Hospital Volume of Immunosuppressed Sepsis Patients and Sepsis Mortality

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ABSTRACT

Rationale: Immunosuppressive medical conditions are risk factors for mortality from severe infections. It is unknown whether hospital characteristics affect this risk.

Objectives: To determine whether the odds of death for an immunosuppressed patient with sepsis relative to a non-immunosuppressed patient with sepsis varies according to the hospital's yearly case volume of immunosuppressed patients with sepsis.

Methods: Patients with sepsis at hospitals in the Vizient database were characterized as immunosuppressed or not immunosuppressed based on diagnosis codes and medication use. Hospitals were grouped into quartiles based on their average volumes of immunosuppressed patients with sepsis per year. Multilevel logistic regression with clustering of patients by hospital was used to determine whether the odds of in-hospital death from sepsis due to a suppressed immune state varied by hospital quartile.

Results: There were 350,183 patients with sepsis at 60 hospitals in the Vizient database from 2010-2012. Immunosuppressed patients with sepsis at the 15 hospitals in the first quartile (64 to 224 immunosuppressed patients with sepsis per year) had an increased odds of in-hospital death relative to non-immunosuppressed patients with sepsis at these hospitals (adjusted OR 1.38, 95% CI 1.27-1.50, p<0.001). The odds of in-hospital death for immunosuppressed patients with sepsis relative to non-immunosuppressed patients with sepsis was similar for patients at hospitals in the second, third, and fourth quartile (225 to 1,056 immunosuppressed patients with sepsis per year). When these 45 hospitals were analyzed as group, the adjusted odds of death from sepsis due to a suppressed immune state of 1.21 (95% CI 1.18-1.25, p<0.001) was significantly lower than that for patients at the 15 hospitals in the first quartile (p=0.004 for difference).

Conclusions: The risk of death from sepsis due to a suppressed immune state was greatest at hospitals with the lowest volume of immunosuppressed patients with sepsis. Further study is needed to determine whether this finding is related to differences in patient characteristics or care delivery at hospitals with varying exposure to immunosuppressed patients.

INTRODUCTION

Sepsis is a leading cause of death among critically ill patients, affecting between one and three million patients in the United States per year and resulting in 250,000 to 350,000 in-hospital deaths (1, 2). Chronic medical conditions significantly increase the risk of developing and dying from sepsis (3, 4). In addition, for patients who survive the initial episode of sepsis, their chronic medical conditions and general health may be worsened, and they carry an increased risk of secondary episodes of sepsis and mortality (5, 6). As a result, health status prior to the development of sepsis may be more influential in determining outcomes than characteristics of the pathogen or the immune response to infection. Patients who are immunocompromised from medical conditions or medications that interfere with normal immune function are considered to be at particularly high risk for developing and dying from sepsis (7, 8). However, the extent of the increased risk is not well characterized and may differ depending on characteristics of the hospital.

Multiple studies have reported that patients with sepsis have better outcomes if they are treated at high case volume centers (9-11). Possible reasons for this association include greater clinician expertise at managing sepsis at high volume hospitals, selective patient referral to high-performing hospitals leading to higher case volume, and organizational factors at the hospital level that allow clinicians to manage sepsis more effectively at higher-volume hospitals.

We sought to determine whether a similar relationship is true with regards to immunosuppression; that is, immunosuppressed patients with sepsis have lower odds of

death at hospitals that manage a larger number of immunosuppressed patients with sepsis per year. Understanding how immunosuppressive conditions affect outcomes from sepsis is important for clinicians who must provide prognostic information to patients and families. It is also important for hospital administrators and researchers who attempt to determine a hospital's expected mortality rate for a given case mix of patients.

MATERIALS AND METHODS

Vizient, formerly the University HealthSystem Consortium (UHC), is an alliance of 117 United States academic medical centers and 300 of their affiliated hospitals. Members that participate in the clinical database/resource manager (CDB/RM) submit demographic data, medication data, and up to 99 ICD-9 diagnosis and procedure codes per encounter for all inpatient and outpatient encounters. Vizient performs rigorous quality assessments of submitted data before it is loaded into the CDB/RM. The University of Chicago Institutional Review Board approved this study.

We used a search strategy described by Angus et al. to identify inpatients at least 18 years of age with sepsis in the Vizient database who were discharged from January 1, 2010 to December 31, 2012 (12). To ensure that each patient was represented once in the dataset, only the first episode of sepsis per patient from 2010-2012 was included. To increase the likelihood that the first hospital admission for sepsis was captured for patients discharged from Jan 1, 2010 to December 31, 2010, we excluded patients who had an episode of sepsis between January 1, 2009 and December 31, 2009.

We used our previously validated approach to categorize patients as immunosuppressed according to presence of discharge diagnosis codes and use of certain medications. In brief, three types of conditions were considered definitely immunosuppressive: human immunodeficiency virus infection (HIV), hematological malignancies, and other intrinsic immune conditions. Patients with three other types of conditions were considered immunosuppressed only if they received an immunosuppressive medication during the studied hospitalization: solid malignancies, solid organ transplantations, and rheumatologic/inflammatory conditions. Compared to the gold standard manual chart review at a single center, we found that this approach had a sensitivity of 87.4% and a specificity of 97.6% for categorizing patients with sepsis as immunosuppressed or not immunosuppressed (13).

Statistical Analysis

We used a multivariable, multilevel logistic regression model to determine the association between a patient's immune state and his or her odds of in-hospital death from sepsis. Patients were clustered within hospital, with a random effect term fit for hospital and intercept. We controlled for each patient's Vizient severity of illness score, which accounts for demographic variables, hospital diagnoses, and comorbid conditions that were present on hospital admission. Investigators have used a similar approach to control for severity of illness at the time of hospital admission (9, 14). We controlled for whether each patient's infection was hospital-acquired (15), and whether the patient was admitted from an external healthcare facility. We also controlled for hospital-level variables that were presumed to be associated with the medical complexity of patients at

the hospital and the overall hospital mortality rate for patients with sepsis: the average number of patients with sepsis at the hospital per year, whether the hospital was a transplant center, whether the hospital had a hospice unit, and geographic location.

We examined whether the association between an individual's immune state and the odds of in-hospital death from sepsis was affected by the number of immunosuppressed patients with sepsis at the hospital after adjusting for variables described above. First, we grouped hospitals into quartiles based on the average number of immunosuppressed patients with sepsis per year. We determined whether the odds of in-hospital death from sepsis due to a suppressed immune state varied by hospital quartile using multivariable, multilevel logistic regression. Second, we determined the expected number of deaths from sepsis at each hospital using the beta-coefficients from our multivariable model. We calculated the ratio of the observed numbers of deaths to the expected number of deaths for immunosuppressed and for non-immunosuppressed patients with sepsis at each hospital. Using linear regression, we determined whether each hospital's observed / expected mortality from sepsis were associated with the hospital's case volume of immunosuppressed patients with sepsis. All tests were two-sided and a p-value ≤ 0.05 was considered to indicate statistical significance. All analyses were performed with STATA 15.1 (StataCorp, College Station, TX).

RESULTS

Of the 289 hospitals in the Vizent database from 2009-2012, 187 were excluded because full patient data were not available during the entire date range. Of the remaining 102

hospitals, 40 were excluded because they did not participate in the pharmacy database **(Supplemental Figure 1).** Two hospitals were excluded from further analysis because the ratio of immunosuppressed to non-immunosuppressed patients with sepsis was greater than two standard deviations above the mean **(Supplemental Figure 2).**

Characteristics of immunosuppressed and non-immunosuppressed patients with sepsis. Of the 350,183 patients with sepsis at 60 hospitals, 70,510 (20%) were classified as immunosuppressed. There were many clinically significant differences in the baseline characteristics of immunosuppressed and non-immunosuppressed patients with sepsis (**Table 1)**. Compared to immunosuppressed patients with sepsis, non-immunosuppressed patients with sepsis were more likely to be older, have congestive heart failure, diabetes, and chronic pulmonary disease, be directly admitted from a hospital or facility, and have genitourinary infections. Compared to non-immunosuppressed patients, immunosuppressed patients were more likely to have unspecified infection types, hospital-acquired infections, and longer lengths of stay in the hospital. Interestingly, immunosuppressed patients were more likely to be discharged home than non-immunosuppressed patients (60% vs. 50% respectively).

A total of 15% of immunosuppressed patients died during the hospitalization compared to 12% of non-immunosuppressed patients. Using multivariable, multilevel logistic regression with clustering of patients by hospital, we found that immunosuppressed patients with sepsis had a 23% increased odds of in-hospital death compared to non-immunosuppressed patients with sepsis (95% CI 20-26%, p<0.001) **(Table 2)**. In this

model, all patients with sepsis had a significantly decreased odds of death as a hospital's case volume of *non-immunosuppressed* patients with sepsis increased. Conversely, all patients with sepsis had a non-significantly increased odds of death as a hospital's case volume of *immunosuppressed* patients with sepsis increased.

Characteristics of hospitals according to their average case volumes of immunosuppressed patients with sepsis per year.

The average number of immunosuppressed patients with sepsis per hospital per year ranged from 63 to 1,056 **(Figure 1)**. The 60 hospitals were grouped into quartiles based on the number of immunosuppressed patients with sepsis per year (**Table 3**). The mean percentage of all patients with sepsis who were immunosuppressed increased across quartiles from 13.7% to 24.1%; this increase was primarily driven by greater percentages of patients with hematological malignancies and solid organ transplants at hospitals with the greatest volume of immunosuppressed patients with sepsis. Patients from hospitals in the lowest quartile were least likely to be admitted directly from hospitals or facilities and least likely to have sepsis from hospital-acquired infections. There were similar discharge dispositions across all hospital quartiles. Hospitals with greater volumes of immunosuppressed patients with sepsis had greater percentages of all inpatients who were immunosuppressed, greater numbers of hospital beds, and were more likely to be transplant centers than hospitals with smaller volumes of immunosuppressed patients with sepsis (**Supplemental Table 1)**.

Effect of hospital case volume of immunosuppressed patients with sepsis on an immunosuppressed patient's odds of death from sepsis.

The hospitals were ranked from one to 60 according to their case volumes of immunosuppressed patients with sepsis per year. The odds of in-hospital death from sepsis due to a suppressed immune state at each hospital was determined using multivariable logistic regression **(Figure 2).** Immunosuppressed patients had increased odds of death at most hospitals, although the association was not statistically significant at many hospitals.

Hospitals were grouped into quartiles based on their case volumes of immunosuppressed patients with sepsis per year. The odds of in-hospital death due to a suppressed immune state at the 15 hospitals within each quartile were determined using multivariable, multilevel logistic regression with clustering of patients by hospital (also displayed in **Figure 2)**. Immunosuppressed patients with sepsis at hospitals with the lowest average case volumes of immunosuppressed patients with sepsis had the greatest odds of in-hospital death relative to non-immunosuppressed patients with sepsis (adjusted OR 1.38, 95% CI 1.27-1.50, $p<0.001$). Immunosuppressed patients with sepsis at hospitals in the second, third, and fourth quartile had similarly increased odds of in-hospital death relative to non-immunosuppressed patients with sepsis; the adjusted odds of death due to a suppressed immune state was 1.21 (95% CI 1.18-1.25, $p<0.001$) at these 45 hospitals. The odds of death due to sepsis from an immunocompromised state at hospitals in the first quartile was significantly higher than the odds of death due to sepsis from an

immunocompromised state at hospitals at the remaining 45 hospitals (p=0.004 difference).

In-hospital mortality for immunosuppressed and non-immunosuppressed patients with sepsis according to hospital case volume of immunosuppressed patients with sepsis.

We determined the odds of death for both immunosuppressed and non-immunosuppressed patients with sepsis by hospital quartile. **(Supplemental Figure 1).** Non-immunosuppressed patients with sepsis at 45 hospitals in quartiles 2 to 4 had similar odds of death to non-immunosuppressed patients at 15 hospitals in quartile 1 (p=0.28). Immunosuppressed patients with sepsis at 45 hospitals in quartiles 2 to 4 had similar odds of death to immunosuppressed patients at 15 hospitals in quartile 1 (p=0.58)

Finally, we determined the observed number of deaths / expected number of deaths for immunosuppressed and non-immunosuppressed patients with sepsis at each hospital **(Figure 3**). The observed / expected mortality from sepsis for immunosuppressed patients was greater than that for non-immunosuppressed patients. There was a significant negative association between a hospital's observed / expected mortality from sepsis for immunosuppressed patients and the hospital's case volume of immunosuppressed patients with sepsis (R^2=0.11, p=0.009). There was no association between a hospital's observed / expected mortality from sepsis for non-immunosuppressed patients and the hospital's case volume of immunosuppressed patients with sepsis (R^2=0.004, p=0.63).

Sensitivity analysis

To confirm that the relationship between hospital volume and odds of death due to a suppressed immune state was not being driven by outcomes from the smallest hospitals, we performed a sensitivity analysis, excluding the six hospitals with less than 150 immunosuppressed patients with sepsis per year **(Supplemental Table 2)**. We also confirmed similar results repeating the primary analysis excluding patients who were admitted from external hospital facilities, and excluding patients who were discharged to hospice or other healthcare facilities.

DISCUSSION

In the largest study to date quantifying the impact of immunosuppressive conditions on the likelihood of death from sepsis, we found that septic patients who were immunosuppressed were 23% more likely to die during the hospitalization than septic patients without immunosuppressive conditions after adjusting for multiple patient- and hospital-level variables. Our novel finding was that the increased odds of death due to a suppressed immune state was greatest at hospitals with the lowest volumes of immunosuppressed patients with sepsis. Immunosuppressed patients at hospitals that managed at least 225 cases of sepsis among immunocompromised hosts per year had similar odds of death relative to non-immunosuppressed patients at these hospitals. Our results suggest that a septic patient may not only benefit from being treated at a hospital that manages the most sepsis, but may also benefit from being treated at a hospital that has certain level of familiarity managing the patient's comorbid conditions, which are risk factors for developing sepsis.

There are many potential reasons that immunosuppressed patients had the greatest odds death from sepsis at hospitals that managed the fewest number of immunosuppressed patients with sepsis. First, the clinical presentation of sepsis may vary based on a patient's immune state (16); clinicians who have the least exposure to immunosuppressed patients may be less able to detect their atypical presentations of sepsis earlier in the disease course and thus may be less likely to comply with the Surviving Sepsis Campaign guidelines (17). Additionally, organizational aspects of hospitals that care for a fewer number of immunosuppressed patients may result to delayed identification and management of all patients with sepsis. Another explanation is that the control of a patient's immunosuppressive medical condition may be worsened in the setting of a severe infection, which may contribute to patient's odds of death. Clinicians with less exposure to immunosuppressed patients may have less experience managing the exacerbations of these conditions in the setting of infection. In addition, these clinicians may have a more pessimistic view of the patient's long-term prognosis and thus may be more likely to recommend against aggressive life-sustaining care than clinicians with greater exposure to immunosuppressed patients. Finally, immunosuppressed patients may be at increased risk for infections with drug-resistant or opportunistic pathogens; clinicians with less familiarity with immunosuppressed patients may be less likely to order an initial regimen of appropriately broad-spectrum antibiotics. Additionally, these clinicians may also be less likely to de-escalate antibiotics appropriately and thereby increase the risk of secondary infections with hospital-acquired pathogens. These possibilities require further study.

Although patients who were immunosuppressed were more likely to die in the hospital than patients without immunosuppression (15% vs. 12%), patients who were immunosuppressed were more likely to be discharged home than patients without immunosuppression (60% vs. 50%). These discordant results suggest that a patient's long-term physical and cognitive outcomes may be more related to factors that were present prior to hospitalization rather than the severity of acute illness (18, 19). That is, patients without immunosuppressive conditions may be more likely to be in declining states of health prior to developing sepsis than patients with immunosuppression. Patients without immunosuppression were more likely to be older and to be admitted directly from a hospital or facility than patients who were immunosuppressed. Further study is needed to investigate differences in long-term outcomes from sepsis according to a patient's immune state.

One limitation of our study is that we were not able to elucidate the reason that immunosuppressed patients had increased odds of death at hospitals with the lowest volumes of immunosuppressed patients. We suspect that immunosuppressed patients with sepsis had improved survival at hospitals where clinicians had greater familiarity caring for immunosuppressed patients for the reasons outlined above. In support of this conclusion, we found that the observed / expected mortality for immunosuppressed patients with sepsis was greatest at hospitals with the lowest volumes of immunosuppressed patients with sepsis. However, we cannot rule out the possibility that non-immunosuppressed patients had worse outcomes at hospitals with a greater proportion of immunosuppressed patients, thereby decreasing the negative effect of being

immunosuppressed at these hospitals. It is likely that both immunosuppressed and non-immunosuppressed patients with more complex medical issues seek out care at larger hospitals. The complexity of a non-immunosuppressed patient's comorbid conditions may be a risk factor for death from sepsis, which is not captured by ICD-9 diagnosis coding. Determining the mechanisms for our findings should be the subject of future studies.

Other limitations of this study are as follows: first, there is no universal definition of clinical immunosuppression (20). Estimations of risk of death from immunosuppression depend on the classification scheme. Second, we previously validated an approach to identify immunosuppressed patients in the Vizient database at a single center. It is possible that the accuracy of our strategy varies by hospital (13). The face validity of our approach was supported by the observation that hospitals with greater volumes of immunosuppressed patients with sepsis were more likely to be larger, more likely to admit patients as transfers from other institutions, and to be transplant centers . Third, all methods to identify patients with sepsis in administrative databases have limitations (1). The approach described by Angus et al. is utilized frequently, but it often overestimates the true prevalence of disease. We cannot exclude the possibility that a hospital's mortality from sepsis was associated with local idiosyncrasies of coding for sepsis. Fourth, we excluded cases of recurrent hospitalizations for sepsis and almost all of the analyzed hospitals were teaching hospitals, which may affect the generalizability of our findings. Fifth, the Vizient model that estimates risk of in-hospital mortality includes diagnoses that were present on hospital admission. In our final model, we controlled for

whether the infection was hospital-acquired, a factor that increased the risk of death. Nevertheless, we were unable to control for severity of acute illness for sepsis that developed in the hospital.

In conclusion, in this large, multicenter study of hospitals in the United States, we quantified the degree to which immunosuppressive conditions were associated with the risk of death from sepsis. The reason most immunosuppressed patients have increased risk of death is likely multifactorial and constantly in flux due to new therapeutic approaches that alter prognoses and risk for severe infection. On average, one of every five septic patients was immunosuppressed. Our finding that the odds of death from sepsis due to immunosuppressive medical conditions was greatest at hospitals with the lowest volumes of immunosuppressed patients is novel and extends the perception that greater familiarity with sepsis at the hospital level is associated with improved outcomes. Further study is required to identify potential differences in care delivery for immunosuppressed patients with sepsis by hospital type.

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Author Contributions
JAG: contributed to the conception and design of the study; data collection and statistical analysis; drafting, critical revision, reading, and approval of the manuscript. JAG is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from incepton to published article.
SHF: contributed to the conception and design of the study; data acquisition, critical revision, reading, and approval of the manuscript.
BDJ: contributed to the statistical analysis, critical revision, reading, and approval of the manuscript
RCS: contributed to the statistical analysis, critical revision, reading, and approval of the manuscript

JBH: contributed to the conception and design of the study, critical revision, reading, and approval of the manuscript.
JPK: contributed to the conception and design of the study, critical revision, reading, and approval of the manuscript.
MZD: contributed to the conception and design of the study, critical revision, reading, and approval of the manuscript.

Figure Legends

Figure 1 - *Number of immunosuppressed and non-immunosuppressed patients with sepsis at 60 hospitals in the Vizient database.* Blue = number of immunosuppressed patients with sepsis per hospital. Grey = number of non-immunosuppressed patients with sepsis per hospital.

Figure 2 – *Adjusted odds of death due to a suppressed immune state for patients with sepsis at 60 hospitals in the Vizient database*. Grey open circle = odds of death due to a suppressed immune state at each hospital.* Hospitals were grouped into quartiles according to the number of immunosuppressed patients with sepsis per year. Black solid circle = adjusted odds of death due to a suppressed immune state within each quartile using multilevel logistic regression.*# Error bars represent 95% confidence intervals.

*OR adjusted for each patient's Vizient risk adjustment score, presence of hospital-acquired infection, and admission directly from another hospital or facility.
OR adjusted for the following hospital characteristics: number of non-immunosuppressed patients with sepsis per year, transplant center, hospice unit, and geographic location.

Figure 3 – *Observed number of deaths relative to expected number of deaths per hospital for immunosuppressed and non-immunosuppressed patients with sepsis*. Blue = immunosuppressed patients with sepsis. Grey= non-immunosuppressed patients with sepsis. Trends were determined using linear regression.

*The expected number of deaths at each hospital was determined using a multilevel, multivariable logistic regression model with the following variables: each patient's Vizient risk adjustment score, patient had a hospital-acquired infection, patient was admitted directly from an external hospital or facility, average number of non-immunosuppressed patients with sepsis per year at the hospital, hospital was a transplant center, hospital had a hospice unit, and geographic location of the hospital.

Supplemental Figure 1 – *Flow diagram of hospital selection.*

Supplemental Figure 2 – *Relationship between the number of immunosuppressed patients with sepsis and the percent of all patients with sepsis who were*

immunosuppressed at each hospital per year. Panel A includes all 62 hospitals. Panel B includes 60 hospitals with two outliers removed.

Supplemental Figure 3 – *Odds of death for immunosuppressed and non-immunosuppressed patients with sepsis*, Hospitals were grouped into quartiles according the number of immunosuppressed patients with sepsis per year. The reference category was non-immunosuppressed patients at hospitals in quartile 1. Blue = immunosuppressed patients with sepsis. Grey= non-immunosuppressed patients with sepsis. Error bars represent 95% confidence intervals.

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