New sepsis definition changes incidence of sepsis in the intensive care unit

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ABSTRACT

Objective: To estimate the impact of adopting the proposed new diagnostic criteria for sepsis, based on Sequential Organ Failure Assessment (SOFA) criteria, on the diagnosis and apparent mortality of sepsis in Australian and New Zealand intensive care units.

Design, setting and participants: A two-stage, post hoc analysis of prospectively collected ICU research data from 3780 adult patients in 77 Australian and New Zealand ICUs on 7 study days, between 2009 and 2014.

Main outcome measures: The proportion of patients who were diagnosed with sepsis using the criteria for systemic inflammatory response syndrome (SIRS) and who met the SOFA criteria for sepsis, and the proportion of patients who were admitted to the ICU with a diagnosis consistent with infection, who meet either, both or neither sets of criteria for sepsis; comparison of the demographic differences and in-hospital mortality between these groups.

Results: Of 926 patients diagnosed with sepsis on a study day using SIRS criteria, 796/923 (86.2% [95% CI, 84.0%–88.5%]) satisfied the SOFA criteria. In-hospital mortality was similar in these groups, with death recorded for 216/872 patients (24.8% [95% CI, 21.9%–27.8%]) who met the SIRS criteria for sepsis, and for 200/747 patients (26.8% [95% CI, 23.6%–30.1%]) who met both the SIRS and SOFA criteria for sepsis. Of 122 patients meeting the SIRS criteria but not the SOFA criteria, 16 (13.1% [95% CI, 7.7%–19.1%]) died. Of 241 patients admitted with infective pathology and complete data, 142 (58.9% [95% CI, 52.4%–65.2%]) satisfied the SIRS criteria for sepsis and 210 (87.1% [95% CI, 82.2%–91.1%]) satisfied the SOFA criteria. Of the 241 patients, 99 (41.1%) were not classified as having sepsis on the study day by SIRS criteria and, of these, 80 (80.8%) met the SOFA criteria.

Conclusions: Adopting the SOFA criteria will increase the apparent incidence of sepsis in patients admitted to the ICU with infective pathology without affecting the mortality rate. Prospective evaluation of the effect of adopting the new definition of sepsis is required.

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Sepsis lacks pathognomonic clinical features and a definitive biochemical or histological diagnostic test.[1] As a result, since 1992, diagnosis of sepsis has been based on the presence of two or more of the criteria characterising the systemic inflammatory response syndrome (SIRS) (Table 1) arising from suspected or proven infection.[2]

In response to data questioning this construct,[3-7] new criteria redefining sepsis, based on the Sequential Organ Failure Assessment (SOFA) score, have been proposed: Sepsis-3[8] (Table 1). The epidemiological and clinical implications of adopting these new criteria are currently unknown. We aimed to estimate the impact of adopting SOFA-based diagnostic criteria for sepsis on the diagnosis and apparent mortality of sepsis in Australian and New Zealand intensive care units.

Methods

Study design and population

We conducted post-hoc analyses of prospectively collected data from the point prevalence program (PPP) of the Australian and New Zealand Intensive Care Society Clinical Trials Group, which consisted of data from single-day point prevalence studies conducted regularly in a large proportion of Australian and New Zealand ICUs. All patients present in participating ICUs at 10 am on seven PPP study days between 2009 and 2014 were included. In this dataset, patients were contemporaneously diagnosed with sepsis if they had a presumed or proven infection and satisfied two or more criteria for SIRS. We assessed this cohort to calculate the proportion who would also satisfy the Sepsis-3 SOFA criteria.

We also analysed the cohort of patients who were admitted to the ICU within the 48 hours before data collection and whose principal reason for ICU admission was infective pathology (see eBox 1, in online appendix at cicm.org.au/Resources/Publications/Journal). We used this cohort to calculate how many patients would satisfy the SOFA criteria even if they did not satisfy the SIRS criteria.

We obtained ethics approval for data collection and use annually at each participating hospital.

Data and statistical analysis

We calculated SOFA scores for patients from worst recorded values on each study day. We made no assumptions about pre-existing organ dysfunction and assumed a baseline SOFA score of 0 (see Methods and eTable 1 in online appendix).[9,10] When data were missing, we excluded the patients from the analysis and reduced the denominator accordingly. We made no assumptions about missing data.

Table 1. Definitions of sepsis

SIRS criteria for sepsis (1992)

Suspected infection *and* at least two of:

- core temperature
  - > 38°C *or*
  - < 36°C
- heart rate > 90 beats per minute
- respiratory rate
  - > 20 breaths per minute *or*
  - $PaCO_2$ < 32 mmHg *or*
  - mechanical ventilation for an acute process
- white blood cell count
  - > 12×10^9/L *or*
  - < 4×10^9/L *or*
  - > 10% immature neutrophils.

SOFA criteria for sepsis (2016)

Suspected infection *and* acute change in SOFA score* of ≥ 2 points consequent to infection (see eTable 1 in supplementary appendix online).

SIRS = systemic inflammatory response syndrome. SOFA = sequential organ failure assessment. * Baseline SOFA score was assumed to be 0 in patients not known to have pre-existing organ dysfunction.

The proportion of patients diagnosed with sepsis using SIRS criteria and SOFA criteria were calculated along with their relative in-hospital mortality. We compared the demographic characteristics of patients determined to have sepsis, based on SOFA criteria, using *t* tests. As there is no gold standard for the diagnosis of sepsis, we did not calculate sensitivity or specificity for either set of diagnostic criteria. We quantified agreement between the criteria using Cohen's kappa. Because the patient groups selected using the new and old criteria were not independent, we did not calculate *P* for the comparison of in-hospital mortality, but drew inferences from the 95% confidence intervals (CIs).

We show data as means and standard deviations (SDs), or frequencies and percentages with 95% CIs, as appropriate. CIs of proportions and Cohen's kappa were calculated using Prism 6 (GraphPad), and *t* tests were performed in SPSS Statistics, version 21.0 (IBM). We defined statistical significance as $P < 0.05$.

Table 2. Characteristics of patients with sepsis on study day, by SOFA score

	SOFA score	
Characteristic	**≥ 2 (*n* = 796)**	**< 2 (*n* = 127)**
Mean age, years (SD)	59.8 (17.0)	53.0 (19.6)
Male, *n* (%)*	508 (63.8%)	82 (63.1%)
Mean APACHE II score (SD)	21.6 (7.5)	17.8 (7.5)
Hospital mortality at Day 28, *n* (%)*	200 (26.8%)	16 (13.1%)

SOFA = sequential organ failure assessment. APACHE = Acute Physiology and Chronic Health Evaluation. * Proportion of cases with recorded outcome.

Results

926/3754 patients (24.7%) were diagnosed with sepsis on study day using SIRS criteria. 796/923 also satisfied the SOFA criteria (86.2% [95% CI, 84.0%–88.5%]) (Figure 1). Patients meeting the sepsis diagnostic criteria for both the SIRS and SOFA definitions were significantly older than patients meeting SIRS criteria alone (SOFA score < 2) (Table 2) (mean age, 59.8 years [SD, 17.0 years] v mean age, 53.0 years [SD, 19.6 years], respectively; $P < 0.003$). Patients meeting both sets of sepsis diagnostic criteria also had higher mean Acute Physiology and Chronic Health Evaluation (APACHE) II scores for severity of disease (21.6 [SD, 7.5] v 17.8 [SD, 7.5], respectively; $P < 0.001$), than patients meeting SIRS criteria alone. In-hospital mortality was similar in patients identified as having sepsis by SIRS criteria alone and in those meeting both SIRS and SOFA criteria: 216/872 (24.8% [95% CI, 21.9%–27.8%]) v 200/747 (26.8% [95% CI, 23.6%–30.1%]) respectively. In comparison, only 16/122 patients (13.1% [95% CI, 7.7%–19.1%]) meeting the SIRS but not the SOFA criteria died.

A total of 1591 patients were admitted to the ICU in the 48 hours before PPP data collection. Of these, 244 (15.3%) had an admission diagnosis indicating infective pathology, of which 142/241 were determined to have sepsis on the study day, based on the SIRS criteria (58.9% [95% CI, 52.4%–65.2%]) (Figure 2). In comparison, 210/241 had sepsis as defined by the Sepsis-3 SOFA criteria (87.1% [95% CI, 82.2%–91.1%]). Patients with a SOFA score ≥ 2 were older (mean age, 62.9 years [SD, 16.6 year] v 56.4 years [SD, 21.7]; $P = 0.168$) with significantly higher disease severity (mean APACHE II score, 19.7 [SD, 7.1] v 13.2 [SD, 6.6]; $P < 0.001$) than those with a SOFA score < 2 (Table 3).

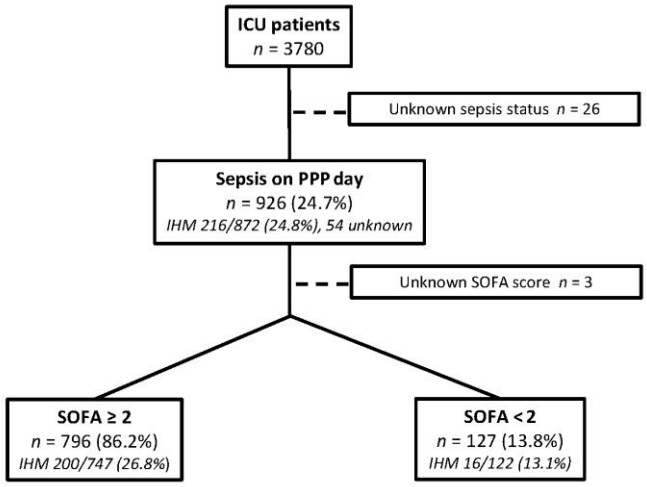
In-hospital mortality was equivalent in patients classified as having sepsis by the SIRS or SOFA criteria (28/135; 20.7% [95% CI, 14.2%–28.6%] v 40/198; 20.2% [95% CI, 14.8%–26.5%]). Of the 99/241 patients (41.1%) not classified as having sepsis on a study day by SIRS criteria, 80/99 patients (80.8%) had a SOFA score ≥ 2 on the study day. We found poor agreement between the diagnostic criteria ($\kappa = 0.12$ [95% CI, 0.02–0.22]).

Patient characteristics, by study day, are shown in eTable 2 in the online appendix.

Discussion

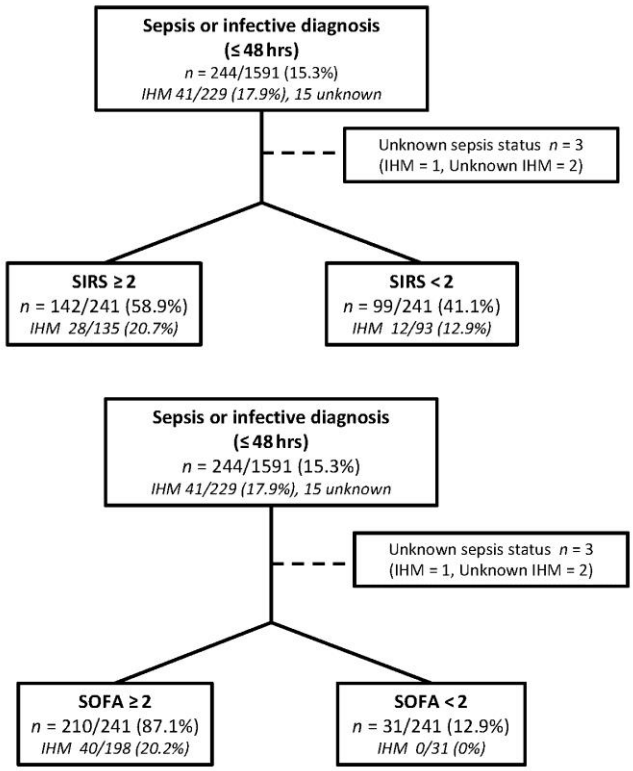
Our data suggest that adopting the Sepsis-3 diagnostic criteria will increase the number of ICU patients diagnosed with sepsis. Of patients admitted to the ICU with an admission diagnosis consistent with infection, substantially more patients will satisfy the new SOFA criteria than the existing SIRS criteria. The in-hospital mortality rate of patients diagnosed with sepsis in the ICU will be unaffected, whether the SIRS or SOFA criteria are used.

Figure 1. Proportion of ICU patients with sepsis on study day with SOFA score ≥ 2 or < 2*



ICU = intensive care unit. SOFA = Sequential Organ Failure Assessment. IHM = in-hospital mortality, censored at 28 days. * Patients diagnosed with sepsis on study day according to the presence of an organism grown in blood or other sterile site, or an abscess, or volume of infected tissue; and by meeting ≥ two criteria for systemic inflammatory response syndrome;[2] scores calculated from five domains (respiratory, coagulation, liver, cardiovascular renal).

Figure 2. Proportion of ICU patients with admission diagnosis consistent with sepsis or infection (≤ 48 hours since admission) meeting SIRS and SOFA diagnostic criteria*



ICU = intensive care unit. SIRS = systemic inflammatory response syndrome. SOFA = Sequential Organ Failure Assessment. IHM = in-hospital mortality, censored at 28 days. APACHE = Acute Physiology and Chronic Health Evaluation. * Patients in the Australian and New Zealand Intensive Care Society point prevalence program registry admitted within 48 hours before data collection, with an APACHE II primary diagnosis consistent with sepsis or infection (see eBox 1 in supplementary appendix online), were divided into patients meeting ≥ two or < two SIRS criteria.[17] Within each group, the proportions of patients meeting the new criteria for sepsis (SOFA score ≥ 2) and not meeting them (SOFA score < 2) were calculated. Outcome was calculated as a proportion of individuals with an infective admission diagnosis overall and patients meeting the current definition of sepsis (≥ two SIRS criteria) or or not meeting it (< two SIRS criteria). SOFA scores were calculated from five domains (respiratory, coagulation, liver, cardiovascular and renal) excluding neurological.

Implications of findings

The aim of the new SOFA-based criteria is to provide a pragmatic tool capable of distinguishing individuals with infection at high risk of adverse outcomes from those with self-limiting, 'uncomplicated' infections, which the SIRS criteria is not capable of.[11,12] Our data show that although the reported mortality rate from sepsis will be unaffected, patients with infective pathology at lower risk of in-patient death who would previously have been diagnosed with sepsis using the SIRS criteria would be excluded from the diagnosis of sepsis using the SOFA criteria. This is in accordance with prior studies showing that the SOFA score has a high predictive value for mortality in ICU cohorts.[13,14]

A recent, large, observational study by Kaukonen and colleagues reported that about 10% of ICU patients with severe sepsis may not be diagnosed with sepsis (and thus "missed") by the established SIRS criteria.[7] The increased proportion of patients with infective pathology diagnosed with sepsis using SOFA criteria, compared with SIRS criteria, along with the low in-hospital mortality rate in patients with a SOFA score ≤ 2, suggests that these patients are captured by the Sepsis-3 definition. It is currently unknown whether this improved sensitivity may be at the cost of reduced specificity.

Table 3. Characteristics of patients with admission diagnosis of infection admitted within 48 hours of study day, by SOFA score

Characteristic	SOFA score ≥ 2 (*n* = 210)	SOFA score < 2 (*n* = 31)
Sepsis on study day, *n* (%)	130 (61.0%)	12 (38.7%)
Mean age, years (SD)	62.9 (16.6)	56.4 (21.7)
Male, *n* (%)	125 (58.7%)	18 (58.1%)
Mean APACHE II score (SD)	19.7 (7.1)	13.2 (6.6)
Hospital mortality at Day 28, *n* (%*)	40 (20.2%)	0

SOFA = Sequential Organ Failure Assessment. APACHE = Acute Physiology and Chronic Health Evaluation. * Proportion of cases with recorded outcome.

The low level of agreement (kappa) observed between the SIRS and SOFA criteria suggests that the Sepsis-3 definition may identify a different patient cohort to the existing criteria. Our data show that this population will be older and sicker (with higher APACHE II scores). The clinical repercussions of designating only patients with infection and established organ failure as having sepsis remain unknown. The mortality of the patients not identified as having sepsis using SOFA criteria may increase if the absence of a diagnosis of sepsis leads to delayed or less intense monitoring and treatment. Further, the implementation of early warning detection systems based on the SIRS criteria, with treatment bundles, has been shown to lead to an enhanced process of care for patients with sepsis in New South Wales. These improved processes were associated with improvements in outcome, including reduced mortality.[15] It is unclear whether integration of the new SOFA-based diagnostic criteria into these algorithms will lead to comparable performance, or whether they will be useful for the early detection of clinical deterioration from non-infective conditions.[16]

Strengths and weaknesses

The PPP data represent bi-national data from self-selected ICUs participating on a voluntary basis. The data are collected prospectively by trained research nurses and coordinators, many of whom have collected data for this program for many years; this suggests that the data are of high quality and the study is of high integrity.

Post-hoc analysis inevitably restricts interpretation of the data. The proportion of patients meeting the SOFA-based definition was not collected as a primary data point. Hence, the proportion of patients with SIRS-negative, SOFA-positive sepsis had to be inferred from patients admitted within 48 hours of a study day, with an admission diagnosis consistent with sepsis or infection. Additionally, as the SOFA score before a study day was not collected, differentiating between patients with an acute increase in SOFA score of ≥ 2 (meeting the new definition of sepsis) and those with a chronically elevated SOFA score of ≥ 2 (not meeting the definition) was not possible. Further, the SOFA scores in the neurological domain were not recorded. Their inclusion could only have increased the reported number of patients diagnosed with sepsis using the SOFA criteria. Mortality status was not known for 5% of patients.

Our estimated mortality rate for patients who did not meet the new criteria for sepsis may be an underestimate. These patients could have received additional monitoring and treatment which would not have occurred without the diagnosis of sepsis. The true outcome of individuals who meet the SIRS but not the SOFA criteria can only be determined prospectively.

Conclusion

Using SOFA-based sepsis diagnostic criteria defines an older patient population with higher disease severity. Retrospectively applying SOFA diagnostic criteria to Australian and New Zealand ICUs increased the number of ICU-treated patients diagnosed with sepsis without altering the apparent in-hospital mortality rate.

Acknowledgements

J F and K T collated, analysed and interpreted the data. J F, K T and A S drafted the manuscript. S F conceived the study, interpreted the data and oversaw manuscript preparation and revision. J F and K T had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to and approved the final version of the manuscript.

Competing interests

None declared.

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