Potential Impact of the 2016 Consensus Definitions of Sepsis and Septic Shock on Future Sepsis Research

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Study objective: The influence of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) on the conduct of future sepsis research is unknown. We seek to examine the potential effect of the new definitions on the identification and outcomes of patients enrolled in a sepsis trial.

Methods: This was a post hoc analysis of the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial of early goal-directed therapy that recruited 1,591 adult patients presenting to the emergency department (ED) with early septic shock diagnosed by greater than or equal to 2 systemic inflammatory response syndrome criteria and either refractory hypotension or hyperlactatemia. The proportion of participants who would have met the Sepsis-3 criteria for quick Sequential Organ Failure Assessment (qSOFA) score, sepsis (an increased Sequential Organ Failure Assessment score $\geq$2 because of infection) and septic shock before randomization, their baseline characteristics, interventions delivered, and mortality were determined.

Results: There were 1,139 participants who had a qSOFA score of greater than or equal to 2 at baseline (71.6% [95% confidence interval {CI} 69.4% to 73.8%]). In contrast, 1,347 participants (84.7% [95% CI 82.9% to 86.4%]) met the Sepsis-3 criteria for sepsis. Only 1,010 participants were both qSOFA positive and met the Sepsis-3 criteria for sepsis (63.5% [95% CI 61.1% to 65.8%]). The Sepsis-3 definition for septic shock was met at baseline by 203 participants (12.8% [95% CI 11.2% to 14.5%]), of whom 175 (86.2% [95% CI 81.5% to 91.0%]) were also qSOFA positive. Ninety-day mortality for participants fulfilling the Sepsis-3 criteria for sepsis and septic shock was 20.4% (95% CI 18.2% to 22.5%) (274/1,344) and 29.6% (95% CI 23.3% to 35.8% [60/203]) versus 9.4% (95% CI 5.8% to 13.1%) (23/244) and 17.1% (95% CI 15.1% to 19.1% [237/1,388]), respectively, for participants not meeting the criteria (risk differences 11.0% [95% CI 6.2% to 14.8%] and 12.5% [95% CI 6.3% to 19.4%], respectively).

Conclusion: Most ARISE participants did not meet the Sepsis-3 definition for septic shock at baseline. However, the majority fulfilled the new sepsis definition and mortality was higher than for participants not fulfilling the criteria. A quarter of participants meeting the new sepsis definition did not fulfill the qSOFA screening criteria, potentially limiting its utility as a screening tool for sepsis trials with patients with suspected infection in the ED. The implications of the new definitions for patients not eligible for recruitment into the ARISE trial are unknown. [Ann Emerg Med. 2017;70:553-561.]

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INTRODUCTION

Background

An international task force of experts in sepsis pathophysiology recently generated a new set of definitions for sepsis and septic shock (Third International Consensus Definitions for Sepsis and Septic Shock [Sepsis-3]).[1] The impetus for revising the definitions was awareness that elements of the 1991 and 2001 consensus conference definitions,[2,3] which incorporated the requirement for 2 or more systemic inflammatory response syndrome (SIRS) criteria, were outdated and did not accurately identify patients with presumed sepsis and septic shock. Data from Australia and New Zealand suggested that 1 in 8 patients admitted to the ICU with infection and new organ failure did not fulfill the SIRS criteria for defining sepsis, despite having substantial mortality.[4]

The new Sepsis-3 definitions use the Sequential Organ Failure Assessment (SOFA)[5] score to identify sepsis and

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Editor's Capsule Summary

What is already known on this topic

International consensus sepsis definitions have recently changed (Third International Consensus Definitions for Sepsis and Septic Shock [Sepsis-3]). The effect of this change on identification and outcomes of patients compared with that of previous sepsis definitions (Sepsis-2) is unknown.

What question this study addressed

How do categories of patients classified by both Sepsis-2 and -3 criteria compare both in terms of definitional overlap and outcomes?

What this study adds to our knowledge

Most patients who met the Sepsis-2 definitions of severe sepsis or septic shock did not meet the Sepsis-3 criteria for septic shock. A quarter of patients meeting Sepsis-3 criteria did not fulfill quick Sequential Organ Failure Assessment (qSOFA) criteria.

How this is relevant to clinical practice

qSOFA appears to have limited utility as a sepsis screening tool in the emergency department. Sepsis-3 may miss patients considered to have sepsis by Sepsis-2 definitions.

septic shock. Moreover, they provide a screening tool, the quick Sequential Organ Failure Assessment (qSOFA) score, to assist in the rapid identification of patients with suspected infection who are at higher risk of mortality. Lacking a criterion standard test for diagnosing sepsis, the qSOFA screening tool and the revised definitions for sepsis and septic shock were based on a systematic literature review, a Delphi study, and retrospective analyses of the Surviving Sepsis Campaign database and 5 electronic health record databases for adult patients with suspected infection in 167 US hospitals and 1 German hospital.[6] The underlying goal was to develop definitions that would lead to more timely identification and resuscitation of patients with sepsis, in particular those with poor outcomes, more reliable epidemiologic data, and less heterogeneity in populations included in clinical sepsis trials.

Importance

The potential research implications of adopting the proposed new definitions for the screening, identification, and inclusion of patients in sepsis trials have not yet been evaluated, in particular for trials involving prompt recognition and early resuscitation. It is not known how the populations of patients included in recent sepsis trials using previous definitions might differ from those likely to be included in future equivalent trials using the new definitions. The effect on key trial design features such as feasibility, sample size calculations, and recruitment is also unknown. Moreover, it is uncertain how informative comparisons of results across trials might be influenced by the variability in selection of patients if different definitions are used.

Goals of This Investigation

We sought to explore the utility and potential effects of the new Sepsis-3 definitions for qSOFA, sepsis, and septic shock on the screening, identification, recruitment, and outcomes of participants, using data from patients previously enrolled in a large, multicenter, randomized, clinical trial conducted in patients presenting to the emergency department (ED) with early septic shock.

MATERIALS AND METHODS

Study Design and Setting

We conducted a post hoc analysis of the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial to determine the proportion of patients enrolled with the SIRS-based criteria that met the new Sepsis-3 definitions for qSOFA, sepsis, and septic shock before randomization; their baseline characteristics; interventions delivered; and outcomes, including mortality, duration of organ support, and ICU and hospital length of stay.[7]

ARISE was a large, multicenter, randomized trial of early goal-directed therapy versus usual care in patients presenting to the ED with early septic shock. The trial was conducted between October 2008 and April 2014 in 51 tertiary (academic) and nontertiary metropolitan and rural hospitals in Australia, New Zealand, Finland, Hong Kong, and the Republic of Ireland. ARISE was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group and Australasian College for Emergency Medicine. The results of the primary analysis have been previously published.[7] We included data from the 1,591 trial participants in the intention-to-treat population in this report.

Selection of Participants

The ARISE trial inclusion criteria were aged 18 years or older, suspected or confirmed infection, 2 or more SIRS criteria (ie, core temperature $<36.0°C$ (96.8°F) or $>38.0°C$ (100.4°F), pulse rate >90 beats/min, respiratory rate >20 breaths/min, or $PaCO_2$ <32 mm Hg or requirement for invasive ventilation for an acute process and WBC count $>12.0\times10^3/\mu L$ or $<4.0\times10^3/\mu L$ or >10% immature bands), and either refractory hypotension

(defined as systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg after an intravenous fluid challenge of 1,000 mL or more administered within a 60-minute period) or hypoperfusion (defined as a blood lactate level of 4 mmol/L or more).[7]

Key exclusion criteria related to an inability to deliver any or all elements of the early goal-directed therapy resuscitation algorithm within the study timeframe, imminent death, or expected death from an underlying condition before 90 days. Patients were eligible for enrollment if they met all the inclusion criteria and none of the exclusion criteria within 6 hours of presenting to the ED.[7]

Time to meeting the final study entry criterion was a median of 1.4 hours (95% confidence interval [CI] 0.6 to 2.5 hours) after presentation to the ED and enrollment occurred 2.7 hours (95% CI 2.0 to 3.9 hours) after presentation.[7]

Data Collection and Processing

Baseline prerandomization characteristics included demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) score, and physiologic, laboratory, and microbiologic variables. We also recorded receipt and duration of organ support (vasopressors, invasive ventilation, and renal replacement therapy), ICU and hospital duration of stay, and mortality at ICU and hospital discharge and at 90 days.

Outcome Measures

The proportion of patients meeting the Sepsis-3 qSOFA criteria (score of ≥2 from respiratory rate ≥22 breaths/min, systolic blood pressure ≤100 mm Hg, Glasgow Coma Scale [GCS] score <15), the SOFA-based definitions for sepsis (an increase of ≥2 in the SOFA score), and the SOFA-based definition for septic shock (an increase of ≥2 in the SOFA score, a requirement for vasopressors, and a blood lactate level >2 mmol/L) were calculated with the worst physiologic, laboratory, and intervention variables obtained after ED presentation and before randomization into ARISE.[7] Missing clinical and laboratory data were assumed to be normal for the purpose of calculating the qSOFA and SOFA scores and for determining the presence of septic shock.

Primary Data Analysis

We performed our analysis with SAS (version 9.4; SAS Institute, Inc., Cary, NC). Categorical data are presented as number and proportion with 95% CIs. Continuous data are presented as mean (standard deviation) or median (interquartile range) as appropriate. All missing values were assumed to be normal. To account for missingness, we conducted a sensitivity analysis using 2 approaches. First, in accordance with Seymour et al[8] and Raith,[9] chained-equations multiple imputation was performed with missingness conditional on observed baseline covariates and assumed to be "missing at random." A total of 11 imputed data sets were created, with median results reported. Furthermore, in contrast to the conventional approach of assigning missing values to be normal, to establish the extreme case scenario, all missing values were assigned to be abnormal.

RESULTS

Characteristics of Study Subjects

Of 1,591 participants included in the ARISE study, 1,139 (71.6% [69.4% to 73.8%]) met 2 or more qSOFA bedside screening criteria before randomization (qSOFA positive) (Figure). The remaining 452 participants (28.4% [26.2% to 30.6%]) were qSOFA negative.

The Sepsis-3 criteria for sepsis were present in 1,347 participants (84.7% [82.9% to 86.4%]) (sepsis positive). A total of 1,010 participants (63.5% [61.1% to 65.8%]) were both qSOFA positive and met the Sepsis-3 definition for sepsis. However, the qSOFA screening tool result was negative in 337 of the 1,347 participants who were Sepsis-3 sepsis positive (25.0% [22.7% to 27.3%]). Finally, only 203 of the 1,591 ARISE participants (12.8% [11.1% to 14.4%]) fulfilled the Sepsis-3 criteria for septic shock (Figure).

Main Results

Of the 1,139 qSOFA-positive participants, 1,099 (96.5% [95.4% to 97.6%]) met the respiratory rate criterion and 1,022 (89.7% [88.0% to 91.5%]) fulfilled the blood pressure criterion. Only 379 qSOFA-positive participants (33.3% [30.5% to 36.0%]) had a GCS score less than 15 before randomization into the ARISE trial. For the 452 qSOFA-negative participants, either the respiratory rate or the blood pressure criteria were present in 241 (53.3% [48.7% to 57.9%]) and 171 (37.8% [33.4% to 42.3%]) participants, respectively. Only 2 participants (0.4% [0% to 1.1%]) who were qSOFA negative met the GCS score criterion of less than 15.

The baseline characteristics and outcomes for qSOFA-positive and -negative participants are shown in Tables 1 and 2, respectively. qSOFA-positive participants had a higher APACHE II score and received more fluid before randomization. They were also more likely to meet the refractory hypotension criteria and receive a vasopressor infusion. More qSOFA-positive participants received a vasopressor infusion during their hospital stay, but receipt of mechanical ventilation and renal replacement therapy was similar to that of qSOFA-negative participants. Mortality in qSOFA-positive participants at 90 days was higher, 20.6%

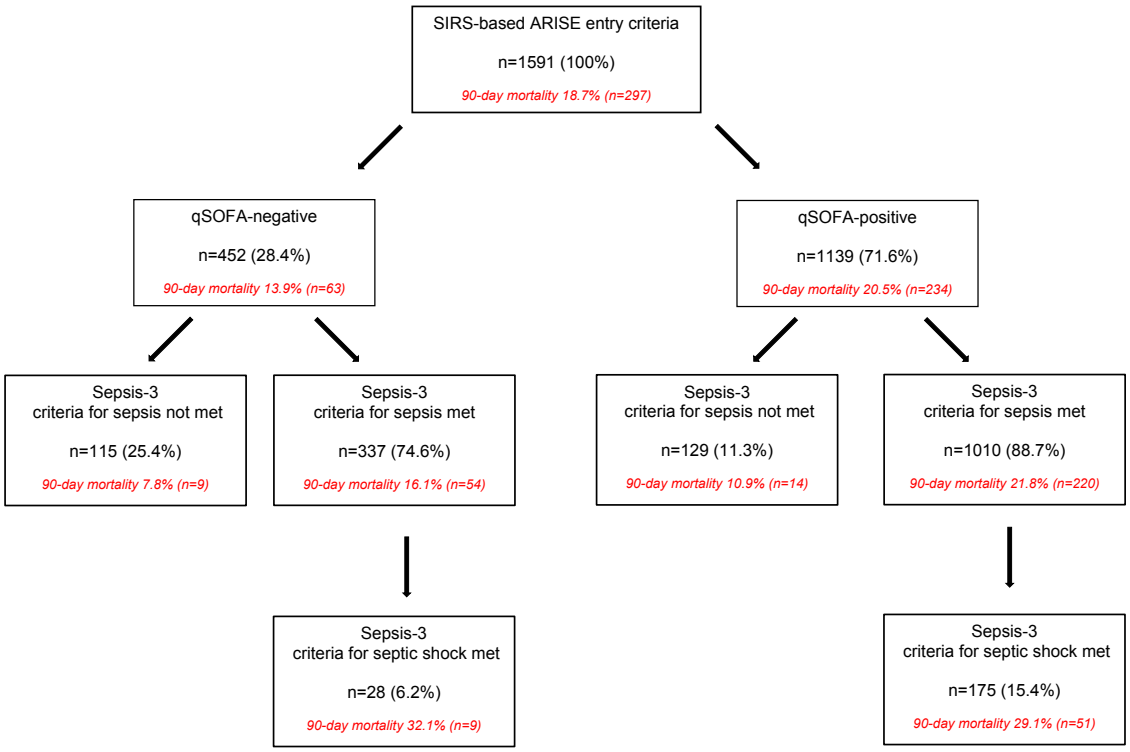

Figure. Proportion of ARISE participants fulfilling the new Sepsis-3 definitions before randomization into the ARISE trial, and 90-day mortality.

(18.2% to 22.9%; 234 of 1,137) versus 14.0% (10.8% to 17.2%; 63 of 451) for qSOFA-negative participants (risk difference 6.6%; 95% CI 2.5% to 10.4%).

A respiratory source of infection was more common in qSOFA-positive participants, with 413 cases (36.3% [33.5% to 39.1%]) versus 138 (30.6% [26.3% to 34.9%]) among qSOFA-negative participants. A positive blood culture result was documented in 440 qSOFA-positive participants (38.6% [35.8% to 41.5%]) and in 161 qSOFA-negative participants (35.6% [31.3% to 40.1%]).

Only 498 of the 1,347 participants (37.0% [34.4% to 39.5%]) who met the Sepsis-3 criteria for sepsis (sepsis positive) achieved a total SOFA score of greater than or equal to 2 with only the bedside cardiovascular or central nervous system components. For the remaining 849 sepsis-positive participants (63.0% [60.5% to 65.6%]), one or more SOFA points were derived from laboratory variables (levels of platelets, bilirubin, creatinine, and PaO_2/FiO_2) from blood drawn before randomization (but results were not necessarily available prerandomization).

For the 337 participants (25% [22.7% to 27.3%]) who were qSOFA negative but sepsis positive, only 44 (13.1% [9.5% to 16.7%]) achieved a total SOFA score of greater than or equal to 2 with just the bedside variables. For the remaining 293 qSOFA-negative but sepsis-positive participants (86.9% [83.3% to 90.5%]) in whom laboratory variables contributed to the total SOFA score, one or more points were derived from the following variables: creatinine level 35.6%, PaO_2/FiO_2 level 29.1%, bilirubin level 23.1%, platelet level 15.1%.

Sepsis-positive participants had a higher APACHE II score, received more fluid resuscitation and organ support before randomization (Table 1), and had higher mortality rates than sepsis-negative participants (Table 2). Ninety-day mortality for sepsis-positive participants was also more than double: 20.4% (18.2% to 22.5%; 274 of 1,344 participants) versus 9.4% (5.8% to 13.1%; 23 of 244 participants) for sepsis-negative participants (risk difference 11.0%; 95% CI 6.2% to 14.8%).

The source of infection was not different between the sepsis-positive and –negative participants: respiratory 466 (34.6% [32.1% to 37.2%]) versus 85 (34.8% [28.9% to 40.8%]), and urinary 257 (19.1% [17.0% to 21.2%]) versus 51 (20.9% [15.8% to 26.0%]), respectively. More sepsis-positive participants were blood culture positive: 540 participants (40.1% [37.5% to 42.7%]) versus 61 (25.0% [19.6% to 30.4%]) for sepsis-negative participants.

Of the 203 participants who fulfilled the Sepsis-3 definition for septic shock before randomization, 175 (86.2% [81.5% to 91.0%]) were also qSOFA positive. Compared with participants who did not fulfill the Sepsis-3 definition for septic shock, those meeting the criteria for

Table 1. Baseline characteristics and interventions for all ARISE trial participants and according to qSOFA, sepsis, and septic shock status.*

Variable	ARISE, n=1,591	qSOFA Negative, n=452	qSOFA Positive, n=1,139	Sepsis Negative, n=244	Sepsis Positive, n=1,347	Septic Shock Negative, n=1,388	Septic Shock Positive, n=203
Baseline characteristics							
Age, y	62.9 (16.5)	61.9 (15.9)	63.3 (16.7)	60.1 (17.1)	63.4 (16.3)	63.1 (16.4)	61.5 (16.8)
Sex, No. (%), male	950 (59.7)	279 (61.7)	671 (58.9)	124 (50.8)	826 (61.3)	823 (59.3)	127 (62.6)
APACHE II score	15.6 (6.5)	13.9 (5.9)	16.3 (6.7)	10.5 (4.2)	16.5 (6.5)	15.1 (6.3)	19.3 (6.8)
Refractory hypotension, No. (%)	1,112 (69.9)	183 (40.5)	929 (81.6)	137 (56.1)	975 (72.4)	947 (68.2)	165 (81.3)
Hypoperfusion, No. (%)	736 (46.3)	293 (64.8)	443 (38.9)	125 (51.2)	611 (45.4)	609 (43.9)	127 (62.6)
Interventions before randomization							
Invasive ventilation, No. (%)	135 (8.5)	31 (6.9)	104 (9.1)	3 (1.2)	132 (9.8)	85 (6.1)	50 (24.6)
Vasopressor, No. (%)	346 (21.7)	50 (11.1)	296 (26.0)	5 (2.0)	341 (25.3)	143 (10.3)	203 (100)
Total intravenous fluid, mL/kg	34.6 (19.8)	30.3 (19.6)	36.4 (19.6)	32.9 (22.9)	35.0 (19.2)	39.4 (20.6)	34.0 (19.6)
Physiologic and laboratory variables before randomization							
Temperature, °C (°F)	37.6 (1.5) (99.7 [34.7])	37.5 (1.5) (99.5 [34.7])	37.6 (1.5) (99.7 [34.7])	37.8 (1.3) (100.0 [34.3])	37.6 (1.6) (99.7 [34.9])	37.7 (1.5) (99.9 [34.7])	37.2 (1.8) (99.0 [35.2])
Pulse rate, beats/min	105 (22)	106 (23)	104 (21)	103 (19)	105 (23)	105 (22)	106 (25)
Respiratory rate, breaths/min	24.8 (7.8)	23.1 (8.0)	25.5 (7.6)	24.6 (7.5)	24.9 (7.8)	24.8 (7.8)	24.8 (7.6)
Mean arterial pressure, mm Hg	69.9 (15.4)	77.4 (15.8)	67.0 (14.3)	73.2 (14.8)	69.3 (15.5)	70.2 (15.3)	68.4 (16.5)
GCS score	14.3 (1.8)	15 (0.4)	14.0 (2.1)	14.9 (0.2)	14.2 (2.0)	14.4 (1.7)	13.8 (2.5)
SpO_2, %	96.6 (4.3)	96.6 (3.7)	96.6 (4.5)	96.9 (3.6)	96.6 (4.4)	96.7 (4.2)	96.0 (5.0)
pH	7.35 (0.12)	7.35 (0.12)	7.35 (0.12)	7.36 (0.10)	7.35 (0.12)	7.36 (0.11)	7.29 (0.15)
Lactate, mmol/L	4.3 (3.1)	4.7 (2.8)	4.1 (3.2)	4.2 (2.4)	4.3 (3.2)	4.1 (2.9)	5.3 (3.8)
Creatinine, median (IQR), μmol/L	131 (93–203)	121 (89–180)	135 (95–210)	85 (69–101)	145 (105–220)	125 (91–188)	204 (126–318)
Urine output, median (IQR), mL/h	50 (0–150)	60 (0–200)	45 (0–145)	100 (20–240)	40 (0–150)	50 (0–160)	30 (0–100)
WBC count$\times 10^9$/L, mean (SD)	13.6 (9.7)	13.6 (8.7)	13.7 (10.1)	13.9 (8.2)	13.6 (9.9)	13.6 (9.5)	13.5 (11.1)
Platelet count$\times 10^9$/L, mean (SD)	206 (114)	215 (120)	203 (111)	256 (100)	197 (114)	210 (115)	181 (100)
Bilirubin, median (IQR), μmol/L	17 (10–27)	17 (10–29)	17 (10–26)	12 (9–16)	17 (11–30)	16 (10–27)	18 (11–30)

IQR, Interquartile range.
*Data are presented as mean (SD) or number (%) unless otherwise indicated.

septic shock had a higher APACHE II score, received more organ support before randomization (Table 1), and had worse outcomes, with higher mortality and greater receipt and duration of invasive ventilation, vasopressor support, and renal replacement therapy (Table 2). Ninety-day mortality was 29.6% (23.3% to 35.8%; 60 of 203) for participants meeting the Sepsis-3 definition for septic shock and 17.1% (15.1% to 19.1%; 237 of 1,388) for those who did not (risk difference 12.5%; 95% CI 6.3% to 19.4%).

There was no difference in the source of infection between participants meeting the Sepsis-3 definition for septic shock and those who did not: respiratory 71 (35.1% [28.6% to 41.7%]) versus 480 (34.6% [32.3% to 37.2%]), and urinary tract 31 (15.3% [10.4% to 20.3%]) versus 277 (20.0% [17.9% to 22.1%]). Blood culture results were positive in 98 participants (48.3% [41.4% to 55.2%]) fulfilling the definition for Sepsis-3 septic shock and 503 (36.2% [33.7% to 39.8%]) who did not.

Data for calculation of the qSOFA and SOFA scores and for determination of septic shock were missing for less than 1% of clinical variables, other than for GCS score, which was not available for 8.2% of participants (Figure E1, available online at http://www.annemergmed.com). For laboratory variables, other than for PaO_2/FiO_2, which was missing for 61.2% of participants, the remainder were available for 84% to 96% of participants.

Assuming all missing values to be abnormal, the proportion of patients meeting the qSOFA (71.6%), sepsis (84.7%), and septic shock (15.2%) criteria increased to 75.5% (73.3% to 77.6%), 99.1% (98.7% to 99.6%), and 28.7% (26.5% to 31.0%), respectively (Table E1, available online at http://www.annemergmed.com). In accordance with multiple imputation sensitivity analysis, the median proportion of patients meeting the qSOFA, sepsis, and septic criteria was 74.1% (71.9% to 76.3%), 96.3% (95.3% to 97.2%), and 16.0% (14.1% to 17.8%), respectively. Sensitivity, specificity, and predictive value of the Sepsis-3 definitions for 90-day mortality using the sensitivity analyses to account for missing data are presented in Table E1, available online at http://www.annemergmed.com.

LIMITATIONS

First, our study was limited to patients presenting to the ED with early septic shock who were eligible for recruitment into the ARISE trial. The number of patients who may have met the new SOFA-based definitions for sepsis and septic shock but did not meet the SIRS-based

Table 2. Outcomes for all ARISE trial participants and according to qSOFA, sepsis, and septic shock status.

Variable	ARISE, n = 1,591	qSOFA Negative, n = 452	qSOFA Positive, n = 1,139	Sepsis Negative, n = 244	Sepsis Positive, n = 1,347	Septic Shock Negative, n = 1,388	Septic Shock Positive, n = 203
90-day mortality, No. (%)*	297 (18.7)	63 (14.0)	234 (20.6)	23 (9.4)	274 (20.4)	237 (17.1)	60 (29.6)
ICU mortality, No. (%)*	164 (11.8)	32 (8.7)	132 (12.9)	7 (3.6)	157 (13.2)	124 (10.4)	40 (20.8)
Hospital mortality, No. (%)*	240 (15.3)	47 (10.4)	196 (17.2)	13 (5.3)	230 (17.1)	189 (13.6)	54 (26.6)
ICU admission, No. (%)	1,387 (87.2)	366 (81.0)	1,021 (89.6)	197 (80.7)	1,190 (88.3)	1,195 (86.1)	192 (94.6)
Median ICU duration of stay, days (IQR)	2.8 (1.5–5.3)	2.6 (1.3–5.0)	2.9 (1.5–5.5)	2.0 (1.0–3.7)	2.9 (1.5–5.8)	2.7 (1.3–5.0)	3.9 (1.9–7.7)
Median hospital duration of stay, days (IQR)	8.3 (4.9–16.7)	7.7 (4.8–15.1)	8.8 (5.0–17.2)	6.9 (4.1-11.5)	8.8 (5.0–17.6)	8.2 (4.9–16.1)	10.1 (4.8–19.9)
Invasive ventilation, No. (%)	491 (30.9)	123 (27.2)	368 (32.3)	37 (15.2)	454 (33.7)	387 (27.9)	104 (51.2)
Median duration of ventilation, h	63.7 (23.6–166.0)	74.0 (20.8–168.2)	62.4 (24.6–162.9)	46.8 (13.7–132.7)	65.5 (24.6–166.7)	59.4 (21.7–154.6)	96 (32.3–236.8)
Vasopressor infusion, No. (%)	1,132 (71.2)	266 (58.8)	866 (76.0)	114 (46.7)	1018 (75.6)	931 (67.1)	203 (100)
Median duration of vasopressor infusion, h (IQR)	31.4 (13.1– 64.5)	28.7 (12.0–61.8)	32.0 (14.0–65.0)	19.1 (7.5–40.3)	32.7 (14.3–67.0)	28.4 (12.9–57.9)	47 (20.5–109.3)
Renal replacement therapy, No. (%)	215 (13.5)	54 (11.9)	161 (14.1)	11 (4.5)	204 (15.2)	156 (11.2)	59 (29.1)
Median duration of renal replacement therapy, h (IQR)	70.5 (25.3–179.0)	73.5 (18.9–207)	69 (27–163)	39.2 (12.9–460)	72.0 (25.3–173)	58 (20.9–167)	90.4 (40.5–221.5)

*Ninety-day mortality available for 1,588 of 1,591 participants; ICU mortality, 1,386 of 1,386 participants; hospital mortality, 1,590 of 1,591 participants.

ARISE entry criteria is not known and potentially underestimates the number of patients eligible for future septic shock trials.[4] The assumption that missing data were within normal limits may also underestimate the potential number of eligible patients. However, for most variables 85% to 100% of data was available, and missing data reflect heterogeneity in clinical practice.

Second, the mortality of patients not eligible for ARISE is also unknown. Patients with imminent death or expected death from an underlying condition before 90 days were not included in ARISE. Accordingly, mortality for participants meeting the new Sepsis-3 definitions is likely to be higher in comparison because there were no such exclusion criteria in the Sepsis-3 development cohorts according to administrative data.

Third, the numbers of patients who would have gone on to meet the new definitions for sepsis or septic shock outside of the context of this clinical trial cannot be reliably determined because subsequent fulfillment of the new criteria, in particular, the cardiovascular SOFA score and the definition of septic shock, both of which depend on the use of vasopressors, would be affected by the study intervention postrandomization. By 6 hours postrandomization, approximately 50% of participants meeting the new criteria for sepsis at baseline met the new criteria for septic shock.

Fourth, no conclusions can be drawn for patients who develop sepsis in either the general ward or in the ICU because ARISE enrolled only patients meeting the study entry criteria in the ED.

DISCUSSION

We found that most ARISE participants fulfilled the Sepsis-3 definition for sepsis before randomization. Accordingly, baseline characteristics and outcomes were similar. However, only 1 in 8 participants met the new definition for septic shock in a trial in which patients were specifically selected because of refractory hypotension (hemodynamic shock), a blood lactate level greater than or equal to 4 mmol/L (cryptic shock), or both. In contrast, more than two thirds of participants enrolled in the ARISE trial met the 2001 Consensus Conference definition of septic shock at baseline (systolic blood pressure <90 mm Hg despite adequate volume resuscitation).[3,7] Although the blood pressure criterion in the Sepsis-3 definition for septic shock is similar to that applied in the ARISE trial, the inclusion of an organ injury score and a blood lactate level greater than or equal to 2 mmol/L in the new definition led to a substantial reduction in the number of participants defined as having septic shock (a greater than 80% decrease in potential participants).

Sample size calculations may be affected by such a change in definition because 90-day mortality for patients meeting the Sepsis-3 definition for septic shock was nearly double that of patients meeting the ARISE refractory hypotension criteria. Thus, for example, in applying the Sepsis-3 definition to a future trial evaluating an intervention with an anticipated 5% absolute risk reduction, 1,618 patients with septic shock would be required (with 80% power and a 2-sided α=.05) compared with 2,560 patients with the 2001 Consensus Conference definition of shock based only on blood pressure.[3] However, counteracting this potential decrease in sample size is the substantial decrease in recruitment rate. Of the 1,591 ARISE participants recruited during 5.5 years, 200 per annum met the criteria for refractory hypotension. In contrast, with the new criteria, only 40 participants per annum would meet the criteria for septic shock. Finally, given the substantial differences in mortality for participants with septic shock between earlier consensus conference definitions[2,3] and the new Sepsis-3 definition, contextualizing the results of future septic shock trials will be problematic.

What effect the Sepsis-3 definition for sepsis would have on sample size and recruitment is less clear because the majority of ARISE participants also fulfilled the new sepsis definition, and therefore 90-day mortality was relatively unchanged (18.7% versus 20.3%, respectively). This observation suggests that, in comparison with earlier consensus conference definitions,[3] the new Sepsis-3 definition may not identify a different or more homogeneous cohort of patients.

The inclusion of patients into trials evaluating sepsis interventions that are time sensitive, such as those assessing the effect of early hemodynamic resuscitation, may also be affected by the new definitions. Although the majority of ARISE participants met the new sepsis definition, less than 40% achieved the SOFA score of greater than or equal to 2 from variables that are readily available at the bedside (blood pressure, vasopressor levels, and GCS score). Data for the majority of participants therefore had to rely on laboratory variables, the results of which may not be available in the same timely fashion as vital signs. This lack of diagnostic immediacy would likely lead to inevitable delays in meeting trial entry criteria and, hence, delivery of any early intervention under investigation. A reported advantage of the SOFA score is that it can be performed retrospectively.[1] However, this feature of the new Sepsis-3 definitions has limited research utility for prospective entry into a randomized clinical trial in which timeliness of identification is a high priority.[10] Delayed identification may also have important clinical implications for early aggressive resuscitation in patients presenting to the ED with a life-threatening infection, particularly because the new definitions require the presence of established organ dysfunction and thus identify a sicker population of infected patients who may be less likely to benefit from early intervention.

Although qSOFA was developed to assist in the early identification of patients with suspected infection who are likely to have a poor outcome, particularly in the ED and other non-ICU settings, 1 in 4 participants meeting the new Sepsis-3 definition of sepsis were qSOFA negative. Also, lactate level, which is not included in the qSOFA score, was higher in qSOFA-negative participants, which may limit the utility of qSOFA to identify higher-risk patients in this population. Furthermore, for qSOFA-positive patients, the GCS score would appear to add very little to the early identification of potentially infected patients.

In summary, our post hoc analysis of the ARISE trial found that the new SOFA-based Sepsis-3 definition for sepsis identified the majority of ARISE participants enrolled with the SIRS-based entry criteria. However, most participants did not meet the new definition of septic shock. Application of the new definitions to future sepsis trials may have a number of potential implications, in particular for sample size, recruitment rate, screening, early identification, and randomization. Prospective observational studies to determine the true effect of the new definitions on key elements of trial conduct are needed.

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Author contributions: SLP, AD, and RB conceived the study. MB conducted the statistical analyses. SLP drafted the article and all authors contributed substantially to its revision. SLP takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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APPENDIX

The ARISE investigators

The ARISE study was a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australasian College for Emergency Medicine and the Australian and New Zealand Intensive Care Research Center, Monash University. The trial was endorsed by the Irish Critical Care Trials Group and the College of Intensive Care Medicine. The trial was funded by the National Health and Medical Research Council (No. 491075 and 1021165) and coordinated by the Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne.

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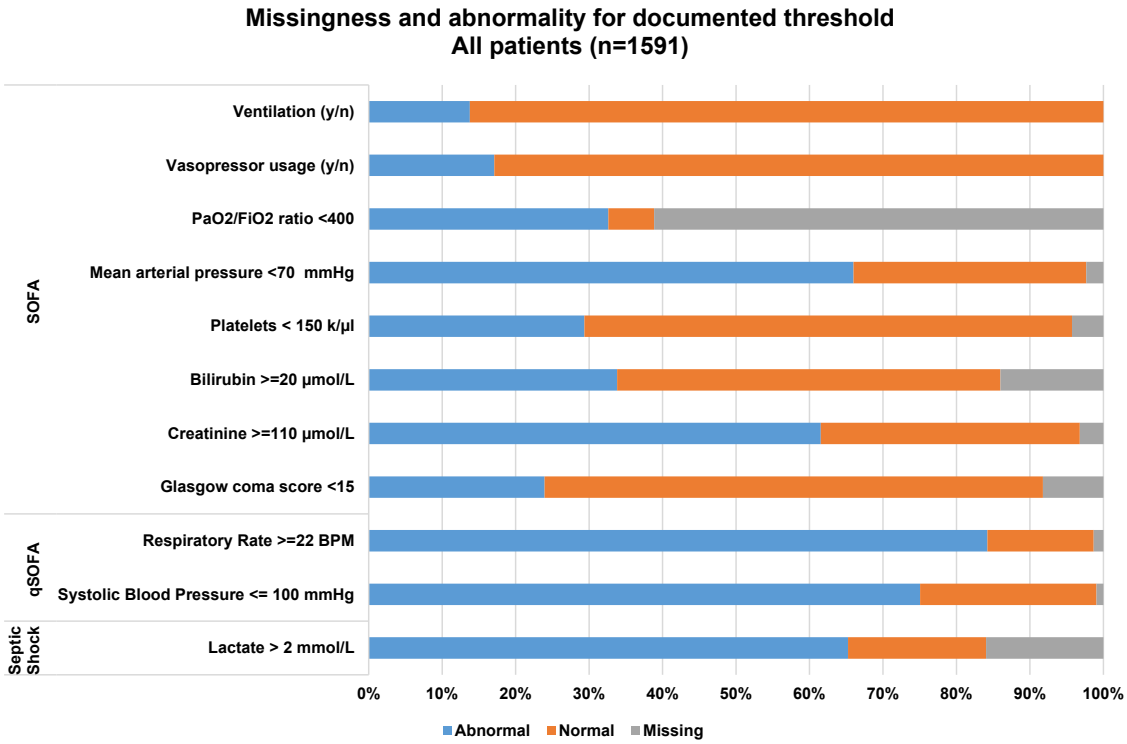

Figure E1. Distribution of variables for calculating the qSOFA and SOFA scores and for determination of septic shock with the Sepsis-3 definition. The blue bars represent the proportion abnormal, orange the proportion normal, and gray the proportion missing for each variable, with the documented threshold defining abnormality. *BPM*, Beats/min.

Table E1. Sensitivity, specificity, and predictive value of the Sepsis-3 definitions for 90-day mortality, with sensitivity analyses for missing data.

Variable	Type	Event Rate	% (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Predictive Value, % (95% CI)	Negative Predictive Value, % (95% CI)
qSOFA	Missing=normal*	1,139/1,588	71.6 (69.3–73.9)	78.8 (74.1–83.5)	30.1 (27.5–32.7)	20.6 (18.2–23.0)	86.0 (82.7–89.3)
qSOFA	Multiple imputation†	1,179/1,588	74.1 (71.9–76.3)	80.8 (76.2–85.4)	27.4 (24.9–29.9)	20.4 (18.1–22.7)	86.1 (82.7–89.5)
qSOFA	Missing=abnormal‡	1,201/1,588	75.5 (73.3–77.6)	81.5 (77–86)	25.9 (23.5–28.3)	20.2 (17.9–22.5)	85.9 (82.4–89.4)
Sepsis	Missing=normal*	1,347/1,588	84.7 (82.9–86.5)	92.3 (89.2–95.4)	17.1 (15–19.2)	20.4 (18.2–22.6)	90.6 (86.9–94.3)
Sepsis	Multiple imputation†	1,532/1,588	96.3 (95.3–97.2)	99.3 (98.3–100.3)	4.4 (3.3–5.5)	19.3 (17.3–21.3)	96.6 (91.9–100)
Sepsis	Missing=abnormal‡	1,577/1,588	99.1 (98.7–99.6)	100 (100–100)	1.1 (0.5–1.7)	18.9 (16.9–20.9)	100 (100–100)
Septic shock	Missing=normal*	203/1,337	15.2 (13.2–17.1)	23 (17.8–28.2)	86.7 (84.6–88.8)	29.6 (23.2–36.0)	82.2 (79.9–84.5)
Septic shock	Multiple imputation†	254/1,588	16.0 (14.1–17.8)	22.6 (17.7–27.5)	85.6 (83.6–87.6)	26.5 (21.0–32.0)	82.8 (80.7–84.9)
Septic shock	Missing=abnormal‡	457/1,588	28.7 (26.5–31.0)	32.3 (26.9–37.7)	72.1 (69.6–74.6)	21.1 (17.3–24.9)	82.2 (79.9–84.5)

*Missing=normal signifies missing data are assumed a normal value or assigned a score of zero.
†Multiple imputation assumed data missing at random. A total of 11 imputed data sets were created and median results are reported.
‡Missing=abnormal signifies missing data are assumed the worst value or assigned a maximum score.