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The Impact of the SEPSIS-3 Septic Shock Definition on Previously Defined Septic Shock Patients

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Abstract

Objective—The Third International Consensus Definitions Task Force (SEPSIS-3) recently recommended changes to the definitions of sepsis. The impact of these changes remains unclear. Our objective was to determine the outcomes of patients meeting SEPSIS-3 septic shock criteria versus patients meeting the 'old' (1991) criteria of septic shock only.

Design—Secondary analysis of two clinical trials of early septic shock resuscitation.

Setting—Large academic emergency departments in the United States.

Patients—Patients with suspected infection, ≥2 SIRS criteria, and SBP <90mmHg after fluid resuscitation.

Interventions—Patients were further categorized as SEPSIS-3 septic shock if they demonstrated hypotension, received vasopressors, and exhibited a lactate >2 mmol/L. We compared in-hospital mortality in patients who met the old definition only to those who met the SEPSIS-3 criteria.

Main Results—470 patients were included in the present analysis. 200 (42.5%) met SEPSIS-3 criteria while 270 (57.4%) met only the old definition. Patients meeting SEPSIS-3 criteria demonstrated higher severity of illness by SOFA score (9 versus 5; $p < 0.001$) and mortality (29% vs 14%; $p < 0.001$). Subgroup analysis of 127 patients meeting only the old definition demonstrated significant mortality benefit following implementation of a quantitative resuscitation protocol (35% vs. 10%, $p = 0.006$).

Conclusion—In this analysis 57% of patients meeting old definition for septic shock did not meet SEPSIS-3 criteria. Although SEPSIS-3 criteria identified a group of patients with increased organ failure and higher mortality, those patients who met the old criteria and not SEPSIS-3 criteria still demonstrated significant organ failure and 14% mortality rate.

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Keywords

septic shock; sepsis; SEPSIS-3; qSOFA; sepsis definition; severe sepsis

Introduction

In 1991, the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) convened with the goal to develop a set of definitions for sepsis to standardized the definition of sepsis and its spectrum of disease, and develop severity of illness scoring systems for prognostication and uniformity in investigations clinical trials.(1) Recommendations included streamlining pseudonyms for sepsis into a “systemic inflammatory response syndrome” (SIRS); “sepsis”, when SIRS results from a infection; “severe sepsis”, when associated with organ dysfunction, hypoperfusion, or hypotension; and “septic shock” when sepsis induced hypotension persists after adequate fluid resuscitation, along with the presence of perfusion abnormalities or organ dysfunction. (1)

Despite these efforts, additional understanding of the pathophysiology of sepsis coupled with the persisting vagaries surrounding the definition of sepsis led to a reassessment of the definitions in 2001.(2) The consensus made no significant changes to the actual definitions of sepsis citing a lack evidence to do so and finding the previous definition were still useful to both clinicians and researchers; however, they did expand the signs and symptoms of sepsis and noted that SIRS criteria were overly sensitive and lacked specificity and that the definitions did not allow for prognostication. (2)

Citing the lack of change in the definitions of sepsis over nearly 20 years despite considerable advances in the pathophysiologic response to sepsis, these definitions were recently reexamined. (3) The Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3) divides sepsis into two distinct categories: sepsis and septic shock. “Sepsis” is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection.” (3) SIRS was deemed unhelpful, and sequential organ failure assessment (SOFA) score and the quick SOFA score (qSOFA) were recommended for prognostic purposes instead.(3;4) As noted in the recommendations of the SEPSIS-3 task force, though qSOFA score was not necessary for diagnostic purposes, ≥2 qSOFA criteria (respiratory rate ≥22 bpm, altered mental status, or systolic blood pressure (SBP) of ≤ 100 mmHg) were recommended for rapid identification of patients with suspected infection who were likely to have poor outcomes. “Severe sepsis” was eliminated, deemed a redundant term. The definition of “septic shock” was altered to “a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.” (3) The authors note this is clinically identified by “vasopressor requirement to maintain a mean arterial pressure of > 65 mmHg and serum lactate level > 2mmol/L in the absence of hypovolemia” and identifies a subset of patients with a hospital mortality rate of > 40%.(3)

Previous data suggests that patients requiring vasopressors who do not exhibit an elevated lactate level may still demonstrate a substantial risk of mortality, between 10 and 20%.(5;6) Furthermore, early resuscitation guidelines are heavily influenced from cohorts of patients

enrolled in clinical trials that based inclusion criteria on the 1991 definition.(7–10) To date, we are aware of no evidence to suggest patients failing to meet the SEPSIS-3 criteria of septic shock or sepsis fail to derive benefit from early recognition and resuscitation. Though we are aware of no evidence that suggests that patients meeting the SEPSIS-3 criteria of septic shock derive a benefit from early resuscitation, presumably, the treatment recommendations for this group, who would still be classified as “septic shock”, would not change. However, should the SEPSIS-3 definition miss-categorize less critically ill patients, therapies may unintentionally be withheld from patients who might otherwise benefit from such therapies. Our objective was to determine the effect of the new SEPSIS-3 septic shock criteria on patients meeting only the ‘old’ (1991) criteria of septic shock

Material and Methods

Study Design

We performed a secondary analysis of two previously completed clinical trials of patients with severe sepsis and septic shock. Both studies were performed in large, academic emergency departments (EDs) and have previously been described in detail. (8;11) In brief, the first study was a single center, before and after study evaluating the clinical effectiveness of an ED based early, protocolized treatment in severe sepsis and septic shock.(11) The second multi-center study (8) was a randomized clinical trial evaluating the non-inferiority of lactate vs central venous oxygen saturation during early resuscitations in sepsis.(8) Inclusion criteria were: age ≥18 years, suspected infection, ≥2 SIRS criteria, and evidence of hypoperfusion defined as hypotension (SBP < 90 mmHg or MAP < 65 mmHg after 20 mL/kg fluid bolus) or a lactate > 4 mmol/L. Exclusion criteria included pregnancy, operative intervention, absolute contraindications to upper central venous catheters, or an advanced directive. The studies were approved by the presiding institutional review boards. (8;11)

Given the objective of the current analysis and to remain consistent with the 1991 consensus definition of septic shock, patients were excluded from this analysis if they had an elevated serum lactate without SBP < 90 mmHg. As all patients in both parent studies did not have a MAP documented, SBP < 90 mmHg was used for determining hypotension in this analysis. Additionally, patients were excluded from the present analysis if they did not have a documented serum lactate.

Data Analysis

Prospectively collected data from the two studies were combined for analysis. Patients were categorized as meeting SEPSIS-3 criteria of septic shock and those who met only the old criteria for septic shock. Patient demographics and markers of severity of illness were calculated and compared between the groups. The primary outcome was in-hospital mortality. Secondary outcomes were intensive care unit (ICU) and hospital length of stay (LOS).

For further evaluation, patients who met the SEPSIS-3 definition of septic shock and those who met only the old definition were further categorized by qSOFA score of <2 and ≥2. Mortality was then calculated for patients who had a qSOFA score of <2 and ≥2 and was

compared between subgroups. Additionally, a subgroup analysis was performed in the cohort of patients from only the implementation study (11), in order to further evaluate the potential effect of implementation of a structured resuscitation protocol on mortality in both patients meeting the SEPSIS-3 septic shock criteria versus those only meeting the old criteria.

Data were analyzed using descriptive statistics, chi-squared, Fischer exact, and Mann Whitney-U tests, as appropriate. All tests were two sided with p-values < 0.05 considered significant. Data were analyzed using StatsDirect ver 3.0.171 (StatsDirect, Cheshire, England).

Results

Of the 587 patients included in the initial trials, 117 were excluded due lack of a documented lactate or patients with elevated lactate levels without hypotension, leaving 470 in the present analysis. Two hundred of 470 (42.6%) met the SEPSIS-3 criteria for septic shock, leaving 270/470 (57.4%) that met only the old criteria (Figure 1). Patients meeting the SEPSIS-3 criteria were slightly older (60+/− 16.7 versus 57 years +/− 17.9 years; p = 0.04) and more likely to have a history diabetes mellitus. Otherwise, there were no significant differences in patient demographics between groups (Table 1).

The SOFA score of patients meeting the SEPSIS-3 criteria for septic shock was significantly higher [9 (IQR 6,12) versus 5 (IQR 3,8);p < 0.001] compared to those who met only the old criteria. Likewise, a significantly higher number of patients who met the SEPSIS-3 criteria had a qSOFA score of ≥ 2 [127/200 (63.5%, 95% CI 56.7 to 70.2)] compared to patients who met only the old criteria [137/270 (50.7%; 95% CI 44.7 to 56.7, p < 0.008)]. (Tables 1).

Though patients who met the SEPSIS-3 criteria had statistically significant higher rates of positive blood cultures (51%), 33% of patients meeting only the old criteria demonstrated positive blood cultures. (Table 1). The primary outcome of mortality among patients meeting the SEPSIS-3 septic shock criteria was 57/200 (28.5%; 95% CI 22.1 to 34.8). While significantly higher than patients meeting only the old definition (p < 0.001), this group still demonstrated a mortality rate of (39/270; 14.4%, 95% CI 10.2 to 18.7). (Table 2)

When patients meeting the SEPSIS-3 criteria of septic shock and patients meeting only the old definition were evaluated by total SOFA score of <2 or ≥ 2, 194/200 (97%, 95% CI 95 to 99) of patients in the SEPSIS-3 septic shock had a total SOFA score of two or more. All of the deaths in this group had a SOFA score ≥ 2. For patients meeting only the “old” criteria of septic shock, 245/270 (91%, 95% CI 87 to 94) of patients had a total SOFA score of ≥ 2. Of the deaths in this group (39/270), one had a SOFA score < 2. When patients meeting the SEPSIS-3 criteria of septic shock and patients meeting only the old definition were further categorized by qSOFA score of <2 or ≥2, patients who met the SEPSIS-3 criteria and had a qSOFA score < 2 had a similar mortality rate (11/73 (15%, 95% CI 7 to 23) to patients who met only the old definition with a qSOFA score <2 (18/133 (14%, 95% CI 8 to 19) and to those who met only the old definition but had a qSOFA score ≥2 (21/137 (13%, 95% CI 9 to 22). Patients who met the SEPSIS-3 criteria and had a qSOFA ≥2, however, had a

significantly higher mortality rate (46/127 (36%, 95% CI 28 to 44, p-value <0.001). (Table 3).

Among patients meeting the SEPSIS-3 criteria of septic shock, hospital and ICU LOS were 8 days (IQR 5,16) and 3.2 days (IQR 1.8, 7), respectively, versus 8 days (IQR 4.5,12, p = 0.47) and 2.6 days (IQR 1,5, p = 0.006) for those patients meeting the old definition only (Table 2). Significant differences were noted in rates of vasopressors use and mechanical ventilation between the groups; however, patients meeting only the old definition had mechanical ventilation rates of over 20% and nearly half of patients required vasopressors (Table 1).

Discussion

In this analysis, we found a majority of patients meeting the old consensus definition of septic shock did not meet the new, SEPSIS-3 criteria of septic shock. (1–3) While the mortality rate and degree of organ dysfunction were significantly higher for patients who met the new criteria, organ failure, intensive care utilization, and mortality rate of those meeting only the old criteria remained significant. These findings suggest that a large number of patients, who were previously considered “septic shock” may be missed utilizing the new definition of septic shock and consequently their severity of illness and risk of mortality potentially under-appreciated following translation of these guidelines into clinical practice.

The past decade has demonstrated significant improvements in the outcomes of patients with sepsis and septic shock.(12;13) While some of this may be artefactual due to changes in coding practices, significant decreases in mortality continue to be observed even after controlling for such factors.(13;14) As no specific molecular therapies for sepsis have been introduced to account for these trends, it can be assumed that the majority of the improvement can be attributed to improvements in early recognition and processes of care. Findings regarding which particular interventions benefit patients with sepsis conflict,(15) though consistent findings of improvements in patient outcomes following process improvement programs suggest that at least one unifying factor is likely increased recognition.

To further explore this, we evaluated the mortality of patients included in this analysis from the implementation study of early quantitative resuscitation (11). Secondary analysis of only patients enrolled in the pre-post resuscitation implementation study showed that mortality of patients meeting the SEPSIS-3 septic shock definition pre- and post-implementation was not significantly different [2/11 (18.2%; 95% CI −9 to 45) and 26/82 (31.7%; 95% CI), respectively, p = 0.39]. Critically, patients meeting only the old definition of septic shock demonstrated a significant decrease in mortality post-implementation [8/23 (34.8%, 95% CI 14 to 56) versus 10/104 (9.6%, 95% CI 4 to 15), p < 0.006].

Interestingly, we found patients who met only the old definition of septic shock had improved mortality post-implementation, while those meeting both criteria failed to derive benefit from the early resuscitation protocol. Though our numbers were small in this sub-

analysis, and further research is needed, our data raise the concerning possibility that the proposed change in the criteria of septic shock may actually decrease emphasis on the very group of patients most likely to derive benefit from early intervention. Excluding this group of patients from the criteria of septic shock may inadvertently lead to under-recognition and treatment delays among a critically ill cohort of patients.

These data are not to suggest that the 1991 and 2001 consensus definitions are not without their limitations. It is well known that SIRS criteria function poorly when deployed in a clinical environment, demonstrating limitations in both sensitivity but more critically specificity for the diagnosis of sepsis.(16) It is reasonable to assume that a diagnosis, based on these criteria, would likewise lead to an overly sensitive definition of sepsis and septic shock. This may lead to unnecessary treatments of patients unlikely to benefit, and potentially at increased risk of harm from overly aggressive care. Singer and colleagues (3) note they aimed to identify a group at higher risk for organ failure and mortality and propose the use of tools to inform the diagnostic criteria of sepsis. Indeed, our results suggest that the authors were successful in this endeavor, as patients meeting the new criteria had significantly higher rates of organ dysfunction and mortality than those who did not. However, patients who were not classified as “septic shock” using the SEPSIS-3 criteria still had a median SOFA score of 5 (IQR 3, 8), indicating a moderate degree of organ dysfunction in this cohort, emphasizing their point that these new definitions and criteria should not replace clinical judgment. (17) Similarly, the mortality rate for patients not meeting the new criteria but only meeting the old criteria for septic shock remained substantial at 14.4%. While less than those who met the SEPSIS-3 criteria, this mortality rate still dwarfs the nationally reported mortality rates for other primary causes of in-hospital death, including stroke (4.7%), heart disease (3.1%), (18) and is on par or exceeds other critical, life threatening conditions including acute myocardial infarction (~5%), ischemic stroke (12%), and submassive pulmonary embolism (15%). (19–21)

Though the SEPSIS-3 criteria of septic shock identifies a high risk cohort, it excludes a group who might still benefit from early recognition and intervention, and subsequently carries with it the risk of erasing the gains made in the past decade in sepsis recognition and mortality. An analogous situation could be imagined where the criteria of acute ST elevation myocardial infarction (STEMI) was changed to require 4 mm of ST elevation in contiguous leads. This would certainly result in identification of a higher risk cohort who are more likely to require prolonged ICU care to die in hospital, and may derive *even greater* clinical benefit than patients with smaller injury patterns. However, such a scenario would exclude patients enrolled in the very clinical trials that proved the efficacy of early thrombolytic and interventional therapies. Precluding clear evidence that the subgroup of patients with the original criteria *do not* benefit from the tested intervention, such a change in the definition may inadvertently lead to the under treatment of patients likely to derive benefit from the tested intervention. Our data, reanalyzed using cohorts of patients that contributed to the literature base supporting early sepsis resuscitative care, raise concern for an analogous situation among sepsis patients.

It is somewhat informative to investigate why patients meeting the old definition of septic shock did not meet the SEPSIS-3 criteria. The requirement of a lactate > 2 mmol/L in

conjunction with hypotension and vasopressors usage excludes a number of patient who are hypotensive and require vasopressor usage, but maintain a normal serum lactate.(3) In this study, over 40% of patients did not meet the new criteria because of a normal lactate measurement. While previous research has shown mortality is associated with an elevated lactate independent or organ dysfunction or shock and even modest lactate elevations are associated with poor outcomes,(22–24) its inclusion in the new criteria of septic shock creates a potential to downgrade a cohort of patients who are hypotensive and require vasopressors but maintain a normal lactate to the diagnosis of “sepsis”.

Our study has several limitations. As pointed out by both the authors of SEPSIS-3 and the authors of previous guidelines, there is no diagnostic test which can confirm the diagnosis of sepsis, leading to ambiguity regarding the criterion standard for sepsis. This is a secondary analysis of previously completed studies, with the inherent limitations of that study design. As a result, because patients were enrolled in an interventional clinical trial, these data are not generalizable to make assumptions regarding the overall incidence, prevalence, and mortality of an unselected cohort of ED patients meeting only the old versus the SEPSIS-3 criteria. Rather, this study focuses on a cohort of patients enrolled in clinical trials that demonstrated clinical efficacy of various early sepsis resuscitation strategies. Also, one of the two studies included in this analysis was an implementation study of early goal directed therapy. Finally, some patients were lacking laboratory values, which limited their full evaluation. 67 patients were excluded from the present analysis due to a lack of lactate measurement, which could have affected our results. Additionally, we had no baseline SOFA score data on patients included in this analysis, and were unable to calculate a true change from baseline SOFA score or acute organ dysfunction, as recommended by the Sepsis-guidelines. Though the 1991 definition of septic shock included tissue hypoperfusion abnormalities or organ dysfunction, we do not have data regarding acute organ dysfunction. The 2001 publication defines septic shock as we do in this investigation, i.e. “persistent arterial hypotension” only without mention of tissue hypoperfusion or organ dysfunction. (1;2) It is possible that inclusion of this data could have identified additional high risk patients. Although we feel this mirrors the typical general emergency medicine practice where baseline lab values may or may not be available either during the acute resuscitation phase or at all, it is possible that this could have affected our results.

Conclusion

In this analysis, we found that the majority of patients who met the old definition for septic shock did not meet the SEPSIS-3 criteria. Although the SEPSIS-3 criteria identified patients with more organ failure and higher mortality, those patients who did not meet the new criteria still carry a significant mortality risk. These results suggest that while SEPSIS-3 identifies a group of patients at greater risk of worse clinical outcomes, it misses a large proportion of subjects with significant disease burden that may benefit from early resuscitative therapy.

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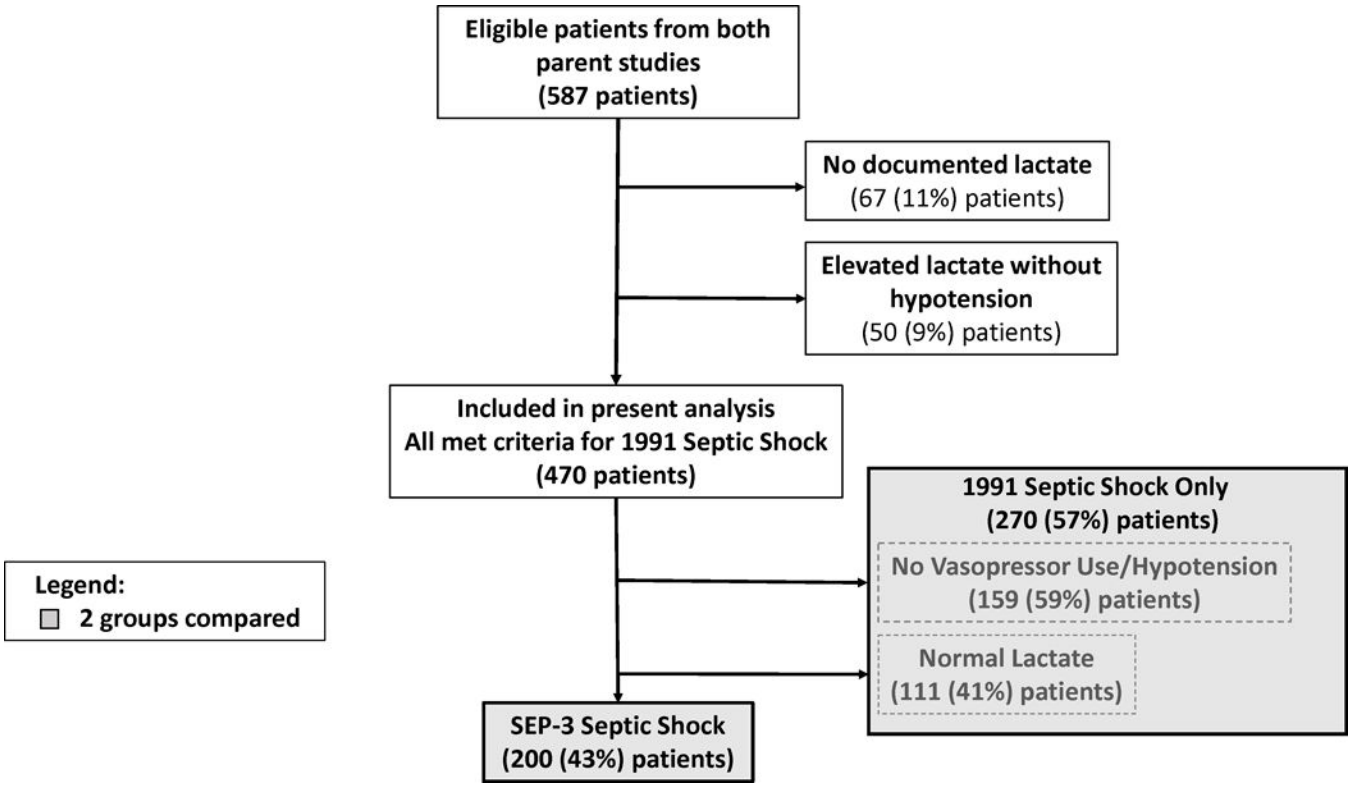

Figure 1.
Flowchart of included patients

Table 1

Patient demographics and clinical characteristics

Variable	*"New" Septic Shock Criteria (SEP-3) (N=200)*	*"Old" Septic Shock Criteria (1991 only) (N=270)*	*p-value*
Age [+]	60 (+/−16.7)	57 (+/−18.0)	0.038
Race (%)			
Caucasian	107 (54)	147 (54)	0.866
Black American	81 (41)	96 (36)	–
Other	12 (6)	27 (10)	–
Comorbidities (%)			
Diabetes mellitus	72 (36)	63 (23)	0.004
Congestive heart failure	30 (15)	39 (14)	0.971
History of Liver Disease/Cirrhosis	9 (5)	7 (3)	0.308
Malignancy	36 (18)	56 (21)	0.533
Human immunodeficiency virus	15 (8)	34 (13)	0.102
Chronic renal disease	32 (16)	41 (15)	0.911
Chronic obstructive pulmonary disease	38 (19)	46 (17)	0.669
Disease Severity [‡]			
Total SOFA score [*]	9 (6,12)	5 (3,8)	<0.001
Respiratory SOFA score	2 (0,3)	1 (0,3)	< 0.001
Coagulation SOFA score	0 (0,1)	0 (0,1)	0.162
Liver SOFA score	0 (0,1)	0 (0,0)	0.001
Cardiovascular SOFA score	3 (3,4)	1 (1,3)	< 0.001
CNS SOFA score	1 (0,3)	0 (0,1)	< 0.001
Renal SOFA score	1 (1,2)	1 (0,2)	0.002
SOFA score ≥ 2 (%)	194 (97)	245 (91)	0.012
SOFA score < 2 (%)	6 (3)	25 (9)	–
≥2 qSOFA criteria (%)	127 (64)	137 (51)	0.037
Lactate (mmol/L) [*]	4 (2.9,6.4)	1.7 (1.1,3.4)	< 0.001
Interventions			
Vasopressors Use (%)	200 (100)	133 (49.2)	< 0.001
Mechanical Ventilation (%)	67 (34)	57 (21)	<0.004
Total ED Fluids (L) [*]	4 (2.8,5)	4.1 (3,6)	0.034
Transfusion of pRBCs (%) [+]	3 (+/− 0.2)	7 (+/−0.3)	0.075
Withdrawal of Care (%)	31 (16)	24 (9)	0.037
Suspected Source of Infection (%)			
Pneumonia	82 (41)	99 (37)	0.391
UTI/pyelonephritis	44 (22)	79 (29)	0.096
Intra-abdominal	42 (21)	36 (13)	0.037

Variable	*"New" Septic Shock Criteria (SEP-3) (N=200)*	*"Old" Septic Shock Criteria (1991 only) (N=270)*	*p-value*
Skin/Soft tissue	23 (12)	33 (12)	0.924
Positive Cultures (%)			
Blood Culture	101 (51)	88 (33)	<0.001
Urine Culture	51 (26)	88 (33)	0.177
Sputum Culture	20 (19)	19 (12)	0.185
Wound Culture	14 (8)	20 (8)	>0.999

Abbreviations: SOFA: Sequential Organ Failure Assessment; qSOFA: Quick Sequential Organ Failure Assessment; CNS: Central Nervous System; ED: Emergency Department; pRBCs: packed red blood cell units; UTI: Urinary tract infection

[+] Mean (SD);

[≠] Disease severity scores calculated at time of enrollment;

[*] Median (IQR)

Table 2

Patient Outcomes

Variable	*"New" Septic Shock Criteria (SEP-3) (N=200)*	*"Old" Septic Shock Criteria (1991 only) (N=270)*	*p-value*
Mortality (%) **	**57 (28.5%) (95% CI 22 to 35)**	**39 (14.4%) (95% CI 10 to 19)**	**<0.001**
Length of Stay (IQR)			
Vasopressors days	**1.3 (0.9,4)** (95% CI 2.3 to 4.2)	**1 (0,2)** (95% CI 0.9 to 1.4)	**<0.001**
Total Hospital days	**8 (5,16)** (95% CI 9.8 to 12.7)	**8 (4.5,12)** (95% CI 9.6 to 12.2)	**0.466**
Total ICU days	**3.2 (1.8,7)** 95% CI 4.9 to 7.1)	**2.5 (1,5)** (95% CI 3.6 to 5.1)	**0.006**

Abbreviations: CI: Confidence Interval; ICU: Intensive Care Unit;

** Primary Outcome

Table 3

qSOFA scores and Mortality

qSOFA Score and Mortality Rate	Septic Shock Criteria		
	"New" Septic Shock Criteria (SEP 3) (n= 200)	***"Old" Septic Shock Criteria (1991 only) (n=270)***	***p-value***
qSOFA < 2	73	133	
Mortality (%)	11 (15)	18 (14)	0.926
qSOFA ≥ 2	127	137	
Mortality (%)	46 (36)	21 (13)	<0.001

Abbreviations: qSOFA: Quick Sequential Organ Failure Assessment