency Department, Centre hospitalo-universitaire, Nîmes, France
14) Emergency Department, CHUV, Lausanne, Switzerland
15) Emergency Department, Barts Health NHS trust, London, United Kingdom
16) Emergency Department, Hôpital Ambroise-Paré, Boulogne, France, and Paris Diderot University, INSERM UMRS 1144, Paris, France

Corresponding author : Dr Yonathan Freund, service d'accueil des urgences, Hôpital Pitié-Salpêtrière, 83 boulevard de l'hôpital, 75013 Paris, France.
yonathan.freund@aphp.fr – tel +331 84827129 – fax +331 42177249

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Yonathan Freund : yonathan.freund@aphp.fr
Najla Lemachatti : lemnajla@gmail.com
Evguenia Krastinova : evguenia.krastinova@aphp.fr
Marie Van Laer : marie.vanlaer@uclouvain.be
Yann-Erick Claessens: yann-erick.claessens@chpg.mc
Aurelie Avondo: aurelie.avondo@chu-dijon.fr
Celine Occelli: celine.occelli@gmail.com
Anne-Laure Feral-Pierssens: feralal@gmail.com
Jennifer Truchot: Jennifer.truchot@aphp.fr
Mar Ortega: mortega@clinic.cat
Bruno Carneiro: Bruno.carneiro@chu-angers.fr
Julie Pernet: juliepernet51@hotmail.com
Pierre-Geraud Claret: pierre.geraud.claret@gmail.com
Fabrice Dami: fabrice.dami@chuv.ch
Ben Bloom: ben.bloom@nhs.net
Bruno Riou: bruno.riou@aphp.fr
Sebastien Beaune: sebastien.beaune@aphp.fr

**Key Points:**

## Abstract

**Importance**: An international task force recently redefined the concept of sepsis. This task force recommended the use of the quick sequential organ failure assessment (qSOFA) score instead of systemic inflammatory response syndrome (SIRS) criteria to identify patients with high mortality risk. However, these new criteria have not been prospectively validated, and their added value in the emergency department setting remains unknown.

**Objective**: To prospectively validate qSOFA as a mortality predictor, and compare the performances of the new sepsis criteria to the previous ones.

**Design, settings and participants:** International prospective cohort study, conducted in France, Spain, Belgium and Switzerland between May and June 2016. In the 30 participating emergency departments, for a four week period, consecutive patients with infection that visited the emergency departments were included. All variables from previous and new definitions of sepsis were collected, and patients were followed up until hospital discharge or death.

**Exposure:** Measurement of qSOFA, SOFA and SIRS.

**Main outcome measure:** In-hospital mortality.

**Result:** Of 1044 patients screened, 879 were included in the analysis. Median age was 67 years (interquartile range 47 – 81), 414 (47%) were women and 379 (43%) had respiratory tract infection. Overall in-hospital mortality was 8%: 3% for patients with a qSOFA <2 vs 24% for qSOFA ≥2 (absolute difference 21%; 95% CI, 15%-26%]). qSOFA performed better than SIRS and severe sepsis to predict in-hospital mortality, with an area under the ROC curve of 0.80 (0.74 – 0.85) vs 0.65 (0.59 – 0.70) for SIRS and severe sepsis ($p<0.001$, incremental AUC 0.15, 95%CI 0.09 – 0.22). The hazard ratio of qSOFA for death was 6.2 (3.8 – 10.3) vs 3.5 (2.2 – 5.5) for severe sepsis.

**Conclusion and relevance:** Among patients presenting to the ED settings with suspected infection, the use of qSOFA resulted in greater prognostic accuracy for inhospital mortality than SIRS or severe sepsis. These findings provide support for the Sepsis-3 criteria in the emergency department setting.

**Registration**: clinicaltrials.gov identifier NCT02738164

## Introduction

Sepsis is a highly prevalent condition that accounts for 10% of admissions to the intensive care unit (ICU), and is associated with a 10-20% in-hospital mortality rate.[1–5] In 2016, an international task force of experts redefined this syndrome in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[6] Due to poor specificity and sensitivity, the systemic inflammatory response syndrome (SIRS), and previous definition of “sepsis” and “severe sepsis” were replaced with the new state of sepsis defined as a life threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis is now identified by an increase of at least two points in the sequential organ failure assessment (SOFA) score in patients with a suspicion of infection. The quick SOFA (qSOFA) score, a surrogate for SOFA in settings where all components of SOFA are not routinely measured, was introduced to screen for patients likely to have sepsis.

The task force derived and validated their criteria on several large patient databases, both inside and outside the ICU. They reported that qSOFA (range 0-3, one point for respiratory rate > 21, systolic arterial blood pressure (BP) ≤ 100 mmHg, or altered mental status) was a better predictor for in-hospital mortality than SIRS or SOFA in non-ICU encounters, and should be used for risk stratification and consideration for sepsis in ED patients with infection. However, it has not been prospectively validated or even studied specifically in the ED. For Sepsis-3 criteria to be globally endorsed, external validation is essential.

The purpose of this study was to assess the external validity of the recently developed Sepsis-3 criteria among patients presenting to the emergency department and to compare these criteria to prior guidelines that utilize the SIRS score and serum lactate levels

## Method

### Design and setting

This was an international multicenter prospective cohort study that recruited from 30 centers in France (27), Switzerland (1), Spain (1), and Belgium (1) – 24 academic centers and 6 non-academic centers. For a four week period from May to June 2016, consecutive patients that visited one of the recruiting EDs with a suspicion of infection were screened and followed until death or hospital discharge after oral (or written in Belgium and Switzerland) consent was obtained. As the study was observational, our institutional review board (IRB) (Comité de protection des personnes, Ile de France VI, Paris, France) approved the study in France, as did local IRBs in Spain, Belgium and Switzerland. The STARD recommendations were followed for the reporting of diagnostic studies.[7]

### Selection of participants, data collection and end points

We included all consecutive adult patients that presented to the ED with a clinical suspicion of infection diagnosed by the treating emergency physicians, based on the identification of an infectious source (whether clinical, radiological or microbiological) or an equivocal presentation (for example, a febrile patient with inflammatory syndrome). After the recruitment and follow up period was over, two experts in each center reviewed all files from each patient's hospital stay and adjudicated whether the acute presentation to the ED was related to an infection or not. Evidence of infection was sought through the analysis of radiological studies, microbiological findings, or clinical context. In cases of disagreement, consensus was sought between the two experts. Patients in whom infection was not confirmed were then excluded from analysis.

We also excluded patients that refused to participate, pregnant women, prisoners or patients in custody, and low acuity patients defined by a localized infection without general symptoms and normal vital parameters (temperature, heart rate, respiratory rate and blood pressure), for which laboratory examinations were not deemed necessary by the emergency physicians (for example tonsillitis, skin abscess or cystitis).

For each recruited patient, the emergency physician collected the three components of the qSOFA in the ED at their worst level during the ED stay (namely highest respiratory rate, lowest systolic blood pressure and lowest Glasgow Coma Scale [GCS] score). As the definition of altered consciousness is not equivalent to a GCS less than 15, the presence of an altered mental status was recorded independently of GCS. The presence of altered mental status was determined clinically by the treating physician. We also recorded data to assess the severity of sepsis using the previous definitions of sepsis (*i.e.* blood lactate and components of the SIRS), and components of the SOFA score when available. Other variables collected by the experts after chart review included the site of infection, means of confirmation (clinical, radiological, or microbiological), and vasopressor administration.

The primary endpoint was in-hospital mortality. As this endpoint could be equivocal for some patients (for example patients transferred to another facility), this endpoint was adjudicated by two experts blinded to each other after reviewing all available medical records. In cases of disagreement, consensus was sought between the two experts. For patients that were still hospitalized after 28 days and outside of ICU, we considered that they did not meet the endpoint of in-hospital mortality. Secondary endpoints included admission to ICU, length of ICU stay > 72h, and a composite of "death or ICU stay > 72h".

**Statistical analysis**

All Gaussian distributed variables are expressed as mean (standard deviation, SD), and non-normally distributed variables as median (interquartile range, IQR). Categorical variables are expressed as number and percentage. We handled missing values for the SOFA score by assuming that they were sithin the normal range for each value.

To assess the performances of the qSOFA to predict the primary endpoint, we calculated diagnostic performances (sensitivity, specificity, negative and positive predictive value) for a qSOFA score equal or higher than 2. We constructed a receiving operator characteristic (ROC) curve and calculated the corresponding area under the ROC curve (AUC). Performances of qSOFA and SOFA to predict the primary and secondary endpoints were compared to those of SIRS and the previous definition of severe sepsis, namely at least 2 elements of SIRS and a blood lactate > 2 mmol/L. The respective hazard ratios for in-hospital death of qSOFA and SIRS that were dichotomized to <2 and ≥2 were estimated with a Cox proportional hazards model after adjustment for measured confounders. The model fit was assessed by the calculation of the concordance probability, which is defined as the probability that predictions and outcomes are concordant. We used the Harrell's C coefficient, which is defined as the proportion of all usable subject pairs in which the predictions and outcomes are concordant.

In line with Seymour et al,[8] the added value of hyperlactatemia to qSOFA (qSOFA + 1 if lactate > 2.0 mmol/l) was also tested, and compared to qSOFA alone. To assess whether the inclusion criteria and primary endpoint were valid, inter-rater agreement

between the two blinded experts that adjudicated these two variables, using Cohen's Kappa was calculated.

To validate the results of the Sepsis-3 consensus paper, the aim was to confirm the hypothesis that patients with a qSOFA score of 2 or higher have an in-hospital mortality of at least 10%.[6] This percentage corresponds to the reported overall mortality rate of infected patients with a SOFA score of 2. For this reason, a difference in mortality of 10% was considered clinically significant in the Sepsis-3 consensus.[6,8] With an estimated overall mortality of 3%,[8] and an assumption that 80% of included patients would have a qSOFA less than 2, and power set at 90%, a target recruitment number of 840 patients was calculated.

All statistical analyses were two-tailed, and a p value less than 0.05 was required for statistical significance. All analyses were performed with NCSS 10.0 (Statistical Solution, Cork, Ireland)

**Results**

A total of 1088 patients were included from 30 EDs during the recruitment period. Following adjudication, 60 patients (6%) were excluded due to not having infection, and 149 patients were excluded due to missing values required to calculate qSOFA, leaving 879 included for the final analysis (Figure 1). A component of the SOFA was missing in 260 patients.The identified infection source was clinical in 79% of patients, radiological in 50%, and microbiological in 37%.

The median age was 67 years (IQR 48 – 81) and the most common site of infection was respiratory (43% cases). Baseline characteristics are summarized in table 1. The qSOFA score was ≥ 2 for 218 patients (25%), SOFA was ≥2 for 324 patients (37%), SIRS was ≥ 2 for 653 patients (74%) and 177 patients (20%) fulfilled the previous criteria of severe sepsis (at least two elements of SIRS and a blood lactate higher than 2.0 mmol/l). Interrater agreement for the diagnosis of infection had a Cohen's Kappa of 0.87 (95% confidence interval [CI] 0.81 – 0.93).

Overall, in-hospital mortality was 8%: mortality for patients with a qSOFA <2 vs ≥ 2 was 3% (95% CI 2% to 5%) vs 24% (95% CI 18% to 30%) respectively (with an absolute difference of 21% [95% CI 15% to 26%]). Secondary endpoints are reported in table 2. Interrater agreement for the primary endpoint had a Cohen's Kappa of 0.99 (95% CI 0.96 – 1). Cumulative incidence of death according to qSOFA is reported in eFigure 1. A ROC curve for the prediction of in hospital death was constructed with new and former definitions of sepsis, namely qSOFA, SOFA, SIRS and severe sepsis (Fig 2). qSOFA and SOFA exhibited the highest AUC with 0.80 (95% CI 0.75 – 0.85) and 0.77 (95% CI 0.71 – 0.82) respectively, vs 0.65 (95%CI 0.59 – 0.70) and 0.65 (95%CI 0.59 – 0.70) for SIRS and severe sepsis respectively (p<0.001 compared to qSOFA). The incremental AUC for qSOFA compared to SIRS

or severe sepsis was 0.15 (95% CI 0.09 – 0.22). We found similar results for the prediction of ICU admission, ICU admission of more than 72h, and a composite of "death or ICU admission > 72h" (eFig 2,3,4). Prognostic performances of these criteria are reported in table 3. For the prediction of in-hospital mortality, qSOFA and SOFA had good sensitivity (70% [95% CI 59% - 80%] and 73% [95% CI 61% - 83%] respectively) and specificity (79% [95%CI 76% - 82%] and 70% [95% CI 67% - 73%] respectively), with a positive likelihood ratio of 3.4 (95% CI 2.8 – 4.17) and 2.4 (95% CI 2.0 – 2.9), and a negative predictive value of 97% (95% CI 95% - 98%) for both.

After adjustment for age and site of infection (respiratory vs others) and using a Cox model, we found that qSOFA ≥ 2 was associated with in-hospital mortality with a hazard ratio (HR) of 6.2 (95%CI 3.8 - 10.3, Harrell's C of 0.83). With the previous definition of severe sepsis, the HR was 3.5 (95% CI 2.2 to 5.5). Other adjusted models for the prediction of in-hospital mortality confirmed the good results of Sepsis-3 criteria (eTable 1).

The AUC ROC of blood lactate was 0.70 (95%CI 0.63 – 0.77). We found no value in adding lactate to qSOFA for the prediction of in-hospital mortality, with a similar AUC ROC for both: 0.80 (95%CI 0.75 – 0.85) for qSOFA and lactate and 0.80 (95%CI 0.74 – 0.85) for qSOFA alone.

In addition, only 30 patients fulfilled the septic shock criteria (presence of hypotension that requires vasoactive drug administration), with a mortality of 40% vs 7% for others (absolute difference 32% (95%CI 15% - 50%)).

## Discussion

The SCREEN international cohort study recruited 879 emergency patients with infection in four European countries to prospectively validate the new Sepsis-3 criteria, and especially the qSOFA score. The latter aimed at identifying patients with sepsis, which is a life threatening situation. This index was derived from large retrospective databases and requires prospective validation.[9] The Sepsis-3 task force estimated that patients with sepsis would have an in-hospital mortality greater than 10%. In the present study, patients with a qSOFA ≥ 2 had an in-hospital mortality of 24% compared with 3% for patients with a qSOFA < 2.

This international study prospectively assessed qSOFA and validated the findings from the derivation cohort. Compared to previous criteria (SIRS and severe sepsis), qSOFA had better discriminative value and hazard ratio for death, ICU admission, and ICU stay longer than 72h. The good prognostic accuracy of qSOFA for mortality was confirmed with an AUC of 0.80 (95% CI 0.74 – 0.85), which was greater than that of SIRS and severe sepsis (AUC 0.65 [95% CI 0.59 – 0.70]) This is in line with the SEPSIS 3 task force study that reported an AUC of 0.81 for qSOFA for non-ICU encounters.[8] Recently, two retrospective studies also confirmed the good prognostic ability of qSOFA to predict mortality and ICU admission.[10,11]

Following the publication of Sepsis-3, a prospective validation study focused on ED patients was required to support the new recommendations and assist in changing the paradigm. In the cohort with SIRS ≥ 2 reported in this paper, the mortality was 11%, and the high sensitivity (93% [95% CI 85% - 98%]) was associated with a poor specificity (27% [95%CI 24% - 31%]). Nearly 75% of patients had at least two points of SIRS, but far fewer had life threatening organ dysfunction. Similarly, previous studies reported that 68 to 93% of patients admitted in the ICU had at least two

elements of SIRS.[12–14] This indicates that having two or more elements of SIRS does not discriminate well enough for organ dysfunction. The very low mortality rate of patients with qSOFA score < 2 is a strong argument to replace SIRS without the risk of missing critically ill patients. Moreover, there was no difference in the rate of false negative of SIRS and qSOFA for the prediction of death or ICU stay > 72h (7% [95% CI 4 % - 10%] and 9% [95% CI 7% - 11%]). Although qSOFA was not meant to replace SIRS in the definition of sepsis but rather help clinicians for early detection of sepsis [15], these results suggest that ED patients with infection and a qSOFA ≥ 2 should be considered for sepsis even in the absence of a SOFA score ≥ 2. More than 70% of patients with a qSOFA ≥ 2 had at least 2 points of SOFA as previously reported. [8]

Of note, although blood lactate was known to be associated with severe outcome in patients with sepsis [16–19], there was no added value of hyperlactatemia to qSOFA. This confirms the findings of the Sepsis-3 task force, which suggested qSOFA performs effectively and there is no added value when stratified by blood lactate level. This along with other findings could result in a complete change of paradigm, because the severity of sepsis has up until now been assessed in emergency department patients using lactate levels.[20,21]

In addition to its better performance, qSOFA is genuinely adapted to the practice of emergency medicine. The endorsement of the Sepsis-3 criteria would allow not only a more accurate recognition of the critically ill, but also an earlier detection as qSOFA can be assessed immediately upon arrival, and doesn’t require any supplemental investigation such as leukocytosis or blood lactate.

The work presented by the Sepsis-3 task force included two major shortcomings that might have contributed to the reluctance of physicians to adopt them: they were not prospectively validated, and they did not involve emergency patient cohorts or emergency physicians. This was particularly criticized because two thirds of patients with sepsis come through the ED. One of the strengths of this study is that it prospectively validates their findings, and highlights how they particularly apply to ED patients with even stronger results.

Our study has some limitations. First, we did not follow up discharged patients and only focused on in-hospital mortality, which was because we used the Sepsis-3 primary endpoint of in-hospital mortality. It is possible that a discharged patient could have been readmitted or could have died in the first 28 days. Second, the worst value of qSOFA criteria during the ED stay of the patient was recorded. This could have biased the results to a higher qSOFA score. Because the qSOFA can vary in a short timeframe, these results could not be extrapolated to the detection of sepsis at the time of the arrival, for instance to be utilized as a nurse triage tool. A specific study on the value at ED entry should be performed to answer this question. Third, there was a substantial part of missing data regarding laboratory results, so the calculation of SOFA may not be accurate. It is possible that with more complete data, the SOFA score may actually perform better than qSOFA. However, qSOFA seems much more appropriate in the ED as an early detection tool. Similarly, one third of patient with at least two SIRS criteria did not have blood lactate measurement, resulting in a possible misclassification in the “severe sepsis” category. Fourth, we did not exclude patients with “do not attempt resuscitation” status or with set limitations of care, and this could have skewed the mortality rate. Fifth, although the study was adequately powered, only 74 patients met the primary endpoint, which may be considered

relatively low. Sixth, experts could not have been blinded to the value of the components of the scores, and this could have influenced their adjudication as to whether the emergency department presentation was related to an infection or not. This could be a source of incorporation bias.

## Conclusion

Among patients presenting to the emergency department setting with suspected infection, the use of qSOFA resulted in greater prognostic accuracy for inhospital mortality than severe sepsis or SIRS. These findings provide support for the Sepsis-3 criteria in the emergency department setting.

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**Authors' contribution**

YF and SB conceived the study. YEC, BR, BB contributed to the study protocol. NL, MVL, YEC, AA, ALFP, JT, FD, MO, PGC, BC and JP recruited patients. YF and EK provided statistical analysis. YF and NL interpreted the results. YF drafted the manuscript. BB, BR, YEC, ALFP and SB provided substantial revisions. All authors have read, revised and approved the manuscript. All authors agree to be accountable for all aspects of the work.

Data analysis was done by YF and EK

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**French society of emergency medicine collaborators group**

Pr Patrick Ray, MD, PhD, Hôpital Tenon, Paris, France
Dr Youri Yordanov, MD, and Dr Pierre-Alexis Raynal, Hôpital Saint-Antoine, Paris, France
Dr Jerome Bokobza, MD, Hôpital Lariboisière, Paris, France
Pr Frederic Adnet, MD, PhD, Pr Frederic Lapostolle, MD, PhD, and Dr Aurelien Guenin, MD, Hôpital Avicenne, Bobigny, France
Dr Florence Dumas, MD, PhD, and Dr Benoit Doumenc, MD, Hôpital Cochin, Paris, France
Pr Sandrine Charpentier, MD, PhD, CHU Toulouse, France
Dr Hery Andrianjafy, MD, Hôpital Nord-Essone, Longjumeau, France
Pr Pierre-Marie Roy, CHU Angers, France

Dr Tahar Chouihed, CHU Nancy, France
Pr Jacques Levraut, CHU Nice, France
Dr Pierre-Arnaud Fort, Centre hospitalier d'Agen, France
Dr Maxime Maignan, CHU Grenoble, France
Dr Sabrina Kepka, CHU Strasbourg, France
Dr Laurent Jacquin, Hospices Civils de Lyon, Lyon, France
Dr Mathias Wargon, Hôpital Saint Camille, Bry sur Marne, France
Dr Mehdi Khellaf, Hôpital Henri-Mondor, Créteil, France
Dr Agnès Ricard-Hibon and Dr Aurélie Ferré, CHIPO, Beaumont sur Oise, France
Pr Said Laribi, CHU Tours, France
Dr Carlos El Khoury, Centre Hospitalier, Vienne, France
Dr Carl Ogereau, Hôpital Saint Louis, Paris, France
Pr Luc-Marie Joly, CHU Rouen, France
Pr Andrea Penaloza, Cliniques universitaires St Luc, Bruxelles, Belgium
Pr Oscar Miro, Hospital clinic, Barcelona, Spain
Pr Olivier Hugli, CHUV, Lausanne, Switzerland

**Data access**

The corresponding author (Y Freund) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All data of the study can be provided upon request to the corresponding author.

## References


1. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840-851. doi:10.1056/NEJMra1208623.

2. Cohen J, Vincent J-L, Adhikari NKJ, et al. Sepsis: a roadmap for future research. *Lancet Infect Dis*. 2015;15(5):581-614. doi:10.1016/S1473-3099(15)70112-X.

3. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16):1496-1506. doi:10.1056/NEJMoa1404380.

4. ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683-1693. doi:10.1056/NEJMoa1401602.

5. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. 2015;372(14):1301-1311. doi:10.1056/NEJMoa1500896.

6. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810. doi:10.1001/jama.2016.0287.

7. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med*. 2003;138(1):W1-12.

8. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762-774. doi:10.1001/jama.2016.0288.

9. Abraham E. New definitions for sepsis and septic shock: Continuing evolution but with much still to be done. *JAMA*. 2016;315(8):757-759. doi:10.1001/jama.2016.0290.

10. Chen Y-X, Wang J-Y, Guo S-B. Use of CRB-65 and quick Sepsis-related Organ Failure Assessment to predict site of care and mortality in pneumonia patients in the emergency department: a retrospective study. *Crit Care Lond Engl*. 2016;20(1):167. doi:10.1186/s13054-016-1351-0.

11. Wang J-Y, Chen Y-X, Guo S-B, Mei X, Yang P. Predictive performance of quick Sepsis-related Organ Failure Assessment for mortality and intensive care unit admission in patients with infection at the ED. *Am J Emerg Med*. June 2016. doi:10.1016/j.ajem.2016.06.015.

12. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA*. 1995;273(2):117-123.

13. Sprung CL, Sakr Y, Vincent J-L, et al. An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence In Acutely Ill Patients (SOAP) study. *Intensive Care Med*. 2006;32(3):421-427. doi:10.1007/s00134-005-0039-8.

14. Dulhunty JM, Lipman J, Finfer S, Sepsis Study Investigators for the ANZICS Clinical Trials Group. Does severe non-infectious SIRS differ from severe sepsis? Results from a multi-centre Australian and New Zealand intensive care unit study. *Intensive Care Med*. 2008;34(9):1654-1661. doi:10.1007/s00134-008-1160-2.

15. Vincent J-L, Martin GS, Levy MM. qSOFA does not replace SIRS in the definition of sepsis. *Crit Care*. 2016;20:210. doi:10.1186/s13054-016-1389-z.

16. Bernardin G, Pradier C, Tiger F, Deloffre P, Mattei M. Blood pressure and arterial lactate level are early indicators of short-term survival in human septic shock. *Intensive Care Med*. 1996;22(1):17-25.

17. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*. 2009;37(5):1670-1677. doi:10.1097/CCM.0b013e31819fcf68.

18. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Med*. 2007;33(6):970-977. doi:10.1007/s00134-007-0563-9.

19. Freund Y, Delerme S, Goulet H, Bernard M, Riou B, Hausfater P. Serum lactate and procalcitonin measurements in emergency room for the diagnosis and risk-stratification of patients with suspected infection. *Biomark Biochem Indic Expo Response Susceptibility Chem*. 2012;17(7):590-596. doi:10.3109/1354750X.2012.704645.

20. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39(2):165-228. doi:10.1007/s00134-012-2769-8.

21. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med*. 2010;36(2):222-231. doi:10.1007/s00134-009-1738-3.

| Characteristics | N | All patients, n | In-hospital death n (%) | Alive and out of hospital, n (%) | p-value |
|---|---|---|---|---|---|
| **All patients** | **879** | 879 | 74 | 805 | |
| **Sex** | | | | | 0.30 |
| female | | 414 (47%) | 31 (42%) | 383 (48%) | |
| male | | 458 (53%) | 43 (58%) | 415 (52%) | |
| **Age (years), median (IQR)** | | 67 (48-81) | 83.5 (72-90) | 66 (47-79) | <0.001 |
| Age <75 | | | 23 (31) | 530 (66) | |
| Age ≥75 | | | 51 (69) | 274 (34) | |
| **Systolic blood pressure (mmHg), median (IQR)** | | 114 (98 - 133) | 93 (76 - 117) | 116 (101 - 133) | <0.001 |
| **Respiratory rate (per min), median (IQR)** | | 20 (16 - 27) | 30 (39 - 24) | 20 (16 - 26) | <0.001 |
| **Heart rate (per min), median (IQR)** | | 102 (88 - 116) | 107 (92 - 126) | 101 (87 - 115) | 0.02 |
| **Glasgow coma scale score < 15** | | 154 (17%) | 41 (56%) | 113 (14%) | <0.001 |
| **Temperature (°C), median (IQR)** | | 38.2 (37.2 - 38.9) | 38 (36.5 - 38.9) | 38.2 (37.2 - 38.9) | 0.06 |
| **Altered mental status** | | 153 (17%) | 39 (53%) | 114 (14%) | <0.001 |
| **Vasoactive drug** | | 36 (4%) | 13 (18%) | 23 (3%) | <0.001 |
| **Site of infection** | | | | | |
| respiratory | | 379 (43%) | 46 (62%) | 333 (42%) | <0.001 |
| urinary | | 236 (27%) | 10 (14%) | 226 (28%) | 0.006 |
| abdominal | | 135 (15%) | 10 (14%) | 125 (16%) | 0.70 |
| cutaneous | | 59 (7%) | 5 (7%) | 54 (7%) | 1.0 |
| neurological | | 15 (2%) | 1 (1%) | 14 (2%) | 1.0 |
| bone and joints | | 15 (2%) | 0 (0%) | 15 (2%) | 0.71 |
| other | | 76 (9%) | 5 (7%) | 71 (9%) | 0.67 |
| **France (vs other countries)** | | 754 (86%) | 67 (91%) | 687 (85%) | 0.22 |
| **Laboratory results, median (IQR)** | | | | | |
| Leucocytes (/µL) | 872 | 12300 (8900 - 6500) | 14900 (10800 - 20500) | 12000 (8900 - 16200) | 0.003 |
| Creatinine (mg/dL) | 861 | 0.83 (0.71 - 1.30) | 1.32 (0.92 - 2.13) | 0.93 (0.71 - 1.23) | <0.001 |
| Bilirubine (mg/dL) | 624 | 0.70 (0.47 - 1.17) | 0.88 (0.41 - 1.70) | 0.70 (0.47 - 1.11) | 0.15 |
| Platelets ($10^3$/µL) | 843 | 222 (168 - 286) | 250 ( 148 - 353) | 222 (169 - 280) | 0.42 |
| Lactate (mmol/L) | 640 | 1.7 (1.4 - 2.6) | 2.6 (1.6 - 4.4) | 1.6 (1.1 - 2.4) | <0.001 |
| **SIRS** | | | | | |
| 0 | | 60 (7%) | 0 (0%) | 60 (7%) | <0.001 |
| 1 | | 166 (19%) | 5 (7%) | 161 (20%) | |
| 2 | | 243 (28%) | 20 (27%) | 223 (28%) | |
| 3 | | 291 (33%) | 32 (43%) | 259 (32%) | |
| 4 | | 119 (14%) | 17 (23%) | 102 (13%) | |
| **SIRS ≥ 2** | | | | | |
| No | | 226 (26%) | 5 (7%) | 221 (27%) | <0.001 |
| Yes | | 653 (74%) | 69 (93%) | 584 (73%) | |
| **Severe sepsis** | | | | | |
| No | | 703 (80%) | 39 (53%) | 664 (82%) | <0.001 |
| Yes | | 176 (20%) | 35 (47%) | 141 (18%) | |
| **qSOFA** | | | | | |
| 0 | | 350 (40%) | 6 (8%) | 344 (43%) | <0.001 |
| 1 | | 311 (35%) | 16 (22%) | 295 (37%) | |
| 2 | | 161 (18%) | 27 (36%) | 134 (17%) | |
| 3 | | 57 (6%) | 25 (34%) | 32 (4%) | |
| **qSOFA ≥ 2** | | | | | |
| No | | 661 (75%) | 22 (30%) | 639 (79%) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| | Yes | 218 (25%) | 52 (70%) | 166 (21%) | |
| **SOFA ≥ 2** | | | | | |
| | No | 582 (66%) | 20 (25%) | 562 (70%) | <0.001 |
| | Yes | 297 (34%) | 54 (75%) | 243 (30%) | |

**Table 1: baseline characteristics.**

IQR: interquartile range. SOFA: Sequential Organ Failure Assessment, 0 to 24. qSOFA: quick SOFA, 0 to 3. SIRS: Systemic inflammatory response syndrome, 0 to 4 Higher scores for higher severity. Severe sepsis = SIRS ≥ 2 AND lactate > 2 mmol/l. Glasgow coma scale score ranges from 3 to 15 – Maximum 4 points for eye response, 5 points for verbal response and 6 points for motor response.

| | All patient | qSOFA<2 (n=661) | qSOFA≥2 (n=218) | difference (95% CI) | SOFA <2 (n=555) | SOFA ≥2 (n=324) | difference (95% CI) | SIRS <2 (n=226) | SIRS ≥2 (n=653) | difference (95% CI) | no severe sepsis (n=703) | severe sepsis (n=176) | difference (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **In-hospital death** | 74 (8%) | 22 (3%) | 52 (24%) | 21% (15% - 26%) | 15 (3%) | 59 (18%) | 15% (10% - 19%) | 5 (2%) | 69 (11%) | 8% (5% - 11%) | 39 (6%) | 35 (20%) | 14% (8% - 20%) |
| **ICU admission** | 131 (15%) | 58 (9%) | 73 (34%) | 25% (18% - 31%) | 38 (7%) | 93 (29%) | 22% (16% - 27%) | 14 (6%) | 117 (18%) | 12% (7% - 16%) | 71 (10%) | 60 (34%) | 24% (17% - 31%) |
| **ICU stay ≥ 72h** | 92 (11%) | 41 (6%) | 51 (23%) | 17% (11% - 23%) | 24 (4%) | 68 (21%) | 17% (12% - 22%) | 12 (5%) | 80 (12%) | 7% (3% - 11%) | 55 (8%) | 37 (21%) | 13% (7% - 13%) |
| **ICU stay ≥ 72h or in-hospital death** | 150 (17%) | 60 (9%) | 90 (41%) | 32% (25% - 39%) | 47 (8%) | 113 (35%) | 28% (22% - 33%) | 16 (7%) | 134 (21%) | 13% (9% - 18%) | 85 (12%) | 65 (37%) | 25% (17% - 32%) |
| **Legnth of hospital stay (days),** median (IQR) | 7 (3 - 11) | 6 (2 - 10) | 9 (5 - 14) | 3.2 (2.1 - 4.3) | 6 (1 - 10) | 9 (5 - 15) | 3.6 (2.5 - 4.6) | 5 (1 - 9) | 7 (3 - 13) | 2.1 (1.0 - 3.2) | 6 (2 - 10) | 9 (5 - 15) | 3.4 (2.2 - 4.6) |

**Table 2: Classification according to sepsis criteria.**

IQR: interquartile range. SOFA: Sequential Organ Failure Assessment, 0 to 24, with increasing score indicating increasing severity of organ failure. qSOFA: quick SOFA, 0 to 3, with increasing score indicating increasing likelihood of having sepsis. SIRS: Systemic inflammatory response syndrome, 0 to 4, with increasing score indicating increasing severity of the syndrome. Severe sepsis = SIRS ≥ 2 and lactate > 2 mmol/l.

| | qSOFA | | SOFA | | SIRS | | Severe sepsis | |
|---|---|---|---|---|---|---|---|---|
| **for prediction of death** | | | | | | | | |
| Sensitivity | 70% | (59% - 80%) | 73% | (61% - 83%) | 93% | (85% - 98%) | 47% | (36% - 59%) |
| Specificity | 79% | (76% - 82%) | 70% | (67% - 73%) | 27% | (24% - 31%) | 82% | (80% - 85%) |
| PPV | 24% | (18% - 30%) | 18% | (14% - 23%) | 11% | (8% - 13%) | 20% | (14% - 27%) |
| NPV | 97% | (95% - 98%) | 97% | (95% - 98%) | 98% | (95% - 99%) | 94% | (92% - 96%) |
| LHR+ | 3.40 | (2.80 - 4.17) | 2.40 | (2.00 - 2.90) | 1.30 | (1.2 - 1.4) | 2.70 | (2.0 - 3.6) |
| LHR- | 0.37 | (0.26 - 0.53) | 0.39 | (0.27 - 0.56) | 0.25 | (0.11 - 0.58) | 0.64 | (0.51 - 0.79) |
| AUC ROC | 0.80 | (0.74 - 0.85) | 0.77 | (0.71 - 0.82) | 0.65 | (0.59 - 0.70) | 0.65 | (0.59 - 0.70) |

**Table 3: Diagnostic performances for the prediction of in-hospital death.**

SOFA: Sequential Organ Failure Assessment. qSOFA: quick SOFA. SIRS: Systemic inflammatory response syndrome. PPV: positive predictive value. NPV: negative predictive value. LHR: likelihood ratio. AUC ROC: area under the receiving operator characteristic curve.

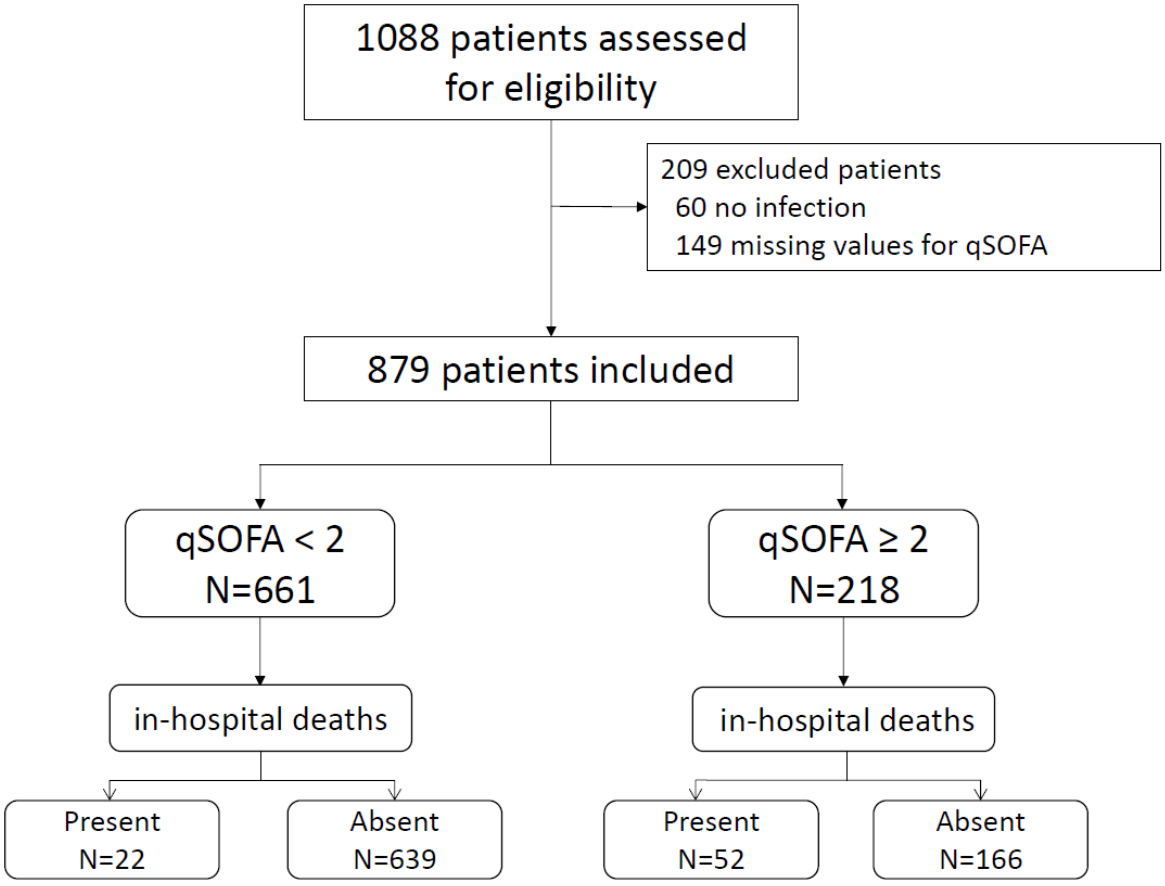
## Figure legends

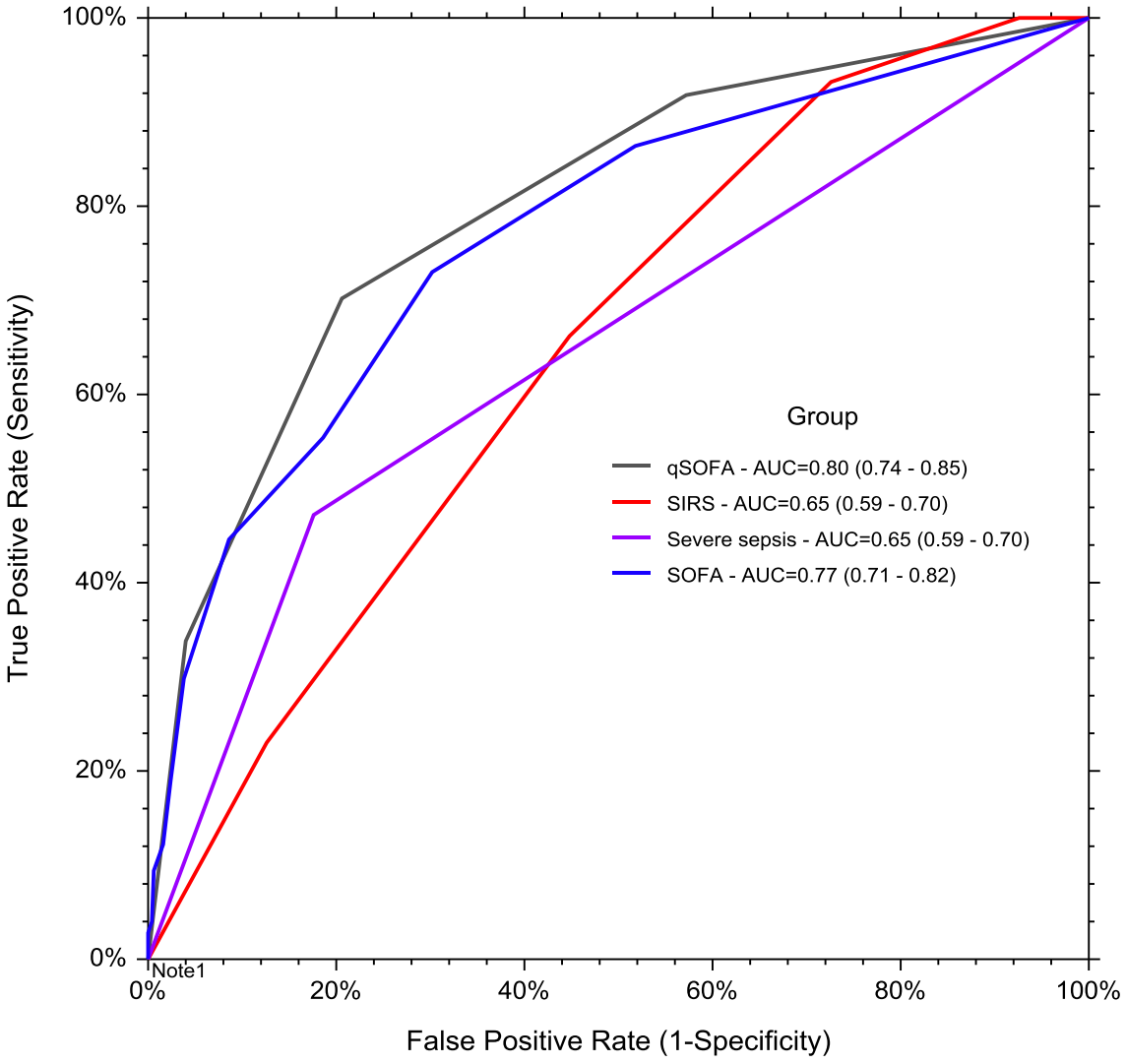
**Figure 1:**

Flow diagram. qSOFA: quick Sequential Organ Failure Assessment.

**Figure 2:**

Receiving operator characteristic curves for in-hospital mortality. AUC: area under the curve. SOFA: Sequential Organ Failure Assessment. qSOFA: quick SOFA. SIRS: Systemic inflammatory response syndrome. AUC for qSOFA=0.80 (0.74 – 0.85), SOFA=0.77 (0.71 – 0.82), SIRS=0.65 (0.59 – 0.70), severe sepsis=0.65 (0.59 – 0.70)


1088 patients assessed for eligibility
209 excluded patients
60 no infection
149 missing values for qSOFA
879 patients included
qSOFA < 2 N=661
qSOFA ≥ 2 N=218
in-hospital deaths
in-hospital deaths
Present N=22
Absent N=639
Present N=52
Absent N=166


100%
80%
60%
40%
20%
0%
True Positive Rate (Sensitivity)
Note1
0%
20%
40%
60%
80%
100%
False Positive Rate (1-Specificity)
Group
qSOFA - AUC=0.80 (0.74 - 0.85)
SIRS - AUC=0.65 (0.59 - 0.70)
Severe sepsis - AUC=0.65 (0.59 - 0.70)
SOFA - AUC=0.77 (0.71 - 0.82)