Hospital Volume of Immunosuppressed Patients with Sepsis 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 nonimmunosuppressed 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 on the basis of 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 owing 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 to 2012. Immunosuppressed patients with sepsis at the 15 hospitals in the lowest quartile (64 to 224 immunosuppressed patients with sepsis per year) had an increased odds of in-hospital death relative to nonimmunosuppressed patients with sepsis at these hospitals (adjusted odds ratio, 1.38; 95% confidence interval, 1.27–1.50; $P < 0.001$). The odds of in-hospital death for immunosuppressed patients with sepsis relative to nonimmunosuppressed patients with sepsis was similar for patients at hospitals in the second, third, and fourth quartiles (225 to 1,056 immunosuppressed patients with sepsis per year). The adjusted odds of death from sepsis owing to a suppressed immune state of 1.21 (95% confidence interval, 1.18–1.25; $P < 0.001$) for patients at these 45 hospitals was significantly less than for patients at the 15 hospitals in the lowest quartile ($P = 0.004$ for difference).

Conclusions: The risk of death from sepsis owing 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 in care delivery at hospitals with different amounts of exposure to immunosuppressed patients.

Keywords: outcomes of intensive care unit management; multiple organ failure; sepsis; immunosuppressed

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Sepsis is a leading cause of death among critically ill patients, affecting between 1 million and 3 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 of sepsis (3, 4). In addition, in patients who survive the initial episode of sepsis, their chronic medical conditions and general health may be worsened, and they carry increased risks of secondary episodes of sepsis and of mortality (5, 6). As a result, health status before 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 as a result of medical conditions or medications that interfere with normal immune function are considered to be at particularly high risk for developing and dying of 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 centers with high case volume (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 exists regarding 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.

Methods

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

We used a search strategy described by Angus and colleagues to identify inpatients at least 18 years of age with sepsis in the Vizient database who were discharged between January 1, 2010, and 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 to 2012 was included. To increase the likelihood that the first hospital admission for sepsis was captured for patients discharged between January 1, 2010, and 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 the presence of discharge diagnosis codes and use of certain medications. In brief, three types of conditions were considered definitely immunosuppressive: human immunodeficiency virus infection, 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 transplants, and rheumatologic/inflammatory conditions. Compared with 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 hospitals, 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 upon 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 owing to a suppressed immune state varied by hospital quartile using multivariable, multilevel logistic regression. In a second analysis, we determined the expected number of deaths from sepsis at each hospital using the β-coefficients from our multivariable model. We calculated the ratio of the observed numbers of deaths to the expected number of deaths for immunosuppressed and nonimmunosuppressed patients with sepsis at each hospital. Using linear regression, we determined whether each hospital's observed/expected mortality from sepsis was associated with the hospital's case volume of immunosuppressed patients with sepsis. All tests were two sided, and a P value less than or equal to 0.05 was considered to indicate statistical significance. All analyses were performed with STATA 15.1 software (StataCorp).

Results

Of the 289 hospitals in the Vizient database from 2009 to 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 (*see* Figure E1 in the online supplement). Two hospitals were

excluded from further analysis because the ratio of immunosuppressed to nonimmunosuppressed patients with sepsis was greater than 2 SD above the mean (Figure E2).

Characteristics of Immunosuppressed and Nonimmunosuppressed 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 nonimmunosuppressed patients with sepsis (Table 1). Compared with immunosuppressed patients with sepsis, nonimmunosuppressed patients with sepsis were more likely to be older; to have congestive heart failure, diabetes, and chronic pulmonary disease; to have been admitted directly from a hospital or facility; and to have genitourinary infections. Compared with nonimmunosuppressed 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 to home than nonimmunosuppressed patients (60% vs. 50%, respectively).

Fifteen percent of immunosuppressed patients died during their hospitalization, compared with 12% of nonimmunosuppressed 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 with nonimmunosuppressed patients with sepsis (95% confidence interval [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 nonimmunosuppressed patients with sepsis increased. Conversely, all patients with sepsis had a nonsignificantly 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. The hospitals were ranked from 1 to 60 according to their case volumes of immunosuppressed patients with sepsis per year (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 driven primarily 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 caused by 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 (Table E1).

Table 1. Characteristics of 350,183 patients with sepsis, grouped by the presence or absence of immunosuppression

	Nonimmunosuppressed (*n* = 279,673)	Immunosuppressed (*n* = 70,510)
Age, yr, mean [SD]	65 [17]	59 [16]
Sex, *n* (%)		
Male	143,536 (51)	36,855 (52)
Female	136,137 (49)	33,655 (48)
Race, *n* (%)		
White	179,969 (64)	44,395 (63)
Black	55,748 (20)	14,678 (21)
Other	43,956 (16)	11,437 (16)
Elixhauser comorbid conditions, *n* (%)		
Congestive heart failure	48,285 (17)	8,738 (12)
Chronic pulmonary disease	63,144 (23)	12,763 (18)
Diabetes	91,599 (33)	18,733 (27)
Chronic liver disease	22,676 (8)	7,460 (11)
Renal failure	69,102 (25)	17,816 (25)
Admitted from a hospital or facility, *n* (%)	74,539 (27)	16,291 (23)
Infection categories, *n* (%)		
Genitourinary infection	111,842 (40)	21,233 (30)
Respiratory infection	91,089 (33)	24,475 (35)
Wound/soft tissue/bone/joint infection	43,302 (15)	9,079 (13)
Abdominal infection	28,941 (10)	9,928 (14)
Bacteremia	13,201 (4.7)	5,189 (7.4)
Device-related infection	12,280 (4.4)	1,938 (2.8)
CNS infection	4,310 (1.5)	1,004 (1.4)
Endocarditis	4,146 (1.5)	620 (0.9)
Other/unspecified infections	158,141 (57)	45,423 (64)
Mean number of infection categories per case [SD]	1.7 [0.8]	1.7 [0.8]
Hospital-acquired infection, *n* (%)	92,319 (33)	27,455 (39)
Length of stay, d, median [interquartile range]	8 [4–16]	10 [5–21]
Discharge location, *n* (%)		
Died	34,528 (12)	10,250 (15)
Home	139,086 (50)	42,590 (60)
Rehabilitation facility including long-term acute care hospital	83,085 (30)	12,776 (18)
Hospice	10,372 (3.7)	2,569 (3.6)
Transfer to other acute care hospital	5,588 (2.0)	1,200 (1.7)
Other	7,014 (2.5)	1,125 (1.6)

Definition of abbreviations: CNS = central nervous system; SD = standard deviation.

Table 2. Association between a patient's immune state and odds of in-hospital death owing to sepsis

	Bivariate Associations between Each Variable and In-Hospital Mortality			Multivariable Model		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Patient is immunosuppressed	1.18	1.15–1.21	<0.001	1.23	1.20–1.26	<0.001
Patient-level adjustment variables						
Vizient severity of illness score (log transformed)	2.23	2.21–2.25	<0.001	2.24	2.22–2.26	<0.001
Hospital-acquired infection	2.02	1.97–2.06	<0.001	1.83	1.79–1.88	<0.001
Admitted directly from other hospital or facility	1.95	1.91–2.00	<0.001	1.02	1.00–1.05	0.08
Hospital-level adjustment variables						
Number of immunosuppressed patients with sepsis at the hospital per yr/1,000	1.38	1.00–1.89	0.05	1.33	0.92–1.93	0.13
Number of nonimmunosuppressed patients with sepsis at the hospital per yr/1,000	1.02	0.91–1.15	0.70	0.86	0.76–0.98	0.02
Transplant center	1.36	1.15–1.61	<0.001	1.15	1.00–1.33	0.05
Hospice unit	0.79	0.68–0.91	0.001	0.86	0.77–0.95	0.004
Midwest region	0.73	0.64–0.84	<0.001	0.85	0.74–0.97	0.01
Northeast region	1.22	1.05–1.41	0.007	1.15	1.01–1.31	0.03
West region	0.99	0.81–1.21	0.95	0.81	0.69–0.95	0.009

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
ORs were determined using multilevel logistic regression with clustering of patients by hospital.

Effect of Hospital Case Volume of Immunosuppressed Patients with Sepsis on an Immunosuppressed Patient's Odds of Death from Sepsis

The odds of in-hospital death from sepsis owing 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 average case volumes of immunosuppressed patients with sepsis per year. The odds of in-hospital death owing 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 nonimmunosuppressed patients with sepsis (adjusted odds ratio, 1.38; 95% CI, 1.27–1.50; $P < 0.001$). Immunosuppressed patients with sepsis at hospitals in the second, third, and fourth quartiles had similarly increased odds of in-hospital death relative to nonimmunosuppressed patients with sepsis; the adjusted odds ratio of death owing 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 owing to sepsis from an immunocompromised state at hospitals in the first quartile (lowest number of immunosuppressed patients with sepsis) was significantly higher than the odds of death owing to sepsis from an immunocompromised state at hospitals at the remaining 45 hospitals ($P = 0.004$ difference).

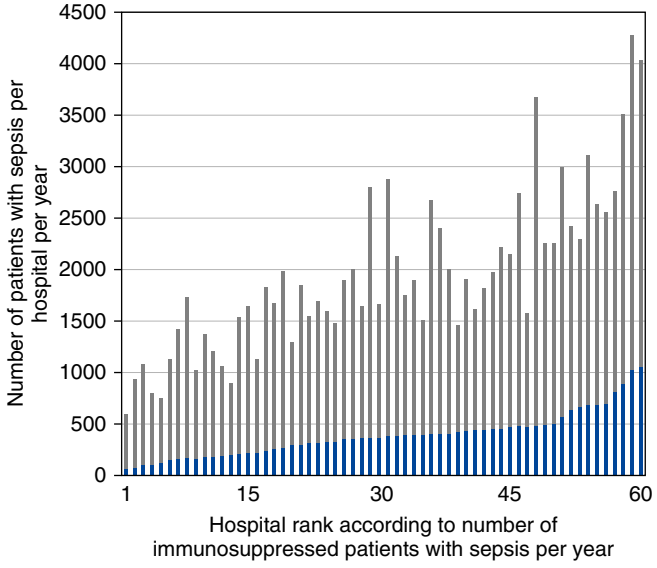

Figure 1. Number of immunosuppressed and nonimmunosuppressed patients with sepsis at 60 hospitals in the Vizient database. Blue = number of immunosuppressed patients with sepsis per hospital; gray = number of nonimmunosuppressed patients with sepsis per hospital.

In-Hospital Mortality for Immunosuppressed and Nonimmunosuppressed Patients with Sepsis According to Hospital Case Volume of Immunosuppressed Patients with Sepsis

We determined the odds of death for both immunosuppressed and nonimmunosuppressed patients with sepsis by hospital quartile (Table E2). Nonimmunosuppressed patients with sepsis at 45 hospitals in quartiles 2 to 4 had

Table 3. Characteristics of 350,183 patients with sepsis, grouped by hospital quartile

	Quartile 1 (*n* = 51,551)	Quartile 2 (*n* = 78,221)	Quartile 3 (*n* = 91,111)	Quartile 4 (*n* = 129,300)
Number of immunosuppressed patients with sepsis per hospital per year (range)	63–224	225–369	383–467	479–1,056
Mean age [SD], yr, per hospital	64 [6]	64 [4]	62 [3]	64 [9]
Sex: percent with each sex per hospital, mean [SD]				
Male	51.1 [0.05]	51.9 [0.02]	51.0 [0.02]	52.0 [0.02]
Female	49.9 [0.05]	49.1 [0.02]	49.0 [0.02]	48 [0.02]
Race: percent of each race per hospital, mean [SD]				
White	62.4 [25.0]	62.5 [24.7]	66.9 [14.8]	62.0 [18.1]
Black	22.1 [24.8]	20.8 [18.2]	20.1 [13.3]	21.3 [14.7]
Other	15.5 [13.2]	16.7 [15.5]	13 [0.09]	16.7 [17.8]
Immunosuppressive conditions: percent with each condition per hospital, mean [SD]*				
HIV	1.9 [1.8]	1.9 [2.7]	1.5 [1.5]	2.0 [1.6]
Hematological malignancy	3.4 [1.7]	5.6 [2.7]	5.8 [2.1]	8.1 [2.7]
Other immune condition	2.7 [1.2]	3.0 [0.9]	3.3 [1.0]	3.3 [0.7]
Solid malignancy and medication	1.0 [0.5]	1.6 [0.5]	1.6 [0.6]	1.8 [0.5]
Solid organ transplant and medication	1.6 [1.7]	2.8 [1.3]	4.7 [2.4]	4.7 [2.3]
Rheumatologic/inflammatory condition and medication	3.1 [0.6]	3.5 [0.7]	4.6 [0.6]	4.2 [0.7]
Any immunosuppressive condition	13.7 [3.8]	18.5 [3.5]	21.5 [4.4]	24.1 [4.8]
Elixhauser comorbid conditions: percent with each condition per hospital, mean [SD]				
Congestive heart failure	16.4 [3.9]	16.6 [3.5]	14.9 [2.9]	15.9 [3.6]
Chronic obstructive pulmonary disease	22.6 [5.2]	21.1 [3.8]	21.6 [3.8]	20.8 [2.9]
Diabetes	32.1 [4.3]	32.2 [2.6]	32.0 [3.3]	30.0 [2.7]
Chronic liver disease	7.9 [3.7]	9.0 [5.0]	9.8 [2.2]	8.6 [2.5]
Chronic renal disease	23.4 [6.4]	24.7 [5.8]	24.2 [4.8]	25.1 [4.2]
Percent admitted from another hospital or facility per hospital, mean [SD]	18.6 [13.4]	27.1 [10.7]	27.9 [11.8]	27.1 [8.0]
Percent with hospital-acquired infections per hospital, mean [SD]	28.0 [7.9]	35.4 [4.3]	34.6 [5.3]	36.5 [4.6]
Discharge location: percent discharged to each location per hospital, mean [SD]				
Died	11.0 [3.3]	13.5 [2.1]	12.6 [2.4]	13.5 [2.8]
Home	51.6 [8.3]	49.1 [4.4]	53.9 [7.9]	52.3 [3.6]
Rehabilitation facility	28.1 [8.6]	29.3 [5.3]	25.8 [7.0]	26.2 [5.2]
Hospice	3.4 [1.8]	4.0 [0.9]	3.6 [1.2]	3.5 [2.0]
Transfer different acute care hospital	2.9 [0.3]	1.9 [2.0]	1.8 [1.7]	2.1 [1.3]
Other location	3.0 [1.7]	2.1 [1.2]	2.3 [1.3]	2.4 [1.9]

Definition of abbreviations: HIV = human immunodeficiency virus; SD = standard deviation.
Hospitals were divided into quartiles based on their volume of immunosuppressed patients with sepsis from 2010 to 2012.
*The six categories of immunosuppressive conditions were mutually exclusive.

similar odds of death relative to nonimmunosuppressed patients at 15 hospitals in the lowest quartile (quartile 1) ($P = 0.28$). Immunosuppressed patients with sepsis at 45 hospitals in quartiles 2 to 4 had similar odds of death relative 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 nonimmunosuppressed patients with sepsis at each hospital (Figure 3). The observed/expected mortality from sepsis for immunosuppressed patients was greater than that for nonimmunosuppressed 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 nonimmunosuppressed 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 owing to a suppressed immune state was not being driven by outcomes from the smallest hospitals, we performed a sensitivity analysis, excluding the six hospitals (10%) with fewer than 150 immunosuppressed patients with sepsis per year (Table E3). We also confirmed similar results by 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 what we believe is the largest study to date quantifying the impact of immunosuppressive conditions on the

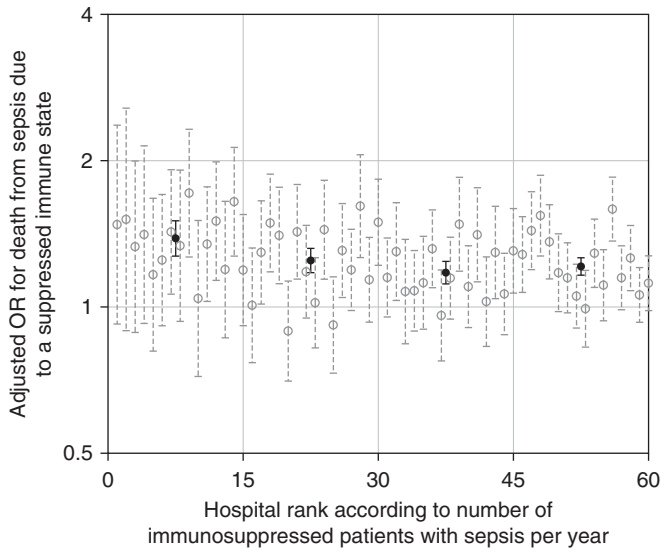

Figure 2. Adjusted odds of death owing to a suppressed immune state in patients with sepsis at 60 hospitals in the Vizient database. Open circles = odds of death owing to a suppressed immune state at each hospital. Hospitals were grouped into quartiles according to the number of immunosuppressed patients with sepsis per year. Solid circles = adjusted odds of death owing to a suppressed immune state within each quartile using multilevel logistic regression. Error bars represent 95% confidence intervals. Open circles: odds ratios (OR) were adjusted for each patient's Vizient risk adjustment score, presence of hospital-acquired infection, and admission directly from another hospital or facility. Solid circles: OR were adjusted for each patient's Vizient risk adjustment score, presence of hospital-acquired infection, admission directly from another hospital or facility, and the following hospital characteristics: number of nonimmunosuppressed patients with sepsis per year, transplant center, hospice unit, and geographic location.

likelihood of death from sepsis, we found that patients with sepsis who were immunosuppressed were 23% more likely to die during their hospitalization than patients with sepsis without immunosuppressive conditions, after adjusting for multiple patient- and hospital-level variables. Our novel finding was that the increased odds of death owing 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 nonimmunosuppressed patients at these hospitals. Our results suggest that a patient with sepsis may benefit not only from being treated at a hospital that manages the most sepsis but also from being treated at a hospital that has a certain level of familiarity with 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 of death from sepsis at hospitals that managed the fewest number of immunosuppressed patients with sepsis. First, the clinical presentation of sepsis may vary depending 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). Second, organizational aspects of hospitals that care for fewer immunosuppressed patients may result in delayed identification and management of all patients with sepsis. Third, the control of a patient's immunosuppressive medical condition may be worsened in the setting of a severe infection, which may contribute to a patient's odds of death. Clinicians with less exposure to immunosuppressed patients may have less experience with managing the exacerbations of these conditions in the setting of infection. Fourth, clinicians at hospitals with less exposure to immunosuppressed patients may have a more pessimistic view of a 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 who have less familiarity with immunosuppressed patients may be less likely to order an initial regimen of appropriately broad-spectrum antibiotics. In addition, these clinicians may 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%, respectively), patients who were immunosuppressed were more likely to be discharged to home than patients without immunosuppression (60% vs. 50%, respectively). These discordant results suggest that a patient's long-term physical and cognitive outcomes may be more greatly associated with factors that were present before hospitalization than with the severity of acute illness (18, 19). That is, patients without immunosuppressive conditions may be more likely to be in declining states of health before 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 with 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 nonimmunosuppressed patients had worse outcomes at hospitals with a greater proportion of immunosuppressed patients,

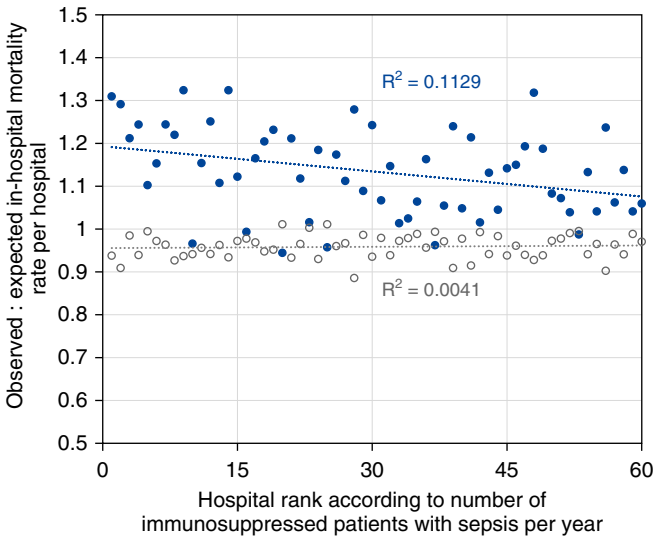

Figure 3. Observed number of deaths relative to expected number of deaths per hospital for immunosuppressed and nonimmunosuppressed patients with sepsis. Blue = immunosuppressed patients with sepsis; gray = nonimmunosuppressed patients with sepsis. Trends were determined using linear regression. The 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 nonimmunosuppressed patients with sepsis per year at the hospital, hospital was a transplant center, hospital had a hospice unit, and geographic location of the hospital. Blue line $P = 0.009$, grey line $P = 0.63$.

thereby decreasing the negative effect of being immunosuppressed at these hospitals. It is likely that both immunosuppressed and nonimmunosuppressed patients with more complex medical issues seek out care at larger hospitals. The complexity of a nonimmunosuppressed patient's comorbid conditions may be a risk factor for death from sepsis that 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 need to be mentioned. 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 more likely to be transplant centers. Third, all methods to identify patients with sepsis in administrative databases have limitations (1). The approach described by Angus and colleagues is used 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 immunosuppressed patients have increased risk of death from sepsis is likely multifactorial and constantly in flux owing to new therapeutic approaches that alter prognoses and risk for severe infection. On average, one of every five patients with sepsis was immunosuppressed. Our finding that the odds of death from sepsis owing 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. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013;41:1167–1174.
2 Vincent JL, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, *et al*.; ICON investigators. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *Lancet Respir Med* 2014;2:380–386.
3 Esper AM, Martin GS. The impact of comorbid conditions on critical illness. *Crit Care Med* 2011;39:2728–2735.
4 Wang HE, Shapiro NI, Griffin R, Safford MM, Judd S, Howard G. Chronic medical conditions and risk of sepsis. *PLoS One* 2012;7:e48307.
5 Yende S, Alvarez K, Loehr L, Folsom AR, Newman AB, Weissfeld LA, *et al*.; Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, and the Health, Aging, and Body Composition Study. Epidemiology and long-term clinical and biologic risk factors for pneumonia in community-dwelling older Americans: analysis of three cohorts. *Chest* 2013;144:1008–1017.
6 Yende S, Iwashyna TJ, Angus DC. Interplay between sepsis and chronic health. *Trends Mol Med* 2014;20:234–238.
7 Poutsiaka DD, Davidson LE, Kahn KL, Bates DW, Snydman DR, Hibberd PL. Risk factors for death after sepsis in patients immunosuppressed before the onset of sepsis. *Scand J Infect Dis* 2009;41:469–479.

8 Tolsma V, Schwebel C, Azoulay E, Darmon M, Souweine B, Vesin A, *et al*. Sepsis severe or septic shock: outcome according to immune status and immunodeficiency profile. *Chest* 2014;146:1205–1213.
9 Walkey AJ, Wiener RS. Hospital case volume and outcomes among patients hospitalized with severe sepsis. *Am J Respir Crit Care Med* 2014;189:548–555.
10 Gu WJ, Wu XD, Zhou Q, Zhang J, Wang F, Ma ZL, *et al*. Relationship between annualized case volume and mortality in sepsis: a dose-response meta-analysis. *Anesthesiology* 2016;125:168–179.
11 Gaieski DF, Edwards JM, Kallan MJ, Mikkelsen ME, Goyal M, Carr BG. The relationship between hospital volume and mortality in severe sepsis. *Am J Respir Crit Care Med* 2014;190:665–674.
12 Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303–1310.
13 Greenberg JA, Hohmann SF, Hall JB, Kress JP, David MZ. Validation of a method to identify immunocompromised patients with severe sepsis in administrative databases. *Ann Am Thorac Soc* 2016;13:253–258.
14 Shaw JJ, Santry HP. Who gets early tracheostomy? Evidence of unequal treatment at 185 academic medical centers. *Chest* 2015;148:1242–1250.
15 Page DB, Donnelly JP, Wang HE. Community-, healthcare-, and hospital-acquired severe sepsis hospitalizations in the University HealthSystem Consortium. *Crit Care Med* 2015;43:1945–1951.
16 Jamme M, Daviaud F, Charpentier J, Marin N, Thy M, Hourmant Y, *et al*. Time course of septic shock in immunocompromised and nonimmunocompromised patients. *Crit Care Med* 2017;45:2031–2039.
17 Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al*. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017;45:486–552.
18 Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, *et al*.; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293–1304.
19 Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787–1794.
20 Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, *et al*.; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;58:309–318.