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The Use of qSOFA for Sepsis in the Emergency Department

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Published Date: October 17, 2017

ABSTRACT

Sepsis is a severe condition that is commonly encountered in the Emergency Department. The disease process encompasses a broad range of symptomatology and is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Recent studies suggest that the quick-Sepsis Related Organ Dysfunction Assessment (**qSOFA**) score is superior to Systemic Inflammatory Response Syndrome criteria for diagnosing sepsis. However, there is still debate about whether the score is applicable to the Emergency Department since several studies have demonstrated conflicting results. In this review, we present a comprehensive summary of studies conducted using Emergency Department patient cohorts to compare the efficacy of both scoring systems for sepsis screening and mortality prediction. The review in this chapter highlights and contrasts the evidence for and against the use of the quick-Sepsis Related Organ Dysfunction Assessment score in the Emergency Department.

Keywords: Sepsis; qSOFA; SIRS; Emergency Department

INTRODUCTION

Worldwide, sepsis impacts millions of patients annually and carries an overall mortality rate of 20-50% [1]. It is estimated that approximately 850,000 ED (Emergency Department) visits in the United States are attributed to the diagnosis of sepsis [2]. In addition to being a common medical condition, there are high costs associated with the disease. The United States Healthcare Cost and Utilization Project reported that hospitalizations related to sepsis cost approximately twenty four billion dollars annually [3].The large healthcare costs and alarming mortality rates attributed to sepsis accentuates its importance as a growing public health concern.

SIRS

With the advent of the term Systemic Inflammatory Response Syndrome (**SIRS**), originally published in 1992 by the American College of Chest Physicians and Society of Critical Care Medicine, greater emphasis was placed on screening and identifying ED patients for sepsis [4]. Sepsis was defined as screening positive for SIRS criteria plus clinician suspecting or confirming infection. SIRS criteria is composed of the following: Temperature > 38˚C or < 36 ˚C, Heart rate > 90 beats per minute, Respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mm Hg, White blood cell count > 12,000/mm^3 or < 4,000/mm^3 or > 10% immature bands. A patient with two or more SIRS criteria screened positive for SIRS. Once meeting criteria for sepsis (SIRS positive plus any suspected infection), the next step would be assessment for hypotension and hypoperfusion by obtaining a lactate and initiating appropriate treatment which includes antibiotics and intravenous fluids resuscitation.

Utilization of SIRS criteria in the ED to screen for septic patients became standard practice. However after years of using SIRS criteria in the ED to screen for sepsis, new publications have challenged the reliability of SIRS in the ED setting, as neither sensitive nor specific. [5-7]. Specifically, recent studies have found that SIRS lacked sensitivity and specificity for identifying an acute infectious process in the critically ill, resulting in unnecessary administration of antibiotics and overutilization of hospital resources. In a retrospective cohort study performed by Liao and colleagues, the exclusive use of SIRS criteria in the ED missed 44% of patients with infection [6]. Additionally, authors Long and Koyfram reported a long list of potential sepsis mimics, for example adrenal insufficiency, heat stroke, pulmonary embolism and thyroid disease, that may be either overlooked or misdiagnosed as sepsis based on abnormal vital signs and laboratory criteria for SIRS [8]. Given that annually approximately sixteen million patients present to United States EDs meeting SIRS criteria, it is extremely important to clarify whether or not SIRS criteria is actually a reliable diagnostic tool for sepsis [5]. The perceived lack of dependability associated with the SIRS based definition of sepsis has inspired researchers and thought leaders to create better sepsis screening tools and rethink the definition of sepsis.

Sepsis-3

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) Task Force introduced a new definition for sepsis, which did not utilize the SIRS criteria. The new sepsis definition is more general and describes sepsis as a condition in which there is, "Life-threatening organ dysfunction caused by a dysregulated host response to infection."In addition to introducing new criteria for defining sepsis, the consensus also recommended the use of the quick-Sepsis Related Organ Dysfunction Assessment (**qSOFA**) score as a tool to readily identify patients with sepsis who are more likely to require critical care or have a higher in-hospital mortality [8-9]. The new recommendations were deduced from an extensive review and meta-analysis of observational studies published from 1992 to 2015 and electronic health record data sets using the Delphi process [11].

The advantage of the qSOFA scoring system over SIRS criteria is its simplicity. qSOFA consists of three components: Altered mental status, Systolic blood pressure ≤ 100 mm Hg and Respiratory rate ≥ 22/min. Each positive component is assigned one point. The qSOFA score ranges from 0 to a maximum score of 3. In those with suspected sepsis, having a qSOFA score ≥ 2 has been shown to have a mortality risk of approximately 10% [8-9]. Patients with a qSOFA score of ≥ 2 have 3 to 14-fold increase in mortality versus a qSOFA score of ≤ 2 [9-10]. The score is easy to utilize as it is based on only three immediately obtainable physical exam findings and does not require any laboratory values [9-10]. Since qSOFA can be calculated rapidly at the bedside, the Taskforce advocated for the score to be applied in high volume settings such as the ED.

The literature regarding the application of qSOFA in the ED setting has to date been controversial as they have yielded conflicting results [12-15]. Prior to the introduction of qSOFA, multiple sepsis scoring systems were evaluated as a way to predict mortality in septic ED patients; including the Mortality in Emergency Department Sepsis (**MEDS**) score, Predisposition, Infection, Response and Organ failure (**PIRO**) score, Mortality in Severe Sepsis in the ED (**MISSED**) score and the SOFA score [16-17]. The qSOFA score is an abbreviated variant of the SOFA score which was initially shown to successfully predict mortality in septic ED and ICU patients [16]. The Sepsis-3 Taskforce advocates for the use of qSOFA as an expeditious clinical tool that ED physicians can use as an adjunct to their clinical judgment to determine which patients are highest risk for organ dysfunction and death [9-10]. They also suggest that the score be used judiciously to, "Initiate or escalate therapy as appropriate, and to consider referral to critical care or increase the frequency of monitoring."

Table 1: Efficacy of qSOFA in the ED.

Outcomes of using qSOFA in the ED	Reference
In-hospital Mortality AUROC=0.81 (95% CI: 0.80-0.82)	Singer et al. [9]
In-hospital Mortality Sensitivity 90.9%, Specificity 45.8% AUROC=0.68 (95% CI: 0.58-0.78)	Haydar et al. [18]
90-day Mortality Sensitivity 80.8%, Specificity 27.4%	Peake et al. [19]
28-day Mortality Sensitivity 39%,Specificity 77% AUROC=0.58 (95% CI: 0.55-0.62)	Hwang et al. [20]
Screening Sensitivity 32%, Specificity 98% *7-day Mortality* Sensitivity 16%, Specificity 96% *30-day Mortality* Sensitivity 13%, Specificity 96%	Askim et al. [21]
Organ Dysfunction Sensitivity 29.9%, Specificity 96.1% AUROC=0.73 (95% CI: 0.72-0.74)	Williams et al. [22]
In-hospital Mortality Sensitivity 89.7% , Specificity 27.4% AUROC=0.66 (95% CI: 0.57-0.76)	April et al. [24]
28-day Mortality AUROC 0.625 (95% CI: 0.579-0.671)	Innocenti et al. [25]
In-hospital Mortality AUC=0.823 (95% CI: 0.707-0.939) *28-day Mortality* AUC=0.848 (95% CI: 0.733-0.963) *Six Month Mortality* AUC=0.62 (95% CI: 0.50-0.74)	Quinten et al. [26]
28-day Mortality AUC=0.666 (95% CI: 0.609-0.723)	Wang et al. [27]
In-hospital Mortality Sensitivity 52%, Specificity 86%	Henning et al. [28]
48-hour Mortality Sensitivity 54%, Specificity 67% AUC=0.65 (95% CI: 0.62–0.66)	Churpek et al. [29]
30-day Mortality Sensitivity 28%, Specificity 94% AUC=0.69 (95% CI: 0.61-0.76)	González Del Castillo et al. [30]
In-hospital Mortality Sensitivity 70%, Specificity 79% AUC=0.80 (95% CI: 0.74-0.85)	Freund et al. [31]
In-hospital mortality Sensitivity 90.8%, specificity 16.1% AUC=0.615 (95% CI 0.560–0.671)	Umemura et al. [32]
In-hospital Mortality Sensitivity 90%, Specificity 42% AUC= 0.74 (95% CI: 0.66-0.81)	Finkelsztein et al. [33]

Organ Failure AUC= 0.814 (95% CI: 0.72-0.91) *In-hospital Mortality* Sensitivity 75%, Specificity 82% AUC= 0.733 (95% CI: 0.64-0.83)	Park et al. [34]
In-hospital Mortality Sensitivity 70%, Specificity 79% AUC=0.80 (95% CI: 0.75-0.85)	Oppert [35]
In-hospital Mortality AUC=0.75 (95% CI: 0.71-0.78)	Singer et al. [36]

METHODS

The aim of this chapter is to review the current sepsis literature regarding the use of qSOFA in the ED patient population and to examine the advantages and disadvantages of this new scoring classification. We conducted a comprehensive review of published research studies that evaluated the sensitivity, specificity and predictive value of qSOFA as a screening tool for sepsis and for predicting mortality outcomes, specifically in ED patients with either known or suspected infection.

RESULTS

A number of studies have compared qSOFA and SIRS as Emergency Department Screening tools [12-13]. In a study performed by Haydar and colleagues looking at mortality for ED patients, qSOFA was 90 % sensitive for mortality versus 95.5% for SIRS criteria [18]. Furthermore in the same study, the median time from ED arrival to SIRS identification was 12 minutes, versus 29minutes when qSOFA was applied leading the authors to conclude that patients with sepsis were identified earlier in the ED using SIRS criteria compared to qSOFA. Such findings suggest that the use of qSOFA in the ED might actually delay identification of septic patients. One explanation of these unexpected findings was that ED practitioners, including triage nurses, lacked familiarity and comfort with qSOFA compared to SIRS which has been utilized in EDs for many years.

Similarly, another study performed by the Australian Resuscitation in Sepsis Evaluation (**ARISE**) investigators evaluated qSOFA as a diagnostic tool for sepsis utilizing retrospective data from their landmark Early Goal Directed Therapy (**EGDT**) trial published in 2014 [19]. The ARISE trial made a considerable contribution to the understanding of sepsis management and EGDT in the ED. The study's inclusion criteria for the trial were based upon the traditional SIRS criteria for defining sepsis. Interestingly, only 63.5% of the patients in the ARISE trial,which consisted of 1,591 subjects, would have screened positive for sepsis by the qSOFA definition of sepsis based on the current Sepsis-3 recommendations. The authors show that using qSOFA to screen for sepsis might have changed the outcome of their landmark trial and its use could significantly impact the results of future trials as well. This reexamination of the ARISE trial using qSOFA as inclusion criteria instead of SIRS markers substantially challenged the utility of the qSOFA scoring system as a research tool for defining and studying sepsis.

Additional research further challenged qSOFA as a reliable screening tool for sepsis in the ED, emphasizing the low sensitivity of the score for detecting sepsis. In a single center retrospective cohort study performed by Hwang and colleagues, the reported sensitivity and specificity of qSOFA was 39% and 77%, respectively for determining a diagnosis of sepsis. Multiple other authors have reported poor sensitivity and specificity of qSOFA as well. Askim et al conducted a single center observational cohort and found that having a qSOFA score ≥ 2 produced a 32% sensitivity and 98% specificity for identifying septic ED patients [20-21].The poor screening value of qSOFA due to low sensitivity has also been reported by Williams and colleagues who concluded that, "Given the relative insensitivity of a qSOFA ≥ 2, it appears inferior to a SIRS score ≥ 2 as a screening test in the ED" [22-23].The same study found that there was no difference between SIRS criteria and qSOFA for predicting sepsis induced organ dysfunction. These studies obviate the findings of Sepsis-3 and question whether qSOFA should replace SIRS as an accurate screening method in the ED.

Although the use of qSOFA in the ED is novel, the score appears to be inadequate for predicting poor outcomes compared to other decision-making rules. For example, April and colleagues determined that the use of SIRS criteria and qSOFA equally predicted in-hospital mortality for ED patients [24]. When compared to other ED scoring systems used to predict mortality, qSOFA outperformed the PIRO score but was determined to be equal or inferior to the MEDS score [25-27]. These results suggest that qSOFA is not currently superior to SIRS criteria or the MEDS score however due to the novelty of qSOFA, further research is still warranted to compare its accuracy to that of PIRO, MEDS and other ED specific scoring systems.

In addition to issues with screening, one of the major limitations of the qSOFA score has been its inconsistent predictive value for identifying which ED patients have the highest risk for in-hospital mortality compared to the use of SIRS criteria. Another study conducted by Henning and colleagues was a secondary analysis of a prospective observational multicenter cohort and found that using qSOFA conferred 52% sensitivity for predicting in-hospital mortality compared to a 83% sensitivity for SIRS criteria [28]. Furthermore, SIRS criteria outperformed qSOFA in a study conducted by Churpek and colleagues which found that ≥ 2 SIRS criteria had a sensitivity of 91% for in-hospital mortality compared with 54% for a qSOFA score ≥ 2 [29]. It should be noted that while this study found SIRS criteria to be very sensitive, the specificity of SIRS was 13%, much lower than the 67% specificity of qSOFA [29]. These findings challenge the recommendations of Sepsis-3 and have ignited a controversial debate regarding the advantage or disadvantage of using qSOFA as a substitute for SIRS criteria.

The controversy regarding qSOFA in the ED was further compounded by a study conducted in Spain by González Del Castillo and colleagues who found that qSOFA was not a reliable predictor of mortality in patients 75 years and older presenting to the ED with sepsis [30]. The multicenter study included 1,071 older patients and found that in this patient population a qSOFA score ≥ 2

had an alarmingly low sensitivity of 28% for predicting 30-day mortality, however the specificity was markedly higher at 94%. The unreliable application of qSOFA in patients 75 years and older may be deemed problematic since older adults make up a significant portion of patients diagnosed with sepsis in the ED [2]. Further studies are required to determine whether qSOFA can be readily applied to older adults with suspected infection.

Controversy exists because there is conflicting data that supports the use qSOFA over SIRS criteria in the ED. For example, in a multicenter international prospective cohort study, Freund and colleagues validated the results presented by the Sepsis-3 consensus by demonstrating that the qSOFA score significantly predicted in-hospital mortality in sepsis patients with a positive predictive value of 24, more than twice of the predictive value of SIRS criteria which was only 11% [31]. Similarly, Umemura and colleagues found that qSOFA was superior to SIRS criteria for detecting sepsis in ED patients in a multicenter study conducted in Japan [32]. In 2017, Finkelsztein et al presented additional evidence for the use of qSOFA over SIRS criteria for predicting mortality in sepsis reporting that qSOFA exhibited a significantly higher predictive value for in-hospital mortality when compared to SIRS criteria [33]. Likewise, Park and colleagues validated the results of Sepsis-3 and confirmed that qSOFA was superior to SIRS criteria for predicting disease severity in ED patients with suspected infection. [34].In a multicenter international prospective cohort study conducted by Oppert in Germany, qSOFA had greater accuracy than SIRS criteria for detecting sepsis in ED patients [35]. For patients presenting to the ED with a suspected infection, Singer and colleagues found that qSOFA was significantly associated with in-hospital mortality [36]. Overall, these results clearly support the 2016 recommendations of the Sepsis-3 Taskforce and add credence to the usefulness of applying qSOFA as a tool to stratify ED patients who are at high risk for death.

The evidence reviewed above is compelling, yet contradictory. The results published are divided on the issue of whether qSOFA is superior, equivocal or inferior to SIRS criteria specifically in ED patients. The conflicting results may perhaps be attributed to population sample since the studies included in this review were conducted using various demographics in multiple countries with differing sample size and inclusion criteria. The articles presented in favor of and against qSOFA as a replacement for SIRS criteria consisted of both single and multicenter studies and spanned over multiple disciples such as Critical Care and Infectious Disease in addition to Emergency Medicine, creating a diverse representation of patients but does not explain differences in study outcomes. The methodologies of the studies were either prospective or retrospective introducing limitations of possible confounding or bias that might also explain why outcomes varied within the literature. Either way, the research generated by the authors does not reach a general consensus about the clinical recourse for SIRS versus qSOFA and paramount questions still remain as to whether qSOFA can successfully replace SIRS criteria in the ED.

CONCLUSION

For over two decades, SIRS criteria plus suspected infection was the mainstay for diagnosing patients with sepsis. Due to problems with sensitivity and specificity, it was determined that using SIRS criteria to define sepsis was insufficient and a better definition was needed. Thus, Sepsis-3 and qSOFA were introduced to solve the problems generated by the application of SIRS criteria in the ED setting.

Unfortunately, qSOFA has been criticized for having marginal sensitivity and inconsistent predictive value, similar to the criticisms cited against its predecessor, SIRS and it has yet to be determined whether the use of qSOFA in the ED will improve patient outcomes, expedite the administration of antibiotics or the initiation of resuscitation. Some argue that using qSOFA to screen patients for sepsis can be harmful and potentially cause a delay of care since it lacks sufficient sensitivity and therefore will miss many sepsis cases, especially cases with occult hypo perfusion. The Sepsis-3 Taskforce does address concerns of uncertainty related to qSOFA and state that, "The Taskforce strongly encourages prospective validation in multiple United States and non-United States health care settings to confirm its robustness and potential for incorporation into future iterations of the definitions" [9].

The variability of qSOFA for screening and determining the risk of mortality for ED patients presenting with sepsis continues to be debated despite the recommendations of the Sepsis-3 Taskforce. The evidence presented in this chapter suggests that qSOFA was not designed as a screening tool and therefore should not be used solely to make a diagnosis of sepsis in the ED. There is however convincing evidence that qSOFA is superior to SIRS criteria and has good prognostic value when used in conjunction with clinical judgment to care for patients who are already deemed to have a source of infection. All of the literature reviewed provides compelling arguments for both the advantages and disadvantages of using qSOFA but a final conclusion remains elusive. The articles reviewed here are a combination of retrospective and prospective cohort studies that either support or debunk the reliability of qSOFA as an adequate ED scoring system. Additional research such as a randomized controlled trial should be performed to validate the results of Sepsis-3 and could help to determine if qSOFA should be permanently implemented into the ED sepsis screening process.

In conclusion, sepsis is a progressive and dynamic process that ranges from a mild adaptive response to florid organ failure and death due to infection. To date, there is no perfect test or gold standard to establish the diagnosis. As stated by the Sepsis-3 Taskforce, "Sepsis is not a specific illness but rather a syndrome encompassing a still uncertain pathophysiology" [9]. Although the qSOFA score is promising, further research is still needed to address the utility of qSOFA in the ED setting and to decide if it is a feasible replacement of SIRS criteria.

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