

The Shock Index as a Predictor of Vasopressor Use in Emergency Department Patients with Severe Sepsis

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Introduction: Severe sepsis is a leading cause of non-coronary death in hospitals across the United States. Early identification and risk stratification in the emergency department (ED) is difficult because there is limited ability to predict escalation of care. In this study we evaluated if a sustained shock index (SI) elevation in the ED was a predictor of short-term cardiovascular collapse, defined as vasopressor dependence within 72 hours of initial presentation.

Methods: Retrospective dual-centered cross-sectional study using patients identified in the Yale-New Haven Hospital Emergency Medicine sepsis registry.

Results: We included 295 patients in the study with 47.5% (n=140) having a sustained SI elevation in the ED. Among patients with a sustained SI elevation, 38.6% (54 of 140) required vasopressors within 72 hours of ED admission contrasted to 11.6% (18 of 155) without a sustained SI elevation (p=0.0001; multivariate modeling OR 4.42 with 95% confidence intervals 2.28-8.55). In the SI elevation group the mean number of organ failures was 4.0 ± 2.1 contrasted to 3.2 ± 1.6 in the non-SI elevation group (p=0.0001).

Conclusion: ED patients with severe sepsis and a sustained SI elevation appear to have higher rates of short-term vasopressor use, and a greater number of organ failures contrasted to patients without a sustained SI elevation. An elevated SI may be a useful modality to identify patients with severe sepsis at risk for disease escalation and cardiovascular collapse. [West J Emerg Med. 2014;15(1):60–66.]

INTRODUCTION

Severe sepsis and septic shock are the 10th leading cause of death in the United States (U.S.) with mortality rates ranging from 28–50%.^{1,2} Over the past several decades the incidence of each has progressively increased^{3,4} with roughly two thirds of patients initially presenting to the emergency department (ED).^{2,5} Of the 2.3 million annual visits to U.S. EDs, severe sepsis represents about 1–3% of all people presenting with an infectious disease related illness^{6,7} and accounts for 1 in 10

admissions to the intensive care unit,⁸ culminating in healthcare costs around 16.7 billion dollars per year.²

Currently for emergency physicians (EP) or other healthcare providers responsible for initial management, there are limited modalities to risk-stratify patients at risk for short-term cardiovascular collapse and escalation of disease (i.e. vasopressor dependence). The shock index (SI, heart rate divided by systolic blood pressure)⁹ is a simple formula useful for detecting changes in cardiovascular performance before the onset of systemic hypotension.^{10–17} A SI elevation greater than

0.8 has a reported 95% sensitivity for predicting shock.¹⁰ It is an easily accessible, non-invasive, and non-costly risk stratification tool that may enhance current EP methods for differentiating severe sepsis patients at risk for imminent cardiovascular collapse. While several studies have evaluated the initial SI value upon presentation to the ED,^{9,11,16} no studies to our knowledge have evaluated the influence of a sustained SI elevation in any clinical environment.

The objective of this preliminary study is to evaluate the role of a sustained SI elevation as a predictor of short-term cardiovascular collapse, defined as vasopressor dependence within 72 hours of ED initial presentation. We hypothesize that severe sepsis patients with a sustained SI elevation greater than 0.8 are at greater risk for short-term vasopressor use, and, that a sustained SI elevation is one instrument that may help to risk stratify patients with severe sepsis at risk for progression to shock.

METHODS

Study Setting and Design

The study was performed at a dual-site teaching hospital ED with nearly 100,000 patient visits annually. It was a retrospective cross-sectional study using patients identified prospectively in the Yale-New Haven Hospital Emergency Medicine sepsis registry. The study was approved by the Yale Human Investigation Committee for the review of medical records by study personnel. The registry is comprised of a patient list created between July 1, 2005, and July 31, 2007. In a systematic and standardized fashion, we prospectively and consecutively identified sepsis registry patients during pre-defined time periods at 2 EDs as a quality improvement initiative tracking sepsis outcomes (i.e., short term mortality) and quality measures (i.e.—lactate measurement, time to antibiotics, implementation of EGDT) for ED patients in the Yale Health System. Over the 2-year time period there were 189,867 cumulative visits at both sites (155,757 patient visits in the Adult Section of the Yale-New Haven Hospital ED; 34,110 visits at the Shoreline Medical Center ED). We screened 5,228 patients, generating a list of 359 septic patients in the registry over the cited time period.

Study Population and Measurements

Inclusion criteria for the study were as follows: at least 18 years of age, fulfillment of at least 2 of the 4 systemic inflammatory response syndrome (SIRS) criteria¹⁸, a documented clinical source of infection, and fulfillment of at least one type of organ dysfunction (i.e.—severe sepsis) at the time of presentation to the ED.

We defined end-organ dysfunction^{19–21} as having at least one of the following: transient hypotension defined as at least one documented systolic blood pressure reading below 90 mmHg in the ED; lactate level greater than 2.0 mmol/mL; unexplained acidosis defined as either an arterial blood gas pH below 7.35 or serum bicarbonate below 21 mg/dl; documented

change in mental status from baseline; a serum platelet count less than 150,000/mm³ with no history of prior thrombocytopenia; a total bilirubin elevation greater than 1.2 mg/dl in the absence of underlying chronic liver disease; an elevation of serum coagulation factors in the absence of chronic liver disease or anticoagulant medications (PT >12sec, PTT>45 sec, INR>1.8); evidence of acute kidney injury defined as a serum creatinine increase above 0.5 mg/dl from baseline or greater than 1.2 mg/dl if no baseline was available; documented hypoxemia with at least one oxygen saturation less than 90%, or an elevated serum troponin above 0.04 mg/dl. We calculated cumulative organ dysfunction scores (i.e., Physiology and Chronic Health Evaluation II [APACHE II], Mortality in Emergency Department Sepsis [MEDS] score) from physiologic parameters and laboratory results acquired in the ED.

We excluded patients from the study if they were discharged to home or to another facility from the ED, if they arrived at the hospital in extremis (defined as having an initial systolic blood pressure less than 80 mmHg and being administered a vasopressor medication within 15 minutes of arrival to the ED), or if they had a pre-existing advance directive for the implementation of comfort care measures prior to ED presentation.

We calculated the SI for each set of vital signs that was documented until admission from the ED or the initiation of a vasopressor in the ED. The percentage of SI elevation for each patient was determined by taking the total number of SI values greater than 0.8 and dividing this number by the total number of vital signs taken. We then used this calculation to estimate the total percentage of time that each patient maintained a SI elevation in the ED. The sustained SI elevation group was defined as having a SI greater than 0.8 for at least 80% of the ED vital sign measurements. The non-sustained SI elevation group was defined as having a SI greater than 0.8 for less than 80% of the vital sign measurements in the ED. As an alternative analysis, we further sub-divided patients based on the total percentage of time each patient had an elevated SI. We also looked at the initial SI for all study patients and compared it to our outcomes of short-term vasopressor use and hospital mortality.

Study Protocol and Measurements

Data were extracted in a standardized and systematic fashion²² from medical records by two medical students (MW, SB) under the supervision of a faculty investigator (CW) with internal procedures to ensure extraction accuracy >90%. Medical students used a customized data collection form and glossary of terms to extract pre-defined demographical and clinical data points. Both electronic and paper records were used for abstraction. We obtained electronic records using MD Link™, Sunrise Clinical Manager™ and Lynx Medical Systems.™ All hard-copy medical charts were reviewed in the Yale-New Haven Hospital office of medical records. Collected

Table 1. Baseline characteristics comparing patients with and without a sustained shock index (SI) elevation in the emergency department.

Chronic Co-morbidities - \pm SD, n (%)	Sustained SI elevation (n=140)	Non-sustained SI Elevation (n=155)	P-value
Age	56.5 \pm 18.7	67.9 \pm 16.6	0.00
Female	76 (54.3)	66 (42.6)	0.05
Congestive heart failure	36 (25.7)	36 (23.2)	0.68
Coronary artery disease	27 (19.3)	47 (30.3)	0.03
Hypertension	57 (40.7)	96 (61.9)	0.00
Chronic obstructive pulmonary disease	21 (15)	30 (30.0)	0.36
Asthma	6 (4.3)	13 (8.4)	0.16
Diabetes (Type 1 or 2)	43 (30.7)	61 (39.4)	0.14
Chronic liver disease	16 (11.4)	11 (7.1)	0.23
History of end stage renal disease	17 (12.1)	17 (11.0)	0.86
Chronic immunosuppression	23 (16.4)	17 (11.0)	0.18
Human immunodeficiency virus or acquired immunodeficiency syndrome	10 (7.1)	10 (6.5)	0.82
History of cancer	41 (29.3)	34 (21.9)	0.18
History of ischemic stroke or transient ischemic attack	15 (10.7)	26 (16.8)	0.18
Chronic altered mental status	13 (9.3)	21 (13.5)	0.28
Extended care facility	28 (20)	49 (31.6)	0.02

data were transcribed from data collection forms into a customized Microsoft Excel database created by the faculty investigator. Patient subjects were randomly assigned study ID numbers to protect personal health information according to guidelines established by our Human Investigation Committee. We conducted weekly meetings to review extracted data and to ensure internal consistency in data extraction. To demonstrate internal accuracy in data extraction, the two medical students collected 551 overlapping data points with 95% agreement.

Data Analysis

Investigators performed statistical analysis in consultation with a statistical consultant from the Yale Department of Emergency Medicine. In performing a 2-tailed post-hoc power calculation (using a Type I error rate of 5%, the total sample size of 295–140 in the sustained SI group; 155 in the group without a sustained SI elevation) we calculated that our study has 100% statistical power, and that it has the appropriate sample size to detect a 12% difference between each group (80% power threshold). Continuous data were reported as the mean and standard deviation. We performed a comparison of means using an unpaired t-test. Fisher's exact test was used to compare groups with categorical variables, including the rates of vasopressor use among patients with a sustained SI elevation contrasted to those without a sustained SI elevation. Statistical significance was indicated by a p-value (or alpha error) <0.05 . To perform statistical analyses, investigators initially used Graph Pad Quick Calcs, GraphPad Software, (San Diego California

USA, www.graphpad.com). Multivariate modeling was performed by a Department of Emergency Medicine faculty member and statistical expert who adjusted for potential confounding variables using SAS software (Cary, NC).

RESULTS

Of the 359 patients identified in the Yale sepsis registry, 82.2% (n=295) met study inclusion criteria. Of the 64 patients excluded from the study, no patients were excluded for age, 7.8% (n=5) were excluded for being in extremis at presentation, 12.5% (n=8) were excluded for having pre-existing comfort measures prior to ED presentation, 23.4% (n=15) were discharged to home or to a facility from the ED, and 57.8% (n=37) were excluded for having fewer than 2 SIRS criteria in the ED or no evidence of end organ dysfunction.

In our cumulative sample, 47.4% (n=140) patients had a sustained SI elevation. Forty-eight percent (142 of 295) were female and the mean age at presentation for all patients was 62.5 \pm 18.5 years (Table 1). Of the 16 co-morbid conditions reviewed, patients with a sustained SI were less likely to have a history of coronary artery disease (19.3 versus 30.3%, $p=0.0319$) and hypertension (40.7 versus 61.9 %, $p=0.0003$). Patients in the sustained SI elevation group had a lower initial systolic blood pressure (102.6 \pm 22.5 versus 127.4 \pm 29.7 mmHg, $p<0.0001$), and higher initial heart rate (112 \pm 21.0 versus 96 \pm 19.7 beats per minute, $p<0.0001$, Table 2).

The mean number of organ dysfunctions at initial presentation was greater in patients with a sustained elevated SI (4.0 \pm 2.1 versus 3.2 \pm 1.6, $p=0.0001$) compared to those without a sustained SI (Table 3). In contrast, there was no

Table 2. Vital signs, systemic inflammatory response syndrome (SIRS) criteria, and localized source of infection in patients with a sustained shock index (SI) elevation and patients without a sustained SI elevation. Results are either reported as the mean \pm SD, or the absolute number (%) of patients with a specific source of infection.

Clinical variables	Sustained SI elevation (n = 140)	Non-sustained SI elevation (n = 155)	P-value
Vital signs and SIRS criteria (mean \pm SD)			
Initial systolic blood pressure – (mmHg)	102.6 \pm 22.5	127.4 \pm 29.7	0.0001
Initial heart rate – (beats per minute)	112.0 \pm 21.0	95.5 \pm 19.7	0.0001
Temperature – (degrees Fahrenheit)	99.2 \pm 2.3	98.8 \pm 2.8	0.1574
Respiratory rate – (breaths per minute)	20.6 \pm 5.0	20.8 \pm 4.2	0.3268
White blood cell count – ($\times 10^3$ per mL)	12.7 \pm 8.3	14.1 \pm 7.9	0.1454
Glasgow Coma Scale (3–15)	14.2 \pm 1.8	13.9 \pm 2.3	0.2302
Localized source of infection- n (%)			
Respiratory	42 (30.0)	47 (30.3)	1.0000
Urinary system	21 (15.0)	23 (14.8)	1.0000
Abdominal	16 (11.4)	18 (11.6)	1.0000
Soft tissue	9 (6.4)	17 (11.0)	0.2178
Line infection	11 (7.9)	2 (1.3)	0.0084
Other - Not otherwise specified	10 (7.1)	6 (3.9)	0.3036

difference in the mean APACHE II (18.8 \pm 7.2 versus 18.1 \pm 6.8, $p=0.3187$) or MEDS score (11.6 \pm 4.8 versus 11.5 \pm 4.4, $p=0.88$ between patients with a sustained elevated SI compared to those without.

Initial laboratory data showed no difference between groups except that there were higher initial lactate levels (2.8 \pm 2.6 versus 2.3 \pm 1.7 mmol/dl, $p=0.0426$) in the sustained SI elevation group. Patients with a sustained SI elevation were more likely to receive blood products in the ED, and they also

received a greater amount of crystalloid fluid volume resuscitation (3.6 \pm 2.4 versus 2.7 \pm 3.9 liters, $p=0.0267$). 42.1% ($n=59$) with a sustained SI elevation underwent central line placement in the ED compared to 27.1% ($n=42$) without a sustained SI elevation ($p<0.005$).

There was no difference in the mean ED length of stay between the sustained SI elevation group and the non-sustained SI elevation group respectively: the time in the ED was 6:27 hours \pm 3:48 hours versus 7:07 hours \pm 4:18 hours ($p=0.287$).

Table 3. End-organ dysfunction in patients with a sustained shock index (SI) elevation versus a non-sustained SI elevation.

End organ failure measures	Sustained SI elevation n=140	Non-sustained SI elevation n=155	P-value
Cumulative organ failure scores			
Total number of organ failures	4.0 \pm 2.1	3.2 \pm 1.6	0.0001
APACHE II	18.9 \pm 7.2	18.1 \pm 6.8	0.3187
MEDS	11.6 \pm 4.8	11.5 \pm 4.4	0.8814
End organ failure - n (%)			
Transient hypotension (SBP<90mmHg)	101 (72.1)	50 (32.3)	0.0001
Lactate elevation >2.0 mg/dl	63 (45.0)	60 (38.7)	0.2891
Unexplained acidosis	74 (52.9)	73 (47.1)	0.3519
Altered mental status from baseline	52 (37.1)	63 (40.6)	0.5522
Platelets <150,000 mm ³	35 (25.0)	26 (16.8)	0.0862
Total bilirubin >1.2 mg/dl	80 (57.1)	57 (36.8)	0.0007
Elevation of coagulation factors	31 (22.1)	20 (12.9)	0.0448
Acute kidney Injury	62 (44.3)	65 (41.9)	0.7245
Hypoxemia	38 (27.1)	42 (27.1)	1.0000
Troponin elevation >0.04 mg/dl	28 (20.0)	34 (21.9)	0.7750

APACHE II, Acute Physiology and Chronic Health Evaluation II; MEDS, Mortality in Emergency Department Sepsis

In our total sample, 24.4% (72 of 295) received a vasopressor agent within 72 hours of initial presentation. Of the 140 patients with a sustained SI elevation, 38.6% (n=54) were placed on vasopressors within 72 hours of presentation, compared to 11.6% (n=18) of the 155 patients who did not have a sustained SI elevation ($p=0.0001$). The proportion of patients placed on vasopressors appeared to be directly related to the total percentage of time patients had a shock index elevation (Figure). Multivariate modeling with correction for potential confounding variables resulted in an OR of 4.42 for vasopressor use within 72 hours among patients with a sustained SI elevation (95% CI 2.28 to 8.55).

In the initial ED presentation, 83.0% (n=245) had an early systolic blood pressure greater than 100 mmHg defined as having at least one of the first 3 systolic blood pressure measurements greater than 100 mmHg. In this subgroup, there was also a significant difference in rates of 72-hour vasopressor use between patients with a sustained SI elevation (n=98) compared to those without a sustained SI elevation (n=147)—30.6% versus 8.2% respectively, ($p<0.0001$).

In further analyses, the isolated initial shock index elevation did not correlate with rates of vasopressor use, in-hospital mortality, or ICU admission. Overall, for our total sample the in-hospital 28-day mortality rate was 15.6% (46 of 295). Patients with a sustained elevated SI had a 19.3% (n=27) mortality, compared to 12.3% (n=19) in patients who did not have an elevated SI ($p=0.1093$). Regardless of SI elevation, all patients placed on vasopressors within 72 hours had higher 28-day mortality rates compared to those who did not receive vasopressors (41.7% versus 7.2%, $p=0.0001$).

DISCUSSION

The SI was first described in the 1960s as the ratio of heart rate to systolic blood pressure.²³ While it was originally designed to identify apparently stable yet critically ill trauma patients, the SI has since been shown to be a simple, non-invasive risk stratification tool useful for detecting changes in cardiovascular performance before the onset of systemic hypotension and cardiorespiratory collapse.¹¹ Since its original description, the SI has been evaluated for this purpose in patients with cardiogenic shock,¹² sepsis,¹³ ectopic pregnancy,¹⁴ gastro-intestinal hemorrhage,²⁴ and pulmonary embolism.¹⁵

In a precursor study,¹³ Rady et al. looked at patients with apparently stable vital signs and divided them into 2 groups based on whether the patient had a SI elevation. The study associated an elevated SI with higher admission rates to hospital floor beds and to ICUs, as well as poorer outcomes. Authors concluded that when used alone, an elevated SI was more sensitive than using heart rate or systolic blood pressure alone to predict the severity of illness, and had a higher specificity.

What is considered an abnormal SI elevation? The reported range in the literature is between 0.8 to 1.0.^{10,13,25} One

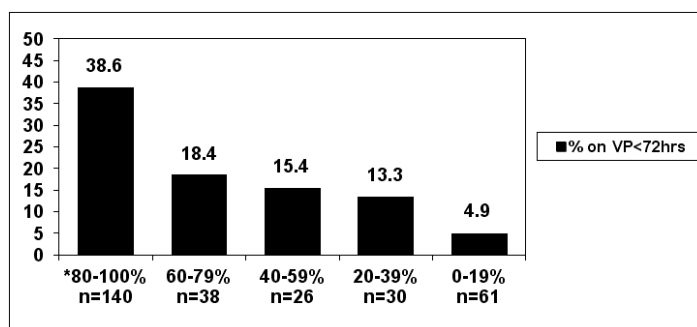


Figure. The rate of vasopressor use within 72 hours in relation to the total percentage of emergency department vital sign measurements with an elevated shock index. (* $P<0.05$ when the 80–100% group is compared to all other groups).

study from Mexico showed an improvement in sensitivity to 95% when using a SI of 0.8, although their population evaluated surgical patients and did not focus specifically on sepsis.¹⁰ Given the variable definition of an elevated SI, there is no established cut-off for an elevated SI above normal (0.5-0.7) that has been routinely applied to critical care literature.

Several areas of focus differentiate our study from others. This is the first study to our knowledge evaluating the impact of a sustained SI elevation. All prior studies evaluating the SI have evaluated single, isolated, initial values rather than taking into account the trajectory of change once fluid resuscitation, antibiotics, and other therapies are instituted. Many have suggested that the SI is potentially a macro-endpoint to resuscitation—but to our knowledge this has also never been studied. We believe there is great merit for the EP using the simple, non-costly, and non-invasive SI measurements to risk stratify patients who are at risk for potential cardiovascular collapse. Also, the sustained SI elevation is something that could be incorporated into future scoring systems aimed at differentiating patients at risk for decompensation versus those that aren't. Furthermore, given the pressure to reduce healthcare costs—a non-costly risk stratification tool for determining which patients truly need the costly resources of an ICU admission is needed.

What further differentiates our research is that while prior studies evaluating the SI have used hospital admission and mortality rates as primary endpoints, we used the endpoint of short-term vasopressor dependence to represent escalation of disease because, for initial providers, progression to vasopressor dependence is a more relevant outcome measure contrasted to overall 28-day mortality. Furthermore, given that the SI is a hemodynamic variable, we believed that short-term vasopressor use was a good marker of hemodynamic decompensation. Although it is still unclear whether the SI is a useful tool when used alone to aid EPs in treatment decisions and triage^{13,25}, it may prove useful in combination with predictors of illness severity and other information routinely available to practitioners.

In this study we identified that a sustained SI elevation in the ED was indeed associated with higher rates of short-term vasopressor use. We also observed a potential relationship between the total percentage of time that patients maintained a SI elevation in the ED and vasopressor use, suggesting that the longer a patient maintains an elevated SI, the more likely they are to require vasopressors within 72 hours.

Similar to the Jones et al study²⁵ we did not find discerning value predictive of outcome when looking only at the initial SI value. There was no difference in vasopressor use or mortality between patients with an initial SI elevation contrasted to those without. Thus, from our data we surmise that a sustained SI elevation may be a more useful measure for risk stratification rather than a single initial SI elevation.

We also found that patients with a sustained SI elevation had a higher mean number of organ failures than those without a sustained elevated SI (4.0 versus 3.1, $p=0.0001$), although there was no difference in APACHE II and MEDS score. This observation does suggest, however, that a sustained SI elevation may serve to identify patients with a potentially greater number of organ failures in the ED, and, could prove to be valuable in clinical settings where laboratory turn-around times for results may approach 60 to 90 minutes.

Looking at other initial vital signs as a predictor of vasopressor use, we found that the initial systolic blood pressure of patients who were placed on vasopressors was lower than those who were not placed on vasopressors (101 versus 120 mmHg). There was also a difference in systolic blood pressure between patients who had a sustained SI elevation and those who did not (102 v. 127 mmHg). While common sense suggests that patients with lower systolic blood pressures would have higher rates of vasopressor use, we identified several points underscoring the potential value of also looking at the SI as a predictor of disease progression. First, nearly 60 percent of the patients with a sustained SI had an initial SBP > 100 mmHg. This finding suggests that a proportion of patients with normal blood pressures and an elevated SI may be at risk for hemodynamic decompensation. Second, the non-sustained SI group had a proportion of patients who were hypertensive in the ED, thus skewing the blood pressure comparison between groups (systolic blood pressure > 170 mmHg, $n=14$, range 170 to 224 mmHg). Third, when we performed a sub-group analysis on patients with an early systolic blood pressure above 100 mmHg ($n=245$), we still found a significant difference in vasopressor use between patients with a sustained SI elevation and those who did not have a sustained SI (30.6% versus 8.2%, $p<0.0001$). Thus, our data suggest that the SI is potentially a valuable and non-costly marker to enhance existing methods to risk stratify septic patients.

LIMITATIONS

General limitations of this study were retrospective data extraction and a relatively small sample size. Additionally, patient selection came from a registry that was not all-inclusive

but did implement procedures (i.e., prospective and consecutive enrollment during predefined time periods) to reduce inclusion or selection bias. There was temporal variability, and variability in the total number of vital sign measurements performed in the ED by the initial providers – the mean number of ED vital sign measurements in our total patient population was 8.06 ± 4.38 , but in a separate analysis this did not depend upon normal or abnormal values. The retrospective data extraction was limited by many factors inherent to the process, including possible errors in the medical record. The 95% accuracy among the 2 data extractors confirmed overall accuracy.

CONCLUSIONS

ED patients with severe sepsis and a sustained SI elevation appear to have higher rates of short-term vasopressor use contrasted to patients without a sustained SI elevation. A sustained SI elevation may be a promising simple, cost-efficient, and non-invasive measurement to help risk stratify patients who present to the ED with severe sepsis, and may complement other predictors of disease progression. A sustained SI elevation may be a useful modality to identify patients with severe sepsis at risk for disease progression.

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