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Risk factors for infection and evaluation of Sepsis-3 in patients with trauma

Emanuel Eguia [a, b, *], Adrienne N. Cobb [a, b], Marshall S. Baker [b], Cara Joyce [c], Emily Gilbert [d], Richard Gonzalez [a, b], Majid Afshar [a, c, d], Matthew M. Churpek [e]

[a] Loyola University Chicago Burn Shock Trauma Research Institute, Maywood, IL, USA
[b] Department of Surgery, Acute Care Surgery Division, Loyola University Chicago, Maywood, IL, USA
[c] Department of Public Health Sciences, Loyola University Chicago, Maywood, IL, USA
[d] Division of Pulmonary and Critical Care Medicine, Loyola University Chicago, Maywood, IL, USA
[e] Division of Pulmonary and Critical Care Medicine, University of Chicago, Chicago, IL, USA

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ABSTRACT

Background: We aim to examine the risk factors associated with infection in trauma patients and the Sepsis-3 definition.
Methods: This was a retrospective cohort study of adult trauma patients admitted to a Level I trauma center between January 2014 and January 2016.
Results: A total of 1499 trauma patients met inclusion criteria and 15% (n = 232) had an infection. Only 19.8% (n = 46) of infected patients met criteria for Sepsis-3, with the majority (43%) of infected cases having a Sequential Organ Failure Assessment (SOFA) score greater on admission compared to the time of suspected infection. In-hospital death was 7% vs 9% (p = 0.65) between Sepsis-3 and infected patients, respectively. Risk factors associated with infection were female sex, admission SOFA score, Elixhauser score, and severe injury ($P < 0.05$).
Conclusion: Patients with trauma often arrive with organ dysfunction, which adds complexity and inaccuracy to the operational definition of Sepsis-3 using changes in SOFA scores. Injury severity score, comorbidities, SOFA score, and sex are risk factors associated with developing an infection after trauma.

Introduction

Sepsis is one of the leading causes of in-hospital death.[1,2] Trauma patients with hospital-acquired infections carry higher mortality, cost, and length of stay.[3] Nearly a quarter of trauma patient admissions develop sepsis during their hospital admission.[1] Approximately 14% of penetrating trauma patients develop sepsis.[4] The mortality rate of those with sepsis is about 13% which increases to 64% in those with septic shock.[4] Improving the identification and treatment of these patients is therefore critical to improving hospital outcomes of patients admitted with trauma.

The current definition of sepsis, established in 2016 by The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), is life-threatening organ dysfunction caused by a dysregulated host response to infection.[5] Organ dysfunction is defined in practice as an increase in the Sequential Organ Failure Assessment (SOFA) score of at least two points from a patient's baseline.[6,7] However, discriminating between the clinical manifestations of severe trauma where many of the SOFA criteria for organ dysfunction are present and SOFA criteria being attributable to infection remains challenging, and there could be a delay in the initiation of antibiotics. For example, patients with severe blunt or penetrating trauma meet SOFA criteria 83% and 17%, respectively, during their hospitalization.[8] Identifying trauma patients at high risk for sepsis may enhance decision making for time-sensitive and appropriate therapy.

Few studies have examined useful approaches to identify patients with trauma that go on to develop sepsis. Many patients with severe trauma present with organ dysfunction attributable to their injuries, which adds complexity to discriminating between infectious and non-infectious organ dysfunction.[9] Therefore, we aim to examine the Sepsis-3 definition for identifying cases of sepsis in

* Corresponding author. Burn Shock Trauma Research Institute, Loyola University Medical Center, 2160 S 1st Avenue, Maywood, IL, 60153, USA.
E-mail address: emanuel.eguia@lumc.edu (E. Eguia).

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patients with trauma and, separately, examine risk factors for the development of sepsis.

Methods

Study design

We identified a retrospective cohort of consecutive trauma patients from Loyola University Medical Center trauma registry (LUMC) between January 1, 2014, and January 1, 2016. LUMC is a 547-bed tertiary academic medical center and Level 1 trauma center. Loyola University Chicago Institutional Review Board approved this study.

Study cohort

All adult (ages 18 or older) trauma patients admitted to the hospital were included for analysis. Suspected infection was defined as meeting the Seymour et al. criteria for suspected infection in the electronic health record (EHR).[10] A patient had to have antibiotic administration preceding body fluid culture obtained within 24 h or body fluid culture obtained first with antibiotic administration within 72 h. Time 0 was defined as the first of these two events. Patients were excluded if they were not admitted for a primary trauma inpatient stay.

Determining the likelihood of infection

All patients with suspected infection underwent detailed manual chart review by trained physician abstractors who rated the likelihood of infection on a five-point Likert scale with the following options: definite (confirmed by cultures and other testing/exams); probable (more likely than other causes); possible (as likely as other causes); unlikely (suspected, but ultimately deemed less likely than other causes); and not infected (neither suspected nor confirmed during admission). Physician abstractors were trained surgery residents (EE and ANC) who conducted the chart review to determine whether or not the subject showed signs of infection, using a structured instrument adapted from Iwashyna et al.[11] The inter-observer agreement was calculated between the resident physicians and an attending critical care physician at the beginning of the study period (MA) to ensure a reliable review using a threshold kappa of $\geq$0.70 between the resident and attending.

SOFA score derivation

The SOFA score at the time of onset of infection was calculated as the highest score in the 48 h before the start of infection to 24 h after the onset of infection. The admission SOFA score was calculated as the highest score in the first 24 h after arriving at the emergency department. The change in SOFA score was the difference between the highest SOFA score at the onset of infection and in the first 24 h. The following variables for the SOFA score were extracted from the EHR[1]: partial pressure of oxygen (PaO2) over the fraction of inspired oxygen (FiO2) or pulse oximetric saturation (SpO2) over the FiO2 if the PaO2 is not available[2]; platelet count ($x10^3/\mu l$)[3]; Bilirubin (mg/dL)[4]; mean arterial pressure or presser dose[5]; Glasgow coma score[6]; creatinine (mg/dL). If values for PaO2/FiO2 or SpO2/FiO2 were missing then it was assumed the patient did not have hypoxic respiratory failure and a score of 0 was imputed. Similarly, bilirubin was missing 19% of values, and a SOFA score of 0 was imputed as a conservative estimate. All other SOFA criteria had at least 96% of the data available.

Outcomes and analytic approach

The primary analysis aimed to identify the risk factors associated with the presence of infection, which was defined as "proven" or "probable" infection based on the detailed chart review. The non-infected group included patients in the possible, unlikely, not infected,and those who didn't meet the Seymour et al. definition of suspected infection. Cases for suspected infection were defined as either patients who had an antibiotic administered no more than 24 h preceding a body fluid culture or a body fluid culture obtained first with antibiotic administration within 72 h.[10] Baseline characteristics were presented as means and standard deviations, medians and interquartile ranges, or counts and percentages. Unadjusted comparisons of two or more proportions between infected and non-infected patients were performed using a chi-squared test, and continuous variables were compared using t-tests or Wilcoxon rank sum tests as appropriate. Both univariable and multivariable analyses to investigate the predictors of infection were performed using logistic regression. Candidate variables in the multivariable analysis included the following: age, gender, Elixhauser comorbidity score, admission SOFA score, diabetes, hypertension, alcoholism, obesity, congestive heart failure (CHF), history of drug abuse, cirrhosis, race/ethnicity, abbreviated injury scores (AIS) for all body regions, injury severity score (ISS), and mechanism of injury. The Elixhauser score is a measure relying on ICD-9 codes to identify patient comorbidities and is associated with in-hospital mortality.[12] An ISS $\geq$15 and AIS >2 were considered severe and serious trauma, respectively, and scores were collapsed into categorical variables for the multivariable analysis. Institutional administrative data was queried to obtain comorbidities using International Classification of Diseases, 9th version (ICD-9) codes. Analyses were performed using STATA 14 software (College Station, TX).

Results

During the study period, a total of 2175 patients had a primary diagnosis of trauma, of which 958 trauma patients met the inclusion criteria for suspected infection and 15% (n = 232) of the suspected infection cohort were identified as having "proven" or "probable" infection after manual annotation (Fig. 1). The median time to infection was five days (IQR 2–7 days). The median age was 49 years old (IQR 48–65), and 31% (n = 458) were female. The most common mechanisms of injury were blunt (84.5%, n = 1267) and penetrating (15.1%, n = 226) trauma. Patients with infection had a higher Elixhauser comorbidity score and a greater proportion with severe injury than the non-infected cohort ($p < 0.01$) (Table 1).

The median SOFA score at the time of admission was higher for infected (4; IQR 1–7) patients compared to non-infected patients (2; IQR 0–3, $p < 0.01$). The sources of infection with the greatest frequencies were urine (44%, n = 101), lung (33%, n = 76), bloodstream (8%, n = 18), skin & soft tissue (8%, n = 18), and bowel (6%, n = 14) (Fig. 2). The most frequently identified organisms in those with suspected infection were non-extended spectrum beta-lactamase *Escherichia coli* (22.9%, n = 54), Methicillin-sensitive Staphylococcus Aureus (9.3%, n = 22), non-multi drug-resistant Pseudomonas (6.8%, n = 16), vancomycin sensitive enterococcus (7.6%, n = 18) , and non-ESBL Klebsiella (7.2%, n = 17) (Fig. 3). The median SOFA score at the time of infection was five (IQR 2–7). The admission SOFA score was greater than the SOFA score at the time of infection in 17% (n = 40) of infected cases. Of those with infection, 19.8% (n = 46) met the Sepsis-3 criteria (Table 1). In patients meeting Sepsis-3 criteria, 7% (n = 3) died, whereas 8% (n = 16) of the infected patients who did not meet Sepsis-3 died during their hospitalization (Table 2).

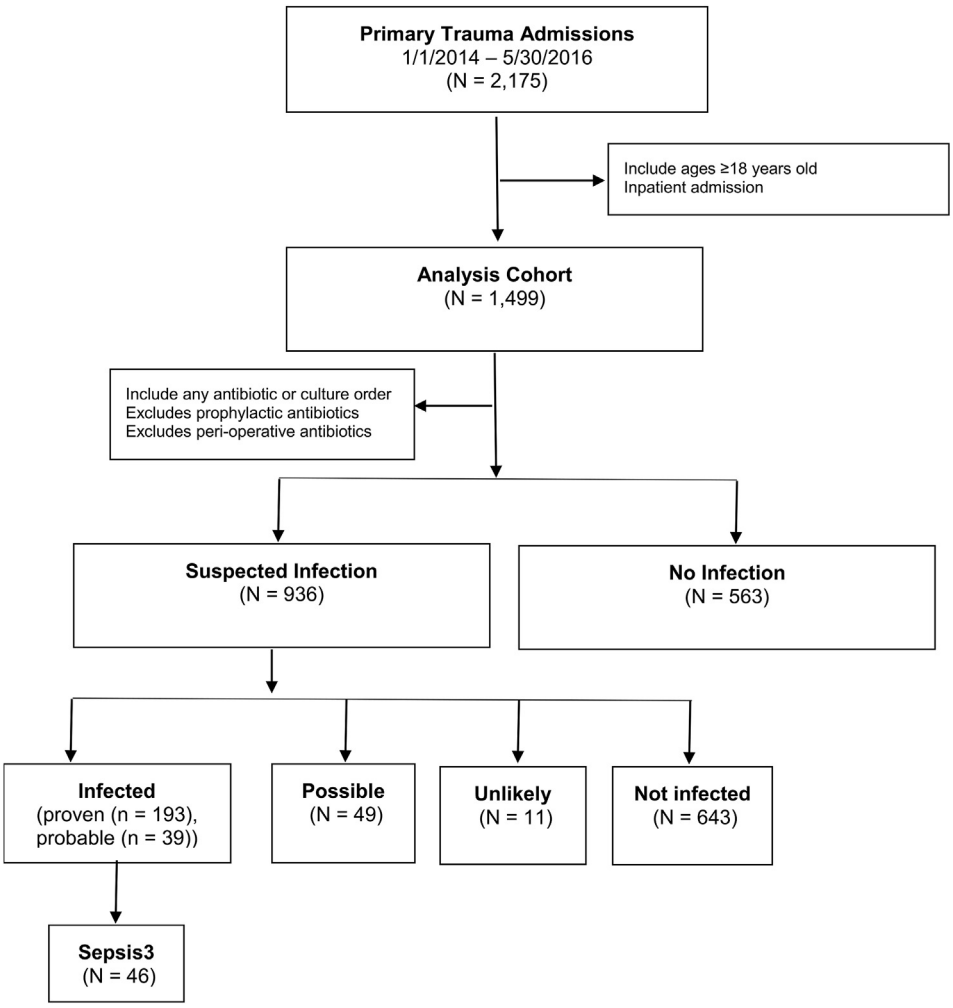

Fig. 1. Patient cohort selection.

In multivariable analysis, the risk factors associated with the development of infection were, female sex (OR 1.52; 95% CI: 1.08–2.15), admission SOFA (OR 1.14% per 1-unit score increase; 95% CI: 1.09–1.20), Elixhauser comorbidity score for mortality (OR 1.07 per 1-unit score increase; 95% CI: 1.04–1.09), and ISS $\geq$ 15 (OR 1.79, 95% CI: 1.25–2.56). (Table 3).

Discussion

In this study, we demonstrated that patients with the greatest odds for infection have more comorbidities at baseline and trauma-related organ dysfunction. The majority of patients with infection continued to have elevated SOFA scores around the time of infection and did not experience a substantial change in score due to their admission injury characteristics. This study reveals potential problems in the application of the Sepsis-3 criteria to trauma patients which have not been previously addressed.[1,2] With infection occurring a median of five days after admission , characteristics unique to trauma patients that place them at risk for sepsis, such as injury characteristics, may be used to risk stratify patients.

We found that a large proportion of trauma patients that go on to develop infection are admitted with high acute and chronic severity of illness scores represented by ISS, SOFA, and Elixhauser comorbidity score. This makes it challenging to parse out the change in SOFA score over time, rendering it less useful in determining organ dysfunction due to infection. The original study by Seymour et al. validating the use of the Sepsis-3 definition had heterogeneity in types of included patients but little mention about trauma[10]; therefore, application of Sepsis-3 in trauma patients who arrive with elevated baseline SOFA scores was not addressed. In our study, few of the patients who developed infection went on to develop sepsis using the SOFA criteria and very few of the patients who met Sepsis-3 criteria died. This may be due in part to the fact that these patients presented with a high admission SOFA score. This would make identifying an infection-associated organ dysfunction using the rule of an increase in SOFA score by two or more problematic. Supporting this contention, infected patients in our dataset that ultimately did meet the sepsis-3 criteria tended to have lower SOFA scores and a smaller proportion with severe injury at admission than their infected but non-septic counterparts. These patients ultimately had no difference in in-hospital death rates. In the end, we found the Sepsis-3 application to be less reliable in identifying cases of sepsis due to confounding from admission injury and severity of illness characteristics. Identifying risk factors for the development of infection becomes essential in patients with trauma if currently published measures for case-identification, such as Sepsis-3, are not reliable.

Prior studies have aimed at developing prediction models for

Table 1
Trauma patient characteristics with and without infection.

	Infected		Not Infected		Total		p
	N = 232		N = 1267		N = 1499		
Age, median (IQR)	53	53–73	49	47–64	49	48–65	0.02
Female n (%)	90	38.8%	368	29.0%	458	30.6%	0.00
Elixhauser mortality score, median (IQR)	3	0–11	0	1–1	0	0–3	0.00
Insurance							
Private	66	28.4%	388	30.6%	454	30.3%	0.00
Medicare	80	34.5%	308	24.3%	388	25.9%	
Medicaid	69	29.7%	372	29.4%	441	29.4%	
Other	17	7.3%	199	15.7%	216	14.4%	
Race/Ethnicity, n (%)							
Non-Hispanic White	133	57.3%	647	51.1%	780	52.0%	0.33
Non-Hispanic Black	48	20.7%	289	22.8%	337	22.5%	
Hispanic	41	17.7%	256	20.2%	297	19.8%	
Other	10	4.3%	75	5.9%	85	5.7%	
Comorbidities, n (%)							
Diabetes	32	13.8%	65	5.1%	97	6.5%	0.05
Hypertension	67	28.9%	268	21.2%	335	22.3%	0.01
Alcohol abuse	33	14.2%	185	14.6%	218	14.5%	0.88
Obese	10	4.3%	46	3.6%	56	3.7%	0.62
Cirrhosis	6	2.6%	41	3.2%	47	3.1%	0.60
CHF	15	6.5%	27	2.1%	42	2.8%	0.00
Type of Injury, n (%)							
Blunt	189	81.5%	1078	85.1%	1267	84.5%	0.16
Penetrating	40	17.2%	186	14.7%	226	15.1%	0.32
Burn	4	1.7%	6	0.5%	10	0.7%	0.03
Other	1	0.4%	11	0.9%	12	0.8%	0.49
Injury Severity Score ≥15, n (%)	99	42.7%	266	21.0%	365	24.3%	0.00
SOFA at Admission, median (IQR)	4	1–7	2	0–3	2	0–4	0.00
SOFA at time of infection, median (IQR)	5	2–7	Na	Na	Na	Na	
Days to infection, median (IQR)	5	2–8	Na	Na	Na	Na	
Sepsis-3, n (%)	46	19.8%	Na	Na	Na	Na	
In Hospital Death, n (%)	19	8.2%	91	12.8%	110	11.6%	0.59

*Elixhauser risk score for mortality. Sepsis 3 criteria adapted from Seymour et al. Abbreviations: congestive heart failure (CHF).

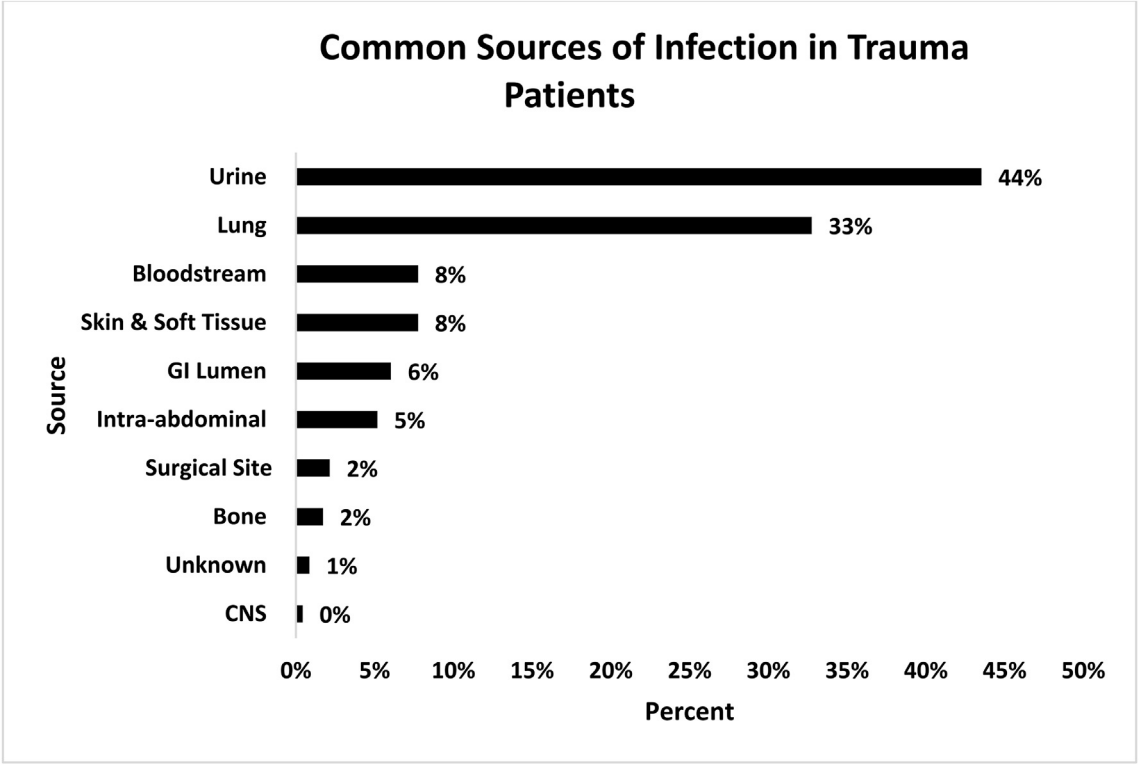

Fig. 2. Common soures of infection in trauma patients.
*Abbreviations: Central Nervous system (CNS) and gastrointestinal (GI).

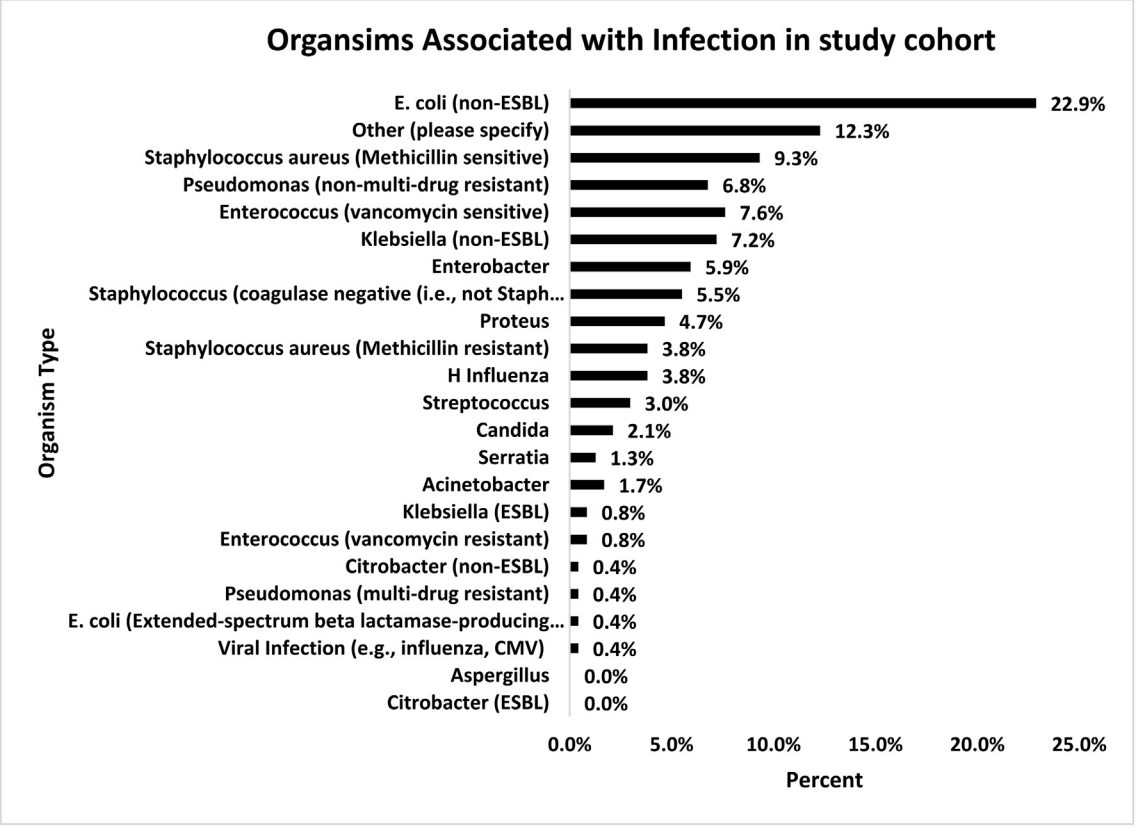

Fig. 3. Organsims Associated with Infection in study cohort.
*Abbreviation: extended-spectrum beta-lactamase positive (ESBL), Haemophilus influenzae (H. Influenza), and cytomegalovirus (CMV).

Table 2
Comparison between those who are infected vs. meet Sepsis3 criteria.

	Sepsis-3		Infected		Total		p
	N = 46		N = 186		N = 232		
Age, median (IQR)	57	38–77	52	30–72	53	32–74	0.12
Female n (%)	17	37.0%	73	39.2%	90	38.8%	0.78
Elixhauser, median (IQR)	1	0–8	3	0–12	3	0–11	0.20
Insurance							
Private	8	17.4%	58	31.2%	66	28.4%	0.14
Medicare	22	47.8%	58	31.2%	80	34.5%	
Medicaid	13	28.3%	56	30.1%	69	29.7%	
Other	3	6.5%	14	7.5%	17	7.3%	
Race/Ethnicity, n (%)							
non-Hispanic White	27	58.7%	106	57.0%	133	57.3%	0.33
Black	7	15.2%	41	22.0%	48	20.7%	
Hispanic	8	17.4%	33	17.7%	41	17.7%	
Other	4	8.7%	6	3.2%	10	4.3%	
Comorbidities, n (%)							
Diabetes	9	19.6%	23	12.4%	32	13.8%	0.21
Hypertension	13	28.3%	54	29.0%	67	28.9%	0.92
Alcohol abuse	17	37.0%	16	8.6%	33	14.2%	0.01
Obese	1	2.2%	9	4.8%	10	4.3%	0.43
Cirrhosis	0	0.0%	6	3.2%	6	2.6%	0.22
CHF	5	10.9%	10	5.4%	15	6.5%	0.18
Type of Injury, n (%) s							
Blunt	39	84.8%	150	80.6%	189	81.5%	0.52
Penetrating	6	13.0%	34	18.3%	40	17.2%	0.40
Burn	2	4.3%	2	1.1%	4	1.7%	0.13
Other	0	0.0%	1	0.5%	1	0.4%	0.02
Injury Severity Score ≥15, n (%)	12	26.1%	87	46.8%	99	42.7%	0.01
SOFA at Admission, median (IQR)	2.4	2–4	5.0	2.7%	4.4	1.9%	0.00
SOFA at time of infection, median (IQR)	6.4	4–8	5.0	2.7%	5.2	2.2%	0.02
Days to infection, median (IQR)	4	1–5	5	2.7%	5	2.2%	0.01
In Hospital Mortality, n (%)	3	6.5%	16	8.6%	19	8.2%	0.65

*Elixhauser risk score for mortality. Sepsis 3 criteria adapted from Seymour et al. Abbreviations: congestive heart failure (CHF).

Table 3
Risk adjusted risk factors associated with infection in trauma patients.

	OR	95% CI	
Age	1.00	0.99	1.01
Female	1.52	1.08	2.15
Sofa, (24hrs)	1.14	1.09	1.20
Elixhauser Mortality Score	1.07	1.04	1.09
Race/ethnicity			
Non-Hispanic white (reference)			
Non-Hispanic Black	1.00	0.64	1.57
Hispanic	1.06	0.68	1.66
Other	0.70	0.32	1.52
Insurance			
Private (reference)			
Medicare	1.63	0.99	2.71
Medicaid	1.06	0.69	1.63
Other	0.67	0.36	1.26
Comorbidities			
Diabetes	0.51	0.27	0.97
HTN	1.35	0.90	2.03
Alcohol	1.44	0.91	2.30
Obesity	1.18	0.53	2.60
Cirrhosis	0.29	0.11	0.82
CHF	1.05	0.46	2.35
ISS >15	1.79	1.25	2.56
Injury Mechanism			
Blunt	0.93	0.25	3.41
Penetrating	1.45	0.39	5.32
Burn	5.69	0.82	39.63
Other injury	0.65	0.05	7.84
AIS >2 by body region			
Head	0.78	0.50	1.22
Face	1.16	0.83	1.61
Thorax	0.85	0.55	1.31
Spine	0.89	0.61	1.31
Upper extremity	0.73	0.52	1.03
Lower extremity	0.74	0.52	1.05
Abdomen	0.61	0.40	0.95

Injury severity score (ISS); abbreviated injury score (AIS); sequential organ failure assessment score (SOFA).

multi-organ failure in trauma patients during their admission, although very few have focused on the development of infection and risk for sepsis.[13,14] Therefore, identifying risk factors unique to trauma patients who develop infection may augment clinical decision making at the bedside when a patient's presenting symptoms may be difficult to distinguish between the onset of infection versus progression of a systemic inflammatory response due to injury. In our study, we found patient sex, acute injury scores with SOFA, ISS, and the Elixhauser comorbidity score were associated with the development of infection. Our study is corroborated by previous studies on sepsis which have found an association of sepsis in elderly patients, female gender, SOFA score, ISS, and pre-existing disease.[4,5,15,16] Previous studies have focused on predicting sepsis in the emergency department, intensive care unit, and general wards[17–19]; however, it remains unclear if these models are helpful in predicting sepsis in trauma patients. Improving the classification of patients at risk for infection and sepsis may lead to a better appropriation of time-sensitive antibiotics, while identification of low-risk patients could improve antibiotic stewardship and decrease unnecessary diagnostics tests. Future research is needed to investigate the pattern of organ dysfunction over time and risk factors for mortality in patients with trauma who develop infection. The model will be in accordance with the guidelines for reporting multivariable prediction models for individual prognosis or diagnosis (TRIPOD).

We also examined the standard sources and organisms of infected trauma patients, with urine and lung representing 77% of the infections. These sources of infection may be unique areas where quality-targeted interventions may play a role in reducing infection in trauma patients (e.g., early discontinuation of Foley catheters).[20–22] Despite quality control measures already in place at our center, including a urinary catheter and central line checklists with daily assessments, the urine was the most frequent source of infection in our study.

This study comes with some limitations. This is a retrospective single-center study so our results may not be generalizable to other trauma centers. Also, our study was limited to adult admissions so the findings may not apply in pediatric trauma. Finally, we did not examine other trauma patient-specific variables, such as pre-hospital and emergency data, labs, vitals, blood product transfusion, and radiologic imaging, to provide a more comprehensive approach to identifying trauma patients at risk of developing an infection.

Conclusion

We demonstrate that trauma patients that develop infection were more severely ill on admission and many arrive with organ dysfunction, which makes the application of the Sepsis-3 definition more challenging and may cause misclassification bias. We identify multiple risk factors unique to trauma patients that may inform future studies aimed at prognostic enrichment strategies for sepsis care in the trauma patient. These results serve as an initial approach to better identify trauma patients who are at risk to develop sepsis so that preventive measures and early treatment may be studied.

Disclosure information

Dr. Churpek has a patent pending (ARCD. P0535US.P2) for risk stratification algorithms for hospitalized patients.

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