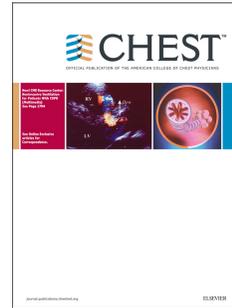# Accepted Manuscript

SIRS, qSOFA and organ dysfunction: insights from a prospective database of emergency department patients with infection

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SIRS, qSOFA and organ dysfunction: insights from a prospective database of emergency department patients with infection.

(Short title: "SIRS, qSOFA and Organ Dysfunction in Emergency")

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Abbreviations: CI = confidence interval, CNS = central nervous system, Cr = creatinine, CVS = cardiovascular system, ED = emergency department, FiO2 = fraction inspired oxygen, GCS = Glascow coma score, GIT = gastrointestinal system, HAEM = haematological system, HR = hazard ratio, ICU = intensive care unit, IQR = inter-quartile range, NA = noradrenaline, OR = odds ratio, PaO2 = arterial oxygen partial pressure (mmHg), RA = room air, RESP = respiratory system, RR = relative risk, SBP = systolic blood pressure, SD = standard deviation, SIRS = systemic inflammatory response syndrome, SOFA = sequential organ function assessment, SpO2 = oximetry saturation, UO = urine output.

ABSTRACT

Objective: A proposed revision of sepsis definitions has abandoned SIRS, defined organ dysfunction as an increase in total SOFA score of ≥2, and conceived "qSOFA" as a bedside indicator of organ dysfunction. We aimed to (1) determine the prognostic impact of SIRS, (2) compare diagnostic accuracy of SIRS and qSOFA for organ dysfunction, and (3) compare standard (Sepsis-2) and revised (Sepsis-3) definitions for organ dysfunction in emergency department patients with infection.

Methods: Consecutive ED patients admitted with presumed infection were prospectively enrolled over three years. Observational data were collected sufficient to calculate SIRS, qSOFA, SOFA, comorbidity and mortality.

Results: 8871 patients were enrolled, 4176 (47.1%) with SIRS. SIRS was associated with increased risk of organ dysfunction (RR 3.5), and mortality in patients without organ dysfunction (OR 3.2). SIRS and qSOFA showed similar discrimination for organ dysfunction (AUROC 0.72 vs 0.73). qSOFA was specific but poorly sensitive for organ dysfunction (96.1%, 29.7% respectively). Mortality for patients with organ dysfunction was similar for Sepsis-2 and Sepsis-3 (12.5%, 11.4%) although 29% of patients with Sepsis-3 organ dysfunction did not meet Sepsis-2 criteria. Increasing number of Sepsis-2 organ dysfunctions was associated with greater mortality.

Conclusions: SIRS was associated with organ dysfunction and mortality, and abandoning the concept appears premature. Although qSOFA≥2 showed high specificity, poor sensitivity may limit utility as a bedside screen. Although mortality for organ dysfunction was comparable between Sepsis-2 and Sepsis-3, more prognostic and clinical information is conveyed using Sepsis-2 regarding number of organ dysfunctions. The SOFA score may require recalibration.

INTRODUCTION

Infectious diseases have plagued mankind for millennia,[1] and remain a major cause of morbidity and mortality.[2] Despite this, the complex pathophysiological response to infection remains to be fully elucidated, and a gold-standard test for serious infection (or colloquially, 'sepsis') does not currently exist. In the absence of a gold-standard test, several groups have attempted to provide clinical criteria for the identification of infected patients at risk of significant mortality.

Consensus conferences in 1991[3] and 2001[4] proposed sepsis be defined as infection with systemic inflammatory response syndrome (SIRS), and severe sepsis as sepsis with consequent organ dysfunction. The sequential organ function assessment (SOFA)[5] score was a suggested means to quantify dysfunction in each of six organ systems. Within this framework, sepsis research has advanced with promulgation of evidence-based guidelines for sepsis management,[6] and global sepsis mortality has been reduced.[7] A recently proposed revision of sepsis definitions ("Sepsis-3")[8] has discarded SIRS, with concerns that most patients with SIRS do not have infection,[9] and that SIRS is absent in some critical care patients with infection.[10] Sepsis-3 has also redefined organ dysfunction as an increase in total SOFA score of two or more, rather than the previous convention of using specified criteria to determine dysfunction in each of several organ systems. A new construct, "qSOFA", has also been introduced in Sepsis-3 as a means to screen for organ dysfunction at the bedside using respiratory rate, blood pressure, and conscious state.

However, the original definitions intended SIRS be regarded as a potential severity indicator in patients with suspected infection, rather than a screening test for infection. In the intensive care unit (ICU), SIRS is common[11] and contributes minimally to mortality risk.[12] As noted in a recent editorial critical of the revised definitions,[13] SIRS is more likely to be useful in the Emergency Department (ED), where patients with infection are common and a parsimonious means to screen for those at higher risk of mortality is required. There are few studies specifically examining the prognostic utility of SIRS in ED patients with infection, and the SOFA and qSOFA scores remain to be evaluated in those patients. The purpose of this study was to determine in ED patients with suspected infection: (1) the prevalence and prognostic impact of SIRS, (2) the diagnostic accuracy of SIRS and qSOFA for organ dysfunction, and (3) the characteristics and utility of the current ("Sepsis-2") and proposed ("Sepsis-3") SOFA-based organ dysfunction criteria.

METHODS

Study design and setting:

The prospective, observational database used for this study was designed to examine the performance of SIRS and SOFA-based organ dysfunction as originally described for Sepsis-2. Following the recent publication of the proposed Sepsis-3 definitions, the study scope was expanded retrospectively to include analysis of the new definitions. The study was undertaken in the ED of a tertiary, university-affiliated Australian hospital with annual census over 72,000 adult presentations. Data were collected over two discrete time periods, October 2007 – December 2008 (unfunded pilot), and June 2009 – May 2011 (funded period), totalling 160 weeks. The Royal Brisbane and Women's Hospital Human Research Ethics Committee approved the study (HREC/09/QRBW/226) and determined patient consent not required.

Participants, methods and measurements:

Methods have been described in detail[14] but are briefly summarized here. On a daily basis, ED patients admitted with a diagnosis indicating presumed or potential infection were identified. The charts of those patients were examined by trained data collectors. Patients were enrolled if the ED and admitting medical staff both indicated infection was the most likely reason for admission. Patients transferred from other hospitals or aged less than 17 years were not enrolled.

Data were abstracted from the paper chart at the time of each patient's enrolment, including physiological measurements and treatment in the ED, presumed source of infection, and co-morbidities. At a later time, results of haematology and biochemistry tests were obtained from computerised hospital databases. Data were entered into a Microsoft Access (Redmond, WA) database and stored on a password-protected secure hospital drive. Regular automated checks for out-of-range entries were conducted, and the principal investigator reviewed accuracy of the data for all patients. The database was designed to comply with the components of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

For each physiological parameter, the most abnormal measurement in ED was recorded. SIRS was defined as two or more of: heart rate >90 minute^{-1}, respiratory rate >20 minute^{-1} or arterial carbon dioxide pressure <32 mmHg, leucocyte count >12,000 or <4,000 microlitre^{-1} and temperature <36 or ≥38 degrees Celsius. The recorded components of qSOFA were respiratory rate ≥22 minute^{-1}, systolic blood pressure ≤100 mmHg, and Glasgow Coma Score (GCS) ≤13. Organ function was assessed using a modified SOFA score (e-Table 1). Hospital records relating to previous admissions, outpatient and ED encounters were used to assess and record baseline organ function, which was assumed normal in the absence of such data. Consistent with definitions in place during data collection (Sepsis-2),

acute organ dysfunction was defined for primary analyses as an increase in SOFA score of two or more in any discrete organ system. For comparison, the proposed new definition of acute organ dysfunction (Sepsis-3) was an increase in total SOFA score of two or more. Shock was defined as hypotension (systolic blood pressure less than 90mmHg) persisting despite at least 1000mL fluid bolus or vasopressor infusion in the ED (corresponding to a cardiovascular SOFA score of two or more). The Charlson Score[15] was calculated to quantify co-morbidity. The primary outcome measure was 30-day mortality, and the secondary outcome was one-year mortality. Both were obtained from a national deaths registry.

Analysis:

Analyses were performed using Stata version 14 (StataCorp, 2015, College Station, TX). In cases of readmission within 90 days, a single representative admission was selected at random from within that period for inclusion in the study dataset. Baseline characteristics of the study sample were reported by vital status at 30 days. Risk ratios and risk differences (with 95% confidence intervals) were calculated to identify the prognostic utility of SIRS for mortality in patients with and without organ dysfunction. Odds ratios adjusted for age and comorbidity also were reported. Due to the nonlinear relationship between age and mortality, age was stratified into 10-year categories for computation of adjusted odds ratios. The Charlson comorbidity index was stratified into 0, 1-2, 3-4 and ≥5 as originally described.[15]

Discrimination of SIRS and qSOFA scores for organ dysfunction and mortality was quantified using receiver operating curves. Sensitivity and specificity corresponding to SIRS≥2 and qSOFA≥2 were reported. Adjusted odds ratios for mortality were calculated for each of the SIRS and qSOFA criteria, each individual (Sepsis-2) organ system dysfunction, Sepsis-2 and Sepsis-3 organ dysfunction, and cumulative (Sepis-2) organ dysfunctions.

A number of sensitivity analyses were conducted. First, analyses were repeated using multiple imputation of missing data to identify whether the assumption of normality in the primary analysis resulted in biased estimates. This resulted in imputation for 21 (0.2%) patients with missing white cell count and 242 (2.7%) patients with any missing SOFA score component. Analyses conducted using multiple imputation yielded similar estimates so were not reported. Second, to inform discussion regarding definitions of acute organ dysfunction, mortality was computed for different SOFA score thresholds.

RESULTS

Patient recruitment and classification into groups according to SIRS and organ dysfunction is outlined in Figure 1. The study cohort comprised 8871 admissions with presumed infection over the total study duration of 160 weeks, after exclusion of 846 readmissions within 90 days. Numbers and characteristics of included and excluded representations are detailed in e-Table 2. Table 1 details characteristics of the study cohort. SIRS was present in 4176 (47.1%) patients and the prevalence of acute organ dysfunction varied according to definition (Sepsis-2: 1534 [17.3%], Sepsis-3: 2166 [24.4%]) (Table 1). However mortality associated with organ dysfunction using Sepsis-2 and Sepsis-3 was similar at 30 days (12.5% [95%CI 10.8-14.2%], 11.4% [95%CI 10.1-12.8%] difference 1.0% [95%CI -1.1-3.2%]) and at one year (25.5% [95%CI 23.3-27.7%], 26.3% [95%CI 24.4-28.2%], difference 0.8% [95%CI -2.1-3.6%]).

Table 2 compares the prevalence and prognostic implications of SIRS in subgroups with and without organ dysfunction, and with shock. In the overall cohort, SIRS was associated with increased risk of (Sepsis-2) organ dysfunction (RR 3.5, 95%CI 3.1-3.8), and increased odds of mortality in patients without (Sepsis-2) organ dysfunction (OR 3.2, 95% CI 2.2-4.7). SIRS had similar implications when Sepsis-3 was used to determine organ dysfunction. SIRS was present in 1157 (75.4%) patients with (Sepsis-2) organ dysfunction and was associated with increased odds of mortality compared to the 377 (24.6%) without SIRS (OR 1.8, 95% CI 1.2-2.7). Similarly, in those with Sepsis-3 organ dysfunction (n=1561 with SIRS and 605 without SIRS), SIRS was associated with increased odds of 30-day mortality (OR 2.2, 95% CI 1.5-3.1). However at one year, there was no association between SIRS and prognosis in patients with organ dysfunction according to either definition. In patients with shock, SIRS was present in 89% and not associated with increased mortality at either endpoint.

Table 2 also allows comparison of sepsis subgroups according to Sepsis-2 and Sepsis-3 definitions (column 2). As defined in this study, patients with Sepsis-2 organ dysfunction comprised a subgroup of those with Sepsis-3 organ dysfunction. The 632 patients that met Sepsis-3 but not Sepsis-2 criteria for organ dysfunction presented with an acute increase in total SOFA of two or more, but that increase occurred in different organ systems. Mortality for those patients was significantly less than for those with Sepsis-2 organ dysfunction at 30 days (difference 3.6%, CI 0.8-6.4%), but not at one year (difference -2.6%, CI -6.8-1.5%). The relationship between study groups according to Sepsis-2 and Sepsis-3 definitions are illustrated graphically in Figure 2. The last four rows of Table 2 and panel D in Figure 2 represent a potential compromise structure which recognises SIRS is associated with

increased mortality in patients without organ dysfunction but prognostically less important when organ dysfunction or shock is present.

SIRS and qSOFA scores showed similar discrimination for Sepsis-3 organ dysfunction [area under receiver operating curves 0.72 vs 0.73, difference 0.01 (95% CI 0.0-0.03)] (Figure 3). A qSOFA score ≥2 had high specificity for Sepsis-3 organ dysfunction but poor sensitivity [96.1% (95.7-96.6%) and 29.9% (27.9-31.8%) respectively]. Specificity and sensitivity for SIRS≥2 were 61.1% (60.0-62.3%) and 72.3% (70.3-74.1%). Supplementary Figure 1 shows results using the endpoint of 30-day mortality.

Using Sepsis-2, the odds of mortality increased with greater number of organ system dysfunctions (Figure 4). Substantial variation was seen in the odds of mortality associated with dysfunction in individual organ systems (Table 3). Central nervous system (CNS) dysfunction was associated with the greatest mortality risk (OR 11.2, 95%CI 7.1-17.7), with haematological dysfunction the lowest and failing to achieve statistical significance (OR 1.6, 95%CI 0.9-2.9). E-Table 3 examines the implications of defining Sepsis-2 organ dysfunction at varying SOFA scores in each organ system. Mortality odds for each of the SIRS and qSOFA components are also presented in Table 3. Among these, altered conscious state was again the most powerful predictor.

DISCUSSION

In this large prospective study of ED patients with suspected infection of all severities, SIRS was found to be a useful marker of organ dysfunction and mortality, while the qSOFA had high specificity for organ dysfunction but poor sensitivity. Organ dysfunction was associated with 30-day mortality just over 10%, without significant difference between values obtained with Sepsis-2 and Sepsis-3. Using Sepsis-2, increasing number of discrete organ system dysfunctions increased mortality, but dysfunction in individual organ systems was associated with a wide variation in mortality risk.

SIRS in the Emergency Department

Previous investigators have found that SIRS is not useful for predicting which patients in hospital wards[9] or the ED[16, 17] have infection. While some components of SIRS may contribute to a clinician's judgement regarding presence of infection, that assessment is ultimately based on a range of physiological, investigational and heuristic criteria, because a gold standard does not yet exist. This paper examined the role of SIRS as a prognostic marker in ED patients with suspected infection. There are few previous studies with this aim. Shapiro and colleagues[18] found no relationship between SIRS and mortality in ED patients with suspected infection without organ dysfunction (OR

0.8, 95%CI 0.4-1.6). The 3102 patients in that study were identified on the basis of blood culture request, and included patients discharged home from the ED. More recently, a larger Danish study[19] also used blood culture request to identify 5499 ED patients admitted with infection, and found SIRS associated with increased mortality (HR 1.5 95%CI 1.2-1.7). Marchik[20] also found SIRS associated with significantly greater mortality in a cohort of 1031 ED patients with suspected infection (6.5% vs. 1.4%, p = 0.02), but those investigators expanded SIRS criteria to include hyperglycaemia and altered mental state. Our study examined the largest prospective cohort of ED patients with suspected infection to date, and found SIRS associated with increased risk of organ dysfunction and mortality at 30 days and one year. The proposed Sepsis-3 definitions discarded SIRS and nominated organ dysfunction as an indicator of deleterious and dysregulated response to infection. Our results establish that SIRS is also associated with increased risk of deleterious response to infection and mortality.

SIRS in patients with organ dysfunction

Depending on method used, we found 24.6% (Sepsis-2) to 27.9% (Sepsis-3) of patients with organ dysfunction did not have SIRS. Other investigators have reported similar figures. [18, 21, 22] In our study, SIRS was associated with a modest increase in 30-day mortality risk in patients with infection and organ dysfunction, but this effect was not evident at one year. We could identify only one previous study designed to examine the prognostic effect of SIRS in ED patients with infection and organ dysfunction. In that study, Henriksen et al[22] found SIRS was present in 75.8% of 1169 ED patients admitted with infection and organ dysfunction, and did not confer increased mortality risk (adjusted HR 1.17, 95% CI 0.84 to 1.64). Studies in ICU patients with infection have concluded SIRS adds little to prognosis in the context of organ dysfunction and shock.[12] Kaukonen[10] examined a large database of ICU patients with serious infection (mortality 23.4%), finding SIRS present in 87.9% and not associated with mortality in an adjusted analysis. In our study, patients with shock (mortality 23.8%) were SIRS-positive in 89%, with SIRS also not associated with mortality.

Organ dysfunction

Overall organ dysfunction according to both Sepsis-2 and Sepsis-3 provided similar estimates of mortality risk. The capacity to denote dysfunction in each of the six SOFA organ systems (Sepsis-2) allowed the identification of patients with dysfunction in multiple organ systems. This classification was important prognostically, with mortality increasing according to the number of organs affected, and could also provide relevant clinical information that may indicate requirement for particular interventions and organ support. Increasing mortality with cumulative organ dysfunction was also

observed in the Shapiro study[18] although the criteria used to determine organ dysfunction were not SOFA-based. Our analyses found that mortality associated with each individual organ dysfunction varied widely (Table 3), despite the same SOFA threshold (increase by two or more) applying to each. E-Table 2 enables comparison of mortality in each organ system as the threshold is increased from one to four. A CNS SOFA cut-off of one (any reduction in consciousness) is associated with outcomes similar to dysfunction in the other major organ systems. Furthermore, even at SOFA cut-offs of 3 or more, gastrointestinal and hematological organ system dysfunction remains less important prognostically than dysfunction in other systems. The poor calibration of the SOFA score between organ systems seen in our study may be related to use in the ED setting and the fact that the SOFA score dates from 1996. Limitations in the SOFA score will also affect Sepsis-3 organ dysfunction criteria, and might be reduced by recalibrating the score with contemporary patient data. The 29% of patients with Sepsis-3 but not Sepsis-2 organ dysfunction presented with an increase in SOFA score by one in two or more different organ systems. Mortality in this group was less than with Sepsis-2 organ dysfunction at 30 days (but similar at one year), creating some uncertainty about whether these patients should be regarded to have organ dysfunction.

SIRS and qSOFA

The qSOFA score has been proposed as a parsimonious bedside tool to screen patients with infection for those at risk of organ dysfunction and death.[8] Overall discrimination for organ dysfunction was similar for SIRS and qSOFA, but specificity and sensitivity differed at operating cutoffs of SIRS≥2 and qSOFA≥2. Despite qSOFA≥2 being highly specific for Sepsis-3 organ dysfunction and mortality (96.1% and 91.3% respectively), sensitivity was poor (29.7% and 49.1%) compared to sensitivity for SIRS≥2 (72.1% and 76.7%). Given the relative insensitivity of qSOFA≥2, it appears inferior to SIRS≥2 as a screening test in the ED where the timely identification of high risk infected patients is paramount.

Study limitations and strengths

The methods used to identify patients may not have identified all ED patients admitted with infection, and not all included patients may have ultimately been shown to have infection. However it is likely that any method chosen to identify patients with infection of all severities in large enough numbers for meaningful analyses would have similar limitations. We aimed to minimise these issues by using a broad list of ED admission diagnoses indicating possible infection to screen for enrolment candidates, and only including those in whom ED and admitting teams concurred infection was the most likely cause for admission. Our methods were entirely observational and therefore data collected were limited to those generated in the course of standard investigation and treatment for

each patient. Despite this, missing data were minimal as reported. Our study was undertaken at a single centre, which may limit generalizability. We utilised a modified SOFA score for ED patients and this may influence the number of patients categorised with organ dysfunction. Derivation of the sepsis-3 sepsis criteria incorporated a secondary endpoint of mortality and/or ICU admission of ≥3 days. Consistent with the primary endpoint of mortality, our analyses have assessed the performance of Sepsis-3 criteria against mortality at 30 days and one year but have not assessed this secondary endpoint.

Strengths of our study include the prospective enrolment of a large cohort of ED patients admitted with suspected infection, and reliable short and long term mortality endpoints, sourced from a national database. Use of the SOFA score has enabled a comparison between alternative definitions for organ dysfunction in the context of infection, and ours is the first assessment of the proposed "Sepsis-3" criteria in the ED.

Conclusions

Our results indicate SIRS is a useful screening tool for organ dysfunction and death in ED patients with suspected infection. SIRS contributed less to prognosis in the context of organ dysfunction or shock, arguing against including SIRS as a requirement for entry into trials enrolling patients with severe sepsis and septic shock. Patients with organ dysfunction according to either Sepsis-2 or Sepsis-3 criteria had similar mortality. Reporting multiple organ dysfunctions (Sepsis-2) allows a description containing more prognostic and clinically relevant information. The wide variation in mortality risk associated with SOFA score of two in each organ system indicates the SOFA score may require calibration for use in the ED.

Acknowledgements

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TABLES

Table 1: Characteristics of the study cohort, by mortality at 30 days

	Total	Alive at 30 days	Deceased 30 days
Entire cohort	8871	8544 (96.3%)	327 (3.7%)
Males	4453 (51.3%)	4369 (51.1%)	184 (56.3%)
Age in years - median (IQR)	49 (30-69)	47 (29-67)	79 (69-86)
ED LOS in hours – median (IQR)	8.3 (5.5-12.2)	8.2 (5.4-12.2)	8.7 (6.0-12.0)
Charlson score - median (IQR)	1 (0-3)	1 (0-3)	4 (2-6)
Total SOFA – median (IQR)	1 (0-2)	1 (0-2)	5 (3-7)
SIRS			
SIRS <2	4695 (52.9%)	4621 (54.1%)	74 (22.6%)
SIRS ≥2	4176 (47.1%)	3923 (45.9%)	253 (77.4%)
SIRS leucocyte count	3933 (44.3%)	3726 (43.6%)	207 (63.3%)
SIRS temperature	2797 (31.5%)	2654 (31.1%)	143 (43.7%)
SIRS respiratory	2009 (22.5%)	1797 (21.0%)	212 (64.8%)
SIRS heart rate	4505 (50.8%)	4274 (50.0%)	231 (70.6%)
qSOFA			
qSOFA <2	7966 (89.8%)	7803 (91.3%)	163 (49.8%)
qSOFA ≥2	905 (10.2%)	741 (8.7%)	164 (50.2%)
GCS ≤13	454 (5.1%)	326 (3.8%)	128 (39.1%)
Respiratory rate ≥22	1868 (21.1%)	1667 (19.5%)	201 (61.5%)
SBP ≤100	2379 (26.8%)	2203 (25.8%)	176 (53.8%)
SEPSIS-2 organ dysfunction			
No organ dysfunction	7337 (82.7%)	7201 (84.3%)	136 (41.6%)
Organ dysfunction	1534 (17.3%)	1343 (15.7%)	191 (58.4%)
Cardiovascular	218 (2.5%)	166 (1.9%)	52 (15.9%)
Respiratory	779 (8.8%)	650 (7.6%)	129 (39.4%)
Renal	279 (3.1%)	214 (2.5%)	65 (19.9%)
Haematological	203 (2.3%)	189 (2.2%)	14 (4.3%)
Gastrointestinal	400 (4.5%)	375 (4.4%)	25 (7.6%)
Central nervous system	129 (1.5%)	86 (1.0%)	43 (13.1%)
SEPSIS-3 organ dysfunction			
No organ dysfunction	6705 (75.6%)	6625 (77.5%)	80 (24.5%)
Organ dysfunction	2166 (24.4%)	1919 (22.5%)	247 (75.5%)

IQR = inter-quartile range, ED LOS = Emergency Department length of stay, SIRS = systemic inflammatory response syndrome, SOFA = sequential organ function assessment, qSOFA = "quick" SOFA, GCS = Glasgow Coma Score, SBP = systolic blood pressure (mmHg).

Table 2: Mortality for sepsis subgroups according to SEPSIS-2 and SEPSIS-3 and the prognostic impact of SIRS in patients with and without organ dysfunction.

Classification	Subgroup	n =	30-day mortality (%)	SIRS vs no SIRS: Mortality difference	SIRS vs no SIRS: Adjusted OR	one year mortality (%)	SIRS vs no SIRS: Mortality difference	SIRS vs no SIRS: Adjusted OR
SEPSIS-2								
All SIRS<2	infection	4695	1.6 (1.2-2.0)			8.4 (7.6-9.2)		
No OD, SIRS≥2	sepsis	3019	3.2 (2.6-3.9)	2.3% (1.6-2.9)	3.2 (2.2-4.7)	11.2 (10.1-12.4)	4.2% (2.5-5.5%)	1.5 (1.2-1.7)
No OD, SIRS<2		4318	0.9 (0.7-1.2)			7.0 (6.3-7.8)		
OD, SIRS≥2	severe sepsis	1157	13.6 (11.6-15.7)	4.6 % (1.1-8.1)	1.8 (1.2-2.7)	26.1 (23.6-28.7)	2.5% (-2.5-7.5%)	1.2 (0.9-1.7)
OD, SIRS<2		377	9.0 (6.3-12.4)			23.6 (19.4-28.2)		
Shock, SIRS≥2	septic shock	194	23.7 (17.9-30.3)	-1.3% (-19.6-17.0)	0.9 (0.3-3.0)	37.6 (30.8-44.9)	-8.2% (-29.3-12.9%)	0.7 (0.2-1.9)
Shock, SIRS<2		24	25.0 (9.8-46.8)			45.8 (25.6-67.2)		
SEPSIS-3								
No OD	infection	6705	1.2 (0.9-1.5)			6.9 (6.3-7.6)		
No OD, SIRS≥2		2615	2.0 (1.5-2.6)	1.3% (0.7-1.9)	2.8 (1.8-4.5)	8.6 (7.5-9.7)	2.7% (1.4-4.0)	1.4 (1.1-1.7)
No OD, SIRS<2		4090	0.7 (0.5-1.0)			5.9 (5.2-6.7)		
OD	sepsis	2166	11.4 (10.1-12.8)			26.3 (24.4-28.2)		
OD, SIRS≥2		1561	12.9 (11.3-14.6)	5.3% (2.6-8.0)	2.2 (1.5-3.1)	26.7 (24.5-29.0)	1.6% (-2.5-5.7)	1.2 (1.0-1.6)
OD, SIRS<2		605	7.6 (5.6-10.0)			25.1 (21.7-28.8)		
OD SEPSIS-3 but not SEPSIS-2		632	8.8 (6.8-11.3)			28.1 (24.6-31.8)		
COMBINATION								
No OD, SIRS<2	infection	4318	0.9 (0.7-1.2)			7.0 (6.3-7.8)		
No OD, SIRS≥2	sepsis	3019	3.2 (2.6-3.9)			11.2 (10.1-12.4)		
OD (SEPSIS-2)	severe sepsis	1534	12.5 (10.8-14.2)			25.5 (23.3-27.7)		
Shock	septic shock	218	23.9 (18.4-30.1)			38.5 (32.0-45.3)		

SIRS = systemic inflammatory response syndrome, OD = organ dysfunction, OR = odds ratio, adjusted for age and co-morbidity (Charlson Score). Figures in parentheses are 95% confidence intervals. 'SEPSIS-2' refers to established definitions[4] and 'SEPSIS-3' to recently proposed definitions.[8] 'COMBINATION' refers to a potential framework which recognises SIRS is associated with substantially increased mortality only in the absence of organ dysfunction.

Table 3: Mortality odds associated with individual SIRS and qSOFA criteria, and organ dysfunctions.

SIRS criteria	n =	OR 30-day mortality unadjusted	OR 30-day mortality adjusted
SIRS respiratory	2009	6.9 (5.5-8.7)	3.7 (2.9-4.8)
SIRS heart rate	4505	2.4 (1.9-3.1)	2.7 (2.1-3.4)
SIRS leucocyte count	3933	2.2 (1.8-2.8)	2.2 (1.7-2.8)
SIRS temperature	2797	1.7 (1.4-2.2)	1.6 (1.3-2.0)
qSOFA criteria			
GCS ≤13	454	16.2 (12.7-20.8)	8.7 (6.6-11.4)
Respiratory rate ≥22	1868	6.6 (5.2-8.3)	3.6 (2.9-4.6)
SBP ≤100	2379	3.4 (2.7-4.2)	3.3 (2.6-4.2)
Organ system dysfunction			
Central nervous	129	14.9 (10.1-21.9)	11.2 (7.1-17.7)
Cardiovascular	218	9.5 (6.8-13.3)	6.3 (4.3-9.1)
Renal	279	9.7 (7.1-13.1)	4.6 (3.3-6.4)
Respiratory	779	7.9 (6.3-10.0)	4.4 (3.4-5.7)
Gastro-intestinal	400	1.8 (1.2-2.7)	1.9 (1.2-3.0)
Haematological	203	2.0 (1.1-3.4)	1.6 (0.9-2.9)

Organ system dysfunction was defined as increase in sequential organ function assessment (SOFA) score of 2 or more in a single organ system. Figures in parentheses are 95% confidence intervals. OR = odds ratio, with figures in final column adjusted for age and co-morbidity (Charlson Score). SIRS = systemic inflammatory response syndrome, qSOFA = "quick" SOFA, GCS = Glasgow Coma Score, SBP = systolic blood pressure (mmHg).

FIGURE LEGENDS

Figure 1: Patient recruitment and classification according to SIRS and organ dysfunction.

SIRS = systemic inflammatory response syndrome. Organ dysfunction (current definition or 'Sepsis-2') is defined as an increase in sequential organ function assessment (SOFA) score of two or more, and shock as cardiovascular system organ dysfunction.

**Figure 2:** Relationships between sepsis subgroups

SIRS = systemic inflammatory response syndrome, SEPSIS-2 and SEPSIS-3 represent patients satisfying organ dysfunction criteria according to respective definitions. Respective ellipse areas are proportional according to the data. **Panel A** demonstrates SHOCK (cardiovascular dysfunction) being a subset of SEPSIS-2 organ dysfunction, which in turn is a subset of SEPSIS-3 organ dysfunction. Each of these groups contains patients with and without SIRS. **Panel B** represents established sepsis definitions[4], with "sepsis" (infection + SIRS) in grey and "severe sepsis" (sepsis + organ dysfunction) cross-hatched. **Panel C** approximates the proposed Sepsis-3[8] definitions, with "sepsis" (infection with organ dysfunction) in grey and "septic shock" cross-hatched. SIRS plays no role in this construct. **Panel D** represents a potential compromise, recognising SIRS is associated with increased mortality in the absence or organ dysfunction, and organ dysfunction (including shock) carries significant mortality risk regardless of SIRS criteria.

Figure 3: Receiver operating curves for SIRS and qSOFA prediction of (Sepsis-3) organ dysfunction

SIRS = systemic inflammatory response syndrome, qSOFA = "quick" sequential organ function assessment, AUC = area under curve, CI = confidence interval. Discrimination for SIRS and qSOFA were similar (AUC difference 0.01, 95%CI 0-0.03). Larger symbols indicate diagnostic characteristics for operating points SIRS≥2 and qSOFA ≥2. Using GCS≤14 rather than GCS≤13 in qSOFA increases AUROC to 0.76 (95%CI 0.75-0.77) with sensitivity 36.5% and specificity 95.4% (p<0.01 for both).
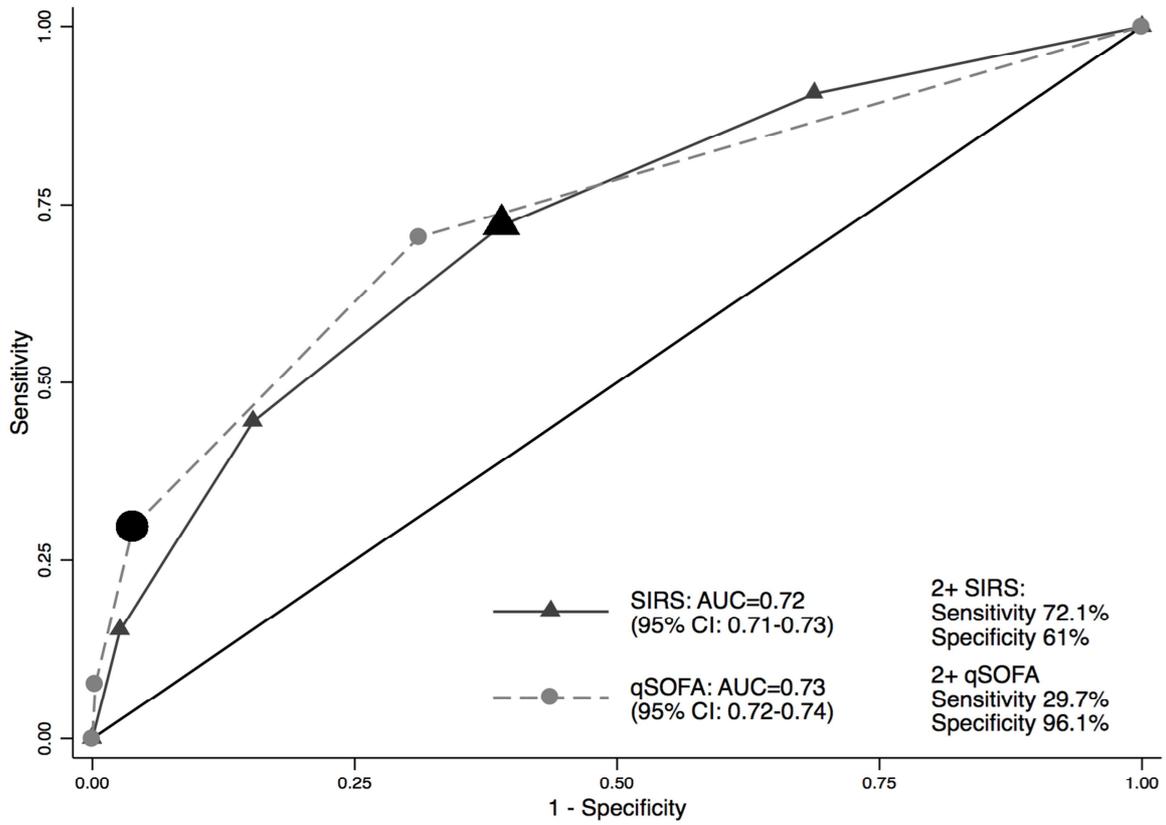
Figure 4: 30-day mortality and adjusted odds ratio for mortality associated with organ dysfunction according to Sepsis-2 and Sepsis-3, and Sepsis-2 cumulative organ dysfunctions.

Mortality = 30-day mortality (%), OR = odds ratio, adjusted for age and co-morbidity (Charlson Score)
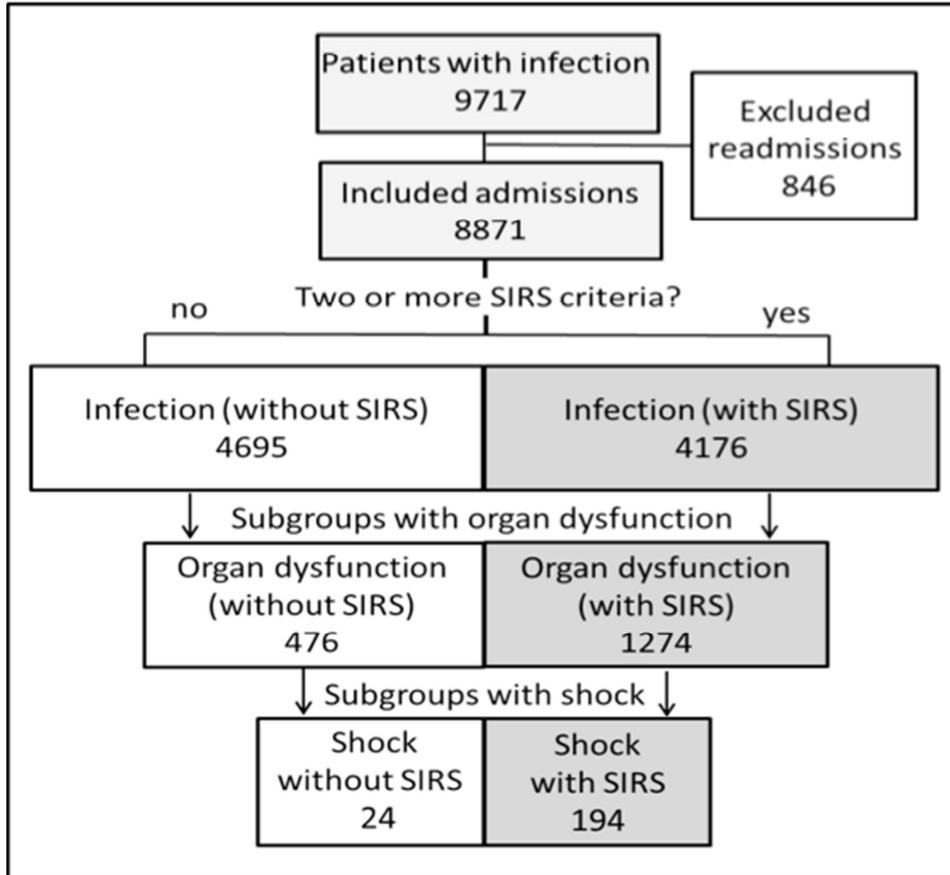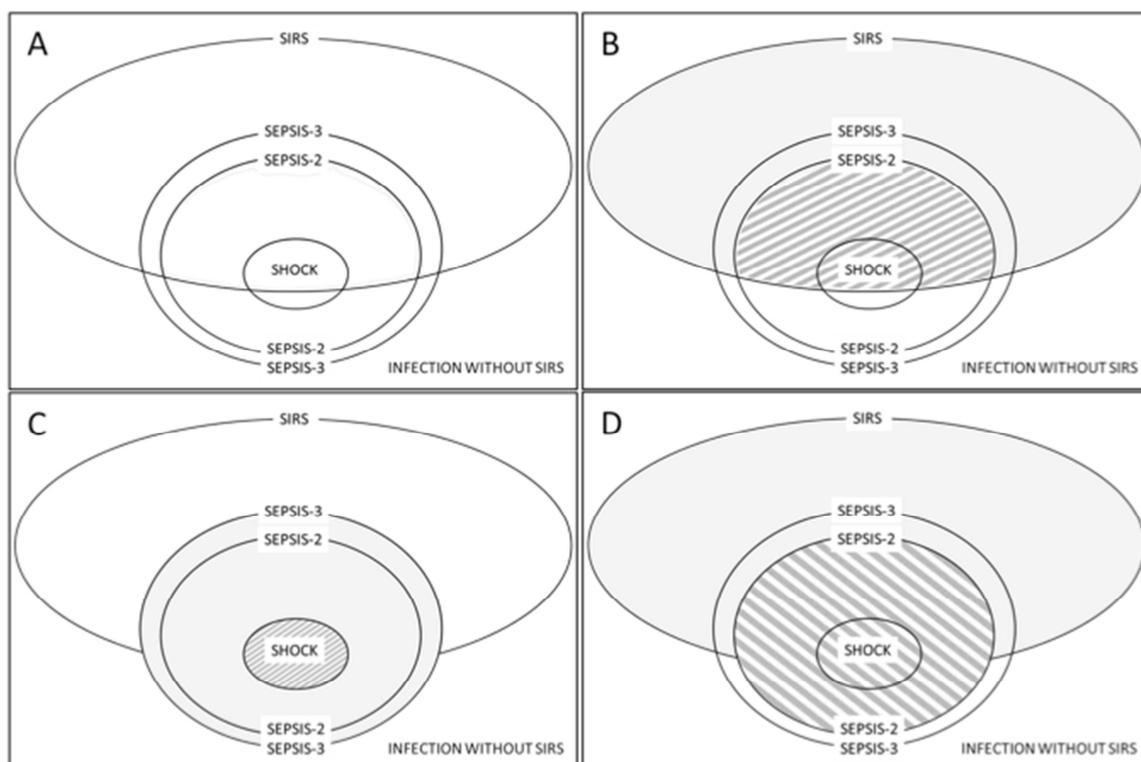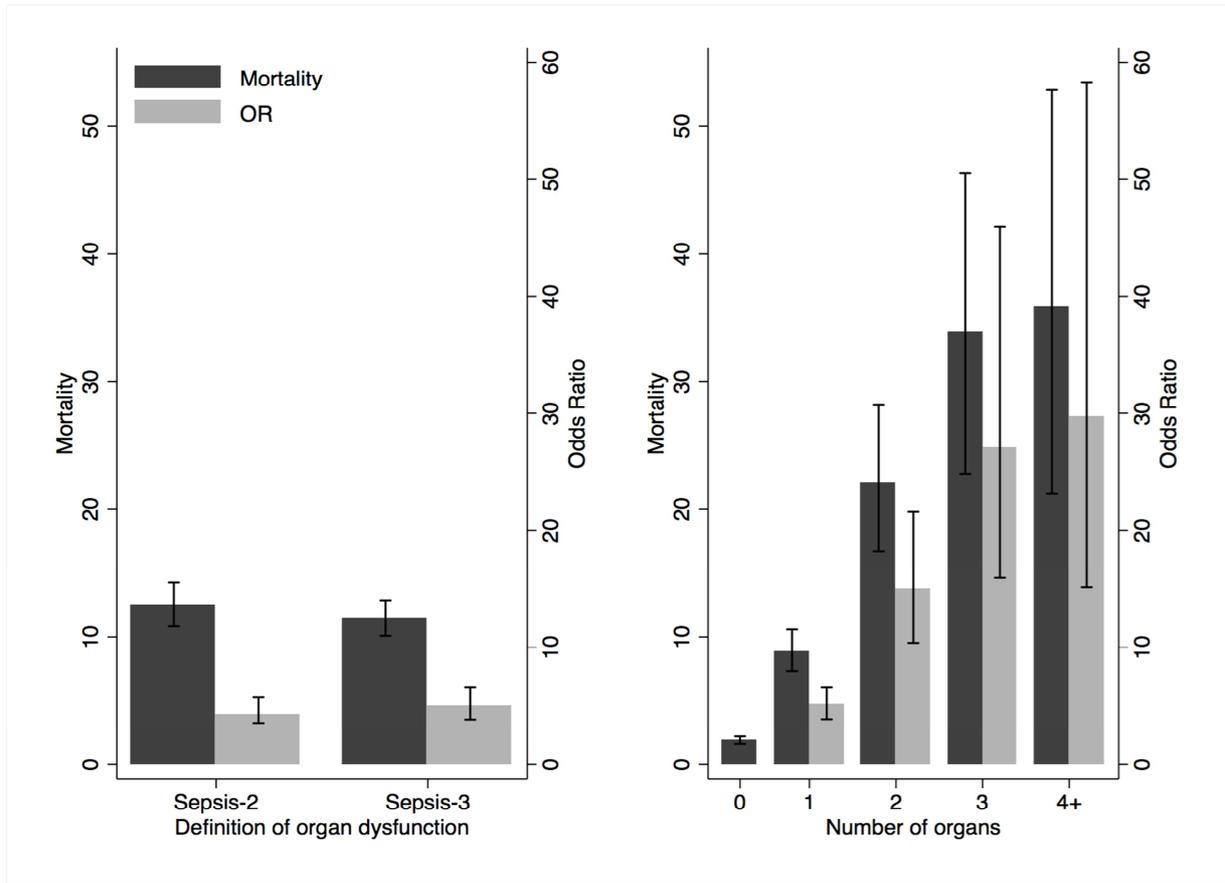
e-Table 1: Modified sequential organ function assessment (SOFA) score

Organ system	Determinants	SOFA SCORE 0	1	2	3	4
RESP	PaO2/FiO2 SpO2%	>400 >94%(RA)	<400	<300 <90%(RA)	<200	<100
CVS	SBP, vasopressors	SBP>90	SBP>90 post bolus	SBP<90 post bolus +/- NA < 8mcg/min	NA 8-15mcg/min	NA >15mcg/min
HAEM	Platelet count (x10⁹/L)	≥150	<150	<100	<50	<20
GIT	Bilirubin (mmol/L)	<20	20-32	33-101	102-204	>204
CNS	Glascow Coma Score (GCS)	15	13-14	10, 11, 12	6, 7, 8, 9	3, 4, 5
RENAL	Cr (mmol/L), Urine output	<120	≥120, UO <0.5 ml/kg over 2 hours	≥170	≥300	≥440

SOFA = sequential organ function assessment, RESP = respiratory system, PaO2 = arterial oxygen partial pressure (mmHg), FiO2 = fraction inspired oxygen, SpO2 = oximetry saturation, RA = room air, CVS = cardiovascular system, SBP = systolic blood pressure (mmHg), NA = noradrenaline, HAEM = haematological system, GIT = gastrointestinal system, CNS = central nervous system, RENAL = renal system, Cr = creatinine, UO = urine output.

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e-Table 2: Comparison of included and excluded presentations for the 618 patients with readmissions within 90 days.

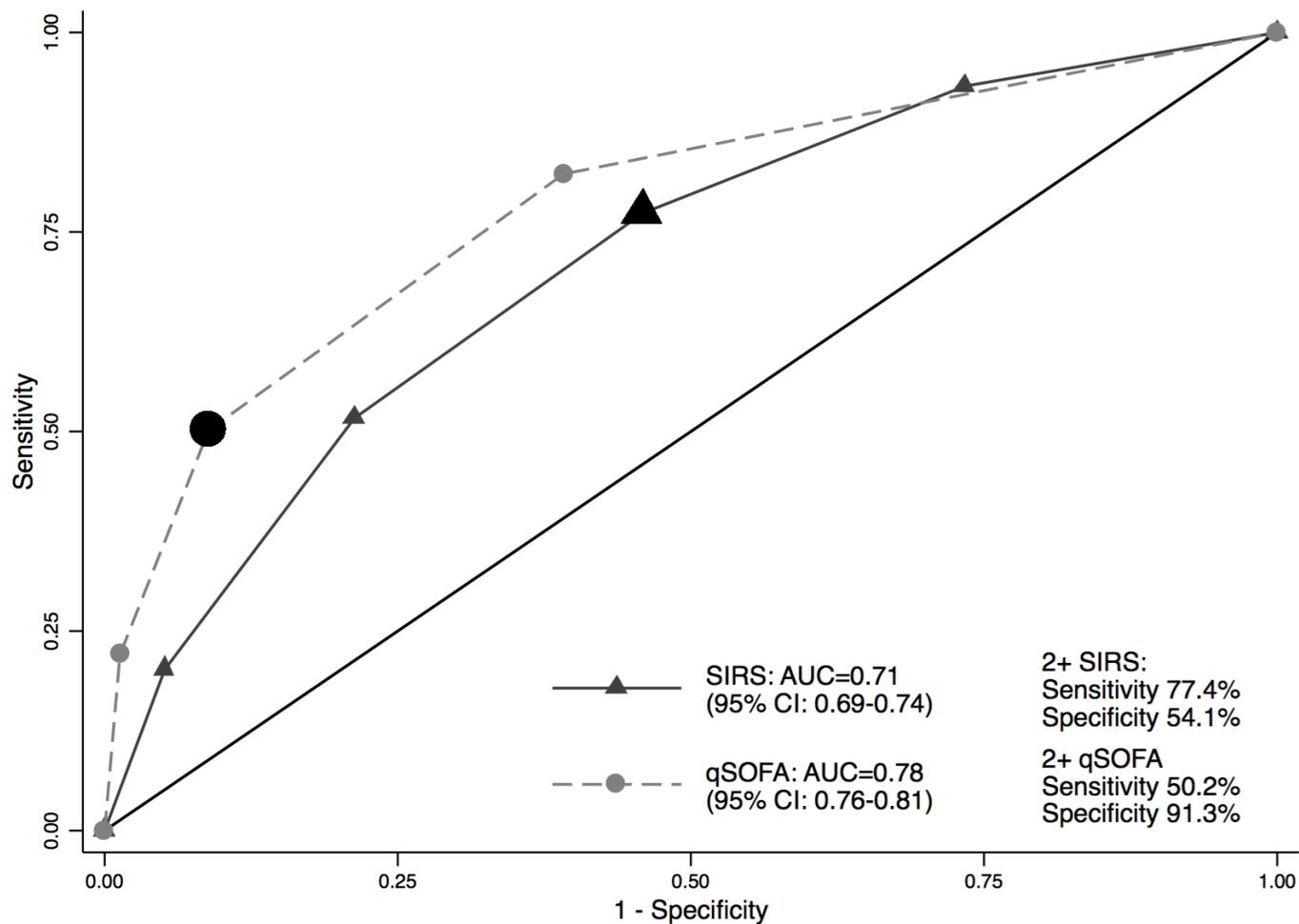|	Included Presentations (884)	Excluded presentations (846)	p =
SIRS ≥2	478 (54.1%)	472 (55.8%)	0.47
qSOFA ≥2	129 (14.6%)	118 (13.9%)	0.70
Sepsis-3 Organ Dysfunction	296 (33.5%)	280 (33.1%)	0.86
Deceased at 30 days	39 (4.4%)	33 (3.9%)	0.60

SIRS = systemic inflammatory response syndrome, qSOFA = "quick" sequential organ function assessment. In cases of readmissions within 90 days, a single admission was chosen at random from that period for inclusion. 472 patients had one representation excluded, 98 had 2 excluded, 27 had 3 excluded, and 19 had 4 or more excluded (total 846 excluded presentations). 429 patients had one representation included, 128 had 2 included, 41 had 3 included, and 18 patients had 4 or more representations included (total 884 included presentations) in the study dataset.

e-Table 3: Mortality and odds ratios for mortality using different SOFA cutoffs to denote organ dysfunction in different organ systems.

SOFA cut-off considered abnormal	CVS	CNS	RESP	HAEM	GIT	RENAL
1+	n=614 16.6% OR: 7.1 (5.5-9.1)	n=789 16.2% OR: 7.7 (6.1-9.7)	n=1639 13.5% OR: 10.5 (8.3-13.3)	n=726 4.8% OR: 1.4 (1.0-2.0)	n=1750 4.6% OR: 1.4 (1.1-1.8)	n=701 15.4% OR: 6.6 (5.2-8.5)
2+	n=218 23.9% OR: 9.5 (6.8-13.3)	n=129 33.3% OR: 14.9 (10.1-21.9)	n=779 16.6% OR: 7.9 (6.3-10.0)	n=203 6.9% OR: 2.0 (1.1-3.4)	n=400 6.3% OR: 1.8 (1.2-2.8)	n=279 23.3% OR: 9.7 (7.1-13.1)
3+	n=60 21.6% OR: 7.5 (4.0-14.0)	n=61 36.1% OR: 15.7 (9.2-26.9)	n=300 20.3% OR: 8.0 (5.9-10.8)	n=66 9.1% OR: 2.6 (1.1-6.2)	n=26 7.7% OR: 2.2 (0.5-9.3)	n=64 25.0% OR: 9.1 (5.1-16.2)
4	n=33 33.3% OR: 13.5 (6.5-28.1)	n=17 41.2% OR: 18.7 (7.1-49.4)	n=72 33.3% OR: 14.0 (8.5-23.2)	n=28 10.7% OR: 3.2 (1.0-10.5)	n=6 16.7% OR: 5.2 (0.6-45.0)	n=25 24.0% OR: 8.4 (3.3-21.1)

SOFA = sequential organ function assessment, CVS = cardiovascular system, CNS = central nervous system, RESP = respiratory system, HAEM = haematological system, GIT = gastrointestinal system, RENAL = renal system, OR = (unadjusted) odds ratio. Table entries comprise number of patients with failure at each cut-off, 30-day mortality and OR for 30-day mortality with 95% confidence intervals in parentheses.

e-Figure 1: Receiver operating curves for SIRS and qSOFA prediction of 30-day mortality

SIRS: AUC=0.71
(95% CI: 0.69-0.74)

qSOFA: AUC=0.78
(95% CI: 0.76-0.81)

2+ SIRS:
Sensitivity 77.4%
Specificity 54.1%

2+ qSOFA
Sensitivity 50.2%
Specificity 91.3%

SIRS = systemic inflammatory response syndrome, qSOFA = "quick" sequential organ function assessment, AUC = area under curve, CI = confidence interval.

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