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Carmen Christina Polito Date

Prehospital Identification of Patients with Severe Sepsis: Derivation and Validation of a Novel Screening Tool

By

Carmen Christina Polito
Master of Science
in
Clinical Research

_____
Jonathan E. Sevransky, M.D., M.H.S., F.C.C.M.
Advisor, Lead Mentor

_____
Alexander Isakov, M.D., M.P.H.
Advisor, Co-mentor

_____
Greg S. Martin, M.D., M.Sc., F.C.C.M.
Advisor, Co-Mentor

_____
Mitch Klein, Ph.D.
Committee Chair

_____
Amit J. Shah, M.D., M.Sc.
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D. Dean of the James T. Laney School of Graduate Studies

_____
Date

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Doctor of Medicine, Medical University of South Carolina, 2007

Advisors: Jonathan E. Sevransky, M.D., M.H.S., F.C.C.P.; Alexander Isakov, M.D., M.P.H.;

Greg S. Martin, M.D., M.Sc., F.C.C.P.

An abstract of
a thesis submitted to the Faculty of
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Master of Science in Clinical Research
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Prehospital Identification of Patients with Severe Sepsis:

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Sepsis is a common, life-threatening inflammatory condition that can occur as a consequence of an active infection. In patients with sepsis, early identification and treatment are key components of reducing morbidity and mortality. Unfortunately, there is no standardized way to identify patients with sepsis in the Emergency Medical Services (EMS) setting, potentially delaying identification and live-saving treatment. The goal of this project was to derive and validate a predictive model and clinical risk prediction score for EMS identification of severe sepsis. We performed a retrospective cohort study of sequential, adult, at-risk patients transported by a city-wide Emergency Medical Services (EMS) system to a 900-bed, urban, public hospital between 2011 and 2012. At-risk patients were defined as having all 3 of the following criteria present in the EMS setting: heart rate >90 beats per minute, 2) respiratory rate >20 breaths per minute, and 3) systolic blood pressure <110 mmHg. Among 66,439 EMS encounters, 555 patients were included for analysis, of which 14% (n=75) had severe sepsis. Severe sepsis (including septic shock) was defined by review of clinical documentation. The cohort was randomly divided into derivation (80%) and validation (20%) subgroups, and logistic regression was performed to determine which EMS characteristics were associated with a diagnosis of severe sepsis. The following six risk factors were found to be EMS predictors of severe sepsis: older age, EMS transport from a nursing home, Emergency Medical Dispatch (EMD) 9-1-1 chief complaint category of "Sick Person", hot tactile temperature, low systolic blood pressure, and low oxygen saturation. The final predictive model showed good discrimination in both derivation and validation subgroups (AUC 0.832 and 0.803, respectively). Sensitivity of the final model was 91% in the derivation subgroup and 78% in the validation subgroup; specificity was 34% and 26%, respectively. Finally, the final predictive model was converted into a prehospital severe sepsis (PreSS) risk prediction score. A PreSS score of ≥2 points performed with a sensitivity of 86% and a specificity of 47%. Further validation of the PreSS score is needed before determining the potential benefit of its use.

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INTRODUCTION

Sepsis is a life-threatening inflammatory syndrome that can occur as a consequence of any severe infection, with severe sepsis defined as sepsis with associated with organ dysfunction [1]. Sepsis is an important and increasing U.S. public health concern. With rates that have more than doubled between 2000 and 2008, sepsis was the most expensive condition treated in hospitals in 2011 [2, 3]. In addition, in-hospital mortality for sepsis was more than eight times higher than other hospital conditions in 2009 [4]. Despite improvements in the treatment of severe sepsis over the past 20 years, mortality remains high, estimated between 12-33% [5-8]. Mortality improvements over this time period have been largely attributable to two core aspects of treatment, namely, appropriate antibiotic therapy and intravenous fluid resuscitation [5, 9, 10]. Substantial evidence suggests that these interventions are most effective when initiated early in the course of disease. In patients with septic shock, the most severe form of sepsis characterized by cardiovascular organ failure, it has been shown that every hour of delay in initiating antibiotic therapy is associated with an average decrease in survival of 8% [10].

The time-sensitive nature of treatment in patients with severe sepsis is similar to other life-threatening conditions including trauma injury, cardiac arrest, heart attack, and stroke. In these other life-threatening, time-sensitive conditions, prehospital identification and treatment is standard of care, as this strategy confers improvements in morbidity and mortality [11-13]. We hypothesize the same is true for severe sepsis. However, there is no accepted method for identifying severe sepsis in the prehospital, Emergency Medical Services (EMS), setting. This is largely due to the fact that sepsis is a complex syndrome that cannot currently be diagnosed with a simple diagnostic test [14].

Although several screening tools have been developed for use in the EMS setting [15-17], these tests have inherent limitations including the need for costly lab assays and/or little epidemiologic data to support their use. Further work is needed to determine how to reliably identify patients in low-resource environments, and ultimately, to determine whether prehospital identification improves patient outcomes. This issue is of critical importance to the nation's health as reflected by the recent ratification of time-sensitive quality measures by the National Quality Forum [18].

As such, the goal of this project is to derive and validate a predictive model and clinical risk prediction score for identification of patients with prehospital severe sepsis.

BACKGROUND

Similar to other life-threatening, time-sensitive conditions including trauma injury, cardiac arrest, heart attack, and stroke, many patients admitted to the hospital with severe sepsis are brought to the Emergency Department by ambulance [19]. It was recently reported that the incidence of Emergency Medical Services (EMS) transport of patients with severe sepsis is higher than the incidence of heart attack or stroke (3.3 cases of severe sepsis per 100 EMS encounters vs. 2.3 cases of acute myocardial infarction per 100 EMS encounters and 2.2 cases of stroke per 100 EMS encounters) [8]. Similar to these other conditions, identification and treatment of severe sepsis is time-sensitive.

Although strong evidence is lacking to support the hypothesis that prehospital identification improves patient outcomes, small observational studies suggest this may be true. Studnek *et al* have reported that EMS identification is associated with a shorter time to initiation of antibiotics in the Emergency Department (70 vs. 122 minutes, $p=0.003$) and a shorter time to initiation of aggressive intravenous fluid resuscitation (69 vs. 131 minutes, $p=0.001$) compared to those in whom sepsis is not identified by EMS personnel [20]. In another prospective cohort study by Guerra et al, prehospital identification that utilized point-of-care (POC) lactate testing was associated with a decrease in unadjusted hospital mortality as compared to those not identified in the prehospital setting (14% vs. 33%, $p=0.045$) [15].

Although several other methods of prehospital identification have been developed, these screening tools are associated with increased cost and complexity due to additional POC blood tests and/or do not have sufficient validation. Existing screening

tools include: 1) the Guerra protocol that utilizes POC lactate, 2) the Robson screening tool, and 3) the BAS 90-30-90 [15-17]. The Guerra protocol utilizes a modified approach to standard diagnostic criteria to identify patients with severe sepsis which includes at least 2 of the following: temperature >38 or <36 degrees Celsius, pulse >90 beats per minutes (bpm), and respiratory rate >20 breaths per minute (bpm) [15]. In addition, patients must have a suspected or documented infection and hypoperfusion manifested by one of the following: systolic blood pressure <90 mmHg, mean arterial pressure <65mm Hg, or POC lactate level ≥4mmol/L. Despite the additional cost and complexity of including POC blood testing, the Guerra protocol only resulted in prehospital identification of 48% of patients with severe sepsis [15].

The Robson screening tool utilizes similar criteria without the use of POC testing [16, 17]. In patients with severe sepsis, the Robson tool has been associated with a sensitivity of 93% (n=13/14 identified) in a small retrospective cohort, making it difficult to draw conclusions regarding its widespread use [17]. Finally, the BAS 90-30-90 is a simple tool that only requires one of the following: systolic blood pressure <90 mmHg, respiratory rate >30 bpm, or oxygen saturation <90%. Because these vital sign criteria may be present in other EMS conditions besides severe sepsis, namely heart failure, asthma and COPD exacerbation, the BAS 90-30-90 only demonstrated a sensitivity for detection of severe sepsis of 70% [17]. Interestingly, the Robson screening tool and BAS 90-30-90 were compared to EMS clinical judgment as the gold standard. In this comparison, clinical judgment demonstrated a sensitivity of 17%.

Given the limitations of these screening tools, we aim to develop an EMS screening tool for severe sepsis that is easy to use, reliable, cost efficient, and supported by epidemiologic data.

METHODS

Study design and patient selection

We conducted a retrospective cohort study of all sequential, adult patients (age ≥18) transported by Grady EMS to Grady Memorial Hospital between January 1, 2011 and December 31, 2012 who were part of our pre-defined risk set [1, 21]. The risk set was defined as having all 3 of the following criteria were present in the EMS setting: heart rate (HR) >90 beats per minute, 2) respiratory rate (RR) >20 breaths per minute, and 3) systolic blood pressure (SBP) <110mmHg [1, 21].

Patients were excluded if any of the following conditions were identified in the EMS setting: trauma injury, cardiac arrest, pregnancy, psychiatric emergency or toxic ingestion. Exclusion criteria were based on the existence of mature care pathways for the condition, or if there was a low likelihood of severe sepsis being present given the exclusion condition. Patients were also excluded if the EMS patient care record could not be linked to a corresponding hospital encounter, or if the patient left the emergency department before being seen by a physician.

Study settings

Grady EMS manages the Emergency Medical Dispatch (EMD) of 9-1-1 medical calls for the portion of the city of Atlanta located in Fulton County, Georgia (88%). Grady EMS provides over 30,000 annual emergency and non-emergency ambulance transports to Grady Memorial Hospital, a 900-bed, urban, public hospital. EMD call takers use an integrated software system, ProQA (Priority Dispatch Corporation; Salt Lake City, Utah), to query

9-1-1 callers in a highly algorithgmic, scripted fashion, and to classify and prioritize caller information. The ProQA algorithm assigns the caller's chief complaint into one of 37 discrete categories. Of note, ProQA is the most frequently utilized EMD classification system in the United States.

Grady EMS ambulances are staffed with personnel licensed to perform their duties at the Emergency Medical Technician, Intermediate and Paramedic levels. Information captured during the on-scene phase of EMS care includes the following: a chief complaint-based patient history, routine vital signs, and a summary clinical impression by EMS providers. This information is directly entered into an electronic medical record, HealthEMS (Sansio Corporation, Duluth, Minnesota), by EMS providers. Although temperature is not routinely measured, a tactile temperature assessment is performed.

Data source

EMS and hospital electronic medical records were linked based on the following criteria: patient name, date of birth and date and time of the EMS and Emergency Department (ED) encounters. Records met all three criteria before a record was considered successfully linked. Potential EMS predictor variables were chosen and abstracted from routinely collected EMS data and included the following categories: patient demographics, past medical history, EMD 9-1-1 dispatch complaint category, EMS vital signs and other EMS characteristics. Data abstraction was performed by trained abstractors who were overseen by a lead abstractor (C.P.) to follow procedures outlined in the study operations manual. Random audit of 5% of all abstracted charts were performed by the lead abstractor to ensure at least 95% consistency with the operations manual.

Outcome of interest

The primary outcome was a clinical diagnosis of severe sepsis, including septic shock, within the first 48 hours of hospital arrival. The time cutoff was selected *a priori* in order to exclude cases of hospital-acquired severe sepsis. Severe sepsis was defined as present if the diagnosis was documented in clinical records by the admitting team. EMS and hospital demographics, biologic and physiologic data, admission diagnoses and hospital outcomes were collected for each patient.

Data storage and descriptive analysis

Data were collected and entered into REDCap, an online, HIPAA-compliant database. For descriptive analysis, mean values with standard deviations are reported for variables that are normally distributed. Median values with interquartile ranges are reported for non-normally distributed variables. Student's t test and Chi-square (or Fisher's exact) tests were used as appropriate to report differences in means and proportions, respectively.

Risk prediction model

The cohort was randomly divided into derivation (80%) and validation (20%) subgroups [22]. To derive the predictive model, univariable logistic regression analysis was performed on routinely collected EMS variables as predictors of severe sepsis. Variables were chosen for univariable analysis based on biologic plausibility, or if there was a significant difference in the distribution in those with and without severe sepsis (**Table 1)**. Infectious symptoms were grouped into a composite category of fever, cough or infection due to small sample size of individual symptoms and instability in the model when symptoms were run individually. Respiratory failure and respiratory arrest were grouped into a composite category for the same reason. Seizure was not modeled as a risk factor due to small cell counts and resultant model instability.

Variables associated with a p-value <0.10 were retained in a multivariable model, and variables associated with a p-value <0.05 were retained in the final model. Forward selection, backward elimination and stepwise selection procedures were performed. Hosmer-Lemeshow test was used to determine goodness of fit of the model with a p-value >0.05 indicating good fit. The final model was tested in both derivation and validation subgroups to plot a receiver operating characteristic (ROC) curve and calculate area under the curve (AUC).

Defining a classification rule

A classification rule was defined and applied to the predictive model in order to classify patients in binary fashion as having or not having severe sepsis, based on an arbitrarily selected cut point. To do this, a classification table of predicted probabilities was reviewed, and a cut point that preserved high sensitivity was selected to minimize false negatives, given that the risks of undertreatment are greater than the risks of overtreatment. Predicted probability ≥3% was selected as the cut point. Preserving high sensitivity in order to rule out disease (low false negative rate) was prioritized to ensure the utility of the screening tool [23].

Clinical risk scoring system

Using a previously described method based on point estimate-weighted values for each predictor, the predictive model was converted into a prehospital, severe sepsis risk prediction score (PreSS) to increase ease of use [24]. Briefly, predictors were organized into categories, and a reference value (W_{iRef}) and referent risk factor profile (W^{ij}) were determined. The distance from each category to the base category was then determined in regression units by multiplying the distance by the parameter estimate (β_i). A constant (B) was chosen

to define one point, and finally the point(s) associated with each predictor were calculated. We chose 10 times the beta estimate for systolic blood pressure to define one point. A maximum score of 24 points was defined. A risk classification table including a range of all possible points was reviewed to arbitrarily select a highly sensitive cut point. The cut point was used to classify scores as increased or low risk for severe sepsis. A cut point of ≥2 points was chosen.

Study approval and software

The study protocol was reviewed and approved by the Emory Institutional Review Board and the Grady Research Oversight Committee. All statistical analysis was performed using SAS (version 9.3; SAS Institute Inc.; Cary, North Carolina).

RESULTS

Descriptive analysis

Among 66,439 EMS transports to Grady Memorial Hospital between January 1, 2011 and December 31, 2012, 555 met entry criteria, of which 14% (n=75) had severe sepsis **(Figure 1).** Baseline characteristics of patients with and without severe sepsis were compared **(Table 2).** Patients with severe sepsis were older (56 vs. 50 years, p=0.002), more likely to have a history of stroke (21% vs. 6%, p<0.0001), and less likely to have a history of asthma (9% vs. 21%, p=0.02).

EMS characteristics of patients are listed and compared in **Table 3.** Patients with severe sepsis were more likely to have an EMD 9-1-1 complaint category of "Sick Person" (40% vs. 16%, p<0.0001) and to be transported from a nursing home (29% vs. 6%, p<0.0001)**.** Patients with severe sepsis were also more likely to have hot tactile temperature (36% vs. 21%, p<0.0001), lower systolic blood pressure [(90mmHg (IQR 83-98) vs. 100mmHg (IQR 90-106), p<0.0001)], higher heart rate [123 (IQR 112-140) vs. 114 (IQR 104-130), p=0.01], lower oxygen saturation [92% (IQR 87-96) vs. 96% (IQR 92-99), p<0.0001)] and lower Glasgow Coma Scale (GCS) [(14 (IQR 9-15) vs. 15 (IQR 14-15), p<0.0001) **(Table 4).**

The following initial EMS impression categories were more frequently documented in patients with severe sepsis: respiratory failure or arrest (4% vs. 0.4%, p=0.02), shock (4% vs 0.6%, p=0.04), altered or loss of consciousness (28% vs. 11%, p<0.0001), and a composite category of fever, infection or cough (15% vs. 8%, p=0.04) **(Table 5).** The following initial EMS impression categories were more frequently documented in patients

without severe sepsis: chest pain (1% vs 11%, p=0.01), asthma (0% vs. 7%, p=0.01), and seizure (0% vs. 8%, p=0.01).

In-hospital mortality for patients with severe sepsis was 31% (n=23) as compared to 9% (n=25) for those without severe sepsis (p<0.0001).

Development and validation of the predictive model

Using univariable logistic regression analysis, the following variables were found to be significant predictors of severe sepsis in the derivation subgroup: older age modeled in tertiles, absent medical history of asthma, medical history of stroke, transport from nursing home, EMD chief complaint category of "Sick Person", initial EMS impression of a composite of shock, respiratory failure or arrest, initial EMS impression of altered or loss of consciousness, hot tactile temperature assessment, low systolic blood pressure, elevated heart rate, elevated respiratory rate, low oxygen saturation, and low GCS **(Table 6).**

In a multivariable logistic regression model, the following 6 predictors remained significant: older age modeled in tertiles, transport from nursing home, EMD chief complaint category of "Sick Person", hot tactile temperature, low systolic blood pressure, and low oxygen saturation **(Table 7)**. These predictors were retained for the final predictive model **(Table 8)**.

In the final model, Hosmer-Lemeshow goodness-of-fit test demonstrated good model fit (Chi-square statistic 6.34; p=0.61). Performance characteristics of the model were determined in both the derivation and validation subgroups (AUC derivation 0.832; AUC validation 0.803) **(Figure 2)**. Using a highly sensitive cut point of predicted probability ≥3%, the sensitivity and specificity were calculated in both the derivation and validation

subgroups (sensitivity: derivation 91%, validation 78%; specificity: derivation 34%, validation 26%) **(Table 9)**.

Development of the Prehospital Severe Sepsis (PreSS) Score

The predictive model was used to generate the PreSS score and an estimate of points-based risk using the same 6 risk factors used in the model: an Emergency Medical Dispatch (EMD) chief complaint category of "Sick Person", EMS transport from a nursing home, patient age, hot tactile temperature assessment, systolic blood pressure and oxygen saturation. Using a highly sensitive cut point of ≥2 points, the PreSS score demonstrated a sensitivity of 86% and a specificity of 47% **(Table 9**). A pre-screening flow sheet and the final PreSS score can be seen in **Figure 3** and **Table 10**, respectively.

DISCUSSION

We have derived and validated a simple, reliable EMS severe sepsis screening tool, the PreSS Score, that demonstrates a sensitivity of 86% and a specificity of 47%. The PreSS score makes use of various types of routinely collected EMS data and includes the following 6 risk factors: an EMD chief complaint category of "Sick Person", EMS transport from a nursing home, older patient age, hot tactile temperature assessment, low systolic blood pressure and low oxygen saturation. Although most of these characteristics have been previously identified as risk factors for severe sepsis, to our knowledge, EMD chief complaint category of "Sick Person" and transport from nursing home are novel additions for a severe sepsis screening tool [5, 25, 26]. The impetus for using a data-based approach stems from the inherent difficulty that comes with identifying complex syndromes, like severe sepsis, in low resource settings. For example, we were surprised to learn that the composite category of EMS impression of fever, infection or cough was not a significant predictor for severe sepsis. Although this finding may be related to small sample size, it may also reflect a potential limitation of using traditional sepsis criteria in low-resource settings.

The potential applications and implications of incorporating screening tools such as the PreSS score into advanced EMS care pathways are promising. Diagnostic challenges currently limit prehospital identification of these patients resulting in potential delay in the initiation of life-saving treatment. In fact, a recent epidemiologic study showed that although the prehospital care interval was, on average, greater than 45 minutes for EMS patients with severe sepsis, only 54% of patients with severe sepsis were transported by paramedics, and only 37% received prehospital intravenous access [19]. These types of basic

interventions are relatively simple to implement and may potentially translate into improvements in the quality of patient care.

To our knowledge, three other screening tools have been developed to identify severe sepsis in the EMS setting [15-17]. However, the PreSS score is unique, in that, it is the only tool that has been developed using a large derivation cohort, whereas other screening tools have adapted standard inpatient diagnostic criteria without determining whether the adapted criteria are useful in the EMS setting. Other unique advantages of the PreSS score compared to other screening tools include the ease of use and cost efficiency. Other screening tools include: 1) the Guerra protocol that utilizes POC lactate, 2) the Robson screening tool, and 3) the BAS 90-30-90 [15-17]. In a small, pilot study, the Guerra protocol demonstrated low sensitivity of 48%, and is also limited by the fact that POC lactate is not routinely available in most EMS systems, including ours. Performing this test also contributes to additional cost.

The Robson screening tool was first described as a perspective piece in 2009 by Robson *et al* and is an adaptation of Surviving Sepsis Campaign Guidelines diagnostic criteria [5, 16]. It utilizes modified systemic inflammatory response syndrome (SIRS) criteria, the presence of a suspected infection, and measures of end-organ dysfunction including systolic blood pressure, oxygen saturation, anuria, lactic acidosis, and prolonged bleeding from injury or gums. In a recent validation study, the Robson screening tool demonstrated a sensitivity of 93%. Finally, the BAS 90-30-90 is a tool recommended for use in Swedish EMS guidelines that uses 3 clinical indicators: systolic blood pressure <90 mmHg, respiratory rate >30 breaths per minute, and oxygen saturation <90% [27]. The BAS 90-30-90 tool has

demonstrated a sensitivity of 81%. Although the sensitivity of the Robson tool and BAS 90-30-90 approach or exceed that of the PreSS Score, the specificity of these tools is unknown.

Our study has several important limitations. Most notably, the PreSS Score was developed from a pragmatic standpoint, in that, its use is not meant for a general EMS population. Rather, all patients in our study had abnormal EMS vital signs (SBP <110, HR>90 and RR>20). Performance of the PreSS score in a general EMS population is unknown, and thus its use in this setting is discouraged. Athough this is not necessarily a limitation of the study design, it is a limitation of the tool that should be taken into account in future studies. In addition, our study is retrospective in nature. Although arguably the only type of design that practically lends itself to building a large predictive model, it also introduces the potential for misclassification bias.

We acknowledge that misclassification of complaints, physical findings and disease may be present in our study. First, classification of EMD 9-1-1 complaint category may vary between medical dispatchers, but we assert that the highly algorithmic, scripted nature of questioning utilized by Grady EMS minimizes this variation. Second, Grady EMS does not routinely measure temperature, but rather performs a tactile temperature assessment. Variation in the method utilized by EMS providers to obtain temperature assessment may lead to variation in results, especially in the case of patients with heart failure, for example. In this situation, cold knees may indicate low cardiac output state rather than a low core temperature. However, in a secondary analysis of our data, our group has previously shown correlation between EMS tactile temperature assessment and the first core temperature measured in the Emergency Department [28].

Finally, misclassification bias may exist in our outcome measure: diagnosis of severe sepsis by the admitting team within 48 hours of hospital arrival. It is possible that a diagnosis by the inpatient team represents severe sepsis that was not present in the EMS setting, but this risk is likely very low. In addition, defining a gold standard for sepsis diagnosis is a topic of ongoing debate [29-31]. As a syndrome defined by a constellation of signs and symptoms, consensus does not currently exist regarding the most valid means of studying the epidemiology of severe sepsis.

Although validated internally, it is also noteworthy that our study was conducted at a single center which limits the external validity of our findings. The PreSS Score will need to be validated in other populations before widespread use can be recommended. Finally, the PreSS Score uses basic prehospital data that is routinely collected. As the EMS environment increasingly incorporates advanced diagnostic capabilities, the PreSS Score should be reassessed to incorporate technologies such as point-of-care biomarker testing in order to further improve performance characteristics of the tool in the future.

In conclusion, the PreSS Score is a prehospital severe sepsis screening tool that has been scientifically derived and validated using EMS clinical data and performs with a sensitivity of 86% and a specificity of 47%. Future validation is needed before testing the potential benefit of the PreSS Score in the early detection of severe sepsis.

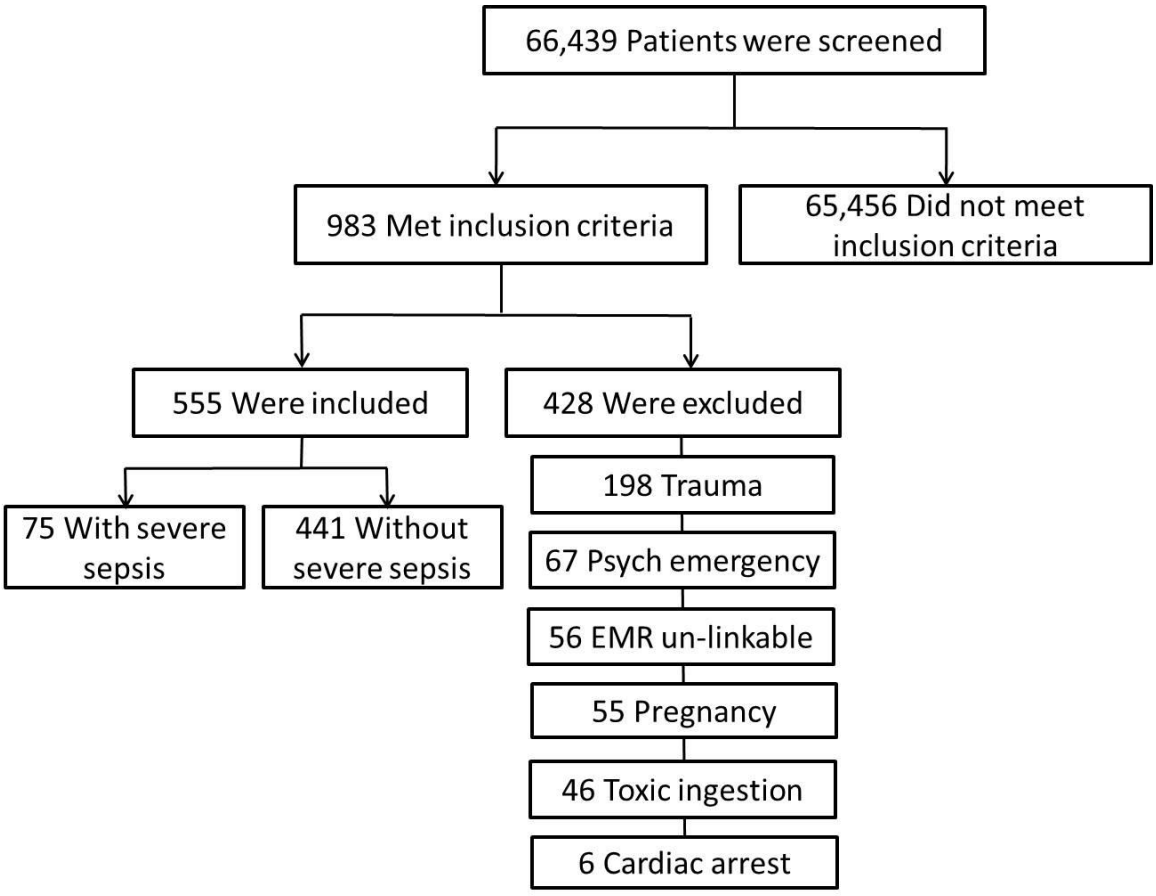
FIGURES AND TABLES

Table 1. EMS Predictor Variables

Demographics	**EMS impression**
Age†*	**RF or arrest†***
Sex†	**Shock†***
Race†	**Difficulty in breathing†***
Past medical history	**Diabetes†***
Asthma*	**Altered or LOC†***
Stroke*	**Fever, infection, cough†***
Cancer†	**EMS vital sign**
HIV†	**Hot tactile temperature†***
Diabetes†	**Systolic blood pressure†***
EMS variables	**Heart rate†***
Transport from nursing home*	**Respiratory rate†**
EMD dispatch complaint:	**Oxygen saturation†***
Difficulty in breathing†	**Blood glucose†**
Diabetes†	**Glascow Coma Scale†***
Sick person†*	
Altered or LOC†	

†Known association and/or biologically plausible. *Significantly different in severe sepsis vs. non-severe sepsis groups.

Figure 1. Patient Selection †



Definitions: EMR – Emergency Medical Record. † Inclusion criteria: age ≥ 18, EMS systolic blood pressure <110 mmHg, EMS heart rate >90 bpm, EMS respiratory rate >20bpm.

Table 2. Patient Characteristics

Patient Characteristics			
Characteristic	**Patients with severe sepsis (N=75)**	**Patients without severe sepsis (N=480)**	**P-value**
Age – years, mean (SD)	56 (15)	49 (16)	0.002
Female sex – no. (%)	35 (47)	252 (53)	0.35
Race and ethnicity – no. (%)			0.57
Caucasian	8 (11)	33 (7)	
African-American	63 (84)	417 (87)	
Hispanic	1 (1)	14 (3)	
Other	3 (4)	16 (3)	
Medical history – no. (%)			
Cardiac	9 (12)	100 (21)	0.07
Hypertension	31 (41)	182 (38)	0.57
Diabetes	16 (21)	93 (19)	0.69
Stroke	16 (21)	30 (6)	<0.0001
Seizure	9 (12)	52 (11)	0.76
Asthma	7 (9)	102 (21)	0.02
COPD	4 (5)	40 (8)	0.37
CKD	5 (7)	26 (5)	0.66
Hemodialysis	4 (5)	21 (4)	0.71
Cancer	8 (11)	49 (10)	0.90
HIV/AIDS	11 (15)	59 (12)	0.56

Definitions: COPD – chronic obstructive pulmonary disease; CKD – chronic kidney disease; HIV/AIDS – human immunodeficiency virus / acquired immunodeficiency syndrome

Table 3. EMS Characteristics

EMS Characteristics			
Characteristic	**Patients with severe sepsis (N=75)**	**Patients without severe sepsis (N=480)**	**P-value**
EMD chief complaint category – no (%)			
Chest pain	4 (5)	58 (12)	0.08
Cardiac symptoms	1 (1)	7 (2)	1.00
Difficulty in breathing	17 (23)	161 (34)	0.06
Diabetes-related complaint	2 (3)	23 (5)	0.56
Stroke	1 (1)	9 (2)	1.00
Unconscious	9 (12)	38 (8)	0.24
Seizure	4 (5)	39 (8)	0.40
Sick person	30 (40)	79 (16)	<0.0001
Abdominal pain	3 (4)	15 (3)	0.72
Hemorrhage	2 (3)	21 (4)	0.76
Other	2 (3)	29 (6)	0.24
Transport from location – no (%)			
Residence	43 (57)	330 (69)	0.05
Nursing home	22 (29)	29 (6)	<0.0001
Other	7 (9)	99 (21)	0.02
Not documented	1 (1)	12 (3)	1.00

Definitions: EMD – Emergency Medical Dispatch. All dispatch categories were defined and determined by use of Priority Dispatch Corporation software.

Table 4. EMS Vital Signs

EMS Vital Signs			
Characteristic	**Patients with severe sepsis (N=75)**	**Patients without severe sepsis (N=480)**	**P-value**
Tactile temperature – no. (%)			
Hot	27 (36)	56 (12)	<0.0001
Normal	38 (51)	358 (76)	<0.0001
Cool	9 (12)	55 (12)	0.92
Cold	1 (1)	5 (1)	0.59
SBP – mmHg, median (IQR)	90 (83-98)	100 (90-106)	<0.0001
HR – bpm, median (IQR)	123 (112-140)	114 (104-130)	0.01
RR – bpm, median (IQR)	26 (22-30)	24 (22-28)	0.07
O2 saturation - %, median (IQR)	92 (87-96)	96 (92-99)	<0.0001
Glucose – mg/dL, median (IQR)	134 (94-165)	123 (102-168	0.70
GCS – median (IQR)	14 (9-15)	15 (14-15)	<0.0001

Definitions: SBP – systolic blood pressure; HR – heart rate; RR – respiratory rate; GCS – Glascow Coma Scale; IQR – interquartile range

Table 5. Initial EMS Impression

Initial EMS Impression			
Impression	**Patients with severe sepsis (N=75)**	**Patients without severe sepsis (N=480)**	**P-value**
Respiratory failure or arrest	3 (4)	2 (0.4)	0.02
Shock	3 (4)	3 (0.6)	0.04
Chest pain	1 (1)	53 (11)	0.01
Difficulty in breathing	14 (19)	87 (18)	0.91
Asthma	0 (0)	34 (7)	0.01
Pulmonary edema	0 (0)	8 (2)	0.60
Abdominal pain	7 (9)	28 (6)	0.30
Nausea, vomiting, diarrhea	2 (3)	19 (4)	0.75
Stroke	0 (0)	1 (1)	1.00
Altered or LOC	21 (28)	52 (11)	<0.0001
Seizure	0 (0)	36 (8)	0.01
Dehydration	3 (4)	20 (4)	1.00
Dizzy or weak	9 (12)	28 (6)	0.05
Diabetes	3 (4)	31 (6)	0.60
Hemorrhage	1 (1)	16 (3)	0.71
Fever	3 (4)	6 (1)	0.11
Infection	8 (11)	29 (6)	0.14
Cough	0 (0)	1 (1)	1.00
Fever, infection, cough	11 (15)	36 (8)	0.04
Other	1 (1)	42 (9)	0.03
Not Documented	1 (1)	7 (1)	1.00

Definitions: LOC – loss of consciousness

Table 6. Univariable Analysis*

Univariable Analysis (N=441)†		
Predictor variable	**Odds Ratio (95% CL)**	**P-value**
Demographics		
Age – (tertiles)		
<40	Reference	--
50-59	7.65 (2.30-25.45)	<0.001
≥60	6.73 (1.92-23.52)	<0.01
Sex (M:F)	1.36 (0.78-2.39)	0.28
Race (AA:C)	0.81 (0.30-2.21)	0.51
Medical History		
Asthma (Y/N)	0.33 (0.13-0.86)	0.02
Stroke (Y/N)	5.10 (2.39-10.91)	<0.0001
Cancer (Y/N)	1.31 (0.56-3.11)	0.53
HIV (Y/N)	0.96 (0.41-2.23)	0.92
Diabetes (Y/N)	1.44 (0.75-2.77)	0.28
EMS Characteristics		
Nursing home transport (Y/N)	8.87 (4.30-18.29)	<0.0001
EMD chief complaint		
DIB (Y/N)	0.70 (0.37-1.31)	0.26
Diabetes (Y/N)	0.90 (0.20-4.02)	0.88
Sick person (Y/N)	3.32 (1.84-6.01)	<0.0001
Altered or LOC (Y/N)	0.96 (0.32-2.85)	0.94
Initial EMS impression		
Shock, RF or arrest (Y/N)	7.17 (1.74-29.53)	0.006
DIB (Y/N)	1.37 (0.70-2.69)	0.35
Diabetes (Y/N)	0.70 (0.16-3.08)	0.64
Altered or LOC (Y/N)	2.91 (1.49-5.68)	0.002
Fever, cough, infection (Y/N)	2.30 (0.87-4.62)	0.11
EMS Vital Signs		
Hot tactile temp (Y/N)	3.81 (2.02-7.18)	<0.0001
SBP – per 1 mmHg increase	0.95 (0.93-0.97)	<0.0001
HR - per 1 bpm increase	1.01 (1.00-1.03)	0.02
RR – per 1 bpm increase	1.04 (1.00-1.08)	0.046
Oxygen saturation – per 1 % inc.	0.94 (0.91-0.97)	<0.0001
Blood glucose – per 1 mg/dL inc.	1.00 (1.00-1.00)	0.12
GCS – per 1 point increase(3-15)	0.86 (0.80-0.92)	<0.0001

Definitions: HIV – human immunodeficiency virus; DIB – difficulty in breathing; EMD – Emergency Medical Dispatch; RF – respiratory failure; LOC – loss of consciousness; SBP – systolic blood pressure; HR – heart rate; RR – respiratory rate; GCS – Glascow Coma Scale; SE- standard error; CL – confidence limit.

† Analysis performed in the derivation subgroup.

* All variables modeled as binary categorical predictors unless otherwise stated. Sex modeled as male vs. female (reference); race modeled African-American vs. Caucasian (reference). Age, SBP, heart rate, respiratory rate, oxygen saturation, GCS and blood glucose modeled as continuous variables.

Table 7. Multivariable Analysis*

Multivariable Analysis (N=441)†		
Predictor variable	**Odds Ratio (95% CL)**	**P-value**
Demographics		
Age (tertiles)		
<40	Reference	--
50-59	3.83 (1.05-14.07)	0.04
≥60	1.63 (0.39-6.75)	0.50
Medical History		
Asthma (Y/N)	0.45 (0.14-4.41)	0.17
Stroke (Y/N)	1.88 (0.65-5.43)	0.24
EMS Characteristics		
Nursing home transport (Y/N)	4.47 (1.77-11.25)	<0.01
EMD dispatch complaint		
Sick person (Y/N)	2.46 (1.12-5.40)	0.03
Initial EMS impression		
Shock, RF or arrest (Y/N)	0.61 (0.05, 6.76)	0.68
Altered or LOC (Y/N)	1.49 (0.55-4.03)	0.43
EMS Vital Signs		
Hot tactile temp (Y/N)	2.52 (1.10-5.74)	0.03
SBP – per 1 mmHg increase	0.96 (0.94-0.99)	<0.01
HR - per 1 bpm increase	1.00 (0.98-1.02)	0.92
RR – per 1 bpm increase	0.98 (0.92-1.05)	0.61
Oxygen saturation – per 1% inc.	0.94 (0.90-0.99)	0.01
GCS – per 1 point inc. (3-15)	0.98 (0.87-1.11)	0.77

Definitions: EMD – Emergency Medical Dispatch; RF – respiratory failure; LOC – loss of consciousness; SBP – systolic blood pressure; HR – heart rate; RR – respiratory rate; GCS – Glascow Coma Scale; CL – confidence limit.

† Analysis performed in the derivation subgroup.

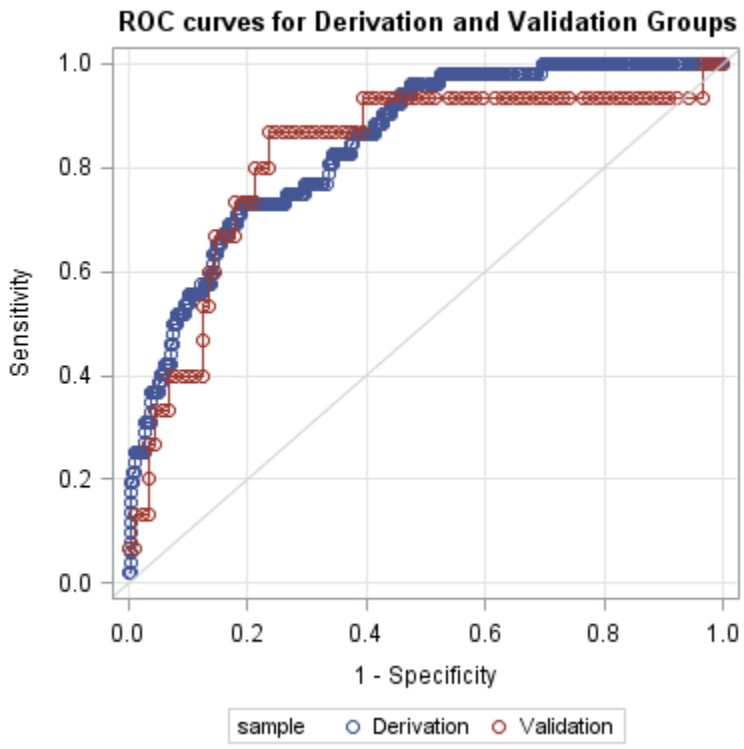
* All variables modeled as binary categorical predictors unless otherwise stated. Sex modeled as male vs. female (reference); race modeled African-American vs. Caucasian (reference). Age, SBP, heart rate, respiratory rate, oxygen saturation, GCS and blood glucose

Table 8. Final Severe Sepsis Predictive Model

Final Predictive Model (N=441)		
Predictor Variable	**Odds Ratio (95% CL)**	**P-value**
Age – (tertiles)		
<40	Reference	--
50-59	4.28 (1.20-15.38)	0.03
≥60	2.19 (0.56-8.66)	0.26
Nursing home transport (Y/N)	4.73 (2.01-11.13)	<0.001
EMD complaint: sick person (Y/N)	3.04 (1.45-6.37)	<0.01
Hot tactile temperature (Y/N)	2.90 (1.35-6.23)	<0.01
SBP – per 1 mmHg increase	0.96 (0.93-0.99)	<0.01
O2 saturation – per 1% increase	0.95 (0.91-0.99)	<0.01

Definitions: EMD – Emergency Medical Dispatch; SBP – systolic blood pressure; CL – confidence limit.

Figure 2. ROC Curves for Derivation and Validation Subgroups*



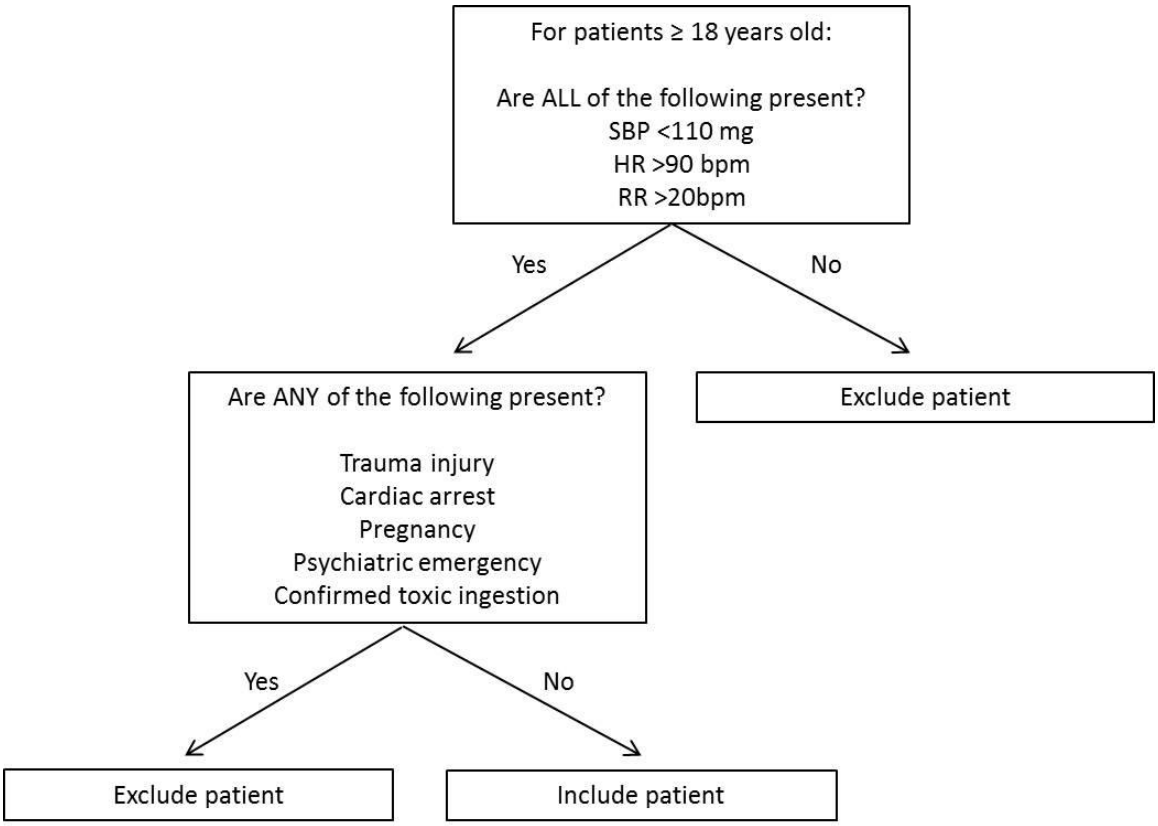
Definitions: ROC – receiver-operating characteristic; AUC – area under curve

*AUC derivation – 0.832; AUC validation 0.803

Table 9. Performance of the Predictive Model and PreSS Score

Performance of the Predictive Model and PreSS Score			
Characteristic	**Model Derivation (N=441)**	**Model Validation (N=114)**	**PreSS Score**
Sensitivity	91%	78%	86%
Specificity	34%	26%	47%
Positive predictive value	17%	16%	19%
Negative predictive value	96%	86%	96%

Figure 3. Pre-screening Flow Sheet



Definitions: SBP – systolic blood pressure; HR – heart rate; RR – respiratory rate

Table 10. Prehospital Severe Sepsis (PreSS) Score

Pre-hospital Severe Sepsis (PreSS) Score**	
**For use in at-risk patients ONLY. See pre-screening flow sheet.	
Risk Factor	**Points**
1. EMD chief complaint: sick person	3
2. Nursing home transport	4
3. Age	
18-39	0
40-59	4
>=60	2
4. Hot tactile temperature	3
5. Systolic blood pressure (mmHg)	
100-109	0
90-99	1
80-89	2
70-79	3
60-69	4
<60	5
6. Oxygen saturation (%)	
≥ 90	0
80-89	1
70-79	3
60-69	4
<60	5
Total Points (0-24):	
Increased risk for severe sepsis = 2 or more points	

Definitions: EMD – Emergency Medical Dispatch

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