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A comparison of screening tools for the early identification of sepsis among EMS patients transported to an urban safety net hospital

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Abstract

A comparison of screening tools for the early identification of sepsis among EMS patients transported to an urban safety net hospital

By Charity Dunn

BACKGROUND: Sepsis is a leading cause of death in the United States and is the most common cause of death in ICU patients. The majority of patients hospitalized for sepsis are admitted through emergency departments (EDs), and nearly half of those are transported to the hospital by emergency medical services (EMS). The purpose of this study is to determine if the Prehospital Severe Sepsis (PRESS) score and quick Sepsis-related Organ Failure Assessment (qSOFA) are useful for identifying septic patients in emergency settings.

STUDY POPULATION: The sample consisted of two cohorts of adult patients transported by EMS to Grady Memorial Hospital in Atlanta, GA between January 2011 and December 2012. Patients were excluded for cardiac arrest, trauma, toxic ingestion, pregnancy, or psychiatric emergency and were stratified into two groups at either high or low risk of sepsis. Patients whose EMS vitals included heart rate greater than 90 beats/min, respiratory rate greater than 20 breaths/min, and systolic blood pressure less than 110 mm Hg were considered high-risk; all else were low-risk.

METHODS AND RESULTS: Thirty-one (27%) of high-risk patients and 12 (2.2%) of low-risk patients had sepsis (p-value <.0001), determined by inpatient diagnosis within 48 hours of hospital arrival. For both cohorts, patient vitals changed between the field and ED, though Glasgow Coma Scale scores did not change (p-values .42 and .81). We retrospectively screened patients with a modified version of PRESS in the field and qSOFA in the ED. Among high-risk patients, PRESS was 90% sensitive and 22% specific; in low-risk patients it was 83% sensitive and 17% specific. qSOFA was 41% sensitive and 88% specific in high-risk patients, and 17% sensitive and 98% specific in low-risk patients. Agreement between screening tools was low, but best for high-risk patients with sepsis (Kappa=0.15, p-value <.0001). Among patients misclassified by either tool, mean heart rate was the most common difference between those with and without sepsis.

CONCLUSION: Further studies are needed to validate PRESS and qSOFA for emergency sepsis screening. PRESS is limited by low specificity, and qSOFA may be unreliable in patients transported by EMS due to low sensitivity.

A comparison of screening tools for the early identification of sepsis among EMS patients transported to an urban safety net hospital

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BACKGROUND/LITERATURE REVIEW

Introduction

Sepsis is a severe syndromic illness associated with high mortality and significant cognitive and functional disability among survivors(1). A complication of infection, it is characterized by organ dysfunction which results from a dysregulated immune response(2). It is the ultimate cause of death from infection and has been an important cause of mortality throughout human history(3). The underlying pathophysiology is not completely understood, and the roles of pro-and anti-inflammatory responses are debated. Many factors influence onset and clinical presentation, making cases of sepsis highly variable and difficult to define.

For decades, physicians have attempted to understand the natural history of sepsis and to devise clinical guidelines for diagnosis and treatment. Despite this, the pathophysiology of sepsis has remained somewhat elusive, and no gold standard diagnosis has been developed. Consequently, multiple case definitions have been published in recent decades to match contemporary clinical theory. More research is needed to further current understanding of the sepsis disease process and to inform guidelines for diagnosis.

It is well known that timely clinical intervention is a key predictor of sepsis-related mortality (4-6). Interventions to facilitate earlier case identification may expedite treatment and so save lives. Prime targets for such intervention are the prehospital and emergency settings, where a large percentage of septic patients are first encountered(7, 8). Two promising protocols for such early sepsis screening have recently been published: the Prehospital Severe Sepsis (PRESS) score and the quick Sepsis-related Organ Failure

Assessment (qSOFA)(2, 9). The use of one or both of these tools may increase case identification, decrease door-to-treatment times, and decrease overall mortality from sepsis.

Pathophysiology

All cases of sepsis begin with infection. The body's innate immune response to infection response involves the localized aggregation of cells which attack pathogens and the release of chemicals which mediate the activity of native and recruited cells. This is called the inflammatory response. In most circumstances, the inflammatory response remains localized and results in eradication of the infecting organism. In some cases, however, the inflammatory response is muted, exaggerated, or imbalanced, and so may become dysregulated. Following may be a systemic disruption of homeostasis extending beyond the immune system to affect cardiovascular, metabolic, neuronal, endocrine, and other functions (2). When such disruption results in clinical organ dysfunction, the condition is termed sepsis. Further progression to multiple organ failure is the cause of death in fatal sepsis cases (10). Despite decades of research, however, the mechanisms by which the host response becomes so dysregulated and leads to sepsis and mortality remain incompletely understood.

Clinically, infection is a "phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms (11)." Stimulated by the presence of microbes, a localized inflammatory response is initiated through innate immunity. Phagocytic cells are recruited, complement and coagulation cascades are initiated, and endothelial cells are activated to cause vasodilation and increase vascular permeability (12). These produce the four classic signs associated with inflammation: warmth (calor), redness (rubor), swelling (tumor), and pain (dolor). Mediating the response are a large group of chemical messengers called cytokines(13).

This initial inflammatory response is primarily a mechanism of containment. Early vasodilation and blood vessel permeability allow the infection site to be flooded with leukocytes such as macrophages and polymorphonucleocytes (PMNs). Leukocytes then act to phagocytize or otherwise neutralize pathogens before they may invade neighboring tissues. Surrounding endothelial cells become activated and express various adhesion factors, which may have affinity for pathogens and leukocytes. The coagulation cascade, induced by activated endothelial cells, increases blood clotting around the infection site as a barrier mechanism. Early theories of pathology perpetuated the notion that sepsis ultimately resulted from the body's failure to contain an infection. This contributed to the frequent synonymous use of *septicemia* and *bacteremia* (or "blood poisoning"), which result from pathogens or their toxins reaching the bloodstream(3).

It is now recognized that sepsis is more than a widespread infection. Organisms are recovered from only about half of all septic patients, and a substantial proportion of patients die despite the underlying infection having been cleared (10, 14). Rather, sepsis refers to a state of metabolic and organ dysfunction *induced* by infection and which stems from the body's inability to properly regulate its immune response. Dysregulation includes excessive immune response as well as induced immunosuppression. In such cases, the body loses its ability to right itself and becomes destructive to its own tissues.

The inflammatory response may become dysregulated for many reasons, most of which remain incompletely understood. Commonly, sepsis may arise when pathogens, their toxins, or inflammatory mediators enter circulation and incite a systemic-wide response. On this larger scale, the changes in blood flow normally associated with localized immune response overwhelm the body's cardiovascular and metabolic functions, leading to organ

damage. For many years, sepsis was thus considered an over-inflammatory response to infection.

Early studies sought to identify a primary mediator of inflammation in hopes of finding a target for therapeutic interventions. Among the most popular candidates were tumor necrosis factor α (TNF-α) and Gram-negative endotoxin(15). TNF-α is a cellular mediator released by macrophages found commonly elevated in patients with sepsis (15). Endotoxins are lipopolysaccharide compounds produced by Gram-negative organisms and which are particularly immunogenic toxins(10). No single major mediator has been identified however, and treatments aimed solely at diminishing the pro-inflammatory response have been ineffective in clinical trials(16, 17). It must also be noted that the body's inflammatory response is not exclusively a response to infection. It may also be triggered in response to burns, trauma, or chemical stimulus (toxins or poisons) (12), suggesting that some driver of disease unique to sepsis must also be present.

While the role of the pro-inflammatory response has long been recognized as important to sepsis pathophysiology, the importance of the anti-inflammatory response has only recently gained significant attention. Rather than simply failing to adequately quell the initial inflammation, anti-inflammatory mediators may contribute to morbidity independently. Sepsis may arise when an appropriate immune response is never mounted or becomes impaired. In fact, studies have shown induced immunosuppression in large proportions of patients who died from sepsis(18, 19). In light of several decades' inability to find an effective mediator of sepsis among pro-inflammatory agents, this evidence has been used to suggest that immunosuppression rather than hyper-inflammation, may be the true driver of sepsis mortality (18).

Several studies of septic patients have found extensive depletion of cells of the immune system, including CD4 and CD8 cells, B cells, follicular dendritic cells, and interdigitating dendritic cells (18). Though the underlying regulatory pathway is not yet known, this depletion is attributed to massive acute apoptosis, suggesting that the cellular die-off is induced by sepsis. This leaves patients with sepsis at heightened risk of succumbing to the original (primary) infection and also of acquiring a second, perhaps more virulent healthcare associated infection (18).

Many host factors also influence the pathogenesis sepsis, and it is associated with a number of comorbidities(14, 20). Persons with increased susceptibility to infection are naturally at increased risk of developing sepsis(14). Such persons may be immunosuppressed by diseases such as HIV/AIDS and lupus, or by induction via clinical therapies such as chronic steroids or chemotherapy. Persons of older or very young age are also at increased risk due to immunosenescence or immunologic immaturity(21). Those with altered metabolic function at baseline may also be more susceptible to metabolic upset. Several studies have identified altered gene expression and synthesis of inflammatory mediators and other proteins in patients with sepsis(22). The severity of sepsis and its outcomes has also been shown to be related to baseline organ function. Those with chronic organ disease are more likely to develop sepsis and experience severe functional impairment afterward (1).

Infection characteristics, including the site and implicated pathogen, are also highly influential. Infections of the respiratory, cardiovascular, gastrointestinal, or central nervous system are more likely to develop organ dysfunction related to sepsis (23). Patients with these infections are also more likely to ultimately develop septic shock. Pathogen-specific factors may also influence what response the host mounts to infection and how effective that response is. Gram-negative lipopolysaccharide (LPS), or endotoxin, is known to

stimulate highly increased levels of inflammatory cytokines which may contribute to excessive inflammatory response(10). Gram-positive organisms have shown decreased susceptibility to innate immunity and so may be more likely to spread, resulting in a systemic response that causes sepsis.

The acute symptoms of sepsis are better understood. The organ dysfunction hallmark of sepsis is caused primarily by inadequate oxygen supply (hypoxia). In patients with sepsis and especially septic shock, circulating cytokines may induce coagulation cascades throughout the body, resulting in widespread clotting of small blood vessels. This condition is known as disseminated intravascular coagulation (DIC)(24). In the small vessels, particularly capillaries, clotting obstructs and decreases blood flow to tissues (hypoperfusion), depriving them of oxygen and nutrients and resulting in cell damage or death. Some early signs of hypoperfusion include lactic acidosis, low urine output (oliguria), and acutely altered mental status (25).

Compounding this condition are several other changes induced by proinflammatory mediators. The metabolic requirement for oxygen is increased in the setting of inflammation (12). Inflammation also stimulates vascular permeability, leading to loss of blood pressure and widespread edema of the interstitial spaces, a condition commonly known as "third spacing." Together, these effects only serve to further decrease end-organ delivery of oxygen and widen the oxygen deficit, which may actually accelerate the onset of organ damage.

Compensatory mechanisms employed by the body manifest as many of the most commonly identified symptoms of sepsis. Tachycardia and tachypnea, increased heart rate and respiratory rate respectively, are among the earliest signs of systemic inflammation. Tachycardia represents the body's attempt to compensate for volume loss (hypovolemia) and increase blood pressure to re-establish proper circulation. Tachypnea is a mechanism to

increase blood-oxygen saturation, thus compensating for low volume delivery. At the cellular level, respiration switches from aerobic to anaerobic, often resulting in a buildup of lactic acid. There is much debate over whether lactate measures may serve as useful indicator of sepsis(6, 26).

Death from sepsis ultimately results from persistent organ failure, usually of multiple organs (27). Acute respiratory distress syndrome (ARDS) is a common acute cause of death, especially in patients with pneumonia(14). Sustained hypotension also frequently causes deaths associated with cardiovascular dysfunction, such as cardiogenic shock and cardiac arrest (14, 27, 28). Differences have been noted in the causes of death among those who die early versus later of sepsis (28).

Relatively few clinical therapies exist for sepsis. In the absence of effective immunomodulation treatments, and the lack of an evidence-based target for such therapy, treatment for sepsis ultimately consists of organ function support and antimicrobial therapy. Current Surviving Sepsis Campaign guidelines state that septic patients with hypotension or who have high serum lactate levels (≥4 mmol/L) should receive intravenous fluid resuscitation no more than three hours after clinical identification(6). Patients with unresponsive hypotension should be treated with vasopressors within 6 hours.

Antibiotics remain the most important clinical intervention available, and multiple studies have associated early antibiotic administration with decreased risk of mortality(4, 29). For every hour's delay in the administration of antibiotics, the risk of mortality has been shown to increase by 8% (4). Current guidelines in the Surviving Sepsis Bundle state that broad spectrum antibiotics should be administered as soon as possible and no later than three hours after clinical identification of a patient with sepsis (6).

This time-sensitivity justifies the prescription of broad-spectrum antibiotics for persons with suspected sepsis but who yet have no positive cultures. Combination therapies with multiple antibiotics may also be used(30). Septic patients may decline rapidly, and so cannot wait for culture samples to be collected, grown, and tested. Such samples may provide no further insight into the disease or even confirm the presence of an infection. Even among patients from whom samples are drawn, isolates are generally recovered from fewer than half of sampled patients(10, 14).

Epidemiology and Public Health Impact

The impact of sepsis in the United States is widely acknowledged. Though the true incidence remains unknown, rates of sepsis are indisputably high and increasing. Estimates of the annual incidence of sepsis range from 300 to 1,031 per 100,000, and most studies agree that this rate is increasing by about 13% per year (31-35). There are various hypothesized drivers of increasing incidence, including aging populations and an increased clinical capacity for life-support, which sustains severely ill patients long enough for sepsis to develop(36).

Sepsis is also associated with high mortality rates. The Centers for Disease Control and Prevention named "septicemia" the 11th leading cause of death in 2011 and bacterial sepsis the 7th leading cause of death of newborns in 2015 (37, 38). In 2014, sepsis was cited as the most frequent cause of death among patients in non-coronary intensive care units (39). Overall estimates of the mortality rate for sepsis range from 14.7% to 29.9% (35). Among patients with septic shock, the mortality rate is estimated to be nearly 50% (39).

Unsurprisingly, sepsis has great economic and social impact as well. Among reasons for inpatient hospitalizations in 2013, septicemia was the most expensive at $23.7 billion in the US alone(40). Global estimates of the cost per of sepsis are variable but reach up to

$50,000 (3). This is due primarily to the intensive care required by septic patients and the often protracted duration of their hospital stays. The median length of stay associated with sepsis hospitalization was recently estimated to be 9 days (20). Following hospitalization, survivors of sepsis often suffer permanent functional disability and may require specialized care, another source of expense. Twenty-five percent of patients discharged from a sepsis-associated hospitalization were discharged to skilled nursing facilities (SNFs) compared to 18% having been admitted from SNFs (20).

Adult persons with sepsis tend to be of much older age (65 years or older) and are most commonly male. Whites and non-whites make up approximately equal proportions of cases, but incidence rates are higher among blacks and Hispanics (41). Mortality is highest among black men (32, 41). Among children and neonates, incidence is highest among infants (5.6 per 1,000) and significantly higher in males (42). In-hospital mortality in this group exceeds 10% (42).

Socioeconomic and geographic associations are less studied, however persons of lower socioeconomic status have higher rates of bacteremic pneumonia, a leading cause of sepsis (43). Higher hospital and case volume have been associated with increased likelihood of sepsis survival, suggesting that more densely populated areas may have higher incidence of sepsis but also better treatment capacity (44, 45). Studies have also suggested some seasonal variation in rates of sepsis, presumably related to concurrent fluctuations in rates of respiratory illness (46).

Many risk factors for sepsis have been identified. Ninety-seven percent of adult septic patients have comorbidities or chronic conditions which increase susceptibility to infections (20). Patients may also be at higher risk due to pre-existing metabolic illnesses or impaired organ function. Common conditions are diabetes, cancer, and chronic pulmonary,

cardiovascular, or renal disease (20, 34). Low birth weight is associated with increased risk of sepsis in children under one year (42). Linked to the presence of comorbidities, most patients have some sort of healthcare exposure within 30 days prior to the septic episode, though the majority of cases are community onset (20).

Respiratory infections, particularly pneumonia, are the overall most common cause of sepsis, though bloodstream infections (BSIs), skin and soft tissue infections (SSTIs), abdominal, and genitourinary infections contribute significantly (34). Genitourinary infections are more common in women (23). Infections may be of viral, fungal, or bacterial etiology. Bacterial infection is the most common cause, though the incidences of fungal and viral sepsis are increasing, particularly among infants and children (47). *Escherichia coli*, *Klebsiella* species, and *Enterococcus* species are the most commonly associated pathogens among adults, young children, and infants, respectively (20). In recent decades, the proportion of cases attributed to Gram-positive organisms has increased significantly, though whether these infections have surpassed the rate of Gram-negative infections remains unclear (10, 32, 48).

Despite much research, the true extent of sepsis-related morbidity and mortality remains unknown. In the past decade, several studies conducted to determine the incidence of sepsis produced widely variable estimates. In 2007, Dombrovskiy et al estimated the annual incidence of sepsis to be as low as 300 per 100,000 population, while Wang estimated published estimates as high as 1,031 per 100,000 (31, 33). Mortalities ranged from about 20% to 50% (32-34). Such discrepancies were primarily due to differences in methodology and case definition as there are no established clinical criteria for sepsis diagnosis (35).

Clinicians and researchers have long struggled to develop a consistent case definition for sepsis. The nature of sepsis is syndromic and non-specific, thus there is no gold standard

diagnostic test by which to ascertain true septic status. Patients may present with any of a number of symptoms, including fever, tachycardia, and hypotension among others, and presentation may vary significantly from case to case(14). Additionally, laboratory confirmation of infection is only obtained in about half of cases (10), presenting difficulty in benchmarking the underlying rate of infections.

Furthermore, the use of unstandardized, redundant jargon is a frequent source of additional confusion. Terms such as "septicemia" and "septic syndrome", in addition to more colloquial phrases such as "blood poisoning", may be misinterpreted or considered vague when recorded in medical records and research publications (2, 3, 11). To remedy these issues, three attempts to clarify sepsis terminology and standardize definitions have been published in the past 25 years.

Definitions

In 1991, the first consensus committee on sepsis was convened by the American College of Chest Physicians and the Society of Critical Care Medicine. The goals of this committee were two-fold: to develop standardized definitions for sepsis and its related conditions, and to provide guidelines for treatment. The committee published criteria for the systemic inflammatory response syndrome (SIRS), and defined sepsis as acute SIRS in the presence of infection(11). It also published definitions for severe sepsis and septic shock, proposing a continuum for the progression of sepsis-related illness.

Four criteria were proposed to assess a patient for SIRS. These were 1) body temperature greater than 38°C or less than 36°C, 2) pulse rate greater than 90 beats per minute, 3) tachypnea, defined as a respiratory rate greater than 20 breaths per minute, or hyperventilation, indicated by a $PaCO_2$ less than 32 mm Hg, and 4) acute changes in white blood cell levels, including counts greater than 12,000 cu mm or below 4,000 cu mm or a

proportion of immature neutrophils greater than 10% (11). SIRS was characterized by acute onset of two or more of these criteria.

When SIRS was present with confirmed infection and no other cause could be identified, the condition was termed sepsis (11). The committee also defined severe sepsis as sepsis associated with acute organ dysfunction, hypoperfusion abnormality, or hypotension, characterized as systolic blood pressure less than 90 mm Hg or a drop of at least 40 mm Hg. When sepsis-induced hypotension persisted despite fluid resuscitation, the condition was called septic shock. These definitions reflected the contemporary understanding of sepsis pathology as existing along a continuum of severity. The committee advised that research be conducted to derive a scoring system for sepsis severity, hypothesizing strong correlations between the three stages and morbidity and mortality.

The European Society of Intensive Care Medicine (ESICM) published the Sepsis-related Organ Failure Assessment (SOFA) score in 1996(49). The SOFA rubric consisted of simple benchmarks of function scored from normal (0) to most abnormal (4) for six organs or organ systems: the liver, kidneys, central nervous system, coagulation system, respiratory system, and cardiovascular system. Respectively, the organ-specific criteria were: serum bilirubin, serum creatinine or urine output, Glasgow Coma Scale (GCS) score, platelet count, and the PaO_2/FiO_2 ratio. Uniquely, cardiovascular criteria were based upon the level of adrenergic infusions needed to maintain sufficient blood pressure. Benchmarks for scoring were based upon dosages of dopamine, epinephrine, and norepinephrine, though an explicit blood pressure that must be maintained with such infusions was not specified.

SOFA was to be calculated daily using the worst measurement in each category for each day. It was the first tool to provide a standardized, objective method for evaluating changes in organ function over time rather than dichotomizing organ failure as merely

present or absent (49). Though the goal of the SOFA was not to predict mortality, initial analyses correlated higher SOFA scores with greater risk of mortality. However, SOFA is calculated exclusively from metabolic results and does not directly account for any underlying comorbidities or risk factors despite the known influence of such risk factors upon the septic disease process.

The 1992 consensus definitions were reviewed at the 2001 International Sepsis Definitions Conference. It was widely felt the 1992 definitions were unclear and that the criteria for SIRS were too broad and non-specific (50). Despite this, only expansions to diagnostic criteria were made. The committee published a list of suggested thresholds for clinical assessment of patients, again emphasizing that any attributed abnormalities should be of acute onset and reasonably attributable to no other cause. To diagnose organ failure, the committee recommended the use of a severity index, but did not specify SOFA or any other as preferred. This approach, as acknowledged by the authors, prioritized facilitating the diagnosis of patients over establishing criteria suitable for research.

Much like the previous definitions committee, conference members acknowledged that the standing definitions were limited and felt the need for an independent staging system for severity. Published in the same paper was the outline for a system of classifying patients called Predisposition, Infection, Response, and Organ Dysfunction (PIRO) (50). Such a system would stratify patients based on the presence of innate risk factors such as diabetes or depressed CD4 count (P), the site, severity, and causal organism of the underlying infection (I), the robustness of the host's immune response (R), and the severity and extent of organ dysfunction and failure (O). It was felt that such a strategy might better recognize and account for the heterogeneity of septic patients and serve to better guide therapies and predict outcomes. Importantly, it might also help to distinguish between

elements of the disease process caused directly by infection and those caused by the host's response. It was hoped that PIRO might ultimately serve as a model for generating hypotheses for research into pathophysiology and treatment (50).

In 2009, Rubolotta et al published the first formalized version of a PIRO scoring system which included independent risk stratifications within the four categories of PIRO (51). Age, pathogen Gram stain result, and the number of failing organ systems were the main drivers of the score. Patient response (R) was stratified into only two levels based solely upon heart and respiratory rate. Despite achieving near-perfect correlation with mortality in both validation cohorts (0.974 and 0.998), this PIRO scoring system was never widely adopted (51). Subsequently developed models have gained no more traction.

The most recent definitions for sepsis were published in 2016. These represented significant changes from previous definitions as well as a shift away from the continuum-based approach to sepsis diagnosis, prognosis, and care. Sepsis and septic shock were redefined, and the committee suggested the term severe sepsis no longer be used. Additionally, the committee derived a new bedside screening tool, the quick sequential organ failure assessment (qSOFA) score, to aid in diagnosis. Unlike previous definitions, some priority was given to developing criteria which could be easily validated with epidemiologic study, and which would facilitate further clinical study.

As currently defined by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, sepsis is "life-threatening organ dysfunction caused by a dysregulated host response to infection (2)." This definition (Sepsis-3) excludes severe but uncomplicated infection and broadens the qualifying host response to include both pro- and anti-inflammatory cascades. In recent years, the importance of the anti-inflammatory response to sepsis pathophysiology has been recognized. SIRS criteria reflect almost

exclusively pro-inflammatory responses, which may be caused by many illnesses besides sepsis. The SIRS-based definition thus suffered from limited specificity. Additionally, as many as 1 in 8 patients with severe sepsis do not meet SIRS criteria, highlighting the lack of sensitivity (52). For these reasons, it was recommended that the use of SIRS criteria to diagnosis sepsis be discontinued.

To qualify organ dysfunction, the Sepsis-3 committee reviewed multiple suggested criteria and scoring systems. It was determined that an acute change of 2 or more SOFA score points should qualify as organ dysfunction. This change should occur in the presence of infection and be unexplained by other causes. Qualifying changes should be relative to patients' individual baselines to account for the presence of chronic or other conditions which may independently alter normal organ function.

The Sepsis-3 definition of septic shock is "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality (2)." The suggested clinical criteria for septic shock thus included 1) that vasopressors be required to sustain a mean arterial pressure of at least 65 mm Hg despite fluid resuscitation, and 2) serum lactate levels exceed 2 mmol/L (2).As opposed to earlier definitions, this definition does not rely solely upon cardiovascular abnormality. Rather, it incorporates the multi-system state of failure and the damage which may be inflicted by it. It also represents a paradigm shift in the understanding of the relationship between sepsis and septic shock, relationship which is neither strictly linear nor inevitable.

Development of Screening Tools

It is known that the timing of clinical intervention is a key predictor of sepsis outcomes. For every hour's delay in antibiotic administration, the risk of mortality from septic shock increases by 8% (4). Accordingly, the 2013 Surviving Sepsis Bundle suggests

that empiric antibiotics and fluid resuscitation be administered within 3 hours of clinical presentation (6).

Recognition of the time-sensitive nature of sepsis has motivated the development of numerous screening tools. Such screening tools have led to faster treatment times and decreased rates of mortality when used to identify patients with other time-sensitive conditions, such as myocardial infarction and stroke. Among EMS encounters, the incidence of severe sepsis surpasses both of these at 3.3 per 100 encounters, and over 40% of ED patients ultimately hospitalized for sepsis arrive by EMS transport (7, 8). However, most studies have found EMS providers identify less than a third of septic patients (53).

Recognizing this opportunity for improvement, a number of studies have developed screening tools for use by EMS or other personnel in prehospital settings. Screening criteria generally include abnormal vital signs, with temperature, heart rate, and respiratory rate incorporated most often (9, 53-55). Such vital sign cut-offs are often the same as or only slightly modified from SIRS criteria. Measures of blood pressure and metabolic measures such as blood glucose and oxygen saturation have also been employed. Regardless of the criteria used, all reviewed screening tools were able to achieve increased sensitivity over provider impression alone (53). Specificities, when reported, were more variable.

In 2015, Polito et al published the Prehospital Severe Sepsis (PRESS) score. The tool was designed to aid EMS providers in the identification of adult patients likely to have severe sepsis using non-laboratory measurements that could be easily quantified in the field. Designed for pragmatism, it is not intended to be used for every patient encountered by EMS personnel. Patients should not be screened in the presence of pregnancy, trauma, psychiatric emergency, toxic ingestion, or cardiac arrest. These conditions were identified by

the study authors as unlikely to be related to sepsis or likely to be addressed using existing coordinated care pathways (9).

The EMS criteria for PRESS screening include heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute, and systolic blood pressure less than 110 mm Hg. The presence of one additional risk factor indicates a positive screen. These risk factors are transport from a nursing home, oxygen saturation less than 90%, age 40 or greater, systolic blood pressure less than 90 mm Hg, EMS tactile temperature assessment of "hot" or measured temperature greater than 38° C, and a recorded chief concern of "sick person" by emergency medical dispatch (EMD) personnel.

The PRESS tool achieved 86% sensitivity and 47% specificity for severe sepsis or septic shock; however, the authors acknowledged several limitations. Because the derivation cohort was restricted to patients bearing the abnormal vital signs listed above, it is not known how well the PRESS tool may perform in the general EMS patient population. The tool may also suffer from limited external validity, as it was derived from the records of patients brought exclusively to Grady Memorial Hospital, a large metropolitan teaching hospital in downtown Atlanta, GA. Finally, the authors used inpatient clinician diagnosis as their gold standard for determining the true sepsis status of patients, which may be subject to misclassification bias. Patients with atypical sepsis phenotypes (i.e., without fever) are frequently missed by providers, and the SIRS criteria used for diagnosis may arise from many etiologies other than sepsis(2, 56).

The Sepsis-3 committee published their own screening tool alongside the updated 2016 definitions. The quick sequential organ failure assessment (qSOFA) score is a simple, 3-criteria screen for persons at risk of severe morbidity or mortality related to infection (2). The derivation outcomes were mortality or ICU stay of 3 or more days in patients with

suspected infection. Thus, like PRESS, qSOFA is not intended to be used for all patients. The tool is recommended for use among patients with suspected infection outside the ICU to prompt providers to investigate for possible sepsis and escalate treatment if necessary. Of note, inside the ICU, standard SOFA criteria were found to be more predictive of sepsis-related outcomes.

The three criteria for qSOFA are respiratory rate of 22 breaths per minute or greater, systolic blood pressure of 100 mm Hg or less, and altered mental status, defined as a Glasgow Coma Scale (GCS) score of 14 or less. The presence of any two or more criteria indicates a positive screen. The authors reported good discrimination among patients with both community and hospital-acquired infections (AUROC 0.71 and 75, respectively) in a test dataset including in- and out-of-hospital encounters (57).

The criteria for qSOFA were derived and validated from a primary cohort of 148,907 patient encounters with suspected infection. Suspicion of infection was based upon the combination of culture sampling and antibiotic administration within 24 or 72 hours, depending on which occurred first. Forty-four percent of patients were located in the emergency room at the time suspicion could be verified. Pre-hospital encounters were not included in the primary cohort. The authors acknowledged these limitations, and suggested further study to validate the use of qSOFA in other settings and among less restricted patient populations.

Of note, the Glasgow Coma Scale was originally developed to evaluate patients with traumatic brain injury and may not always be calculated(58). Accordingly, no GCS data was available in a cohort of VA patients used to validate qSOFA, though discrimination remained robust in this group (AUROC 0.78) (57). The availability and use of all screening criteria remains ideal. Sepsis has been associated with acute brain dysfunction and altered

mentation, and the Glasgow Coma Scale remains an established, reliable, and easily calculable score for evaluating altered mental status (11, 58-60).

Forward Directions

The burden and severity of sepsis in the United States warrants further research into methods to improve clinical outcomes. The underlying pathophysiology of sepsis remains incompletely understood, which hampers the ability of clinicians to accurately diagnosis and effectively treat afflicted patients. Still, contemporary efforts to intervene where possible have much merit. The prehospital setting provides a window of opportunity to effect great improvements in sepsis diagnosis and care. As with other critical conditions, the use of a reliable screening tool in such settings is likely to improve provider recognition and facilitate earlier administration of treatment.

Both PRESS and qSOFA are promising screening tools which have yet to be validated. It is unknown whether either or both may be effective in all settings, or if one is superior to the other among select patient groups. Analysis to compare predictive values and assess agreement between the two may inform recommendations for use in the field.

A comparison of screening tools for the early identification of sepsis among EMS patients transported to an urban safety net hospital

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Abstract

BACKGROUND: Sepsis is a leading cause of death in the United States and is the most common cause of death in ICU patients. The majority of patients hospitalized for sepsis are admitted through emergency departments (EDs), and nearly half of those are transported to the hospital by emergency medical services (EMS). The purpose of this study is to determine if the Prehospital Severe Sepsis (PRESS) score and quick Sepsis-related Organ Failure Assessment (qSOFA) are useful for identifying septic patients in emergency settings.

STUDY POPULATION: The sample consisted of two cohorts of adult patients transported by EMS to Grady Memorial Hospital in Atlanta, GA between January 2011 and December 2012. Patients were excluded for cardiac arrest, trauma, toxic ingestion, pregnancy, or psychiatric emergency and were stratified into two groups at either high or low risk of sepsis. Patients whose EMS vitals included heart rate greater than 90 beats/min, respiratory rate greater than 20 breaths/min, and systolic blood pressure less than 110 mm Hg were considered high-risk; all else were low-risk.

METHODS AND RESULTS: Thirty-one (27%) of high-risk patients and 12 (2.2%) of low-risk patients had sepsis (p-value <.0001), determined by inpatient diagnosis within 48 hours of hospital arrival. For both cohorts, patient vitals changed between the field and ED, though Glasgow Coma Scale scores did not change (p-values .42 and .81). We retrospectively screened patients with a modified version of PRESS in the field and qSOFA in the ED. Among high-risk patients, PRESS was 90% sensitive and 22% specific; in low-risk patients it was 83% sensitive and 17% specific. qSOFA was 41% sensitive and 88% specific in high-risk patients, and 17% sensitive and 98% specific in low-risk patients. Agreement between screening tools was low, but best for high-risk patients with sepsis (Kappa=0.15, p-value <.0001). Among patients misclassified by either tool, mean heart rate was the most common difference between those with and without sepsis.

CONCLUSION: Further studies are needed to validate PRESS and qSOFA for emergency sepsis screening. PRESS is limited by low specificity, and qSOFA may be unreliable in patients transported by EMS due to low sensitivity.

Keywords: sepsis, emergency medical services (EMS), emergency department (ED), Prehospital Severe Sepsis (PRESS) score, quick Sepsis-related Organ Failure Assessment (qSOFA)

1. Introduction

Sepsis is a non-specific syndrome characterized by a dysfunctional immune response to infection that leads to organ failure (2). Incidence in the United States is estimated to be between 300 and 1,031 per 100,000, and mortality estimates reach as high as 30% or 60% for those with septic shock (31-34). It is the leading cause of death among intensive care unit (ICU) patients (48). It is also time-sensitive (4, 5). Current Surviving Sepsis Campaign guidelines recommend intravenous fluids and broad spectrum antibiotics be administered no more than three hours after clinical identification of sepsis, and each hour's delay in antibiotic treatment is associated with an 8% increase in risk of mortality (4, 6). However, failure to identify septic patients remains a key barrier to implementing these guidelines.

EMS and ED settings are ideal targets for interventions to increase sepsis identification. The majority of patients hospitalized for sepsis are admitted through emergency departments (EDs), and up to half of these cases are transported to the hospital by emergency medical services (EMS) (7, 8). Studies have suggested that EMS personnel identify less than a third and ED providers about two-thirds of septic patients, but that identification increases when a structured screening protocol is implemented (53, 56). Screening tools for other emergency conditions such as stroke and myocardial infarction have also been implemented successfully. The use of similar screening tools could potentially have great impact upon EMS and ED patients with sepsis.

Two screening tools have recently been published to facilitate simple, early identification of patients who are or are at risk of becoming septic. In 2015, Polito et al. developed the Prehospital Severe Sepsis (PRESS) score to identify patients with severe sepsis or septic shock in the EMS setting. In patients with abnormal vital signs, the tool achieved 86% sensitivity and 43% specificity (9). In 2016, the Society of Critical Care Medicine and European Society of Intensive Care Medicine redefined sepsis and septic shock, and published a screening tool to identify patients at risk of infection-related in-hospital mortality or illness requiring ICU care. The quick Sepsis-related Organ Failure Assessment (qSOFA) was 81% sensitive in non-ICU patients with suspected infection (2).

The burden and severity of sepsis in the United States warrants further research to improve diagnosis and care, and emergency settings provide ideal windows of opportunity to achieve earlier recognition. Both PRESS and qSOFA are promising tools which may be suitable for such uses. It is unknown whether either or both may be effective in all settings, or if one is superior to the other among select patient groups. The purpose of this study is to evaluate the performance of PRESS and qSOFA as screening tools for sepsis in two populations, and to identify the potential strengths and weaknesses of each. It was not our intent to develop a new screening tool or to derive new cut points for PRESS or qSOFA.

2. Methods

2.1 Study Design and Population

This study is a secondary analysis of an existing dataset from a retrospective cohort study conducted with approval of the Emory Emergency Medicine Departmental Review Committee, the Emory Institutional Review Board, and the Grady Research Oversight Committee. The study population consisted of adult patients (age ≥ 18 years) transported by

Grady Emergency Medical services (GEMS) to Grady Memorial Hospital between January 1, 2011 and December 31, 2012 meeting the eligibility criteria detailed below. Grady Memorial Hospital is a 900-bed public teaching hospital located in downtown Atlanta, Georgia. GEMS serves the 88% of Atlanta's population in Fulton County and transports approximately 30,000 patients per year. The annual incidence of sepsis among these patients is unknown.

The patient sample was identified using exclusion and inclusion criteria assessed in the EMS setting by electronic medical record review. Patients were excluded if the electronic EMS record indicated any of the following: traumatic injury, cardiac arrest, pregnancy, psychiatric problem, or toxic ingestion. These conditions were excluded due to the existence of mature treatment pathways or because they are uncommonly associated with sepsis. Patients were enrolled in two groups, one at high risk of sepsis and one at low risk of sepsis, hereafter referred to as Phase I and Phase II. Risk stratification was based upon modified systemic inflammatory response syndrome (SIRS) criteria and systolic blood pressure. SIRS criteria have been used to define and diagnose sepsis for over 20 years, and hypotension is a common symptom of sepsis (11, 50).

Patients more likely to be septic were enrolled during Phase I. Inclusion criteria were 1) auscultated or palpated systolic blood pressure (SBP) less than 110 mm Hg, 2) heart rate (HR) greater than 90 beats per minute, and 3) respiratory rate greater than 20 breaths per minute. Of 66,439 EMS encounters screened, 983 met inclusion criteria. Of these, 372 had exclusion criteria. An additional 56 were excluded because the qualifying EMS encounter could not be linked to an inpatient encounter. Overall, 555 patients were enrolled during Phase I. The PRESS tool was derived from a random sample of 441 of these patients and validated in the remaining 114. Refer to Polito et al for a complete description of PRESS

development (9). In the current study, only the validation group of patients from Phase I were included for analysis (n=114).

Patients less likely to be septic were enrolled in Phase II. Data abstractors returned to each Phase I EMS encounter in the EMS database and enrolled the next sequential encounter which failed to meet inclusion criteria (for Phase I) and which did not meet exclusion criteria. A total of 555 patients were enrolled during Phase II. During data cleaning, one Phase I patient in the derivation group was found to have been enrolled improperly due to documentation of trauma. This patient and the corresponding Phase II patient were excluded. Thus, the final analysis dataset consisted of 114 Phase I patients and 554 Phase II patients. A flowchart of patient selection appears in Figure 1.

2.2 Data Collection

All data was collected manually from electronic EMS and hospital medical records by trained personnel using guidelines defined in the study protocol. ED and hospital records were linked using patient name and birth date and the time and date of the EMS encounter. Demographics and medical histories were collected, and vital sign, treatment, and diagnosis data were recorded for the EMS field, ED, and if admitted, first 48 hours of hospitalization after arrival. All personal identifiers and encounter dates were removed from the dataset prior to this analysis.

2.3 Outcome of Interest

Because there is no gold standard diagnosis for sepsis, we used inpatient provider diagnoses to determine septic status. Patients were considered truly septic if manual review of the inpatient record reflected a diagnosis of sepsis, severe sepsis, or septic shock. Qualifying diagnoses were restricted to the first 48 hours following ED arrival to exclude cases of infection that originated in the hospital. Patients with no such diagnosis or who

were not admitted were considered not septic. Four patients expired in the ED; for these patients, ED provider diagnoses were substituted for inpatient diagnoses.

2.4 Sepsis Screening

Phase I and II patients were screened for sepsis using the PRESS and qSOFA tools. PRESS screen results were generated using EMS data, and qSOFA screen results were generated using initial ED data.

The PRESS tool is comprised of six criteria assessed in the EMS setting. Patient scores range from 0-24, and a score of two or more is considered positive. Recognizing the limited practicality of such a tool in the field, we simplified the PRESS tool by dichotomizing each criterion. Patients screened positive if any one or more of the following criteria were present: 1) systolic blood pressure less than 90 mm Hg, 2) age greater than or equal to 40 years, 3) tactile temperature of "hot", 4) blood oxygen saturation less than 90%, 5) dispatch chief concern of "sick person", or 6) transport from a nursing home. PRESS is recommended for use in patients who have abnormal vital signs, defined as HR > 90, RR > 20, and SBP < 110. Thus by definition, all Phase I patients qualified for screening. PRESS screens were also generated for Phase II patients to assess how PRESS might perform in patients without abnormal vitals.

The qSOFA score ranges from 0-3 and consists of three criteria worth one point each: 1) systolic blood pressure less than or equal to 100 mm Hg, 2) respiratory rate greater than or equal to 22 breaths per minute, and 3) Glasgow Coma Score (GCS) less than or equal to 14. Screen results were generated using initial ED data collected within 1 hour of arrival, and a score of two or more was considered positive. Due to a high percentage of missing ED GCS values (79% in Phase I and 82% in Phase II), the worst GCS obtained within 48 hours of patient arrival was substituted if available. qSOFA screens were not

generated for patients still missing two or more qSOFA criteria (2.6% in Phase I and 2.7% in Phase II).

The qSOFA is recommended for use in patients with suspected infection, so we conducted a subset analysis among patients with a record of orders for blood cultures *and* antibiotics prior to hospital admission or ED discharge. Though an anachronistic approach, we also screened these patients with PRESS for comparison.

2.5 Statistical Analysis

Demographic characteristics and inpatient medical histories (where available) were quantified for Phase I and II patients. Multivariable logistic regression was used to generate p-values for differences between groups, adjusting for all demographic factors and comorbidities. The proportions of patients with suspected infection and sepsis were also calculated, and differences were assessed using unadjusted χ^2 tests. Clinical characteristics were compared for patients between EMS and ED settings. Significance testing was performed using paired student t-tests or Wilcoxon signed-rank tests as appropriate.

Performance statistics including sensitivities, specificities, positive predictive values, and negative predictive values were computed for PRESS and qSOFA screens among Phase I and II patients. Patients were considered septic if an inpatient diagnosis of sepsis, severe sepsis, or septic shock was found in the medical record within the first 48 hours after hospital arrival. ED provider diagnosis was substituted for patients who expired in the ED. One-sample z-tests of proportion were used to generate confidence intervals and two-tailed p-values for sensitivity and specificity (H_o: $p=0.5$). Receiver operating characteristic (ROC) curves were produced from multivariable logistic regression models of each screening tool to assess overall tool discrimination. We used the same methods to quantify screening performance in the subsets of Phase I and II patients with suspected infection. Cohen's

kappa statistics were calculated to assess the agreement of PRESS and qSOFA screening for patients with and without sepsis.

For each screening method, patients with false positive screens were characterized and compared to those who were truly septic. Patients with false negative screens were compared to patients who were truly not septic. Comparisons were restricted to characteristics which could be assessed quickly in the field or ED without laboratory testing, including age and gender, medical history, and routine vital signs. Mantel-Haenszel, student t, and Wilcoxon rank sum tests were used to determine significance as appropriate. All statistical analysis was performed using SAS 9.4 (Cary, NC).

3. Results

3.1 Characteristics of Study Population

The final dataset contained 114 patients from Phase I and 554 patients from Phase II. Patient characteristics are summarized in Table 1. Phase I patients were more likely to have suspected infection (21.9% vs. 7.2%, p-value <0.0001) and to be diagnosed with sepsis after admission (27.2% vs. 2.2%, p-value <.0001), though data needed to establish suspicion was missing for 45 (39.5%) and 14 (2.5%) of Phase I and II patients, respectively. Phase I patients were also more likely to be female (57.9% vs. 49.3%, p-value .034) and to have histories of cancer (15.8% vs. 6.3%, p-value .0001), HIV (20.2% vs 8%, p-value .0002), or hemodialysis (5.3% vs. 2.4%, p-value .021). In both groups, mean age was similar (48.6 and 51.4 years, p-value .17) and the overwhelming majority of patients were black (83.3 % vs. 89.5%, p-value .07).

For both groups, clinical characteristics differed significantly between EMS and ED settings. Heart rate and respiratory rate were lower in the ED, while SBP and blood oxygen saturation were higher. Only GCS scores, while more variable, were overall not significantly

different between the prehospital field and ED (Phase I p-value .42, Phase II p-value .81). Table 2 details these characteristics for patients in Phase I and II.

3.2 Performance of PRESS Screening Tool

Table 3 displays the performance characteristics of PRESS and qSOFA among patients overall and with suspected infection. PRESS was up to 90.3% sensitive in Phase I patients and up to 83.3% sensitive in Phase II patients. However, PRESS specificity was consistently poor in both patient groups (Phase I 21.7%, Phase II 17.2%), and was worse in those with suspected infection (Phase I 14.3%, Phase II 3.1%). In logistic regression, the areas under the receiver operating characteristic (AUROC) curves indicated good discrimination among Phase I patients and acceptable discrimination among Phase II patients (AUROC .82 and .72, respectively).

The characteristics of patients with false positive PRESS screens (Phase I n=65/114 [57%], Phase 2 n=449/554 [81%]) and negative screens (Phase I n=3/114 [2.6%], Phase II n=2/554 [.3%]) are detailed in Tables 5 and 6. Compared to those with true sepsis, Phase I patients with false positive PRESS screens had lower mean heart rates (120.1 vs. 130.5 bpm) and higher median GCS scores (15 vs. 14), and were less likely to have a history of stroke (7.7% vs. 32.2%). In Phase II, patients with false positive screens had higher systolic blood pressure (140.0 vs. 109.5) and lower heart rate (92.9 vs. 114.7), and were less likely to have a history of stroke (2.2% vs. 16.7%). Two-thirds of patients with false negative screens in Phase I were HIV positive versus 16.9% of patients who were not septic (p-value .03). No other significant associations were found, though this is likely due to small sample size.

3.3 Performance of qSOFA Screening Tool

qSOFA demonstrated low sensitivity in both patient groups, but was higher among Phase I patients (41.4% vs. 16.7%). Specificity was much higher in both groups (Phase I

87.8%, Phase II 97.1%). Sensitivities were similar in the subsets of patients with suspected infection (Phase I 43.7%, Phase II 12.5%), though specificities were lower (Phase I 71.4%, Phase II 90%). Overall model performance was acceptable in Phase I and Phase II (AUROC 0.77 and 0.786), but was excellent in Phase I patients with infection (AUROC 0.993). Among Phase II patients with suspected infection, however, the AUROC dropped to 0.637.

Patients with false positive qSOFA screens (Phase I n=10/114 [8.8%], Phase II n=12/554 [2.2%]) and negative qSOFA screens (Phase I n=17/114 [1.5%], Phase II n=10/554 [1.8%]) are characterized in Tables 7 and 8. Compared to those with sepsis, Phase I patients with false positive screens had lower ED heart rates (96.4 vs 120.0) and systolic blood pressure (93.5 vs 111.2). In Phase II, false positive patients tended to have lower ED heart rate (99.4 vs 114.7), and higher systolic blood pressure (139.9 vs 109.5) and respiratory rate (23.8 vs 20.5), and were more likely to have pulmonary disease (50% vs 8.3%). Compared to true negatives, Phase I false negatives had higher heart rates (123.5 vs 120.9), and were more likely to be female (64.7% vs. 57.8%), and or have histories of stroke (41.2% vs 6%) or HIV (41.2% vs 16.9%). In Phase II, false negative patients had higher ED heart rate (116.6 vs 92.7) and respiratory rate (21.5 vs 19.3), and lower systolic blood pressure (120.4 vs 138.), than patients who were truly not septic.

3.4 Comparison of Screening Tools

There was little more than chance agreement between PRESS and qSOFA screens in either patient group. The greatest agreement was found among Phase I patients with sepsis ($\varkappa = 0.151$, p-value <0.0001); however, agreement was less than 10% in Phase I patients without sepsis and Phase II patients with sepsis; it was less than 1% in Phase II patients without sepsis. In both Phase I and II patients, disagreement between screening tools occurred almost exclusively when PRESS was positive and qSOFA was negative. Only one

patient in Phase II screened negative by PRESS in the field but positive by qSOFA in the ED. Results are detailed in Table 4.

Discussion

4.1 Implications

PRESS and qSOFA demonstrated limited efficacy in this study. As expected, the PRESS tool performed best when used as recommended in patients with abnormal vital signs. Peak sensitivity in these patients was 90.3%. However, PRESS specificity was less than 25% in all patient groups, and positive predictive values were consistently low. qSOFA also performed best in patients with abnormal vitals, consistent with recommendations that it be used for those with suspected infection. Nevertheless, though specificity reached 97.9% in Phase II, overall identification by qSOFA was poor, with sensitivities less than 50% in all patient groups, including the subsets of those with suspected infection.

We suspect clinical interventions contributed to the low sensitivity of qSOFA. As shown in Table 2, patient vitals appeared more normal in the ED than in the field, perhaps reflecting the effectiveness of EMS interventions. Similarly, worst 48-hour GCS scores were substituted for over three-quarters of patients in both groups, and these may not be reflective of patients' true mental status upon arrival due to subsequent hospital interventions. qSOFA alone may therefore be unreliable for assessing ED patients arriving by EMS.

Historically, screening tools have prioritized sensitivity to ensure all patients at risk of disease are identified (61). By this criterion, PRESS was more valuable than qSOFA for sepsis screening in this study. However, there is no gold standard diagnostic by which to confirm PRESS screening, and PRESS demonstrated very low specificity. The ultimate goal of PRESS screening is to expedite treatment for septic EMS patients, yet there are known

risks associated with inappropriate antibiotic use and excessive fluid resuscitation in patients without sepsis or infection (6, 62, 63). We therefore cannot yet recommended either PRESS or qSOFA for widespread use based upon the results of this study.

Because PRESS and qSOFA were assessed at different points of care, it was of interest to know if patients with sepsis would be identified by both screening tools, and if the use of both tools in succession might increase predictive value. Our study found little to no agreement between PRESS and qSOFA ($\varkappa$ .15 to .005). We suspect the low agreement is due to the high false-positive rate for PRESS and the changes in clinical presentation between the field and ED which may have decreased qSOFA sensitivity (see Table 2). Additionally, only 40% of patients for whom both screening results were positive also truly had sepsis. However, of 43 septic patients in this study, 38 (88.4%) were identified by at least one screening tool, suggesting there may be value in using both screening tools together.

Improvements to individual screening tools might focus upon modifying screening criteria. Mean heart rate was the most common difference between misclassified patients and truly septic or non-septic patients (as were appropriate for comparison, see Table 5 and 6). This includes Phase I patients, for whom inclusion criteria included a minimum heart rate of 90 bpm. Though PRESS is recommended for use in patients who meet Phase I criteria, heart rate is not directly included as a screening criterion for either PRESS or qSOFA. Other common significant differences included age, SBP, and history of stroke or HIV, though SBP is already included in qSOFA, and both age and SBP are included in PRESS.

4.2 Limitations

In the absence of a gold standard diagnostic, we relied upon clinician diagnoses to determine septic status, which may be subject to misclassification bias. The 2001 consensus definitions for sepsis, severe sepsis, and septic shock were still in use during the period

covered by this study, and these definitions have since been revised to include only patients with more severe illness. It is therefore likely that some patients classified as septic in this study would not be considered septic according to current clinical guidelines. This and the modifications made to PRESS criteria may explain the differences in PRESS performance reported in our study and the original article (9)

Because this analysis was restricted to particular subsets of EMS patients at a single institution, the external validity of our results may be limited. Our results do not represent the performance of PRESS or qSOFA in all EMS patients and do not apply to children or those with excluding conditions. The setting of this study was a single urban teaching hospital, the patient population of which likely differs from that of other institutions. Additionally, the study sample is drawn from the same population which was sampled to derive the PRESS tool. Though the current sample consists of different individuals, overall similarities between ours and the original derivation sample may exaggerate PRESS sensitivity. We would expect lower sensitivity in external studies.

Conclusion

Among EMS patients, the PRESS tool demonstrated high sensitivity but low specificity for sepsis in the field. Among the same patients after ED arrival, qSOFA demonstrated low sensitivity but high specificity. There was little agreement between screening tools. Further research is needed to improve the performance of the PRESS and qSOFA screening tools and to validate their use in broader patient populations.

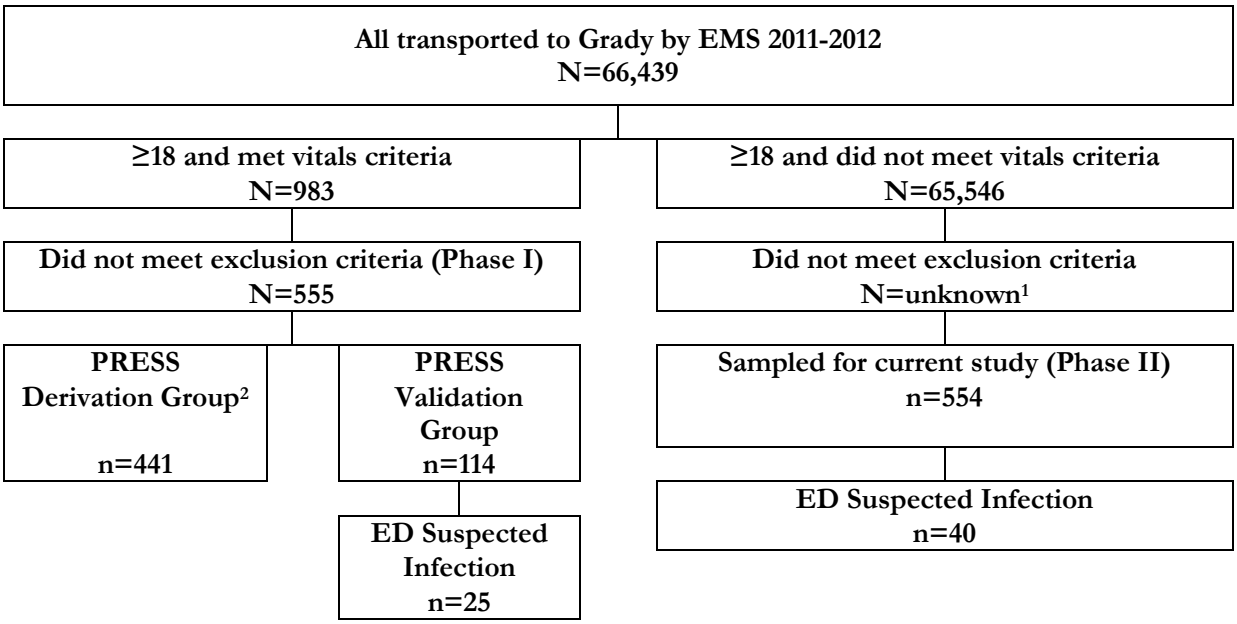

Figure 1. Flowchart of patient selection, Phases I and II

[1]The EMS database query design prevents this population from being quantified directly. Patients were screened and excluded from Phase II catchment on a case-by-case basis.

[2]One patient was later excluded; however, this did not affect the current study beyond changing the number of Phase II patients enrolled.

Table 1. Demographic characteristics of Phase I and Phase II patients.

Characteristic	Phase I (n=114)	Phase II (n=554)	p-value[d]
Female, n (%)	66 (57.9)	272 (49.3)	.03
Age, Mean (SD)	48.6 (16.2)	51.4 (16.6)	.16
Race/Ethnicity, n (%)			.07
White	13 (11.4)	37 (6.7)	
Black	95 (83.3)	493 (89.5)	
Hispanic	3 (2.6)	9 (1.6)	
Other/Unknown	3 (2.6)	12 (2.2)	
Medical History, n (%)			
Pulmonary Disease[a]	40 (35.1)	151 (27.3)	.29
Cardiovascular Disease[b]	19 (16.7)	88 (15.9)	.23
Hypertension	51 (44.7)	301 (54.3)	.23
Stroke	15 (13.2)	61 (11.0)	.34
Cirrhosis	1 (0.9)	4 (0.7)	.64
Diabetes	19 (16.7)	139 (25.1)	.22
Cancer	18 (15.8)	35 (6.3)	.0001
HIV/AIDS	23 (20.2)	44 (8.0)	.0002
Dialysis	6 (5.3)	13 (2.4)	.02
Immunosuppression[c]	3 (2.6)	12 (2.2)	.46
Suspected Infection	25 (21.9)	40 (7.2)	<.0001
Diagnosis of Sepsis	31 (27.2)	12 (2.2)	<.0001

[a]Includes chronic obstructive pulmonary disease and asthma

[b]Includes congestive heart failure, deep vein thrombosis (DVT), and pulmonary embolism (PE)

[c]Includes chronic steroids, chemotherapy, organ transplant, and diseases such as lupus

[d]Except for sepsis and suspected infection, p-values for covariates were obtained via logistic regression adjusting for all other covariates.

Table 2. Clinical Characteristics of Phase I and Phase II Patients in the EMS and ED Settings

Characteristic	EMS, Mean (SD) or Median (IQR)	ED, Mean (SD) or Median (IQR)	p-value[a]
PHASE I			
Heart rate	123.5 (23.4)	105.8 (22.3)	<.0001
Respiratory rate	26.7 (7.2)	20.7 (5.3)	<.0001
Systolic blood pressure	95.1 (11.5)	115.7 (19.6)	<.0001
GCS	15 (1)	15 (4)[b]	.42
Blood O2 saturation	93.2 (9.5)	96.3 (6.1)	.0004
PHASE II			
Heart rate	93.2 (19.7)	88.6 (18.0)	<.0001
Respiratory rate	19.3 (3.8)	18.9 (3.7)	.05
Systolic blood pressure	137.5 (28.3)	141.3 (28.9)	<.0001
GCS	15 (0)	15 (0)[b]	.81
Blood O2 saturation	96.7 (6.8)	98.0 (2.6)	<.0001

[a]P-values generated by paired t-test or Wilcoxon signed-rank test as appropriate

[b]Worst GCS recorded within 24 hours was substituted if no GCS was recorded within 1 hour of arrival

Table 3. Performance of PRESS and qSOFA screening in Phase I and Phase II patients overall and restricted to those with suspected infection[c]

	Phase I		Phase II	
Parameter	All (n=114)	Suspected Infection (n=25)	All (n=554)	Suspected Infection (n=40)
PRESS Screening				
Sensitivity	90.3	88.9	83.3	75.0
Specificity	21.7	14.3	17.2	3.1
Positive PV[a]	30.0	72.7	2.2	16.2
Negative PV	85.7	33.3	97.9	33.3
AUROC[b]	0.819	0.887	0.721	0.772
qSOFA Screening				
Sensitivity	41.4	43.7	16.7	12.5
Specificity	87.8	71.4	97.9	90.0
Positive PV[a]	54.5	77.8	14.3	25.0
Negative PV	80.9	35.7	98.1	79.4
AUROC[b]	0.770	0.933	0.786	0.637

[a]Predictive value

[b]Area under the receiver operating characteristic curve

[c]Suspected infection indicates blood cultures drawn and antibiotics ordered in the ED

Table 4. Agreement of PRESS and qSOFA Screens among Phase I and II patients with and without sepsis[a].

	Phase I		Phase II	
	With sepsis (n=29)	Without sepsis (n=83)	With sepsis (n=12)	Without sepsis (n=527)
Kappa	0.151	0.070	0.077	0.0049
p-value	.0002	<.0001	.005	<.0001

[a]Kappa calculations do not include those for whom no qSOFA result could be generated.

Table 5. Characteristics of Phase I and II Patients False Positive by PRESS

Characteristic	False Positives Mean (SD) or N (%)	True Septic Mean (SD) or N (%)	p-value[a]
Phase I (n=114)	65 (57.0)	31 (27.2)	
Age	50.6 (14.2)	56.3 (14.9)	.71
Female	33 (50.8)	18 (58.1)	.51
EMS SBP	95.3 (11.3)	91.1 (12.8)	.10
EMS HR	120.1 (21.0)	130.5 (18.4)	.02
EMS RR	26.4 (6.5)	28.5 (9.3)	.15
EMS O2	93.6 (8.7)	89.4 (12.4)	.11
EMS GCS[b]	15 (0)	14 (6)	.001
Pulmonary Disease[c]	27 (41.5)	7 (22.6)	.07
Cardiovascular Disease[d]	12 (18.5)	5 (16.3)	.78
Hypertension	30 (36.2)	18 (58.1)	.28
Stroke	5 (7.7)	10 (32.3)	.002
Cirrhosis	1 (1.54)	0	.49
Diabetes	10 (15.4)	7 (22.6)	.39
Cancer	10 (15.4)	7(22.6)	.39
HIV/AIDS	13 (20.0)	9 (29.0)	.33
Dialysis	4 (6.2)	2 (6.5)	.96
Immunosuppression[e]	2 (3.1)	1 (3.2)	.97
Phase II (n=554)	449 (81.0)	12 (2.2)	
Age	55.5 (14.7)	57.9 (19.5)	.58
Female	221 (49.4)	5 (41.7)	.60
EMS SBP	140.0 (29.1)	109.5 (23.8)	.0004
EMS HR	92.9 (19.6)	114.7 (19.6)	.0002
EMS RR	19.3 (3.8)	20.5 (4.2)	.19
EMS O2	96.5 (7.4)	97.1 (3.0)	1.00
EMS GCS[b]	15 (0)	15 (0)	.46
Pulmonary Disease[c]	130 (29.0)	1 (8.3)	.12
Cardiovascular Disease[d]	84 (18.7)	1 (8.3)	.36
Hypertension	279 (62.1)	6 (50.0)	.39
Stroke	56 (12.5)	4 (33.3)	.03
Cirrhosis	4 (0.9)	0	.74
Diabetes	124 (27.6)	4 (33.3)	.66
Cancer	32 (7.1)	1 (8.3)	.87
HIV/AIDS	37 (8.2)	2 (16.7)	.30
Dialysis	10 (2.2)	2 (16.7)	.002
Immunosuppression[e]	11 (2.5)	0	.58

[a]P-values are for significance differences versus Phase I patients with true sepsis

[b]Reported measures are median and interquartile range

[c]Includes chronic obstructive pulmonary disease and asthma

[d]Includes congestive heart failure, deep vein thrombosis (DVT), and pulmonary embolism (PE)

[e]Includes chronic steroids, chemotherapy, organ transplant, and diseases such as lupus

Table 6. Characteristics of Phase I and II Patients False Negative by PRESS

Characteristic	False Negatives Mean (SD) or N (%)	True non-Septic Mean (SD) or N (%)	p-value[a]
Phase I (n=114)	3 (2.6)	83 (72.8)	
Age	29.3 (7.1)	45.7 (15.8)	.08
Female	2 (66.7)	48 (57.8)	.76
EMS SBP	101.3 (5.8)	96.6 (10.6)	.45
EMS HR	140 (22.7)	120.9 (24.7)	.19
EMS RR	25.3 (2.3)	26.1 (6.1)	.53
EMS O2	98.0 (2.0)	94.5 (7.9)	.36
EMS GCS[b]	15 (0)	15 (0)	.38
Pulmonary Disease[c]	0	33 (39.8)	.17
Cardiovascular Disease[d]	0	14 (16.9)	.44
Hypertension	0	33 (39.8)	.17
Stroke	0	5 (6.0)	.66
Cirrhosis	0	1 (1.2)	.85
Diabetes	0	12 (14.5)	.48
Cancer	0	11 (13.3)	.50
HIV/AIDS	2 (66.7)	14 (16.9)	.03
Dialysis	0	4 (4.8)	.70
Immunosuppression[e]	0	2 (2.4)	.79
Phase II (n=554)	2 (.004)	542 (97.8)	
Age	33.5 (0.7)	51.3 (16.5)	.13
Female	1 (50.0)	267 (49.4)	.99
EMS SBP	108.0 (5.7)	138.1 (28.1)	.13
EMS HR	117.5 (6.4)	92.7 (19.4)	.07
EMS RR	23.0 (7.1)	19.3 (3.8)	.36
EMS O2	98.5 (0.7)	96.7 (6.8)	.56
EMS GCS[b]	15 (0)	15 (0)	.46
Pulmonary Disease[c]	0	150 (27.7)	.38
Cardiovascular Disease[d]	0	87 (16.1)	.54
Hypertension	0	295 (54.4)	.12
Stroke	0	57 (10.5)	.63
Cirrhosis	0	4 (0.7)	.90
Diabetes	0	135 (24.9)	.42
Cancer	0	34 (6.3)	.72
HIV/AIDS	0	42 (7.8)	.68
Dialysis	0	11 (2.0)	.84
Immunosuppression[e]	0	12 (2.2)	.83

[a]P-values are for significance differences versus Phase I patients with true sepsis

[b]Reported measures are median and interquartile range

[c]Includes chronic obstructive pulmonary disease and asthma

[d]Includes congestive heart failure, deep vein thrombosis (DVT), and pulmonary embolism (PE)

[e]Includes chronic steroids, chemotherapy, organ transplant, and diseases such as lupus

Table 7. Characteristics of Phase I and II Patients False Positive by qSOFA

Characteristic	False Positives Mean (SD) or N (%)	True Septic Mean (SD) or N (%)	p-value[a]
Phase I (n=114)	10 (8.8)	31 (27.2)	
Age	46.0 (10.6)	56.3 (14.9)	.05
Female	4 (40.0)	13 (41.9)	.33
ED SBP	93.5 (12.7)	111.2 (20.7)	.02
ED HR	96.4 (34.0)	120.0 (22.35)	.02
ED RR	22.3 (5.1)	22.2 (7.1)	.48
ED O2	94.9 (3.7)	94.1 (9.4)	.31
ED GCS[b]	14.0 (6)	14.0 (6)	.73
Pulmonary Disease[c]	3 (30.0)	7 (22.6)	.64
Cardiovascular Disease[d]	1 (10.0)	5 (16.1)	.64
Hypertension	4 (40.0)	18 (58.1)	.33
Stroke	0	10 (32.3)	.04
Cirrhosis	0	0	-
Diabetes	2 (20.0)	7 (22.6)	.87
Cancer	0	7 (22.6)	.10
HIV/AIDS	2 (20.0)	9 (29.0)	.58
Dialysis	1 (10.0)	2 (6.5)	.71
Immunosuppression[e]	0	1 (3.2)	.57
Phase II (n=554)	12 (2.2)	12 (2.2)	
Age	55.8 (15.8)	57.9 (19.5)	.77
Female	6 (50.0)	5 (41.7)	.69
ED SBP	139.9 (28.3)	109.5 (23.8)	.02
ED HR	99.4 (21.3)	114.7 (19.6)	.04
ED RR	23.8 (2.2)	20.5 (4.2)	.01
ED O2	97.4 (3.1)	97.1 (3.0)	.97
ED GCS[b]	10.5 (6)	15 (0)	.46
Pulmonary Disease[c]	6 (50.0)	1 (8.3)	.03
Cardiovascular Disease[d]	3 (25.0)	1 (8.3)	.28
Hypertension	9 (75.0)	6 (50.0)	.22
Stroke	1 (8.3)	4 (33.3)	.14
Cirrhosis	0	0	-
Diabetes	4 (33.3)	4 (33.3)	1.00
Cancer	2 (16.7)	1 (8.3)	.55
HIV/AIDS	0	2 (16.7)	.15
Dialysis	0	2 (16.7)	.15
Immunosuppression[e]	0	0	-

[a]P-values are for significance differences versus Phase I patients with true sepsis

[b]Reported measures are median and interquartile range

[c]Includes chronic obstructive pulmonary disease and asthma

[d]Includes congestive heart failure, deep vein thrombosis (DVT), and pulmonary embolism (PE)

[e]Includes chronic steroids, chemotherapy, organ transplant, and diseases such as lupus

Table 8. Characteristics of Phase I and II Patients False Negative by qSOFA

Characteristic	False Negatives Mean (SD) or N (%)	True non-Septic Mean (SD) or N (%)	p-value[a]
Phase I (n=114)	17 (14.9)	83 (72.8)	
Age	55.5 (18.4)	45.7 (15.8)	.03
Female	11 (64.7)	48 (57.8)	.60
ED SBP	113.8 (19.2)	96.6 (10.6)	.50
ED HR	123.5 (20.7)	120.9 (24.7)	<.0001
ED RR	19.1 (1.8)	26.1 (6.1)	.65
ED O2	96.4 (5.8)	94.5 (7.9)	.78
ED GCS[b]	15.0 (2.5)	15 (0)	.41
Pulmonary Disease[c]	4 (23.5)	33 (39.8)	.21
Cardiovascular Disease[d]	1 (5.9)	14 (16.9)	.25
Hypertension	10 (58.8)	33 (39.8)	.15
Stroke	7 (41.2)	5 (6.0)	<.0001
Cirrhosis	0	1 (1.2)	.65
Diabetes	3 (17.7)	12 (14.5)	.74
Cancer	5 (29.4)	11 (13.3)	.10
HIV/AIDS	7 (41.2)	14 (16.9)	.03
Dialysis	2 (11.8)	4 (4.8)	.27
Immunosuppression[e]	1 (5.9)	2 (2.4)	.45
Phase II (n=554)	10 (1.8)	542 (97.8)	
Age	57.1 (21.4)	51.3 (16.5)	.27
Female	4 (40)	267 (49.4)	.55
ED SBP	120.4 (21.4)	138.1 (28.1)	.02
ED HR	116.6 (15.6)	92.7 (19.4)	<.0001
ED RR	21.5 (3.5)	19.3 (3.8)	.002
ED O2	98.1 (2.0)	96.7 (6.8)	.91
ED GCS[b]	15.0 (1)		.62
Pulmonary Disease[c]	1 (10.0)	150 (27.7)	.22
Cardiovascular Disease[d]	1 (10.0)	87 (16.1)	.60
Hypertension	5 (50.0)	295 (54.4)	.78
Stroke	2 (20.0)	57 (10.5)	.34
Cirrhosis	0	4 (0.7)	.79
Diabetes	3 (30.0)	135 (24.9)	.71
Cancer	1 (10.0)	34 (6.3)	.63
HIV/AIDS	2 (20.0)	42 (7.8)	.16
Dialysis	1 (10.0)	11 (2.0)	.09
Immunosuppression[e]	0	12 (2.2)	.63

[a]P-values are for significance differences versus Phase I patients without true sepsis

[b]Reported measures are median and interquartile range

[c]Includes chronic obstructive pulmonary disease and asthma

[d]Includes congestive heart failure, deep vein thrombosis (DVT), and pulmonary embolism (PE)

[e]Includes chronic steroids, chemotherapy, organ transplant, and diseases such as lupus

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SUMMARY, IMPLICATIONS, AND FUTURE DIRECTIONS

Summary

This study analyzed the performance of two screening tools for sepsis in high- and low-risk EMS patients of an urban safety net hospital. The Prehospital Severe Sepsis (PRESS) score demonstrated high sensitivity but low specificity for patients in the EMS setting. The quick Sepsis-related Organ Failure Assessment (qSOFA) demonstrated low sensitivity but high specificity for the same patients after ED arrival. Both tools performed better among high-risk patients than low-risk patients, though combined sensitivity approached 90% overall. There was little agreement between screening methods. For both screening tools, the heart rates of patients who were misclassified differed significantly from the heart rates of those with true sepsis (versus false positives) or those without true sepsis (versus false negatives). Neither PRESS nor qSOFA can yet be recommended for wide use based on the results of this study alone.

Implications

Proper, timely diagnosis is critical to avoiding death from sepsis, and screening tools have been developed to increase provider recognition both in and out of hospitals. However, the results of this study do not support the widespread implementation of PRESS or qSOFA for sepsis screening. Neither tool performed with sufficient sensitivity or specificity to have practical value.

PRESS demonstrated impressive sensitivity in both high- and low-risk EMS patients, yet sacrificed substantial specificity. Positive predictive value ranged from just 2% to 30%. Historically, screening tools have prioritized sensitivity over specificity to ensure all patients at risk of disease are identified. When there is a cost-effective, gold standard diagnostic to

confirm screening, this approach is effective. However, there is no definitive diagnostic test for sepsis, and due to the time-sensitive nature of the syndrome, screening tools must have sufficient specificity to justify treatment for patients with positive screens. There are known risks associated with the inappropriate use of therapies for sepsis. Patients receiving empiric antibiotics are at greater risk of developing resistant infections. Especially when secondary to sepsis, these greatly increase the risk of mortality. Fluid overload has also been associated with increased mortality in mistreated patients and even in patients with sepsis. The specificity of the PRESS tool therefore must be increased to ensure its practical utility.

For patients misclassified by PRESS, average heart rate was the most common difference between false positives and true septic patients as well as between false negatives and truly non-septic patients. In general, septic patients had higher heart rates than non-septic patients regardless of screening results. While PRESS is recommended for use only in patients with heart rate greater than 90 bpm, this relationship still held true among Phase I patients who met suggested screening criteria. However, a very broad of range of heart rates were observed for patients in this study, therefore the potential value of heart rate as a predictor of sepsis remains questionable.

Conversely, qSOFA demonstrated very low sensitivity for sepsis. This nullifies its practical use as a screening tool. However, qSOFA demonstrated high specificity and negative predictive value, indicating it may have some merit as a check against overly sensitive tools such as PRESS. In this study the combined sensitivity of PRESS and qSOFA (where at least screen was positive) was 88%, and combined specificity (where at least one tool was negative) was 95%. This combined performance is better than either screening tool alone, though such an approach would require a tie-breaker for discordant screens and therefore is unlikely to be practical.

It is worth mentioning that agreement between PRESS and qSOFA was very low. Seventy-five percent of patients had discordant screening results. It is unclear whether this is due to intrinsic patient factors or to changes which occur between the times of PRESS and qSOFA screening. The PRESS and qSOFA tools are built primarily around vital signs, which changed significantly between the field and ED in this study (see Table 2). Common EMS interventions such as supplemental oxygen and intravenous fluids may directly affect the vital signs which comprise qSOFA criteria (SBP, RR, and GCS). This could be a cause of the low sensitivity of qSOFA among patients in this study. Further studies may investigate this relationship and lead to recommendations that qSOFA not be used in patients transported by EMS.

Future Directions

The results of this study are not representative of screening tool performance for all patients in all settings. Key limitations include small sample size and restriction to select patients of a single institution. Tool performance may be significantly different in rural populations or in more general urban populations. PRESS and qSOFA should therefore be validated in larger, more diverse populations in order to determine the true potentials for impact. Additional studies may be needed to refine screening criteria for PRESS and qSOFA and improve screening performance.