Sepsis-Related Hospitalizations and Outcomes in HIV-Infected Veterans

By

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BS, University of Kansas, 2018

Submitted to the graduate degree program in Clinical Research and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Master of Science.

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Date Defended: 28 April 2020

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ABSTRACT

Introduction: Sepsis continues to be a significant cause of hospitalizations and death especially among HIV-infected patients. However, little is known about the impact of sepsis hospitalizations, hospital mortality, and hospital length of stay (LOS) in HIV-infected patients in the modern era of HIV and sepsis care.

Methods: This was a multicenter, retrospective cohort study of 3,449,329 veterans admitted to a Veterans Health Administration (VHA) hospital between January 1st, 2012 and December 31st, 2018. Sepsis was defined using criteria consistent with current definitions set forth by the Surviving Sepsis Campaign (SSC). The proportion of sepsis-related hospitalizations and hospital outcomes were compared between HIV-infected patients and HIV-uninfected patients. A number of potential risk factors including demographics, comorbidities, clinical characteristics of sepsis, and CD4 lymphocyte count were assessed for their impact on mortality in HIV-infected patients by univariable and multivariable analyses adjusting for other risk factors.

Results: The proportion of sepsis-related hospitalizations was significantly greater among HIV-infected patients compared to HIV-uninfected patients (5.8% vs. 3.8%; Risk Ratio [RR], 1.51; $p < 0.01$). Sepsis-related hospital mortality was not different between groups (16.4% vs. 16.0%; RR, 1.02; $p = 0.59$), while median hospital LOS was longer in HIV-infected patients (10 days vs. 9 days; $p < 0.01$). In the multivariable logistic regression analysis, cancer (Odds Ratio [OR] 2.24; 95% CI, 1.33-3.77; $p < 0.01$), hospital onset infection (OR, 2.04; 95% CI, 1.08-3.79; $p = 0.03$), vasopressor initiation (OR, 12.46; 95% CI, 7.54-20.95; $p < 0.01$), hepatic injury (OR 2.48; 95% CI, 1.43-4.26; $p < 0.01$), and hyperlactatemia (OR 2.15; 95% CI, 1.33-3.54; $p < 0.01$) were associated with increased odds of hospital mortality in HIV-infected patients, while diabetes (OR, 0.42; 95% CI, 0.22-0.78; $p < 0.01$) was associated with decreased odds of hospital

mortality. Decreased CD4 lymphocyte count (< 200 cells/μL) was not associated with increased odds of mortality when adjusting for other risk factors (OR 1.13; 95% CI, 0.66-1.89; p = 0.65).

Conclusions: Sepsis disproportionally affects HIV-infected patients and results in increased hospital LOS compared to HIV-uninfected patients. Despite sepsis occurring more frequently per hospitalization, sepsis-related hospital mortality does not differ between HIV-infected and HIV-uninfected patients. Certain comorbidities and clinical characteristics may affect risk of sepsis-related hospital mortality in HIV-infected patients.

ACKNOWLEDGEMENTS

I would like to thank Dr. Nick Britt for his amazing mentorship. It has been an absolute joy to work with and learn from him during this experience, and I sincerely hope to continue doing so in the future. I want to thank Dr. Sue Min Lai and Dr. Wissam el Atrouni for their support and guidance throughout this process. Without instrumental direction from these individuals, this project would not have been possible.

I would like to thank all the faculty in the Departments of Population Health and Biostatistics and Data Science at the University of Kansas Medical Center. Their teaching and expertise are paramount in developing aspiring researchers, and it has been a fantastic experience learning from them over the past year. I would especially like to thank Dr. Won Choi and Amy Smith for their dedication to maintaining the Master of Science in Clinical Research program to the highest standards.

Finally, I would like to thank my family for their unconditional love and tremendous support throughout my scholastic career. Words cannot express how fortunate I am to have them in my life. Plainly stated, they rock.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION

Sepsis is a life-threatening syndrome characterized by immune dysregulation in response to an infection. Incidence of sepsis continues to increase[1] and is estimated to be greater than 30 million annual cases worldwide.[2] In the US, an estimated $24 billion are spent on management of these patients every year,[3] and approximately one-third of hospital deaths are associated with sepsis.[4] Current understanding of the biology of sepsis illustrates that a number of factors involved in host immune response are fundamental in the pathophysiology and outcomes.[5,6] In populations that have existing immune dysfunction, such as those with Human Immunodeficiency Virus (HIV), this response may be significantly altered[7] and confer unique clinical characteristics and sepsis-related outcomes.[8] Human Immunodeficiency Virus is a retrovirus that replicates primarily within host lymphocytes and leads to impaired cellular immunity. As the disease progresses, decreasing host CD4 lymphocyte counts and mounting viral reservoirs lead to blunted immune response and increased susceptibility to invasive pathogens.[9-11] This has historically translated to worse sepsis-related outcomes[12-14] and potentially greater risk of sepsis compared to HIV-uninfected patients. Unfortunately, these studies provide little insight into the current impact of sepsis in HIV-infected patients as they include exclusively critically ill patients or data that precedes the era of modern antiretroviral therapy. To further complicate our understanding of sepsis in HIV, there do exist studies that have shown no significant difference in outcomes,[15,16] namely mortality, and there is currently no published comparison of the relative proportion of sepsis-related hospitalizations by HIV-status.

Due to its complexity, a uniform definition of sepsis syndrome has been difficult to establish. In 2016 the Surviving Sepsis Campaign (SSC) published an update of sepsis and septic shock definitions.[17] Prior to this change, Systemic Inflammatory Response Syndrome (SIRS) criteria were used to differentiate an uncomplicated infection from an infection accompanied by

a dysregulated immune response. Due the poor performance of SIRS criteria in this regard, the SSC recommended using the presence of an Acute Organ Dysfunction (AOD) identified using the Sequential Organ Failure Assessment (SOFA) score instead. This fundamental change has resulted in a recent attempt to adopt this definition into clinical care and research; however, the majority of sepsis research has historically defined cases using SIRS criteria. Sepsis research using currently accepted case definitions is lacking especially in populations like HIV-infected patients that may be at an increased risk of developing sepsis or experiencing worse outcomes.

While advances in sepsis care has led to a reduction in overall mortality,[18,19] certain subpopulations like HIV-infected patients may remain at high risk for development and further complications of sepsis.[14,20,21] Furthermore, it is unclear if common laboratory markers of immune function including CD4 lymphocyte count can be used to predict adverse outcomes such as mortality in HIV-infected patients with sepsis.[14,22] The objectives of this study were to compare proportion of sepsis-related hospitalizations, hospital mortality, and hospital length of stay (LOS) between HIV-infected and HIV-uninfected veterans and to identify novel risk factors that were predictive of sepsis-related hospital mortality in HIV-infected patients.

CHAPTER 2: METHODS

1.1 Study Population

This was a multicenter, retrospective cohort study of hospitalized veterans utilizing data in the Corporate Data Warehouse (CDW), within the Veterans Informatics and Computing Infrastructure (VINCI). The cohort consisted of all patients under acute inpatient care at a Veterans Health Administration (VHA) facility that were admitted after January 1st, 2012 and discharged before December 31st, 2018. Patients who were under nursing home, psychiatric, or domiciliary care were not included in order to capture acute care episodes only. Defining a patient as HIV-infected was based on the following criteria: i) an International Classification of Diseases (ICD)-9 or ICD-10 code indicating a diagnosis of HIV at any point prior to discharge,[23] or ii) a plasma HIV viral load of >100 copies/mL before or during the hospitalization if patients did not have an explicit ICD-9 or ICD-10 code listed during the encounter. Sepsis was defined according to previously described criteria and consistent with recent SSC definitions.[4] Briefly, a hospitalization was considered sepsis-related if the patient had a blood culture performed irrespective of positivity, consistent antibiotic therapy starting within 2 days of the blood culture, and ≥ 1 marker of AOD within 2 days of the blood culture. Patients were defined as having presumed infection if they met blood culture and antibiotic therapy criteria without meeting AOD criteria. Markers of AOD included mechanical ventilation, vasopressor use, elevated lactate, and an increase from baseline in serum creatinine, glomerular filtration rate, bilirubin, or platelet count.[4] For patients with multiple sepsis-related cases during the study period, only the first case was analyzed. Onset of infection was determined by the first day in a hospitalization that a blood culture was performed or the day on which consistent antibiotic therapy began. Onset of sepsis was likewise determined by the first day in a hospitalization that a blood culture

was drawn, consistent antibiotic therapy began, or a marker of AOD was observed. Patient comorbidities were determined using ICD-9 and ICD-10 codes.

1.2 Outcome Measures and Statistical Analysis

Baseline characteristics were summarized by frequency count and percentage of cases for dichotomous variables. Continuous variables were described using the mean or median depending on the skewness of the data and the interquartile range. Baseline characteristics were compared using Pearson's chi-squared test or Fisher's exact test for categorical variables and Welch's *t* test or Mann-Whitney U test for continuous variables. Proportion of sepsis-related hospitalizations was calculated as the number of patients meeting sepsis criteria out of the total number of inpatient admissions during the same time period. Hospital mortality was defined as death any time after the date of blood culture but before or on the date of discharge. The proportion of sepsis-related hospitalizations and hospital mortality were both compared using Pearson's chi-squared test. The impact of HIV status on proportion of sepsis-related hospitalizations and hospital mortality was measured by calculating a risk ratio. Hospital LOS was defined as the number of days from the date of admission to the date of discharge. Hospital length of stay was compared using the Mann-Whitney U test. A process of purposeful selection was used to create the final logistic regression model identifying variables associated with hospital mortality.[24] Univariate logistic regression was used to identify variables that were independently associated with hospital mortality in HIV-infected patients. Individual coefficients were assessed for their impact on risk of hospital mortality using the Wald test, and those with a p-value of less than 0.20 in the univariable analysis were selected for initial inclusion in the multivariable model. Variables that were no longer statistically significant at an alpha level of 0.05 were then excluded from the multivariable model. Goodness of fit of the final multivariable

model was assessed using the Hosmer-Lemeshow test. Variables of interest included CD4 count and baseline comorbidities including diabetes, chronic kidney disease, cancer, hepatitis B infection, hepatitis C infection, heart failure, ischemic heart disease, and chronic pulmonary disease. In all analyses, CD4 count was assessed as a categorical variable being < 200 cells/μL or ≥ 200 cells/ μL and was determined using the closest lab value within 6 months prior to admission. Only data from patients admitted on or after January 1st, 2013 were included in the regression analysis to ensure that each patient had an equal window of time from which CD4 count was determined as data before January 1st, 2012 was not available. Aside from determining inclusion in the multivariable regression analysis, findings with a p-value of < 0.05 were considered statistically significant. To determine the impact of organ dysfunctions occurring early in the course of sepsis, a sensitivity analysis of the final multivariable logistic regression model was performed using only markers of AOD that were met within 24 hours of patients meeting all sepsis criteria. Data extraction from the CDW was performed in Microsoft SQL Server Management Studio 17 (Microsoft Corporation, Redmond, WA, USA), and statistical analysis was performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA) and R Studio (R: A Language and Environment for Statistical Computing, Vienna, Austria). This study used only de-identified data and was deemed exempt from IRB approval.

CHAPTER 3: RESULTS

Selecting only acute care inpatient encounters, 3,449,329 hospitalizations were identified and included in the proportion of sepsis-related hospitalizations analysis. Of those, 504,381 cases met criteria for presumed infection. In total, 162,233 cases from 133,046 patients met criteria for sepsis-related hospitalization, including 3,849 cases from 2,895 HIV-infected patients.

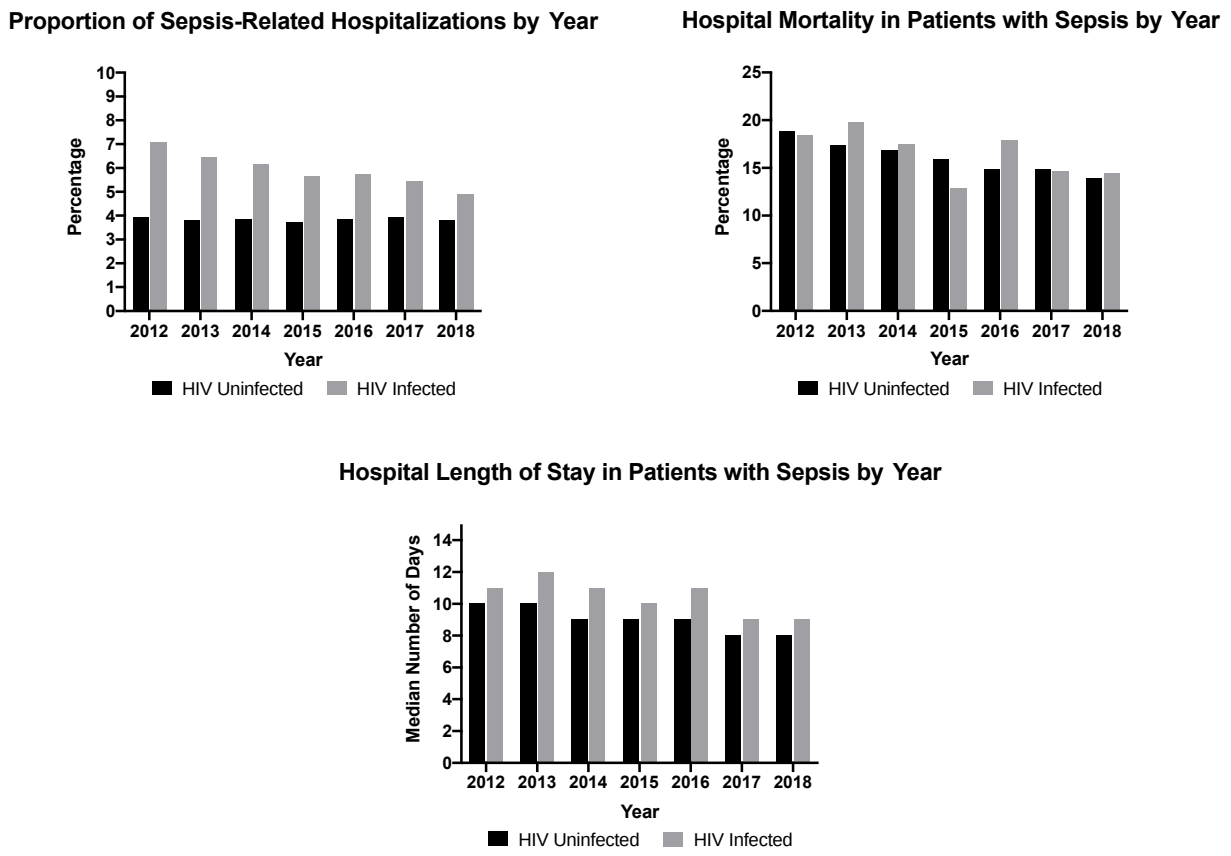
Results from analyses of the proportion of sepsis-related hospitalizations, hospital mortality, and hospital LOS are found in Table 1. The proportion of sepsis-related hospitalizations was higher among HIV-infected patients compared to HIV-uninfected patients (5.8% vs. 3.8%) resulting in a risk ratio greater than 1 (RR, 1.51; 95% CI, 1.46-1.57; $p < 0.01$). Hospital mortality rates were numerically greater among HIV-infected patients (16.4% vs 16.0%) but resulted in no significant difference in risk compared to HIV-uninfected patients (RR, 1.02; 95% CI, 0.94-1.11; $p = 0.59$). Hospital LOS was on average greater in the HIV-infected group compared to the HIV-uninfected group (10 days vs 9 days; $p < 0.01$). A similar relationship in proportion of sepsis-related hospitalizations, hospital mortality, and hospital LOS were seen in each year included in the analysis (Figures 1).

TABLE 1. Sepsis-related hospitalizations, hospital mortality, and hospital length of stay by HIV-status

Outcome	HIV-Infected	HIV-Uninfected	Relative Risk (95% CI)	P value
Sepsis-Related Hospitalizations[a], *n* (%)	2,895 (5.8)	130,151 (3.8)	1.51 (1.46-1.57)	<0.01[c]
Hospital Mortality[b], *n* (%)	475 (16.4)	20,868 (16.0)	1.02 (0.94-1.11)	0.59[c]
Hospital LOS (days)[b], median (IQR)	10 (13)	9 (11)	----	<0.01[d]

CI, confidence interval; LOS, length of stay.
[a] Sample sizes were 49,983 for HIV-infected patients and 3,399,346 for HIV-uninfected patients
[b] Sample sizes were 2,895 for HIV-infected patients and 130,151 for HIV-uninfected patients
[c] Calculated by χ^2 test
[d] Calculated by Mann-Whitney U test

FIGURE 1. Sepsis-related hospitalizations, hospital mortality, and hospital length of stay by year



Baseline characteristics of sepsis cases according to HIV-status are found below in Table 2. In general, HIV-infected patients were younger than their HIV-uninfected counterparts. A greater proportion of HIV-infected patients were black or African American and a smaller proportion were white. Chronic conditions such as diabetes mellitus, heart failure, ischemic heart disease, and chronic pulmonary disease were less common in the HIV-infected group. HIV-infected patients were more likely to have comorbid infection with hepatitis B and hepatitis C viruses. Rates of cancer diagnoses and chronic kidney disease were similar between groups. The place of infection onset was similar between groups, while sepsis onset occurred more frequently in the hospital in the HIV-infected group compared to the HIV-uninfected group. HIV-infected patients on average met a higher number of AOD criteria. Organ dysfunction characteristics were

similar between groups for vasopressor initiation and hyperlactatemia, while mechanical ventilation, acute kidney injury, hepatic injury, and thrombocytopenia rates were higher in HIV-infected patients.

TABLE 2. Baseline characteristics of patients meeting sepsis criteria by HIV-status

Characteristic	HIV-Infected (*n* = 2,895 patients)	HIV-Uninfected (*n* = 130,151 patients)	P value
Age (years), mean (IQR)	57.8 (13.0)	66.9 (16.0)	<0.01[c]
Sex (female), *n* (%)	90 (3.1)	4,452 (3.4)	0.36
Race, *n* (%)			
White	1,283 (44.3)	93,411 (71.8)	<0.01
American Indian or Alaskan Native	33 (1.1)	1,255 (1.0)	0.34
Asian	19 (0.7)	601 (0.5)	0.13
Black or African American	1,362 (47.1)	26,478 (20.3)	<0.01
Native Hawaiian or Other Pacific Islander	27 (0.9)	1,095 (0.8)	0.60
Unknown	171 (5.9)	7,311 (5.6)	0.50
Comorbidities, *n* (%)			
Diabetes mellitus	802 (27.7)	50,238 (38.6)	<0.01
Chronic kidney disease	722 (24.9)	33,127 (25.5)	0.53
Cancer	652 (22.5)	30,601 (23.5)	0.21
Hepatitis B virus infection	141 (4.9)	787 (0.6)	<0.01
Hepatitis C virus infection	642 (22.2)	8,988 (6.9)	<0.01
Heart failure	479 (16.6)	30,549 (23.5)	<0.01
Ischemic heart disease	539 (18.6)	39,603 (30.4)	<0.01
Chronic pulmonary disease	586 (20.2)	33,957 (26.1)	<0.01
Infection Onset, *n* (%)			
Hospital	475 (16.4)	20,920 (16.1)	0.63
Present on admission	2,420 (83.6)	109,231 (83.9)	0.63
Sepsis Onset, *n* (%)			
Hospital	1,228 (42.4)	47,547 (36.5)	<0.01
Present on admission	1,667 (57.6)	82,604 (63.5)	<0.01
Shock, *n* (%)	205 (7.1)	10,079 (7.7)	0.19
No. of AOD, median (IQR)	1.0 (2.0)	1.0 (1.0)	<0.01[d]
Vasopressor initiation, *n* (%)	685 (23.7)	29,848 (22.9)	0.36
Mechanical ventilation initiation, *n* (%)	605 (20.9)	24,510 (18.8)	<0.01
Acute kidney injury, *n* (%)	1,608 (55.5)	63,982 (49.2)	<0.01
Hepatic injury, *n* (%)	629 (21.7)	22,870 (17.6)	<0.01
Thrombocytopenia, *n* (%)	786 (27.2)	25,198 (19.4)	<0.01
Hyperlactatemia, *n* (%)	1,443 (49.8)	66,795 (51.3)	0.12
CD4 count < 200 cells/μL, *n* (%)[a]	247 (29.5)	----	----
HIV viral load < 50 copies/mL, *n* (%)[b]	1,507 (71.2)	----	----

IQR, interquartile range; AOD, acute organ dysfunction.

[a] Data was available for 838 patients

[b] Data was available for 2,116 patients

[c] Calculated by Welch's t test

[d] Calculated by Mann-Whitney U test

A number of clinical characteristics and comorbidities were independently associated with hospital mortality in HIV-infected patients with sepsis. Baseline characteristics for HIV-infected patients with sepsis by hospital mortality as well as results for all univariable logistic regression analyses can be found in Table 3. Out of 2,895 HIV-infected patients with sepsis, 2,525 were admitted on or after January 1st, 2013. Patient cases with any incomplete data were excluded from all regression analyses. As such, lack of CD4 count in the 6 months prior to admission resulted in the further exclusion of 1,811 HIV-infected patients with sepsis leaving 714 patient cases to be included in the regression analysis. All 2,895 patient cases were included in bivariate analyses of characteristics by hospital mortality. There were no significant differences in age, gender, or race between groups with the exception of a higher proportion of nonsurvivors whose race was unknown (8.8% vs. 5.3%; $p < 0.01$). Nonsurvivors were less likely to have diabetes (21.9% vs. 28.8%; $p < 0.01$) and more likely to have cancer (34.4% vs. 20.2%; $p < 0.01$) compared to survivors. Hospital onset infection (34.3% vs. 12.9%; $p < 0.01$), hospital onset sepsis (80.0% vs. 35.0%; $p < 0.01$), and septic shock (22.3% vs. 4.1%; $p < 0.01$) were more common among nonsurvivors compared to survivors. On average, nonsurvivors met a higher number of AOD criteria (1.0 vs 3.0; $p < 0.01$), and rates of each individual AOD were far greater among nonsurvivors compared to survivors. A larger proportion of nonsurvivors had recent CD4 counts that were below 200 cells/μL (36.2% vs. 28.3%; $p = 0.07$) though this difference was not statistically significant, while a similar proportion had a suppressed HIV viral load of less than 50 copies/mL (74.6% vs. 72.2%; $p = 0.49$).

TABLE 3. Characteristics of HIV-infected patients with sepsis by hospital mortality and univariate logistic regression results

Characteristic	Hospital Mortality				
	Yes (*n* = 475)	No (*n* = 2,420)	P Value	Odds Ratio (95% CI)	P Value
Age (years), mean (IQR)	57.9 (12)	57.8 (13)	0.94	1.00 (	0.89
Sex (female), *n* (%)	12 (2.5)	78 (3.2)	0.42	0.88 (0.13-3.27)	0.86
Race, *n* (%)					
White	208 (43.8)	1,075 (44.4)	0.80	0.82 (0.54-1.23)	0.34
American Indian or Alaskan Native	8 (1.0)	25 (1.7)	0.22	2.66 (0.37-13.80)	0.26
Asian	2 (0.4)	17 (0.7)	0.77[a]	----	----[b]
Black or African American	209 (44.0)	1,153 (47.6)	0.15	0.97 (0.65-1.44)	0.87
Native Hawaiian or Other Pacific Islander	6 (1.3)	21 (0.9)	0.41	1.76 (0.09-13.89)	0.63
Unknown	42 (8.8)	129 (5.3)	<0.01	2.49 (1.05-5.46)	0.03
Comorbidities, *n* (%)					
Diabetes mellitus	104 (21.9)	698 (28.8)	<0.01	0.52 (0.30-0.86)	0.02
Chronic kidney disease	102 (21.5)	620 (25.6)	0.06	0.86 (0.54-1.34)	0.52
Cancer	163 (34.3)	489 (20.2)	<0.01	1.79 (1.17-2.71)	<0.01
Hepatitis B virus infection	27 (5.7)	114 (4.7)	0.37	1.67 (0.79-3.29)	0.15
Hepatitis C virus infection	108 (22.7)	534 (22.1)	0.75	1.36 (0.87-2.08)	0.17
Heart failure	90 (19.0)	389 (16.1)	0.12	1.08 (0.60-1.83)	0.79
Ischemic heart disease	101 (21.3)	438 (18.1)	0.11	1.29 (0.75-2.12)	0.34
Chronic pulmonary disease	103 (21.7)	483 (20.0)	0.39	0.80 (0.47-1.31)	0.39
Infection Onset, *n* (%)					
Hospital	163 (34.3)	312 (12.9)	<0.01	4.12 (2.50-6.72)	<0.01
Present on admission	312 (65.7)	2,108 (87.1)	<0.01	Ref	Ref
Sepsis Onset, *n* (%)					
Hospital	380 (80.0)	848 (35.0)	<0.01	7.53 (4.77-12.27)	<0.01
Present on Admission	95 (20.0)	1,572 (65.0)	<0.01	Ref	Ref
Shock, *n* (%)	106 (22.3)	99 (4.1)	<0.01	10.25 (5.32-20.32)	<0.01
No. of AOD, median (IQR)	3.0 (3.0)	1.0 (1.0)	<0.01	2.62 (2.21-3.14)	<0.01
Vasopressor initiation, *n* (%)	330 (69.5)	355 (14.7)	<0.01	11.52 (8.61-15.53)	<0.01
Mechanical ventilation initiation, *n* (%)	278 (58.5)	327 (13.5)	<0.01	10.62 (7.94-14.28)	<0.01
Acute kidney injury, *n* (%)	321 (67.6)	1,287 (53.2)	<0.01	2.08 (1.58-2.76)	<0.01
Hepatic injury, *n* (%)	170 (35.8)	459 (19.0)	<0.01	2.54 (1.89-3.40)	<0.01
Thrombocytopenia, *n* (%)	197 (41.5)	589 (24.3)	<0.01	2.19 (1.65-2.88)	<0.01
Hyperlactatemia, *n* (%)	300 (63.2)	1,143 (47.2)	<0.01	2.03 (1.54-2.69)	<0.01
CD4 count < 200 cells/μL, *n* (%)	47 (36.2)	200 (28.3)	0.07 [c]	1.49 (0.97-2.26)	0.07
HIV viral load < 50 copies/mL, *n* (%)	141 (74.6)	790 (72.2)	0.49 [d]	1.48 (0.86-2.70)	0.17[e]

CI, confidence interval; SD, standard deviation; AOD, acute organ dysfunction.
Odds ratios were calculated based on data from 714 patients.
[a] *Calculated using Fisher's exact test*
[b] *No patients experienced mortality*
[c] *Data was available for 838 patients*
[d] *Data was available for 1,284 patients*
[e] *Data was available for 579 patients*

All variables included in the final multivariable logistic regression as well as results from the sensitivity analysis using AOD criteria met within 24 hours of sepsis determination are listed in Table 4. Main effects for unknown race and ischemic heart disease were not significantly associated with hospital mortality in the final model as determined by p-values greater than 0.05 and were removed. Hospital onset sepsis and shock were not included in the final model due to shared variance with hospital onset infection, vasopressor initiation, and hyperlactatemia. Variables that remained significantly associated with increased odds of hospital mortality in the final multivariable model were diabetes (Adjusted Odds Ratio [AOR], 0.42; 95% CI 0.22-0.78; $p < 0.01$), cancer (AOR, 2.24; 95% CI, 1.33-3.77; $p < 0.01$), hospital onset infection (AOR, 2.04; 95% CI, 1.08-3.79; $p = 0.03$), as well as vasopressor initiation (AOR, 12.46; 95% CI, 7.54-20.95; $p < 0.01$), hepatic injury (AOR, 2.48; 95% CI, 1.43-4.26; $p < 0.01$), and hyperlactatemia (AOR, 2.15; 95% CI 1.33-1.89; $p < 0.01$). In the final multivariable model, CD4 count < 200 cells/μL was not associated with hospital mortality. Estimates for diabetes, cancer, hospital onset infection, and vasopressor initiation changed very little in a sensitivity analysis using only AOD criteria met within 24 hours of meeting all sepsis criteria. Adjusted odds ratios for hepatic injury and hyperlactatemia were no longer statistically significant in the sensitivity analysis, and the AOR for CD4 count < 200 cells/μL trended closer to significance but still resulted in a p-value greater than 0.05.

TABLE 4. Final multivariable logistic regression model and sensitivity analysis for variables associated with sepsis-related hospital mortality in HIV-infected patients

Variables	Primary Analysis		Sensitivity Analysis	
	Adjusted Odds Ratio (95% CI)	**P value**	**Adjusted Odds Ratio (95% CI)**	**P value**
Diabetes	0.42 (0.22-0.78)	<0.01	0.44 (0.24-0.79)	<0.01
Cancer	2.24 (1.33-3.77)	<0.01	2.14 (1.32-3.47)	<0.01
Hospital onset infection	2.04 (1.08-3.79)	0.03	2.71 (1.49-4.85)	<0.01
AOD				
Vasopressor initiation	12.46 (7.54-20.95)	<0.01	12.35 (6.77-22.99)	<0.01
Hepatic injury	2.48 (1.43-4.26)	<0.01	1.58 (0.80-2.96)	0.17
Hyperlactatemia	2.15 (1.33-3.54)	<0.01	1.50 (0.94-2.39)	0.09
CD4 count < 200 cells/μL	1.13 (0.66-1.89)	0.65	1.47 (0.90-2.37)	0.12

CI, confidence interval.
Hosmer-Lemeshow goodness of fit test, p value = 0.604.

CHAPTER 4: DISCUSSION

In this retrospective, multicenter analysis of veterans with sepsis, we found that on average the proportion of sepsis-related hospitalizations among HIV-infected patients is 51% greater than among HIV-uninfected patients. While previous research has found that a significant proportion of patients with sepsis presented with comorbid HIV-infection,[4,20] there has been little investigation of the proportion of sepsis-related hospitalizations among patients living with HIV.[25] Estimates of sepsis-related hospitalizations in HIV-infected patients has largely been described in the intensive care unit (ICU), where proportions have ranged from 13-33%.[21,22,26] However, nearly half of all patients with sepsis do not require admission to the ICU.[4] Therefore, these estimates would only capture a subset of patients with sepsis in the hospital. Additionally, these studies were all conducted prior to the 2016 SSC update and could be over-estimates due to inclusion of patients that met overly sensitive case definitions such as those based on SIRS criteria. This study is, to our knowledge, the largest assessment of sepsis-related hospitalizations using in HIV-infected patients current case definitions to date.

Although hospitalized HIV-infected patients more commonly experienced sepsis in this analysis, risk of hospital mortality was no different compared to that of HIV-uninfected patients. This stands in contrast to previous research that has suggested that HIV-infected patients with sepsis are at an increased risk for hospital mortality compared to their HIV-uninfected counterparts.[12-14] However, the majority of patients in these studies were exclusively in the ICU, and due to recent efforts to screen patients across all areas of the hospital,[17] it is likely that these estimates do not accurately represent all HIV-infected patients with sepsis but rather only a subset of higher risk patients. Moreover, data in these studies spans from 1999 to 2010. Over the past few decades, advances in sepsis care such as timely administration of broad spectrum antibiotics, resuscitation with crystalloid fluids, and early recognition of potentially high risk

patients have resulted in a significant decrease in hospital mortality overall.[4] Therefore, it is likely that these studies, while relevant when they were published, are no longer an accurate representation of the burden of mortality in patients with sepsis regardless of HIV-status. It is important to note that prior research has also found that HIV-infected patients are at a similar risk for sepsis-related hospital mortality.[15,16] In addition to advances in sepsis care, continued improvement in care of HIV-infected patients has likely played a role in mitigating adverse outcomes related to infections including: improved effectiveness of antiretroviral therapy, improved access to HIV care, opportunistic infection prophylaxis, and increased testing to identify HIV-infected patients earlier in the course of disease.

Hospital LOS has been used as a sepsis outcome to measure of morbidity and consumption of hospital resources. In this study, we found a difference in hospital LOS between HIV-infected and HIV-uninfected patients that resulted in a p-value that was less than the prespecified threshold for statistical significance. Hospital LOS has previously been found to be shorter in critically ill HIV-infected patients if it was different at all.[12-14] The substantially higher mortality rate among the HIV-infected patients in such studies was likely the driver for shorter hospital LOS. Conversely, in our study, the markedly lower mortality rates led to a longer hospital LOS in HIV-infected patients compared to HIV-uninfected. Though the difference in median hospital LOS was only one day, patient level differences could vary resulting in much longer relative hospital stays for some patients. Assessing differences in recovery from sepsis was outside the scope of this study, but future research should investigate reasons for HIV-infected patients requiring longer sepsis-related hospitalizations.

The purpose of the multivariable logistic regression model was to identify novel risk factors associated with hospital mortality in HIV-infected patients with sepsis. Specifically of

interest were common comorbidities and CD4 lymphocyte count as to assess the effect of specific comorbidities and immune function on sepsis-related hospital mortality. A cutoff of 200 cells/mL, the same that is used for diagnosis of Acquired Immunodeficiency Syndrome (AIDS), was selected for CD4 count to assess the impact of severe suppression of cellular immunity. Previous studies have found conflicting results for the impact of CD4 count on hospital mortality in critically-ill HIV-infected patients.[14,21,22,26,27] In this study, CD4 count was associated with hospital mortality in the univariable analysis, but this relationship did not hold when adjusted for other significant variables including markers of AOD which are established risk factors for mortality in sepsis.[17] Low CD4 counts increase a patient's risk for acquiring invasive opportunistic infections.[28] It is therefore possible that the association of CD4 count with sepsis-related hospital mortality is driven by direct effects of more invasive or difficult to treat infections, more profound AOD in the presence these pathogens, or some combination of the two. Future investigation into the role of CD4 counts on outcomes in sepsis is warranted. Unsurprisingly, presence of cancer and hospital onset of infection greatly increased odds of hospital mortality before and after adjustment. Patients undergoing active treatment for cancer would likely suffer from further impairment of the immune system in addition to the effects caused by HIV infection. Hospital onset of infection implies a greater likelihood that the source of infection is nosocomial in nature. Across multiple infectious etiologies, healthcare-acquired organisms carry a higher rate of morbidity and mortality.[29,30] Therefore, the finding that hospital onset of infection significantly increased the risk for hospital mortality in HIV-infected patients with sepsis was consistent with current knowledge of these infections.

There are several limitations associated with this study. The retrospective design of this study limits the interpretation of these findings. Sepsis is difficult to identify in large cohorts,

and, although we employed case selection methods that have been validated in the general population, misclassification is likely to be present in a small proportion of cases. This study included veterans using only VHA data sources. The study population differs inherently from the greater population of patients with sepsis or HIV infection. Mortality data was only available for patients that passed away in the hospital. As short-term mortality rates continue to decrease in sepsis, effect on long-term outcomes are of increasing interest to many clinicians. Future studies should address differences in mortality between HIV-infected and HIV-uninfected patients at time points extending beyond hospital discharge. As HIV-infected patients had a greater degree of AOD in this study, these patients could still be at a greater risk for mortality after discharge from the hospital. Factors impacting hospital mortality were only assessed among HIV-infected patients with complete sets of data. Therefore, patients without recent CD4 counts were excluded from this analysis which could bias regression analysis findings. Future studies should investigate outcomes in these patients further.

This study evaluated proportion of sepsis-related hospitalizations, sepsis-related outcomes, and risk factors for sepsis-related hospital mortality in HIV-infected veterans. These results indicate that as incidence in sepsis is increasing in the overall population, HIV-infected patients may be at an even greater risk for sepsis hospitalization. Despite a greater proportion of sepsis-related hospitalizations, hospital mortality in HIV-infected patients is similar to their HIV-uninfected counterparts. However, patients with HIV-infection have longer hospital LOS compared to HIV-uninfected patients. Factors that increase the odds of hospital mortality in HIV-infected patients include AOD, cancer, and hospital onset of infection. These findings suggest improved sepsis and HIV care has had a beneficial impact on outcomes in sepsis, but HIV-infected patients remain at an increased risk of developing sepsis. Additionally, these

findings provide evidence for the roles of common HIV lab monitoring, comorbidities, and clinical characteristics in assessing risk of hospital mortality in HIV-infected patients with sepsis.

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