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Non-utility of sepsis scores for identifying infection in surgical intensive care unit patients

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ABSTRACT

Background: The Sequential Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) scores replaced the Systemic Inflammatory Response System (SIRS) criteria for defining sepsis, and are often utilized to identify infection, however remain understudied in surgical populations.
Methods: Daily SOFA, qSOFA, and SIRS scores were prospectively collected in a surgical/trauma intensive care unit (ICU), comparing scores between patients with and without new infection. Multivariable analysis controlled for ICU type and pre-existing infection.
Results: Scores were recorded for 1942 patient-days, including 1385 (71%) with no infection, 439 (23%) with existing/treated infection, and 120 (6.2%) with new infection. Scores were globally elevated, with 98% having SOFA score ≥2, 82% with qSOFA score ≥2, and 92% meeting ≥2 SIRS criteria. Neither univariate nor multivariate analysis revealed a correlation between SOFA, qSOFA, or SIRS score and infection.
Conclusion: No scores correlated with new infection, potentially related to increased existing inflammation in this population.
Summary: The Sequential Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) have replaced the Systemic Inflammatory Response System (SIRS) criteria for sepsis, however are not well investigated in surgical populations or for identifying infections, as they are often used in practice. In this study, neither daily SOFA, qSOFA, nor SIRS criteria correlated with new infection in a population of critically ill surgical patients. Scores were globally elevated in non-infected patients, potentially related to high levels of existing inflammation in this population.

Introduction

Sepsis is prevalent throughout intensive care units (ICU), emergency departments, and acute care wards, with approximately 30 million cases per year worldwide.[1] Despite treatment advances, sepsis remains a major cause of death in surgical and trauma patients, in part due to difficulty defining and accurately diagnosing the condition.[2–4] Efforts to define sepsis began in 1991 with The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus conference, culminating in the initial definition of sepsis as a systemic inflammatory response syndrome (SIRS) combined with known infection and introducing the familiar SIRS criteria.[5] These definitions were then reviewed in 2001 by the International Sepsis Definitions Conference. Though the 2001 conference felt the SIRS-based definitions were "overly sensitive and non-specific" they opted to leave the existing definitions in place, primarily due to lack of evidence for additional metrics.[6]

In 2016, the Sepsis Definitions Task Force met and formulated the Sepsis-3 guidelines, a set of updated definitions for sepsis and septic shock that define sepsis as "a life-threatening organ dysfunction caused by a dysregulated host response to infection."[7] In these consensus guidelines, the Sequential Organ Failure Assessment Score (SOFA) and quickSOFA (qSOFA) scores were provided as clinically applicable assessment criteria for identifying septic patients, particularly those with a higher risk of death and were meant to replace the SIRS criteria.[5,7]

The SOFA score (originally sepsis-related organ failure

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assessment score) was initially developed in 2004 and takes into account the degree of failure of 6 separate organ systems, assigning each a score of zero to 4.[8,9] The score has been primarily used as a measure of organ dysfunction in both septic and non-septic patients. In the new Sepsis-3 definitions, a change in SOFA score of 2 or more points is used to define sepsis.[7] In contrast, the qSOFA score, with points for altered mentation, tachypnea, and hypotension, was developed during the validation of these new sepsis criteria, with variables selected for their combined ability to predict mortality in infected patients.[10]

Prior to their inclusion in the Sepsis-3 definitions, SOFA and qSOFA criteria were evaluated in a large multi-institutional database of combined medical/surgical patients, and subsequently were validated in 4 additional mixed patient databases.[10] These studies concluded the SOFA score was predictive of in-hospital mortality among patients with suspected infection in the ICU, while a higher qSOFA score was a stronger predictor of mortality for patients outside of the ICU setting.[10] Subsequent multi-institutional studies have reported similar results, finding higher SOFA scores predictive of increased mortality and ICU length of stay in hospitalized patients, and higher qSOFA scores predictive of mortality in the emergency department setting.[11,12] All of these studies included only patients with suspected infection—as defined by obtaining cultures or starting antibiotics—and focused on the scores' ability to identify poor outcomes and multisystem organ failure. However, even though the scores were not designed to detect infection, they are often used for this purpose in practice, and the initial derivation papers suggest that qSOFA criteria may have utility for this purpose.[7] Additionally, none of these aforementioned studies have utilized a purely surgical patient population, though these scores are frequently used in these populations.

We therefore aimed to evaluate the SOFA score, qSOFA score, and SIRS criteria in surgical ICU patients, specifically as these measurements pertain to the identification of new infection, with the hypothesis that one of these scores would correlate with the presence of a new ICU-acquired infection in surgical patients.

Methods

This was a prospective study of all patients admitted to the surgical/trauma ICU or postoperative cardiothoracic ICU at the University of Virginia Medical Center over a 90-day period from May to July of 2016. The surgical/trauma ICU admits patients following multisystem trauma, post-surgical patients requiring intensive care, and patients with diseases meriting management by a surgical team. The postoperative cardiothoracic ICU admits patients following cardiac or thoracic surgery, with the majority of patients admitted directly from the operating room. Each patient was treated as a separate data point for each day, in order to fully evaluate the scores' ability to predict infection at a particular moment in time. Data was therefore collected in a deidentified fashion each day rather than trended over time. Hence, individual data points are referred to as patient-days.

For each patient-day, a SOFA score was calculated using values for PaO2/FiO2, platelets, Glasgow Coma Scale, bilirubin, mean arterial pressure, and creatinine.[7,8] Quick SOFA scores were calculated using respiratory rate, altered mentation, and systolic blood pressure.[7,10] SIRS criteria were calculated using temperature, heart rate, respiratory rate, and white blood cell count, using the highest score for each day.[5] Each patient-day was additionally categorized as either a new infection, existing infection undergoing treatment, or no infection. Infection status was determined by expert analysis using CDC definitions for infection, and taking into account available culture and imaging data, when available.[13,14]

Univariate statistical analyses using Wilcoxon rank sum and Chi-Square tests were performed to evaluate differences between values of SOFA, qSOFA, and SIRS criteria across the 3 ICU populations. Univariate analysis also compared patient-days with a new ICU-acquired infection to those without a new infection (patient-days with either no infection or days with an existing infection already being treated with antibiotics). Multivariable regression analyses evaluated the association between elevated SOFA score, qSOFA score ≥ 2, or SIRS criteria ≥ 2 and new infection. Due to anticipated differences in score distribution across ICU populations, as well as expected score elevations in patients with existing/treated infection, each logistic regression controlled for trauma or cardiothoracic ICU status as well as ongoing existing infection. Statistical significance was defined with the alpha value of <0.05. All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC).

Table 1
Distribution of scores across ICU's.

	Trauma ICU (n = 532)		Surgical ICU (n = 653)		Cardiothoracic ICU (n = 757)		p-value
No Infection	382	71.8%	417	63.9%	586	77.4%	<0.001
Existing/Treated Infection	118	22.2%	187	28.6%	147	19.4%	<0.001
New Infection	37	7.0%	54	8.3%	29	3.8%	0.002
SOFA score	6	[4–8]	6	[4–9]	7	[4–10]	<0.001
qSOFA score	2	[2–3]	2	[1–3]	2	[2–3]	<0.001
SIRS criteria	3	[2–3]	2	[2–3]	3	[2–3]	<0.001
qSOFA Scores							<0.001
0	4	0.8%	23	3.5%	6	0.8%	
1	63	11.8%	153	23.4%	110	14.5%	
2	291	54.7%	282	43.2%	360	47.6%	
3	174	32.7%	195	29.9%	281	37.1%	
SIRS Criteria							<0.001
0	0	0.0%	4	0.6%	0	0.0%	
1	29	5.4%	74	11.3%	49	6.5%	
2	178	33.5%	269	41.2%	262	34.6%	
3	228	42.9%	249	38.1%	345	45.6%	
4	97	18.2%	57	8.7%	101	13.3%	

Outcomes reported as n, % for categorical variables and median, interquartile range for continuous variables.

Results

From May to July 2016, data from 1942 total patient-days were collected. Of these, there were 532 trauma ICU, 653 non-trauma surgical ICU, and 757 postoperative cardiothoracic ICU patient-days. A total of 1385 of these patient-days (71%) had no infection, while 437 (23%) had an existing/treated infection, and 120 (6.2%) included the initiation of therapy for a new episode of ICU-acquired infection (Table 1). Of the patient-days with new infection, 15 (0.77%) also had existing/treated infection; these were counted with the new infection group for univariate analyses. The majority of all scores were elevated, with 98% of patients having a SOFA score ≥2, 82% having a qSOFA score ≥2, and 92% meeting ≥2 SIRS criteria.

Between the three ICUs studied, 532 (27%) patient-days were in the trauma ICU, 653 (34%) were in the surgical ICU, and 757 (39%) were in the cardiothoracic ICU. The 3 ICUs demonstrated differing incidences of new infection (7.0% vs. 8.3% vs. 3.8%, $p = 0.002$), with the surgical ICU having the highest number of patient-days with new infection (Table 1). The 3 ICUs also demonstrated differing distributions of SOFA, qSOFA, and SIRS scores, with trauma and cardiothoracic ICU patients generally demonstrating higher scores, while surgical ICU patients had lower, though still elevated scores (Table 1).

When comparing patient-days with new infection to those without infection or with existing/treated infection, there was no difference in median SOFA score (7 vs. 6, $p = 0.22$), qSOFA score (2 vs. 2, $p = 0.14$), or SIRS criteria met (3 vs. 3, $p = 0.47$). There was also no difference in the overall distribution of qSOFA scores or SIRS criteria in patient-days with and without new infection ($p = 0.52$, $p = 0.94$.) The distributions of SOFA, qSOFA, and SIRS scores between patient-days with and without infection are shown in Table 2.

Multivariable regression models evaluating the independent association of elevated sepsis scores with infection are shown in Table 3. When controlling for trauma status, cardiothoracic status, and presence of existing infection, elevation of SOFA score was not associated with new-onset infection [OR 1.04 (0.99–1.09), $p = 0.10$, C-statistic 0.65]. Elevation in qSOFA score ≥2 was also not associated with new infection [OR 1.44 (0.85–2.43), $p = 0.17$, C-statistic 0.64]. Likewise, presence of ≥2 SIRS criteria was not associated with new infection [OR 1.30 (0.62–2.73), $p = 0.49$, C-statistic 0.63].

Table 2
SOFA, qSOFA, and SIRS scores by Infection Status.

	No Infection (n = 1385)		Existing/ Treated Infection (n = 437)[a]		New Infection (n = 120)		p-value[b]
SOFA score	6	[4–9]	7	[4–10]	7	[4.5–10]	0.219
qSOFA score	2	[2–3]	2	[2–3]	2	[2–3]	0.142
SIRS criteria	3	[2–3]	2	[2–3]	3	[2–3]	0.468
qSOFA Scores							0.517
0	25	1.8%	6	1.4%	2	1.7%	
1	224	16.2%	86	19.7%	16	13.3%	
2	651	47.0%	227	52.0%	55	45.8%	
3	485	35.0%	1118	27.0%	47	39.2%	
SIRS Criteria							0.942
0	3	0.2%	1	0.2%	0	0.0%	
1	101	7.3%	43	9.8%	8	6.7%	
2	491	35.5%	176	40.3%	42	35.0%	
3	598	43.2%	171	39.1%	53	44.2%	
4	192	13.9%	46	10.5%	17	14.2%	

Outcomes reported as n, % for categorical variables and median, interquartile range for continuous variables.

[a] Not including those who also had new infection.

[b] P-value compares new infection to the combined group of patients with no infection and patients with existing/treated infection.

Discussion

This analysis identified a high percentage of surgical ICU patients with elevated SOFA, qSOFA, and SIRS scores, indicating significant systemic inflammation and organ dysfunction. However, contrary to our hypothesis, no correlation between new infection and increased SOFA, qSOFA, or SIRS scores was identified—even when controlling for existing infection and patient population. This suggests that in surgical patients these criteria are unable to differentiate sterile from infectious inflammation. Our investigation did differ slightly from prior studies of sepsis scores, as we investigated a possible correlation between new infection and elevated scores rather than studying outcomes in a group of patients with suspected or identified infection. In practice, however, practitioners use sepsis definitions to identify infection, and the newest sepsis guidelines suggest that qSOFA criteria may have utility as a marker for infection.[7]

Patients in our study had grossly higher SOFA, qSOFA, and SIRS scores than patients in prior studies of these metrics. In the initial studies for the new Sepsis-3 guidelines, Seymour et al. investigated these scores in a large database of patients from multiple University of Pittsburgh Medical Center (UPMC) hospitals, then verified the scores in 4 additional multi-hospital databases.[10] Patients included from these databases comprised either a medical/surgical or entirely surgical population. While the UPMC cohort's ICU population had 91% of patients with SOFA score ≥2, our population had 98% of patient-days with SOFA score ≥2, and while 84% of their patients had SIRS of ≥2, our population had 92% with SIRS ≥ 2.[10] In a subsequent follow-up study, Raith et al. evaluated SOFA, qSOFA, and SIRS criteria in mixed ICU patients at 182 hospitals in New Zealand and Australia.[11] Compared to their mixed study population, our population again had grossly elevated scores. Their population had 90.1% of patients with SOFA score ≥2 (compared to our 98% of patient-days), 54.4% with qSOFA score ≥2 (compared to our 81%), and 86.7% with ≥2 SIRS criteria (compared to our 92%).

There have been limited prior studies of the SOFA score in strictly surgical patients, all of which have primarily focused on its ability to discern multiple organ failure. Two studies in cardiac surgery populations have found the score to be a reliable predictor of worsened outcomes in this population, though they noted shortcomings, including increased values for the effect of sedation on mental status and the broad use of inotropes postoperatively.[15,16] An investigation of the use of SOFA scores in trauma patients found them to be more sensitive, though less specific, for mortality than other scores, and ultimately recommended the Denver Postinjury Multiple Organ Failure Score rather than SOFA score in this population.[17] While these studies differed methodologically from the current analysis, they do highlight the concern that surgical patients demonstrate different illness patterns related to significant sterile systemic inflammation with the implication that the SOFA score—and other scores designed for mixed populations— may be inferior to scores developed specifically for surgical patients.[15–17]

The differences in score distributions among surgical patients may reflect the inherent differences between medical and surgical/trauma populations. Postoperative and trauma patients have multiple non-infectious reasons to have systemic inflammation and organ failure leading to elevated individual components of these scores. For example, many patients have severe pain contributing to tachypnea and tachycardia while the post-anesthesia state and opioid pain medications contribute to confusion. Postoperative cardiac surgery patients, in particular, routinely arrive to the ICU sedated and intubated, with many requiring inotrope support.[16] Importantly, postoperative patients exhibit a known physiologic inflammatory response that leads to elevation of these scores, even

Table 3
Multivariable sepsis score models.

3a. SOFA Score Model		95% CI OR	Wald Chi-square	p-value
Variable	OR			
SOFA Score	1.042	0.992–1.094	2.705	0.100
Treated Infection	0.410	.0235–.715	9.89	0.002
Trauma ICU	0.806	0.520–1.249	0.9336	0.334
Cardiothoracic ICU	0.393	0.246–0.630	15.064	<0.001
*C-statistic 0.647				
3b. qSOFA Score Model				
Variable	OR	95% CI OR	Wald Chi-square	p-value
qSOFA score ≥2	1.439	0.852–2.429	1.8522	0.174
Treated Infection	0.418	0.240–0.729	9.4738	0.002
Trauma ICU	0.755	0.486–1.174	1.5556	0.212
Cardiothoracic ICU	0.396	0.247–0.633	14.936	<0.001
*C-statistic 0.640				
3c. SIRS Score Model				
Variable	OR	95% CI OR	Wald Chi-square	p-value
SIRS ≥2	1.299	0.617–2.733	0.4738	0.491
Treated Infection	0.421	0.242–0.733	9.3392	0.002
Trauma ICU	0.780	0.508–1.209	1.2343	0.267
Cardiothoracic ICU	0.408	0.256–0.651	14.1363	<0.001
*C-statistic 0.633				

when not related to infection or a dysregulated host response. Because of these differing baseline characteristics, SOFA and qSOFA scores may not discriminate septic patients as successfully as in a strictly medical population.

While the Sepsis-3 guidelines direct the focus of sepsis scores towards identifying patients at risk for poor outcomes rather than infection itself, there remains a need to identify infection and sepsis early and accurately in surgical patients. A recent review identified several scores used to identify sepsis, including the sepsis screening score (SSS; a score based on magnitude of physiologic derangement of the SIRS criteria), the St. Johns sepsis agent (SJSA; developed by Cerner and designed to be interfaced with an electronic medical record), and the modified early warning score (MEWS).[18–22] However, many of these scores both incorporate and were tested against the SIRS criteria for sepsis and have not been tested against the revised Sepsis-3 definitions.[19] Furthermore, the majority of these screening tools do not have a means of differentiating between non-infectious (sterile) inflammation, common in surgical patients, and inflammation caused by infections, though the SSS does weight the degree of physiologic derangement.[18] Potential alternatives to sepsis scoring systems include molecular tests, such as tests for rapid pathogen detection and gene expression biomarkers.[23,24] Tests designed to identify markers of aberrant immune activation could potentially distinguish infection-related inflammation from existing surgical inflammation, proving especially useful in these populations.[23] Conversely, tests designed for rapid pathogen detection could quickly identify patients with culture proven infection early in their treatment course.[25] Though the Sepsis-3 criteria do not correlate well with new infection, they may be of value as a comparison benchmark for continued studies of these existing scores and detection methods.

Our study includes several important limitations. While treating each patient each day as a separate data point allowed for a greater sample size and for analysis of the daily predictive value of the score, this may have introduced selection bias and necessitated the use of a daily SOFA score rather than serial SOFA scores. Because long term follow-up data were not collected, this study does not provide a picture of the long term predictive abilities of these scores—such as for length of stay or mortality or length of stay—although these outcomes were not the object of this investigation. Finally, this was a single institution study and thus results may not be generalizable to other institutions. However, the inclusion of 3 types of surgical ICU patients gives confidence that results will apply to a number of surgical ICUs, and we have no reason to believe our surgical ICU population behaves differently than those at other academic medical centers.

Conclusion

This analysis found no correlation between SOFA, qSOFA, or SIRS criteria and the diagnosis of a new infection in a population of critically-ill surgical patients. These results emphasize the importance of differentiating between criteria meant to *define* sepsis and criteria meant to *identify* sepsis and infection inpatients. While these scoring systems have been validated as markers of mortality, they may not be reliable tools for clinical decision making in this population. Additionally, the majority of patients in this population of exclusively surgical patients had elevated SOFA, qSOFA, and SIRS scores from significant underlying (usually sterile) inflammation alone, regardless of infection. Since infection identification based solely on measures of systemic inflammation or organ dysfunction remains inadequate, new research emphasizing rapid pathogen detection, molecular techniques, and degree of physiologic derangement may improve sepsis survival in critically ill surgical patients.

Conflicts of interest

All authors report no relevant conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.11.044.

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