Early variation of quick sequential organ failure assessment score to predict in-hospital mortality in emergency department patients with suspected infection

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Background **The quick sequential organ failure assessment (qSOFA) score showed good prognostic performance in patients with suspicion of infection in the emergency department (ED). However, previous studies only assessed the performance of individual values of qSOFA during the ED stay. As this score may vary over short timeframes, the optimal time of measurement, and the prognostic value of its variation are unclear. The objective of the present study was to prospectively assess the prognostic value of the change in qSOFA over the first 3 h (ΔqSOFA = qSOFA at 3 h − qSOFA at inclusion).**

Patients and methods **This is an international prospective cohort study conducted in 17 EDs in France, Belgium, and Spain. From November 2016 to March 2017, patients with a suspected infection and a qSOFA score of 2 or higher were included and followed up until death or hospital discharge. qSOFA was measured at inclusion, 1 h and 3 h. Primary end point was in-hospital mortality, truncated at 28 days.**

Results **Of 534 recruited patients, 512 were included in the analysis. The qSOFA was improved at 3 h (ΔqSOFA < 0) in 287 (55%) patients. Overall in-hospital mortality was 27%: 44% when ΔqSOFA greater than 0, 36% when ΔqSOFA = 0, and 18% when ΔqSOFA less than 0. A positive ΔqSOFA was independently associated with reduced in-hospital mortality (adjusted hazard ratio of 0.48, 95% confidence interval: 0.34–0.68). After modeling qSOFA kinetics in the first 3 h, there was a significant difference in adjusted slopes between patients who died and those who survived (0.15, 95% confidence interval: 0.09–0.22, $P < 0.001$).**

Conclusion **In patients with suspected infection presenting to the ED with a qSOFA of 2 or higher, the early change in qSOFA is a strong independent predictor of mortality.** ***European Journal of Emergency Medicine*** **00:000–000**

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Introduction

Background

In 2016, the SEPSIS-3 task force redefined sepsis and introduced the quick sequential organ failure assessment (qSOFA) score aimed at raising awareness on patients at risk of sepsis. qSOFA includes three clinical binary components: a systolic arterial blood pressure less than or equal to 100 mmHg, a respiratory rate greater than 21 breaths/min, and an altered mental status (one point for each, range: 0–3) [1,2]. A qSOFA score of 2 or higher has been reported to be independently associated with increased mortality [3–5], and its validity has been confirmed in emergency department (ED) patients [6].

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Importance

In previous studies that evaluated qSOFA, only one measurement was taken into account during the study period (whole ED stay, or first 24 h). The analyzed value was either the value measured at triage, or the worst qSOFA value during the ED stay, or the only value entered in an electronic database for the day [1,4,6,7]. However, physiological values may change during ED attendances, especially for patients with sepsis receiving fluid resuscitation [8]. Hwang *et al.* [9] recently reported that qSOFA may vary in a short timeframe during the early period after ED presentation. It is unclear at which point qSOFA should be measured for optimizing its prognostic accuracy. Furthermore, similar to early changes in lactate concentration, a change in the qSOFA during the first hours of management in the ED could refine risk stratification in patients with an initial qSOFA of 2 or higher [10,11].

Goal of this investigation

The aims of this study were to evaluate the variation of qSOFA during the first 3 h of management of patients with suspected infection in the ED, and to assess the prognostic value of this early variation to better predict in-hospital mortality. We hypothesize that in patients with an initial qSOFA greater than or equal to 2, an improvement of qSOFA during the first 3 h in the ED is independently associated with improved survival.

Patients and methods

Design and setting

This was an international prospective cohort study that recruited patients from 17 centers in France ($n=11$), Spain ($n=5$), and Belgium ($n=1$). From 1 November 2016 for a 4-month period, all adult patients with suspected infection who presented to the ED were screened. After evaluation by an emergency physician, if their qSOFA was 2 or higher and after verbal consent (or written in Belgium), they were recruited in the study and followed up until death or hospital discharge. Because the study was observational, written informed consent was not required in France. Institutional review boards of each country approved the study (Comité de protection des personnes Ile-de-France 6 in France, Comité d'ethique des cliniques universitaires St Luc, Bruxelles, Belgium, and local research ethics committees in each of the five Spanish centers; Clinicaltrials.gov NCT02926664). The TRIPOD recommendations were followed for the reporting of diagnostic studies [12].

Selection of participants, data collection, and end points

We included all consecutive adult patients who presented to the ED with a clinical suspicion of infection and a qSOFA score of 2 or higher. As in our previous study, the suspicion of infection was based on identification of an infection source (whether clinical, radiological or microbiological) or an equivocal presentation [6]. We excluded patients who refused to consent, prisoners, and pregnant women. After completion of the follow-up period, a local expert investigator adjudicated if the acute presentation was caused by an infection or not. This method has been reported to be reliable, with an inter-rater κ agreement of 0.87 [6]. The local investigator also adjudicated the site of infection on the basis of clinical, radiological, and microbiological findings.

Measurement

The qSOFA was measured by the emergency physician at the time of inclusion: during the first contact between the patient and the emergency physician. If an infection was suspected, the emergency physician measured qSOFA to seek potential inclusion in the study. If the patient fulfilled the inclusion criteria (qSOFA ≥ 2 and no exclusion criteria), qSOFA measurement was repeated at 1 and 3 h following inclusion. The timeframe of 3 h was arbitrarily chosen, consistent with what is done for lactate clearance (i.e. after at least 2 h [13]), without risking exceeding the length of ED stay. Furthermore, this is consistent with the 3-h bundle recommended by the 'Surviving Sepsis Campaign' [14].

As described previously, the presence of an 'altered mental status' was determined clinically by the treating emergency physician [6]. Patients receiving vasopressors were assigned one point for the sBP component, and intubated patients were assigned one point for the respiratory component plus one point for the mental state component. The total volume of fluid resuscitation at 1 h and 3 h was also recorded, as were site of infection, 'treatment limitation decisions' or 'do not resuscitate' orders, vasopressor administration, and biological variables including lactate and leukocyte concentration, and components of the SOFA score when available.

Outcomes

The primary objective of the study was to assess the prognostic performances of ΔqSOFA at 3 h for the prediction of in-hospital mortality. The primary end point was in-hospital mortality, truncated at 28 days. The secondary end points were ICU admission, length of ICU stay, ICU stay of greater than 72 h, and a composite of ICU stay longer than 72 h or death. We also assessed the prognostic performances of the value of qSOFA at 3 h, and of ΔqSOFA at 1 h ($\Delta qSOFA_{H1}$).

Statistical analysis

Categorical variables were expressed as number (percentage). Baseline characteristics were compared with the χ^2-test and the Wilcoxon rank sum test for dichotomous and continuous variables, respectively. The change in qSOFA over 3 h (ΔqSOFA) was defined as qSOFA at 3 h minus qSOFA at inclusion. We tested ΔqSOFA as a binary variable (<0 or not, i.e. lowered qSOFA at 3 h) and as a categorical variable. As there was a very small number of patients with a ΔqSOFA of -3 ($n=7$, 1.3%), we handled ΔqSOFA as the following

categorical variables: 1, 0, −1, or −2. Patients with missing data to calculate qSOFA at inclusion or at 3 h were excluded.

Kaplan–Meier survival curves were used to analyze survival according to qSOFA. Curves were compared using the log-rank test. Univariate and multivariate analyses were performed with Cox proportional hazards models. The proportionality assumptions were assessed by checking the log cumulative survival plots.

The qSOFA evolution (using measurements at inclusion, 1 h, and 3 h) was modeled using piecewise linear mixed effects models to take into account the correlation between measurements in a given subject. The models included both fixed and random effects for the intercept and slope. Plotted prediction of the mixed modeling analysis was used to give a visual illustration of the qSOFA dynamics though the first 3 h. The best model (Akaike's criterion) was chosen. Multivariate analysis was performed after adjusting for sex, age, site of infection, and the center of inclusion.

In the clinicaltrial.gov registry, we initially wrongly reported 'infection ruled out by the expert after chart review' whereas the protocol reported that only 'patients in whom the emergency physician ruled out infection during ED management were excluded'. For the purpose of transparency, we report our main results both with the whole population, and in the population after excluding 'patients with infections ruled out by the expert after chart review'. As patients with treatment limitation decisions may be of less interest, we also report our main analysis after excluding these patients. We also assessed the change in qSOFA over 1 h, defined as $\Delta qSOFA_{H1}$ = qSOFA at1 h–qSOFA at inclusion, and subsequent prognostic performances.

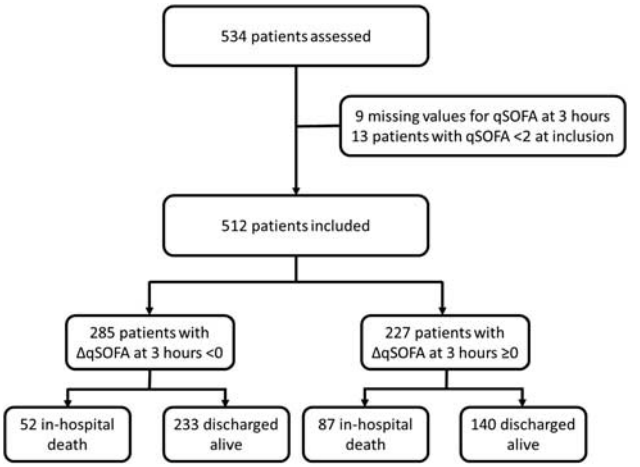
Our hypothesis was that an improved qSOFA after 3 h was associated with an absolute decrease of 15% in-hospital mortality. On the basis of our previous study, we assumed a 23% baseline mortality risk, and also estimated that ΔqSOFA will be negative in half of the patients [6]. With a power of 90% and with alpha risk set at 0.05, we needed to analyze at least 322 patients (PASS 14; Statistical Solution Ltd, Cork, Ireland).

Results

During the study period, 534 patients were included. Nine had missing values for qSOFA at 3 h, and 13 had an initial qSOFA less than 2, leaving 512 patients for analysis (Fig. 1). The median age was 76 years (IQR: 62–85 years), 226 (44%) were women, and the most common sites of infection were respiratory (n = 238, 46%) and urinary (n = 107, 21%; Table 1). After 3 h in the ED, patients received a median of 1500 ml (IQR: 1000–2000) of fluid, and 89 (17%) received vasoactive drugs. At 3 h, qSOFA was less than 2 in 222 (45%) patients.

The overall in-hospital mortality was 27% [95% confidence interval (95% CI): 23–31%]. In the 287 (55%) patients whose ΔqSOFA less than 0, the in-hospital mortality rate was 18%, versus 38% in the group whose ΔqSOFA was greater than or equal to 0 (absolute difference 19%; 95% CI: 12–28%) (eFigure 1). Secondary end points are also reported in Table 2. A decrease of one point of ΔqSOFA at 3 h was significantly associated with a lower in-hospital mortality (Fig. 2a). At 3 h, individual qSOFA scores were also associated with in-hospital mortality (Fig. 2b). The qSOFA evolution (using measurements at inclusion, 1 h, and 3 h) was modeled using piecewise linear mixed effects models to take into account the correlation between measurements in a given subject. The qSOFA slope for surviving patients was significantly lower than that of deceased patients: −0.25 (SD: 0.01) versus −0.09 (SD: 0.02), difference 0.16 (95%CI: 0.10–0.21). Figure 3 gives a visual insight of the qSOFA evolution in the first 3 h after plotting the predictions of the mixed modeling (Fig. 3).

Fig. 1



Flow diagram. ΔqSOFA = qSOFA at 3 h−qSOFA at admission. qSOFA, quick sequential organ failure assessment.

After adjustment for age, center, and site of infection, a negative ΔqSOFA at 3 h was independently associated with improved outcomes in a Cox model, with an adjusted HR of 0.48 (95% CI: 0.34–0.68; Table 3). Each point of qSOFA improvement was independently associated with decreased in-hospital mortality (Table 3). We found similar results for patients in whom an infection was confirmed (n = 453), where a negative ΔqSOFA was still an independent predictor of decreased in-hospital mortality (adjusted HR: 0.47, 95% CI: 0.33–0.68, Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A218*). However, after excluding patients with treatment limitation decisions (n = 136), similar results were observed only for patient with ΔqSOFA less than −1 (adjusted HR: 0.32, 95% CI: 0.11–0.95, Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/EJEM/A218*), and qSOFA at 3 h less than −1 (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/EJEM/A218*).

Table 1 Baseline patients' characteristics

Characteristics	*N*	All patients [*n* (%)]	In-hospital death [*n* (%)]	Discharged alive [*n* (%)]	*P* value
All patients	512	512	139 (27)	373 (73)	
Sex					
Female	512	226 (44)	58 (42)	168 (45)	0.62
Male		286 (56)	81 (58)	205 (55)	
Age [median (IQR)] (years)	512	76 (62–85)	82 (71–88)	72 (57–84)	< 0.001
Age <75		246 (47)	42 (30)	204 (53)	
Age ≥ 75		277 (53)	99 (70)	178 (47)	
Systolic blood pressure [median (IQR)] (mmHg)	512	95 (84–102)	93 (80–104)	95 (85–101)	0.30
Respiratory rate [median (IQR)] (breaths/min)	512	26 (23–31)	29 (24–35)	26 (22–30)	< 0.001
Heart rate [median (IQR)] (beats/min)	491	102 (86–120)	100 (80–120)	103 (87–120)	0.20
Temperature [median (IQR)] (°C)	484	38 (37–38.7)	37.8 (36.2–38.5)	38.1 (37.2–38.7)	< 0.001
Altered consciousness	512	323 (62)	105 (74)	218 (57)	< 0.001
Vasoactive drug	512	89 (17)	30 (22)	59 (16)	0.20
Site of infection [*n*(%)] (*N* = 512)					
Respiratory		238 (46)	74 (53)	164 (44)	0.06
Urinary		107 (21)	25 (18)	82 (22)	0.20
Abdominal		72 (14)	22 (16)	50 (13)	0.60
Cutaneous		19 (4)	5 (4)	14 (4)	0.70
Neurological		12 (2)	0 (0)	12 (3)	
Bone and joints		4 (0.8)	2 (1)	2 (0.5)	0.34
Other		37 (7)	11 (8)	26 (7)	0.70
France (vs. other countries)	512	384 (75)	111 (80)	273 (73)	0.12
Laboratory results [median (IQR)]	512				0.07
Leukocytes (G/l)	510	12.9 (8.5–18.8)	13.8 (8.7–21)	12.6 (8.5–17.8)	0.20
Creatinine (μmol/l)	511	121 (80–185)	170 (84–240)	112 (79–165)	< 0.001
Bilirubin (μmol/l)	436	12 (7–21)	13 (7–24)	12 (7–20)	0.40
Platelets (G/l)	507	200 (136–289)	203 (133–322)	199 (136–278)	0.28
Lactate (mmol/l)	329	2.3 (1.4–3.8)	2.7 (1.6–4.8)	2.2 (1.3–3.3)	0.002
Volume of fluids received [median (IQR)] (ml)		1500 (1000–2000)	1500 (1000–2000)	1500 (1000–2000)	0.75
qSOFA at inclusion					
2	512	375 (71)	86 (62)	289 (75)	< 0.001
3		137 (26)	53 (38)	84 (22)	
qSOFA at 3 h					
0	512	64 (13)	6 (4)	58 (16)	< 0.001
1		158 (32)	24 (18)	134 (36)	
2		200 (39)	64 (45)	136 (36)	
3		90 (17)	45 (32)	45 (11)	
ΔqSOFA at 3 h					
> 0	512	227 (44)	87 (63)	140 (38)	< 0.001
≤ 0		285 (56)	52 (37)	233 (62)	
ΔqSOFA at 3 h					
1	512	42 (8)	20 (14)	22 (6)	< 0.001
0		185 (36)	67 (48)	118 (32)	
−1		202 (39)	42 (30)	160 (43)	
−2		83 (22)	10 (7)	73 (20)	
ΔqSOFA at 1 h					
> 0	505	291 (58)	88 (63)	203 (56)	0.10
≤ 0		214 (52)	51 (37)	163 (44)	

ΔqSOFA = qSOFA at 3 h–qSOFA at admission.
IQR, interquartile range; qSOFA, quick sequential organ failure assessment.

ΔqSOFA performed equally well for the secondary outcome of 'ICU stay greater than 72 h or in-hospital death'; however, there was no significant difference in length of ICU stay and proportion of patients who stayed greater than 72 h in the ICU (Table 2). A negative ΔqSOFA at 3 h was an independent predictor of the combined end point of 'death or ICU stay longer than 72 h', with an adjusted HR of 0.47 (95% CI: 0.33–0.67, Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/EJEM/A218*).

Discussion

The qSOFA score is quick and easy to calculate at the bedside but may change during the short time the patient is in the ED. This raises the questions of which qSOFA value should be used for risk stratification, and whether the value of the change (ΔqSOFA) has prognostic power. In the present study, we analyzed early changes in the qSOFA scores of 512 patients with suspected infection and an initial qSOFA of 2 or more. We found that ΔqSOFA was less than 0 (i.e. improved qSOFA) over 3 h in 55% of patients, and that was independently associated with reduced in-hospital mortality (18 vs. 37%, HR = 0.48). This large international study also confirmed that ED patients with suspected infection and an initial qSOFA greater than or equal to 2 have a high in-hospital mortality risk (27%) which is similar to the result of our previous study (23% in the SCREEN study) [6].

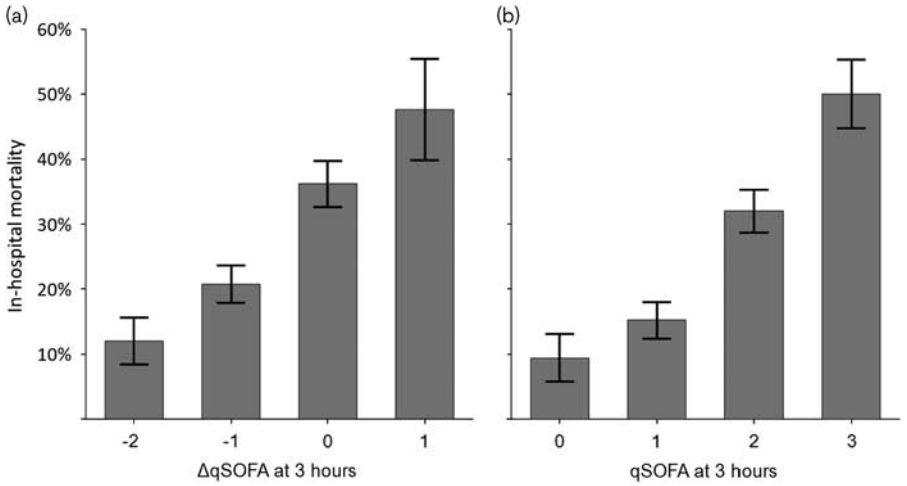
In the present study, the improvement of one point of the qSOFA score was found to be an independent predictor of

Table 2 Primary and secondary end points for the whole population, patients without treatment limitation decision, and patients with confirmed infection

Total population	All patients ($n=512$) [n (%)]	ΔqSOFA < 0 ($n=285$) [n (%)]	ΔqSOFA ≥ 0 ($n=227$) [n (%)]	Effect size[a] (95% CI)	P
In-hospital death	139 (27)	52 (18)	87 (38)	20 (12 to 28%)	< 0.001
ICU admission	201 (39)	112 (39)	89 (39)	0% (−9 to 9%)	0.9
ICU stay > 72 h	147 (29)	81 (28)	66 (29)	0% (−9 to 8%)	0.9
In-hospital death or ICU stay > 72 h	264 (52)	122 (43)	142 (63)	20% (11 to 28%)	< 0.001
Length of ICU stay [median (interquartile range) (days)	4 (2–11)	4 (2–7)	5 (2–13)	3.6 (0.6 to 6.7)	0.12
Patients without TLD	$n=376$	$n=229$	$n=147$		
In-hospital death	63 (17)	32 (14)	31 (21)	7 (0 to 15%)	0.06
ICU admission	194 (52)	107 (47)	87 (59)	12 (2 to 23%)	< 0.01
ICU stay > 72 h	142 (38)	78 (34)	64 (44)	9 (0 to 20%)	0.06
In-hospital death or ICU stay > 72 h	183 (43)	99 (43)	84 (57)	13 (3 to 24%)	< 0.01
Length of ICU stay [median (interquartile range)] (days)	4 (2–11)	4 (2–7)	5 (2–13)	3.6 (0.6 to 6.7)	0.10
Patients with confirmed infection	$n=453$	$n=250$	$n=203$		
In-hospital death	126 (28)	46 (18)	80 (39)	21 (13 to 29%)	< 0.001
ICU admission	187 (41)	104 (42)	83 (41)	−1 (−9 to 8%)	0.88
ICU stay > 72 h	138 (31)	75 (30)	63 (31)	1 (−10 to 8%)	0.81
In-hospital death or ICU stay > 72 h	244 (54)	112 (45)	132 (65)	20 (11 to 29%)	< 0.001
Length of ICU stay [median (interquartile range)] (days)	4 (2–10)	4 (2–7)	5 (3–13)	2.7 (0.3 to 5.12)	0.10

CI, confidence interval; qSOFA, quick sequential organ failure assessment.
[a]Effect size: difference in proportions with its 95% CI, or mean difference with its 95% CI.
ΔqSOFA = qSOFA at admission−qSOFA at 3 h.

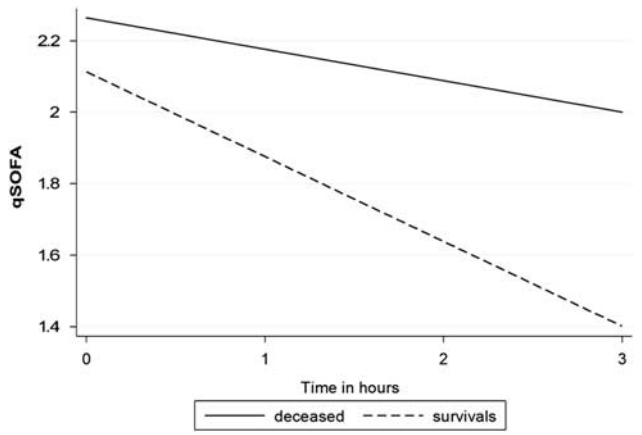
Fig. 2



Error bars of in-hospital mortality with SD. (a) Association of ΔqSOFA at 3 h and in-hospital mortality; (b) association of qSOFA at 3 h and in-hospital mortality. ΔqSOFA = qSOFA at admission−qSOFA at 3 h. qSOFA, quick sequential organ failure assessment.

improved outcomes in patients with suspected infection. The significant difference in in-hospital mortality between patients whose qSOFA improved and those whose qSOFA did not could be a useful added value for risk stratification. The main results of the present study were also confirmed in two sensitivity analyses, and for the prediction of the secondary end point, which increases its validity. These results could therefore be used as part of a clinical decision tool for choosing the site of care in infected patients with an initial qSOFA greater than or equal to 2. We found that this group had an overall in-hospital mortality of ~ 25%, which is high enough to consider management in an ICU. However, after 3 h of ED care, 83 (16%) patients improved their qSOFA by at least two points, and their in-hospital mortality rate was lower than 10%. This concomitant reduction in mortality with improvement in qSOFA implies that the indication for ICU admission, identified at initial qSOFA, could be reassessed after 3 h, and that ΔqSOFA may contribute to the decision of site of care. A ΔqSOFA less than 0 confers a lower mortality risk, and conversely, ΔqSOFA greater than or equal to 0 was associated with an in-hospital mortality of 38%, which is similar to that of patients in septic

Fig. 3



Plotted predictions of the qSOFA evolution from the piecewise linear mixed effects model according to deceased or survival status. qSOFA, quick sequential organ failure assessment. Slope difference: $P < 0.001$.

Table 3 Adjusted hazard ratios for prediction of in-hospital mortality

Variables	aHR	95% CI
ΔqSOFA at 3 h		
≥ 0 (reference)	1	
< 0	0.48	(0.34–0.68)
ΔqSOFA at 3 h		
1	1.35	(0.82–2.23)
0 (reference)	1	
−1	0.57	(0.39–0.85)
−2	0.35	(0.18–0.68)
qSOFA at 3 h		
0 (reference)	1	
1	1.47	(0.60–3.6)
2	3.09	(1.33–7.18)
3	5.19	(2.20–12.27)
0 (reference)	1	
ΔqSOFA at 1 h		
1	1.18	(0.63–2.23)
0 (reference)	1	
−1	0.87	(0.59–1.26)
−2	0.87	(0.40–1.89)

Adjustments were made on age, sex, site of infection, and center of inclusion.
ΔqSOFA = qSOFA at admission−qSOFA at 3 h.
aHR, adjusted hazard ratios; CI, confidence interval; qSOFA: quick sequential organ failure assessment.

shock, and thus may increase the indication for ICU admission [15].

The results of this study are similar to those reported on early lactate clearance: Nguyen *et al.* [16] showed that an early lactate clearance greater than 10% was associated with decreased in-hospital mortality (33 vs. 68% for those with lactate clearance <10%). Similar results were later reported for lactate clearance, including the inclusion of lactate clearance greater than 10% as a goal in the 'early goal-directed therapy' bundle [10,17,18]. The assessment of lactate shift is incorporated in the recent surviving sepsis campaign guidelines [14]. As early variation in qSOFA seems to have good prognostic performance, and that this score is easily obtainable at the bedside of the patient with no turnaround time, this measurement could substitute for lactate measurement. The comparison between the prognostic utility of ΔqSOFA and lactate clearance is analogous to that of lactate clearance versus $ScvO_2$ measurement, and a prospective study should assess their respective values [14].

In this cohort, the median volume of fluid resuscitation within 3 h was 1500 ml, which was below the recommendation of the Surviving Sepsis Campaign guidelines (30 ml/kg). This delay in the completion of initial fluids bolus has been recently highlighted by Seymour *et al.* [1], where less than 40% patients received the recommended fluid volume within 3 h in the ED. Of note, the cornerstone trials of early goal-directed therapy had similar fluids volume in the control groups than patients in the present study [19–21]. We report here that 17% of patients received vasoactive drugs, a similar rate than previously described in similar settings [6].

The Surviving Sepsis Campaign recommends reassessment of volume status and tissue perfusion using either invasive measurement (ScvO2 and central venous pressure), passive leg raising, echocardiography, or through repeated clinical examination after fluid resuscitation [14]. The reassessment of qSOFA could be a structured tool for clinical re-evaluation, and may be a guide for further resuscitation. However, although we report here an independent association between ΔqSOFA and mortality, the clinical utility of measuring early changes in qSOFA should be evaluated in future prospective clinical studies, in a similar manner to early lactate clearance.

Limitations

Our study has some limitations. First, we did not compare the performances of ΔqSOFA with those of previously validated techniques such as ScvO2, lactate clearance, or passive leg raise. However, the promising results of our study advocate for the conduction of comparative trials to assess whether ΔqSOFA is noninferior to these other assessments of response to resuscitation. Second, our study was observational, and we did not compare the care patients received. Although we did not find any significant association between the volume of fluid resuscitation and outcomes, we cannot rule out that unmeasured confounding variables, such as delay to antibiotic administration may have biased our findings. Other unmeasured confounding variables could have inflated our estimates, such as pre-existing illness and comorbidities. A further limitation is that a substantial proportion of patients had treatment limitation decisions, including vasopressor use, ICU admission, or mechanical ventilation. The analysis following exclusion of these patients may be underpowered to show a treatment effect similar to that found in the whole sample, with a nonsignificant trend toward lowered in-hospital mortality

(difference 7%, 95% CI: 0–15%, $P=0.06$). Furthermore, our multivariate analysis did not include this confounder variable, which can be a source of bias. The confirmation of infection was made by a local investigator, not blinded to the data of the patients. This could be a source of selection bias. However, as our results remain unchanged regardless as to whether patients with or without confirmation of infection were included, we believe that the extent of this potential bias was limited. A further limitation lies in the choice of our primary end point. This end point does not take into consideration patients who were discharge but died at home before day 28, or those that died in the hospital after the 28-day censoring timeframe. We, however, chose this end point to be consistent with previous studies on qSOFA and SEPSIS-3 definitions. We performed a sensitivity analysis with patients with in-hospital mortality beyond day 28 ($N=10$) and found no difference for the independent association between the primary end point and a negative ΔqSOFA.

Finally, there may be prognostic value in ΔqSOFA in patients with infection and with initial qSOFA of 0 or 1. However, we did not include these patients in the study as their reported mortality rate is low (3%), and these patients are considered to be 'well' and may often be managed in a primary care setting, so that measuring the change in qSOFA would not be possible.

Conclusion

In patients with suspected infection and initial qSOFA greater than or equal to 2, the early variation of qSOFA in the first 3 h of ED care was significantly and independently associated with in-hospital mortality. Future studies should assess whether ΔqSOFA could be used to guide fluid resuscitation and decisions regarding site of care in patients with high mortality risk.

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Y.F. conceived the study; Y.F., B.R., P.H., and L.N. contributed to the study protocol; L.N., O.M., P.A., P.L.B., P-G. C., C.O., A-L.F.-P., S.B., J.T., H.A., F.D., and Y.Y. recruited patients; Y.F. and E.K. provided statistical analysis; Y.F. and E.K. interpreted the results; Y.F. drafted the manuscript; B.B. and B.R. 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 Y.F. and E.K.

Conflicts of interest

There are no conflicts of interest.

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