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Admission characteristics predictive of in-hospital death from hospital-acquired sepsis: A comparison to community-acquired sepsis

Teresa Padro [a], Carmen Smotherman [b], Shiva Gautam [b], Cynthia Gerdik [a], Kelly Gray-Eurom [a], Faheem W. Guirgis [a,*]

[a] University of Florida College of Medicine-Jacksonville, Department of Emergency Medicine, Jacksonville, FL, United States of America
[b] University of Florida College of Medicine-Jacksonville, Center for Health Equity and Quality Research, Jacksonville, FL, United States of America

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ABSTRACT

Purpose: Healthcare associated (HA) sepsis is associated with increased resource utilization and mortality compared with community acquired (CA) sepsis. The purpose of this study was to identify independent predictors of in-hospital mortality from HA-sepsis.
Materials and methods: Retrospective study of adult patients admitted with HA or CA-sepsis. Predictors were identified using logistic regression.
Results: There were 3917 sepsis encounters, of which 3186 were CA and 731 were HA. History of stroke (83/731, 11%) and myocardial infarction (70/731, 10%) were higher in HA than CA-sepsis (stroke: 258/3186, 8%, $p = .005$; myocardial infarction: 213/3186, 7%, $p = .007$). HA-sepsis patients required more mechanical ventilation (153/731, 21%) than CA-patients (218/3186, 7%, $p < .001$) and had a higher rate of vasopressor use (334/731, 46%) than CA patients (832/3186, 26%, $p < .001$). The HA group had longer ICU lengths of stay (LOS) than CA patients did at 9 days and 2.8 days, respectively ($p < .0001$). Moderate to severe liver disease (OR = 27, 95%CI 1.4, 513, $p = .031$) and congestive heart failure (CHF, 5.81, 95% CI 1.3, 26, $p = .025$) were predictive of in-hospital mortality from HA-sepsis.
Conclusions: Liver disease and CHF were independent predictors of in-hospital mortality in HA-sepsis. HA-sepsis patients had increased prevalence of previous stroke, myocardial infarction, and liver disease.

1. Introduction

CDC statistics from 1999 to 2014 reported about 2.5 million sepsis-related deaths in the United States (6% of all deaths), of which 22% were directly due to sepsis [1]. Sepsis has important consequences; a study with two large independent cohorts showed that sepsis was responsible for 33–50% of hospital mortality, and most mortality cases were associated with sepsis on admission to the hospital [2]. Sepsis accounted for 23.7 billion dollars in health care expenses in 2013 [3], making it the most expensive condition treated in hospitals in 2013 [4-6].

Importantly, research has shown that there are differences between patients admitted for community-acquired (CA) sepsis and those who develop hospital-acquired (HA) sepsis after admission. Rothman and colleagues noted differences in incidence and mortality between CA-sepsis and HA-sepsis in a study of over 250,000 adult inpatient cases from four centers [7]. They showed that the group with CA-sepsis represented 77% to 93% of hospital sepsis with an average 12% mortality rate, and the group with HA-sepsis represented 7% to 23% of all hospital sepsis with a mortality rate of 35% [7]. HA-sepsis is also associated with a higher use of resources than CA-sepsis and healthcare-associated sepsis [8].

Given the significant societal burden and cost related to sepsis, identifying the differences between patient admitted for sepsis, and patients who develop sepsis after admission is important for devising strategies for early recognition and prevention. The overall goal of this study was to determine differences in demographics and baseline characteristics between patients with CA and HA-sepsis. We hypothesized that patients with HA-sepsis would have a higher chronic disease burden and severity of illness with poorer outcomes than patients with CA-sepsis.

2. Methods

2.1. Study design

This was a secondary analysis of a retrospective data set of patients admitted to UF Health Jacksonville who were treated for sepsis. UF Health Jacksonville is a 696-bed, urban, Level 1 trauma center with

* Corresponding author at: Department of Emergency Medicine, UF Health Jacksonville, 655 West 8th Street, Jacksonville, FL 32209, United States of America.
E-mail address: Faheem.Guirgis@jax.ufl.edu (F.W. Guirgis).

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142 ICU beds. The hospital Institutional Review Board approved the study.

2.2. Study patients

The sample consisted of all patients 18 years and older with a diagnosis of sepsis at discharge and who were admitted to all patient care units from October 1, 2013 to November 10, 2015. Cases were identified using ICD-9 diagnosis codes for sepsis, severe sepsis, or septic shock as in previous studies [9]. Sepsis was categorized as present on admission, or CA-sepsis, if the patient was confirmed to have sepsis at the time of admission and at discharge. Patients were considered to have HA-sepsis if they did not have an admission diagnosis of sepsis but had a discharge diagnosis of sepsis. The categorization of sepsis present on admission was made in the electronic health record (EHR) after careful chart review and verification by healthcare professionals trained in data abstraction for billing purposes and with inquiries to admitting providers.

2.3. Chart review and data collection

Demographics including age, race, sex, and comorbidities were obtained from the EHR as were data on Systemic Inflammatory Response Syndrome (SIRS), Sequential Organ Failure Assessment (SOFA), quick Sequential Organ Failure Assessment (qSOFA) scores, mechanical ventilation, vasopressor use, and length of stay (LOS) and mortality. SIRS, SOFA and qSOFA scores were calculated from the first set of values obtained at the time of ED presentation. The Charlson Comorbidity Index (CCI), a mortality predictor based on chronic disease burden was also recorded [10]. The CCI has been used by others to predict mortality from sepsis [11]. The variables examined were demographics (Age, Sex, Race), CCI, mechanical ventilator and vasopressor use; SIRS criteria and SOFA scores; ICU LOS and overall hospital LOS.

2.4. Statistical methods

The primary outcome was HA-Sepsis in-hospital mortality. Univariate and multivariable analyses were performed to evaluate individual associations. Categorical variables were summarized using counts and percentages and analyzed using the Pearson's Chi-square test. Continuous data were summarized using means, standard deviations, and median; and analyzed using Wilcoxon rank sum test. Some patients in the data set had multiple encounters during the data collection period, so in order to account for the possibility of repetition of data points, repeated measure models were fit to these data points in the multivariable analyses. For in-hospital mortality, mechanical ventilation, and vasopressor use, generalized linear mixed models with a logistic link function were fit using a random intercept for each subject. For LOS the log-transformed data was close to normal, so a mixed model repeated analysis was performed and for ICU days, zero-inflated negative binomial models were each fit to these data.

In the multivariable analyses, generalized linear mixed models using a logistic link function were fit with a random intercept for each subject, to determine whether factors (all with $p < .1$ in univariate analyses), such as sex, race (white vs non-white), myocardial infarction (MI), congestive heart failure (CHF), stroke, moderate or severe liver disease, SOFA score, qSOFA score, and SIRS, were associated with in-patient mortality. Five different variance-covariance structures (including first-order auto-regressive, compound symmetry, and "unstructured") were fit, and the structure with the smallest corrected Akaike Information Criterion (AICC) was selected. All statistical models were fit using SAS® 9.4 Stat Version 13.1.

3. Results

There were 3917 sepsis encounters of which, 3186 were CA and 731 were HA-sepsis. For the CA-sepsis group, the most common admitting diagnosis was unspecified septicemia (1919 cases), followed by septicemia due to *E. coli* (124), methicillin resistant *Staphylococcus aureus* septicemia (92), infection and inflammatory reaction due to indwelling urinary catheter (84), HIV (73) other septicemia due to gram negative organisms ($n = 71$), and septicemia due to anaerobes (70). The most common diagnosis in the HA group was HIV disease ($n = 98$), indicating that approximately 1/8th of the HA-sepsis group were immunocompromised. Frequencies of the top non-infectious admitting diagnoses in the HA group included "care involving specified rehabilitative procedure" (37), ischemic or hemorrhagic stroke (30), congestive heart failure (27), acute respiratory failure (25), acute kidney failure (22), trauma (21), and myocardial infarction (19).

The results of the demographics comparison between CA and HA-sepsis showed that in the HA group there were fewer females (322/731, 44%) than in the CA group (1629/3186, 51%, $p < .001$). History of stroke was higher in the HA group (83/731, 11%) than the CA group (258/3186, 8%, $p = .005$), and moderate to severe liver disease was also higher in the HA group (26/731, 4%) than the CA group (75/3186, 2%, $p = .064$). History of MI was higher in HA sepsis as well (70/731, 10%) when compared with CA sepsis (213/3186, 7%, $p = .007$). Finally, though not statistically significant, the presence of CHF was higher in HA-sepsis patients (177/731, 24%) than CA-sepsis patients (668/3186, 21%, $p = .055$). Demographics and comorbidities for all patients are presented in Table 1.

In general, patient acuity at the time of emergency department presentation was lower in the HA-sepsis group than in the CA-sepsis group. Though not clinically significant, CA-sepsis patients had higher

Table 1
Demographics and comorbidities for all patients.

Variable	Overall (3917, 100%)	CA-sepsis (3186, 81%)	HA-sepsis (731, 19%)	P-Value*
Age, median (Q1, Q3)		58 (47, 69)	58 (46, 67)	0.287**
Charlson Comorbidity Index		2 (1, 4)	2(0, 4)	0.010**
Sex				
Female	1951 (50)	1629 (51)	322 (44)	<0.001
Race				
Black	2006 (51)	1669 (52)	337 (46)	0.009
White	1727 (44)	1371 (43)	356 (49)	
Other	184 (5)	146 (5)	38 (5)	
Insurance				
Uninsured	560 (14)	458 (14)	102 (14)	<0.001
Medicaid	1037 (26)	842 (26)	195 (27)	
Medicare	1900 (49)	1600 (50)	300 (41)	
Private	420 (11)	286 (9)	134 (18)	
Comorbidities				
AIDS	184 (5)	167 (5)	17 (2)	<0.001
Cancer (all types)	448 (11)	358 (11)	90 (12)	0.411
CHF	845 (22)	668 (21)	177 (24)	0.055
COPD	1299 (33)	1064 (34)	235 (32)	0.514
Stroke or TIA	341 (9)	258 (8)	83 (11)	0.005
DM (no complications)	1125 (29)	928 (29)	197 (27)	0.238
DM (complications)	283 (7)	229 (7)	54 (7)	0.853
Dementia	123 (3)	110 (3)	13 (2)	0.019
Liver (mild)	441 (11)	359 (11)	82 (11)	0.967
Liver (moderate/severe)	101 (3)	75 (2)	26 (4)	0.064
MI	283 (7)	213 (7)	70 (10)	0.007
Metastatic cancer	156 (4)	131 (4)	25 (3)	0.388
Dialysis	376 (10)	302 (9)	74 (10)	0.594
ESRD	351 (9)	296 (9)	55 (8)	0.131
Mechanical Ventilation	371 (9)	218 (7)	153 (21)	<0.001
Vasopressor use	1166 (30)	832 (26)	334 (46)	<0.001

Data are counts (%); *Pearson's Chi-square test; unless otherwise specified by **Wilcoxon rank sum test.
Abbreviations: Q1, 1st quartile; Q3, 3rd quartile; AIDS, acquired immunodeficiency syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; DM, diabetes mellitus; ESRD, end-stage renal disease.

admission heart rates, temperatures, and initial white blood cell counts than HA-sepsis patients (Table 2). There was a smaller proportion of patients with total SOFA score ≥ 2 in the HA-sepsis group (349/731, 48%) than in the CA-sepsis group (1722/3186, 54%, $p = .002$). The number of patient with ≥2 SIRS criteria was also lower in the HA-sepsis group (455/731, 64%) than the CA-sepsis group (2751/3186, 87%, $p < .001$) (Table 3).

Conversely, HA-sepsis patients had greater severity of illness and resource utilization after development of sepsis during their index hospitalization (Table 2). HA-sepsis patients required more mechanical ventilation (153/731, 21%) than CA patients did (218/3186, 7%, $p < .001$) and had a higher rate of vasopressor use (334/731, 46%) than CA patients (832/3186, 26%, p < .001). The HA group also had a longer ICU LOS than CA patients at 9 days and 2.8 days, respectively ($p < .0001$). Mean hospital LOS was higher in HA-sepsis at 23 days compared with 11 days for CA-sepsis (p < .0001). Mortality of HA-sepsis was nearly double that of CA-sepsis at 19% and 9%, respectively (Table 4).

3.1. Mortality prediction

For the prediction of the primary outcome of HA-sepsis mortality, a multivariable model containing age, sex, all Charlson Comorbidity Index components, SOFA score, qSOFA score, and SIRS criteria was generated. Significant independent predictors of in-hospital HA-sepsis mortality included moderate or severe liver disease (OR = 27.16, 95%CI 1.44, 512.7, $p = .031$) and CHF (OR = 5.81, 95%CI 1.31, 25.90, $p = .025$) (Table 4).

4. Discussion

In this retrospective study comparing HA-sepsis to CA-sepsis, we have shown that patients who develop HA-sepsis have a higher prevalence of moderate to severe liver disease, cardiovascular disease and stroke and that presenting patient acuity was lower than patients with CA-sepsis. In contrast, overall resource utilization and mortality was significantly higher in HA-sepsis. Clinical predictors of HA-sepsis mortality included moderate to severe liver disease and CHF. These findings may provide a basis for future studies aimed at preventing HA-sepsis and may facilitate earlier recognition of HA-sepsis in at-risk admitted patient populations.

Our findings regarding differences in comorbidities between the two populations may have implications for screening for HA-sepsis. History of stroke was higher in HA-sepsis than CA-sepsis, and history of CHF also showed a trend toward being significantly higher in the HA-sepsis group. There are some possible explanations for this finding; stroke patients with a history of stroke who have neurological sequelae, including dysphagia, tend to have impaired mobility that places them at risk for respiratory infections that can lead to sepsis [12]. Berger and colleagues showed that when patients with a history of stroke were admitted to an ICU, the risk for infections and sepsis was even greater due to the instrumentation inherent to the ICU [13]. Perhaps, most interesting is the evidence that the immune suppression mounted to protect the brain after a stroke can have detrimental effects on the immune response of stroke patients, which predisposes them to infection [12]. The observation that AIDS as a comorbidity was lower in HA-sepsis patients than CA-sepsis patients may be explained by a higher suspicion for acute infections in AIDS patients combined with the higher incidence of acute infections in this population. These factors may have raised suspicion for infection in the CA group and an admission diagnosis of sepsis.

In general, HA-sepsis patients had less severe elevations in SIRS, SOFA or qSOFA in comparison to CA-sepsis. These findings are consistent with the absence of sepsis on presentation in HA-sepsis patients as expected. There were also distinct differences between HA and CA-sepsis patients concerning outcomes, including a much greater rate of adverse outcomes in the HA group. HA-sepsis patients were 3 times more likely to require mechanical ventilation than CA-sepsis patients, nearly twice as likely to require vasopressors, they also required longer ICU and hospital stays and had twice the in-hospital mortality compared to CA-sepsis. It is unclear if the increased rate of adverse outcomes and resource utilization shown in HA-sepsis were due to delays in sepsis detection or if they were related to their underlying reason for hospitalization. In all likelihood, it was probably a combination of delayed recognition and chronic disease burden.

The finding that moderate to severe liver disease was a significant independent predictor of HA-sepsis mortality may have implications for sepsis screening and prevention in admitted patients. Daviaud and colleagues demonstrated that sepsis mortality was independently associated cirrhosis among other factors [14]. Moreover, liver disease can affect lactate clearance, which can be severely reduced in patients with liver disease who are undergoing sepsis resuscitation [15]. This is not an unpredictable finding given the well-documented association between liver disease and infection seen in several studies [16-18]. Patients with advanced liver disease or cirrhosis are prone to bacterial and fungal infections due weakened innate and adaptive immune response, bacterial overactivity, dysbiosis, and translocation of intestinal bacteria and bacterial derivatives [19]. Nonetheless, these findings underscore the importance of directing the focus to detect and prevent the development of sepsis in admitted patients.

Our finding that cardiovascular disease (MI and CHF) was more prevalent in the HA-sepsis population echoes the work of Capp and

Table 2
Encounter characteristics for community or hospital acquired sepsis.

Variable	Overall (3917, 100%)	CA-sepsis (3186, 81%)	HA-sepsis (731, 19%)	P-Value*
Initial vital signs and laboratory findings				
Heart rate (beats/min)	101.3 (23.6)	102.4 (23.3)	95.7 (24.1)	<0.001
Respiratory rate (breaths/min)	19.7 (5.3)	19.7 (5.3)	19.5 (5.3)	0.098
Temperature (°F)	98.9 (2.3)	99.0 (2.3)	97.9 (2.1)	<0.001
Initial WBC count (thous/mm^3)	13.6 (8.1)	14.0 (7.7)	11.5 (9.8)	<0.001
Resource utilization and outcomes				
Mechanical Ventilation	371 (9)	218 (7)	153 (21)	<0.001
Vasopressor use	1166 (30)	832 (26)	334 (46)	<0.001
ICU days	4.0 (10.2)	2.8 (8)	9 (16)	<0.001
Hospital days	13.4 (19.9)	11.2 (15.2)	23.1 (31.8)	<0.001
In-hospital mortality, n (%)	428 (11)	288 (9)	140 (19)	<0.001**

Data are means (standard deviation); Abbreviations: CA, community-acquired sepsis; HA, hospital-acquired sepsis; WBC, white blood cell; ICU, intensive care unit. * Wilcoxon's Rank Sum Test; unless otherwise specified by **Pearson's Chi-square test.

Table 3
Sepsis scores (qSOFA, SIRS, and SOFA) by community or hospital acquired sepsis.

Variable	Overall (3917, 100%)	CA-sepsis (3186, 81%)	HA-sepsis (731, 19%)	P-Value*
qSOFA ≥ 2	594 (15)	506 (16)	88 (13)	<0.001
SIRS ≥ 2	3206 (83)	2751 (87)	455 (64)	0.098
SOFA ≥ 2	2071 (53)	1722 (54)	349 (48)	<0.001

Data are counts (%); * Pearson's Chi-square test. Abbreviations: CA, community acquired; HA, hospital-acquired; qSOFA. quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

Table 4
Independent Predictors of Mortality from Hospital-Acquired Sepsis.

Predictor	Odds Ratio (95% CI)	P-value
Moderate-severe liver disease	27.2 (1.44, 512.7)	0.031
Congestive heart failure	5.8 (1.31, 25.90)	0.025

Abbreviations: CI, confidence interval.

colleagues who identified clinical predictors of progression to septic shock in patients admitted from the ED with sepsis [20]. Out of 1316 patients, 111 patients with sepsis (8.4%) progressed to septic shock between 4 and 48 h of ED arrival. Coronary artery disease was found to be a significant predictor of progression to shock. Similarly Wang and colleagues showed an association between sepsis and history of MI or coronary artery disease among other diseases [21]. And Hsiao and colleagues demonstrated that patients with a history coronary artery disease, CHF, and acute kidney injury were more likely to progress to septic shock when hospitalized for urinary tract infections [22].

It is important to note that HA sepsis may also be associated with in-hospital interventions such as central venous catheters, indwelling urethral catheters, or surgical interventions. Our institution has undergone continuous process improvements in order decrease hospital-acquired infections. In the last 3 years, the hospital has seen a 66% decrease in central venous catheter infections, a 74% decrease in urinary tract infections, a 70% decrease in surgical infections to name a few. Overall however, we believe the trends identified in this study are not unique to our institution and are likely to be validated in other settings.

This study has a number of limitations. This was a single-center, retrospective study of patients with a diagnosis of sepsis. Therefore, patients without an explicit diagnosis may have been missed as this study identified only those patients with a diagnosis of sepsis, severe sepsis or septic shock from ICD-9 codes. In addition, the diagnosis of HA-sepsis was made based on the absence of an admission diagnosis of sepsis for HA-sepsis patients. Though this could be perceived as a major limitation of this study due to the potential for missed diagnoses of sepsis upon admission, all sepsis admission diagnoses were verified by healthcare billing professionals after careful chart reviews. Our study did not have specific data on interventions such as time to fluids, quantity of fluids, or time to antibiotics. Finally, this study provides an epidemiological contrast between CA and HA-sepsis but does not explore the microbiological and pathophysiological differences between CA and HA-sepsis.

5. Conclusions

In this study, moderate to severe liver disease and CHF were independent predictors of increased odds of death from HA-sepsis. HA-sepsis patients more commonly had a past medical history of CHF, stroke, moderate to severe liver disease, and myocardial infarction and had higher rates of mechanical ventilation, vasopressor use, and longer ICU and overall hospital lengths of stay. Further multicenter studies are needed to confirm these findings.

Study site

All patients were enrolled at UF Health Jacksonville, 655 West 8th Street, Jacksonville, FL 32209.

Conflicts of interest and financial disclosures

The authors have no conflicts of interest or financial interests to disclose.

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