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Epidemiology of Bloodstream Infections in a Multicenter Retrospective Cohort of Liver Transplant Recipients

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Background. Although some studies have examined the epidemiology of bloodstream infections after liver transplantation, they were based in single centers and did not identify bloodstream infections treated in other hospitals. **Methods.** We retrospectively examined a cohort of 7912 adult liver transplant recipients from 24 transplant centers using 2004 to 2012 *International Classification of Diseases, Ninth Revision, Clinical Modification* billing data from 3 State Inpatient Databases, and identified bloodstream infections, inpatient death, and cumulative 1-year hospital costs. Multilevel Cox regression analyses were used to determine factors associated with bloodstream infections and death. **Results.** Bloodstream infections were identified in 29% (n = 2326) of liver transplant recipients, with a range of 19% to 40% across transplant centers. Only 63% of bloodstream infections occurring more than 100 days posttransplant were identified at the original transplant center. Bloodstream infections were associated with posttransplant laparotomy (adjusted hazard ratio [aHR], 1.52), prior liver transplant (aHR, 1.42), increasing age (aHR, 1.07/decade), and some comorbidities. Death was associated with bloodstream infections with and without septic shock (aHR, 10.96 and 3.71, respectively), transplant failure or rejection (aHR, 1.41), posttransplant laparotomy (aHR, 1.40), prior solid-organ transplant (aHR, 1.48), increasing age (aHR, 1.15/decade), and hepatitis C cirrhosis (aHR, 1.20). The risk of bloodstream infections and death varied across transplant centers. Median 1-year cumulative hospital costs were higher for patients who developed bloodstream infections within 1 year of transplant compared with patients who were bloodstream infection-free (US $229 806 vs US $111 313; $P < 0.001$). **Conclusions.** Bloodstream infections are common and costly complications after liver transplantation that are associated with a markedly increased risk of death. The incidence and risk of developing bloodstream infections may vary across transplant centers.

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Liver transplantation has a 1- and 5-year graft survival rate of 90% and 70%, respectively, that has been enabled by refinements in surgical technique and advances in immunosuppressive and preventive anti-infective therapy.[1] However, bloodstream infections can limit posttransplant patient survival by culminating in multiorgan failure, septic shock, and death.[2-5]

Recently published single-center studies show that bloodstream infections occur in 17% to 29% of liver transplant recipients[6-9] and are associated with an increased risk of death.[8,9] Commonly isolated microorganisms were *Staphylococcus aureus*, *Enterococcus* species, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and frequently

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originated from abdominal, pulmonary, and urinary tract sources.[7,8] Patients infected with carbapenem-resistant *K. pneumoniae* had a particularly high mortality rate.[9] Although these studies increase our understanding of the incidence, microbiology, and outcomes of bloodstream infections after liver transplantation, they are based in single transplant centers that may have missed bloodstream infections treated in other hospitals.

To determine the epidemiology of bloodstream infections after liver transplantation, we assembled a large and more representative cohort of liver transplant recipients from multiple centers using the Healthcare Cost and Utilization Project State Inpatient Databases (SID). The SID comprise of demographic and billing data that capture inpatient diagnoses and procedures through *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) coding[10] and has been used in the field of liver transplantation to study perioperative complications of live liver donors,[11] delayed-onset cytomegalovirus disease,[12] and relationships between hospital/surgeon volume and inpatient mortality.[13] The ICD-9-CM codes used to identify bloodstream infections in this study have been validated, with a positive predictive value of 89% and a negative predictive value of 80%.[14] Our approach allowed us to follow a large number of patients for a long period, identify bloodstream infections regardless of whether patients were readmitted to the transplant hospital or a different hospital, and determine hospital costs. We hypothesized that a significant proportion of bloodstream infections are treated in hospitals other than the original transplant center, and that bloodstream infections are associated with increased hospital costs and death.

METHODS

Data Sources

We used the SID from California (2003 to 2011), Florida (2005 to 2013), and New York (2005 to 2012) because of the availability of encrypted patient-level identifiers that link admissions across hospitals over time within a state. The ICD-9-CM diagnosis and procedure codes used in this study are listed in **Table S1** (**SDC**, http://links.lww.com/TXD/A21).

Study Design and Patient Population

We performed a retrospective cohort study of persons 18 years or older who underwent liver transplantation in nonpediatric hospitals (identified by the American Hospital Association Annual Hospital Survey) from 2004 to 2010 in the California SID, 2006 to 2012 in the Florida SID, and 2006 to 2011 in the New York SID (n = 9096). We chose the cohort inception years to accrue 1 year of preexisting data to determine comorbidities and at least 1 year of follow-up data. We excluded persons who lived outside of the state where the transplant was performed because we would not be able to track bloodstream infections during readmission in those individuals (n = 1088), and persons who died 2 days or less posttransplant because they would not have had the opportunity to develop bloodstream infections (n = 96). The final study population consisted of 7912 liver transplant recipients (Figure 1). This study was considered exempt by the Washington University Institutional Review Board.

Patient Characteristics

Demographic data were determined at the time of liver transplantation. Possible reasons for liver transplant, prior solid-organ transplant, and Elixhauser comorbidities were identified within 1 year before liver transplant and during the transplant hospitalization.[15]

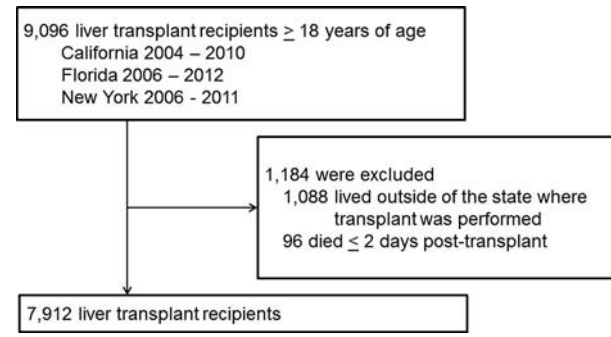

FIGURE 1. Cohort inception of 7912 liver transplant recipients.

Transplant Center Characteristics

We determined the mean annual number of liver transplants at each transplant center and classified hospitals as either small (<25 transplants/yr), medium (26 to 75 transplants/yr), or large (>75 transplants/yr) transplant centers by volume. We used American Hospital Association Annual Survey data to determine the number of adult acute-care medical/surgical beds at each transplant center and identify its teaching status (presence or absence of residents-in-training).

Bloodstream Infections

Bloodstream infections that occurred posttransplant were identified using ICD-9-CM codes in **Table S1** (**SDC**, http://links.lww.com/TXD/A21). Bloodstream infections that occurred during the transplant hospitalization were defined as occurring after transplantation if it was not the primary diagnosis coded for the hospitalization and if 15 days or less elapsed from day of admission to day of transplant, to minimize the probability of capturing bloodstream infections occurring before transplant. The time of bloodstream infection was defined as the midpoint between the day of transplant and the day of discharge for bloodstream infections that occurred during the transplant hospitalization, and the day of admission for bloodstream infections that were identified on readmission. Bloodstream infections were empirically categorized as either early-onset (occurring < 100 days posttransplant) or delayed-onset (occurring > 100 days posttransplant) based on the median onset of bloodstream infection, and as perioperative (occurring < 30 days post-transplant) or nonperioperative (occurring > 30 days posttransplant). Possible sources of infection were defined as concurrent coding for intra-abdominal infections, pneumonia, empyema, and other chest infections, urinary tract infection, endocarditis, and other blood vessel infections, septic arthritis and osteomyelitis, and central nervous system infections. Possible complications of bloodstream infection were defined as concurrent coding for acute organ dysfunction and septic shock.[14] The hospitals where bloodstream infections were identified indicated whether patients were treated at the original transplant center or another hospital.

Death and Other Conditions

Time of inpatient death was determined using the discharge status variable. Other conditions identified on follow-up were

newly coded transplant failure or rejection, posttransplant laparotomy, hemodialysis, and repeat solid-organ transplant during readmission (**Table S1, SDC**, http://links.lww.com/TXD/A21).

Hospital Costs

Hospital costs for the transplant hospitalization and any subsequent readmission 1 year or less after transplantation were summed to arrive at cumulative 1-year hospital costs for the study population, after converting hospital charges to costs using the Healthcare Cost and Utilization Project cost-to-charge ratio file,[16] and adjusting for inflation to 2013 US dollars with the medical care component of the Consumer Price Index.[17] Hospital costs were then compared between persons who developed bloodstream infection 1 year or less posttransplant and persons who were bloodstream infection-free.

Statistical Analysis

Descriptive statistics were used to describe the demographic and clinical characteristics of the study population. Kruskall-Wallis testing was performed to determine if cumulative 1-year hospital costs were statistically significantly higher for persons who developed bloodstream infection 1 year or less posttransplant compared with persons who were bloodstream infection-free. Spearman rank-order testing was performed to determine if incidence of bloodstream infections and death across transplant centers was correlated. Multilevel Cox regression analyses with random intercepts by transplant center were performed to identify patient-level and transplant center-level factors associated with bloodstream infection and death while accounting for shared frailties in developing bloodstream infection and death in persons from the same transplant center. Clinically meaningful patient-level and transplant center-level variables that could be potential risk factors for bloodstream infection and death were specified and evaluated for proportionality and time dependency using visual inspection of log-log survival curves and examination of Schoenfeld residuals.[18] A series of Cox regression models starting with a hierarchically well-formulated initial model followed by iterative backward elimination resulted in a penultimate model that was assessed for confounding and precision to arrive at the final model.[19] Statistical significance was set at a P value of 0.05 or less. All analyses were performed using SAS Enterprise Guide 5.1 (Cary, NC).

RESULTS

Patient Characteristics

The study population consisted of 7912 adult liver transplant recipients (Table 1). The median age was 56 years; 33% were women, 56% were white, 22% were Hispanic, 74% lived in large metropolitan areas, and 52% had private insurance. Commonly identified possible reasons for liver transplant were hepatitis C cirrhosis (44%), hepatocellular carcinoma (36%), and alcoholic cirrhosis (34%). Two percent of patients had prior solid-organ transplantation. Commonly identified comorbidities were hypertension (49%), diabetes mellitus (34%), and renal failure (19%). The median duration of follow-up was 4 years (interquartile range, 2.1-5.9 years).

TABLE 1.

Demographic and clinical characteristics of liver transplant recipients in the study cohort at the time of organ transplantation

Variables	All recipients, n = 7912
Age, y	
Mean ± SD	54.38 ± 10.01
Median (interquartile range)	56 (50-61)
Female sex (%)	32.95
Race (%)	
White	56.31
Black	6.95
Hispanic	22.00
Asian or Pacific Islander	8.06
Other or missing	6.67
Patient location (urban-rural) (%)[a]	
Large metropolitan	74.89
Small metropolitan	20.34
Micropolitan	3.37
Not metropolitan or micropolitan, or missing	1.40
Median income of patient ZIP code (%)	
First quartile (poorest)	20.70
Second quartile	23.10
Third quartile	23.90
Fourth quartile (wealthiest)	23.95
Missing	8.34
Expected primary insurance payer (%)	
Medicare	26.93
Private insurance	51.50
Medicaid, self-pay, no charge, other, or missing	21.56
Possible reasons for liver transplant, %	
Hepatitis C cirrhosis	43.69
Hepatocellular carcinoma	36.29
Alcoholic cirrhosis	34.11
Cirrhosis, no viral etiology identified	16.92
Hepatitis B cirrhosis	9.37
Nonalcoholic steatohepatitis	8.34
Biliary cirrhosis	4.97
Prior transplant, %	2.14
Liver	1.86
Other comorbidities, %	
Hypertension	49.34
Diabetes mellitus	33.99
Renal failure	19.40
Depression	14.21
Chronic pulmonary disease	12.87
Obesity	10.62
Drug abuse	9.31
Hypothyroidism	9.31
Neurologic disorders	6.96
Pulmonary circulation disease	6.74
Congestive heart failure	6.08
Valvular disease	5.46
Duration of follow-up, years	
Mean	4.0
Median (interquartile range)	4.0 (2.1-5.9)

[a] Large metropolitan—at least 1 million residents; small metropolitan—less than 1 million residents; micropolitan—adjacent to large or small metropolitan area.

Transplant Center Characteristics

There were 24 hospitals that performed liver transplants for the study population (Table 2). The mean number of liver transplants performed by each hospital per year was 49, and the mean number of acute-care beds was 404. Six hospitals were small (<25 transplants/year), 12 were medium (26-75 transplants/year), and 6 were large (>75 transplants/year) transplant centers. Ninety-two percent of transplant centers were teaching hospitals.

Bloodstream Infections

Bloodstream infections were identified in 29% of liver transplant recipients, with a range of 19% to 40% across transplant centers (Figure 2A). Fifty-two percent of bloodstream infections occurred 100 days or less posttransplant (early-onset), and 48% occurred more than 100 days posttransplant (delayed-onset) (Table 3). Thirty-four percent of bloodstream infections occurred 30 days or less posttransplant (perioperative), and 66% occurred more than 30 days posttransplant (nonperioperative). Coding for Gram-negative or anaerobic bacteria, Gram-positive bacteria, multiple microorganisms, and fungus accounted for 23%, 22%, 8%, and 3% bloodstream infections, respectively, whereas unspecified microorganisms (eg, "bacteremia") were coded in 44%. Common possible sources of infection were intra-abdominal infections (55%), pneumonia, empyema, and other chest infections (37%), urinary tract infection (22%), endocarditis, and other blood vessel infections (7%). Significantly more early-onset bloodstream infections had concurrent coding for intra-abdominal and pulmonary infections than delayed-onset bloodstream infections (70% vs 40% and 42% vs 31%, respectively). Acute organ dysfunction, multiorgan failure, and septic shock were identified in 78%, 54%, and 19% of bloodstream infection hospitalizations, respectively. Renal (64%), cardiovascular (27%), respiratory (27%), and hematologic (26%) dysfunction commonly occurred. Eighty-one percent of patients with bloodstream infection were diagnosed and treated in the original transplant center. Although 97% of early-onset bloodstream infections were identified at the original transplant center, only 63% of delayed-onset bloodstream infections were identified at the original transplant center. Thirty-four percent of patients with bloodstream infections died, with a median time to death of 47 days from the bloodstream infection hospitalization (interquartile range, 15-206 days).

TABLE 2.

Hospital characteristics of liver transplant centers

Variables	All hospitals, n = 24
No. liver transplants performed per year	
Mean ± SD	48.96 ± 34.15
Median (range)	43 (2-139)
Transplant center size by mean number of liver transplants performed per year (%)	
Small (<25)	6 (25.00)
Medium (26-75)	12 (50.00)
Large (>75)	6 (25.00)
Number of adult acute-care medical/surgical beds	
Mean ± SD	403.62 ± 262.20
Median (range)	338 (80-1081)
Transplant center size by bed number	
Small (<250)	7 (29.17)
Medium (251 to 500)	10 (41.67)
Large (>500)	7 (29.17)
Teaching hospital (%)	22 (91.67)

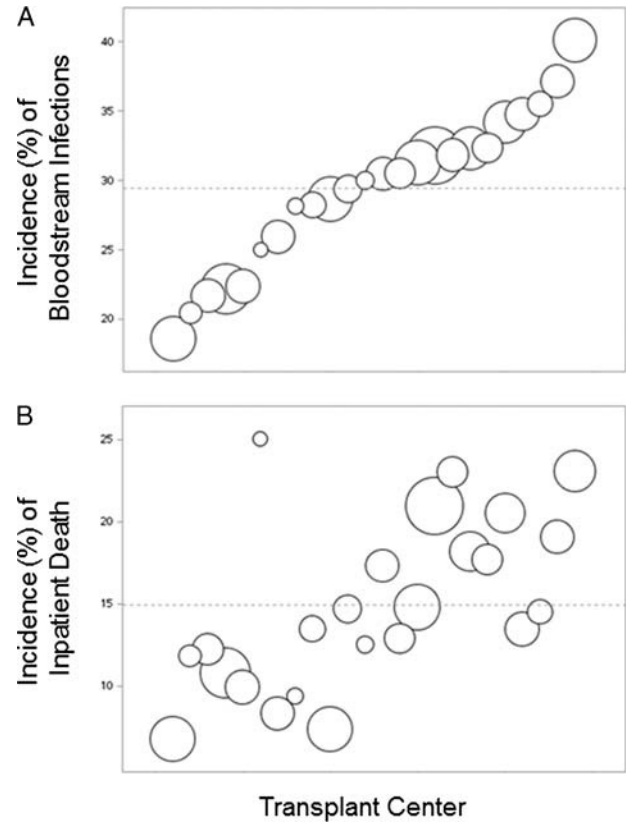

FIGURE 2. Incidence of bloodstream infections (A) and inpatient death (B) stratified according to transplant center. Bubbles signify relative sizes of transplant centers by mean number of liver transplants per year. Dashed line indicates the mean incidence for the population.

Risk factors for bloodstream infections are in Table 4. In multivariate analysis, posttransplant laparotomy (hazard ratio [HR], 1.52), increasing age at time of transplantation per decade (HR, 1.07), female sex (HR, 1.13), prior liver transplant (HR, 1.42), diabetes mellitus (HR, 1.12), renal failure (HR, 1.27), chronic pulmonary disease (HR, 1.22), and congestive heart failure (HR, 1.23) were associated with an increased risk of bloodstream infections. Hepatocellular carcinoma (HR, 0.80) was associated with a decreased risk of bloodstream infections. Of 24 transplant centers, 4 were significantly more likely than average to have populations that developed bloodstream infections and 3 were significantly less likely than average to have populations that developed bloodstream infections (Figure 3A).

Median 1-year cumulative hospital costs were higher for patients who developed bloodstream infections within 1 year of transplant compared with patients who were bloodstream infection-free (US $229 806 vs $111 313; $P < 0.001$) (Figure 4).

Inpatient Death

Inpatient death was identified in 15% of patients, with a range of 7% to 25% across transplant centers (Figure 2B). The incidence of bloodstream infections and death across transplant centers were strongly correlated (Spearman

TABLE 3.

No. patients with bloodstream infections and inpatient death coded during hospitalization in a cohort of 7912 liver transplant recipients

	All	Early (<100 d posttransplant)	Delayed (>100 d posttransplant)
Bloodstream infections			
No. patients (%)	2326 (29.40)	1212 (52.11)	1114 (47.89)
Microorganism			
Gram-negative or anaerobic bacteria	524 (22.53)	251 (20.71)	273 (24.51)
Gram-positive bacteria	518 (22.27)	281 (23.18)	237 (21.27)
Multiple organisms	192 (8.25)	131 (10.81)	61 (5.48)
Fungus	62 (2.67)	38 (3.14)	24 (2.15)
No specific microorganism	1030 (44.28)	511 (42.16)	519 (46.59)
Possible source of infection			
Intra-abdominal infections	1290 (55.46)	847 (69.88)	443 (39.77)
Pneumonia, empyema, other chest infections	858 (36.89)	510 (42.08)	348 (31.24)
Urinary tract infection	506 (21.75)	250 (20.63)	256 (22.98)
Endocarditis, other blood vessel infections	165 (7.09)	73 (6.02)	92 (8.26)
Septic arthritis, osteomyelitis	20 (0.86)	*	*
Meningitis, brain abscess, spinal abscess	11 (0.47)	*	*
No identifiable possible source of infection	436 (18.74)	160 (13.20)	276 (24.78)
Acute organ dysfunction			
Renal	1479 (63.59)	786 (64.85)	693 (62.21)
Cardiovascular	632 (27.17)	352 (29.04)	280 (25.13)
Respiratory	622 (26.74)	369 (30.45)	253 (22.71)
Hematologic	614 (26.40)	384 (31.68)	230 (20.65)
Metabolic	427 (18.36)	217 (17.90)	210 (18.85)
Hepatic	416 (17.88)	297 (24.50)	119 (10.68)
Neurologic	262 (11.26)	138 (11.39)	124 (11.13)
Multiorgan failure (>2 acute organ dysfunction)	1256 (54.00)	730 (60.23)	526 (47.22)
Septic shock	453 (19.48)	252 (20.79)	201 (18.04)
Admitted to the original liver transplant center	1877 (80.70)	1174 (96.86)	703 (63.11)
Died	802 (34.48)	412 (33.99)	390 (35.01)
Median time to death in days after admission with bloodstream infection (interquartile range)	47 (15-206)	44 (16-227)	51 (15-176)
Inpatient death			
No. patients (%)	1180 (14.91)	380 (32.20)	800 (67.80)
Bloodstream infection	756 (64.07)	264 (69.47)	492 (61.50)
Transplant failure or rejection	628 (53.22)	174 (45.79)	454 (56.75)
Dialysis	497 (42.12)	204 (53.68)	293 (36.63)

[a] AHRQ-HCUP prohibits reporting cell sizes <11 in number.

AHRQ-HCUP, Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project

correlation coefficient, 0.66; $P < 0.001$). Thirty-two percent of deaths occurred 100 days or less posttransplant, and 68% occurred more than 100 days posttransplant (Table 3). Common conditions during the death hospitalization were bloodstream infections (64%), transplant failure or rejection (53%), and hemodialysis (42%).

Risk factors for death are in Table 5. In multivariate analysis, bloodstream infections without septic shock (HR, 3.71), bloodstream infections with septic shock (HR, 10.96), transplant failure or rejection (HR, 1.41), posttransplant laparotomy (HR, 1.40), increasing age at time of transplantation per decade (HR, 1.15), hepatitis C cirrhosis (HR, 1.20), and prior solid-organ transplant (HR, 1.48) were associated with an increased risk of death. Of 24 transplant centers, 4 were significantly more likely than average to have populations that died and 2 were significantly less likely than average to have populations that died (Figure 3B). Bloodstream infections with or without septic shock (HR, 4.8), early-onset bloodstream infections (HR, 5.3), and delayed-onset bloodstream infections (HR, 4.3) were associated with increased risk of death after adjusting for the same covariates.

DISCUSSION

We found that bloodstream infections were common and costly complications after liver transplantation that were associated with a nearly 5-fold increased risk of death. These results identify bloodstream infections as significant impediments to successful liver transplantation across multiple transplant centers and highlight the need for more clinical and translational research into how bloodstream infections in these vulnerable hosts can be better prevented and treated.

Interestingly, almost half of first episodes of bloodstream infection were identified more than 100 days posttransplant, of which nearly 40% were treated at a hospital other than the original transplant center. This finding underscores the ability

TABLE 4.

Cox proportional hazard model of risk factors for bloodstream infections

	Univariate analysis		Multivariate analysis	
Risk factor	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Patient-level variables				
Previous exploratory laparotomy	1.59 (1.43-1.77)	<0.001	1.52 (1.36-1.70)	<0.001
Increasing age at time of transplantation per decade	1.04 (1.00-1.09)	0.053	1.07 (1.02-1.11)	0.004
Female sex	1.20 (1.10-1.30)	<0.001	1.13 (1.04-1.24)	0.004
Possible reasons for liver transplant				
Hepatitis C cirrhosis	1.00 (0.92-1.08)	1.000		
Hepatocellular carcinoma	0.76 (0.70-0.83)	<0.001	0.80 (0.73-0.88)	<0.001
Alcoholic cirrhosis	1.05 (0.97-1.14)	0.249		
Cirrhosis, no viral etiology identified	1.10 (0.99-1.22)	0.089		
Hepatitis B cirrhosis	0.84 (0.73-0.98)	0.022		
Non-alcoholic steatohepatitis	1.15 (1.00-1.32)	0.048		
Biliary cirrhosis	1.02 (0.85-1.23)	0.797		
Prior liver transplant	1.67 (1.31-2.13)	<0.001	1.42 (1.10-1.82)	0.006
Other comorbidities				
Diabetes mellitus	1.14 (1.04-1.24)	0.003	1.12 (1.02-1.22)	0.015
Renal failure	1.44 (1.31-1.59)	<0.001	1.27 (1.15-1.41)	<0.001
Chronic pulmonary disease	1.30 (1.16-1.46)	<0.001	1.22 (1.08-1.36)	0.001
Obese	1.18 (1.04-1.34)	0.010		
Congestive heart failure	1.47 (1.27-1.71)	<0.001	1.23 (1.06-1.43)	0.008
Transplant center-level variables				
Transplant center size by volume				
Small (<25 transplants/y)	1.00			
Medium (26 to 75 transplants/y)	1.10 (0.92-1.32)	0.275		
Large (>75 transplants/y)	1.00 (0.84-1.19)	0.988		
Transplant center size by bed number				
Small (<250)	1.00			
Medium (251-500)	0.87 (0.79-0.96)	0.006		
Large (>500)	0.90 (0.82-1.00)	0.047		
Teaching hospital	1.07 (0.83-1.38)	0.587		

of our analysis to identify bloodstream infections over a long period, and regardless of whether patients were readmitted to the transplant center or another hospital. Delayed-onset bloodstream infections were less commonly concurrently coded with intra-abdominal infections than were early-onset infections, likely reflecting a shift away from the surgical site as an obvious source of infection as time elapses after transplant.[7,8] In contrast, urinary tract, endovascular, bone and joint, and central nervous system infections were more commonly concurrently coded with delayed-onset bloodstream infections than early-onset bloodstream infections. Acute organ dysfunction, multiorgan failure, and septic shock occurred commonly in hospitalizations wherein bloodstream infections were identified, and possibly reflect significant morbidity caused by bloodstream infections.[7,20,21]

Posttransplant laparotomy and prior liver transplant were the strongest risk factors for bloodstream infections in our analysis. Return to surgery and prior liver transplant have previously been shown to be associated with bloodstream infections in single-center studies.[8,20,22] Return to surgery is typically performed for technical complications that arise posttransplant, and include biliary leak or stricture, portal vein or hepatic artery thrombosis, hemorrhage and infarction.[23,24] Disrupted anatomy coupled with critical illness, complex surgery, and prolonged hospitalization may predispose patients to develop intra-abdominal, pulmonary, urinary tract, and vascular catheter infections that culminate in bloodstream infections. Repeat liver transplantation has higher rates of allograft failure compared with primary liver transplantation,[25,26] which can result in an increased risk of bloodstream infections. Other risk factors were increasing age, diabetes mellitus, renal failure, chronic pulmonary disease, and congestive heart failure, which indicate that comorbidities can contribute to increasing the risk of bloodstream infections among liver transplant recipients. Hepatocellular carcinoma was associated with a decreased risk of bloodstream infections, likely because patients who underwent transplantation for early-stage hepatocellular carcinoma as defined by the Milan criteria[27-29] had lower model for end-stage liver disease (MELD) scores than patients who underwent transplantation for end-stage liver disease.[30,31] Single-center studies indicate that higher MELD scores are associated with increased bloodstream infection risk.[8,20]

We found variability in the shared susceptibilities of liver transplant recipients clustered within transplant centers in developing bloodstream infections, after accounting for patient-level factors that included posttransplant laparotomy, prior liver transplant, age, sex, and several comorbidities. The most likely reason for variability is residual confounding given our inability to capture all patient-level factors that can be associated with bloodstream infections. Some transplant centers operate on sicker and more complicated patients than others,

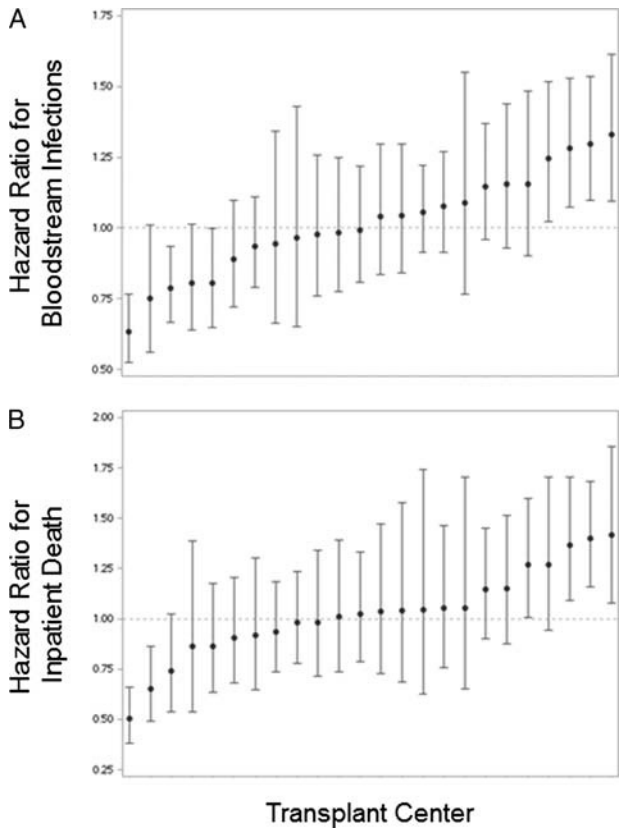

FIGURE 3. Transplant center-level effects for bloodstream infection (A) and death (B). Blue circles represent point estimates, and red bars indicate 95% confidence intervals. Dashed line indicates the average risk for the population.

which can result in more morbid cohorts who are at greater risk of bloodstream infections and death than average. Other possible reasons for variability include shared antibiotic resistance patterns for bacteria among patients transplanted in the same transplant center,[9,20-22,32-34] shared infection control policies,[8,35] and shared surgical teams.[23,24] Patients transplanted in hospitals with high rates of multidrug-resistant bacteria, such as methicillin-resistant *S. aureus*, extended spectrum β lactamase-producing *P. aeruginosa* and carbapenem-resistant *K. pneumoniae* may be at increased risk of developing bloodstream infections given the reduced efficacy of first-line antibiotics in treating sources of infection.[9,21] Aggressive infection control policies that have been shown to reduce the transmission of methicillin-resistant *S. aureus* among liver transplant recipients (active surveillance, contact isolation and decolonization) may be more effectively implemented in some transplant centers than others.[8,35] Surgical teams in different transplant centers may have varying levels of technical proficiency, which can lead to different biliary and vascular complication rates[23,24] and different risks of bloodstream infection. Variability in bloodstream infection risk across transplant centers should be confirmed with more granular clinical data.

We found that bloodstream infections, multiorgan failure, and septic shock were strongly associated with death, supporting recently published single-center studies.[8,9] Some bloodstream infections can initiate a rapidly vicious circle of cytokine-driven hyperinflammation, septic shock, and death within a few days of onset,[9,36] whereas others can result in protracted hospitalization, persistent organ dysfunction, immune exhaustion, and frailty followed by death after several weeks or months.[37] Alternatively, bloodstream infections may be markers for more direct determinants of death, such as posttransplant technical complications or acute allograft rejection. Although we adjusted for posttransplant laparotomy and transplant failure or rejection in our Cox regression models, residual confounding may have been present. The precise role of bloodstream infections in the causal pathway to death cannot be determined in this retrospective population-level epidemiologic study.

The strengths of our study are the large size of the study population, long duration of follow-up, and identification of bloodstream infections regardless of admission to the transplant center or another hospital. It however has some limitations. Comorbidities and clinical events were identified using ICD-9-CM codes which are not perfectly accurate.[38] However, the ICD-9-CM codes used to identify bloodstream infections in this study have been validated and found to have reasonable accuracy.[14] Moreover, misclassification stemming from occasionally inaccurate ICD-9-CM coding will result in more conservative estimates of associations between bloodstream infections and death, or bloodstream infections and potential risk factors, thereby maintaining the validity of our results. The data source used in this study contains only demographic and inpatient hospital ICD-9-CM billing data occurring within a state and does not have microbiology information, laboratory test results, MELD scores, medications prescribed, or information regarding the presence of

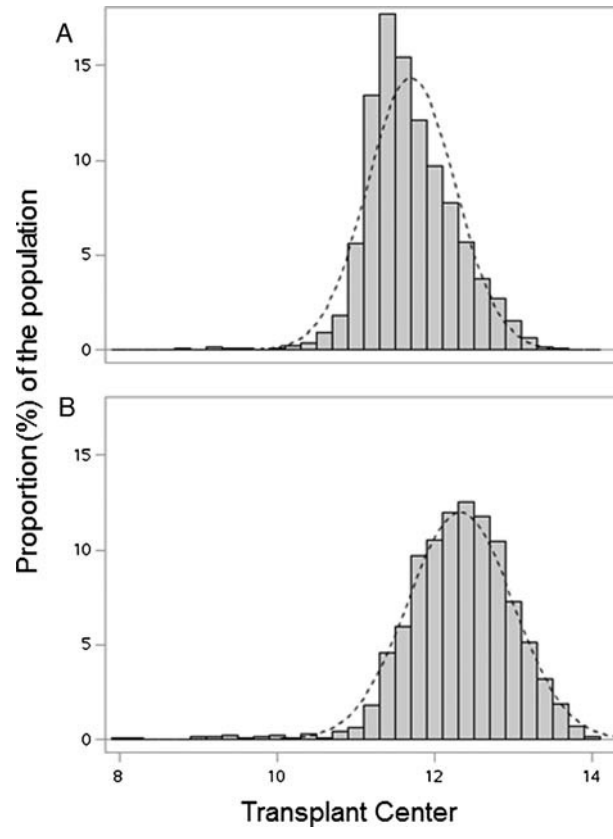

FIGURE 4. Natural log of cumulative 1-year hospital costs stratified according absence (A) or presence (B) of bloodstream infection within 1 year posttransplant.

TABLE 5.

Cox proportional hazard model of risk factors for inpatient death

	Univariate analysis		Multivariate analysis	
Risk factor	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Patient-level variables				
Bloodstream infections	5.73 (5.07-6.48)	<0.001		
Microorganism				
Gram-negative or anaerobic bacteria	5.34 (4.46-6.40)	<0.001		
Gram-positive bacteria	4.73 (3.93-5.70)	<0.001		
Multiple organisms	7.58 (5.97-9.62)	<0.001		
Fungus	5.40 (3.44-8.46)	<0.001		
No specific microorganism	6.17 (5.35-7.12)	<0.001		
Without multiorgan failure	2.96 (2.50-3.50)	<0.001		
With multiorgan failure	8.70 (7.64-9.90)	<0.001		
Early-onset (<100 days posttransplant)	6.19 (5.38-7.12)	<0.001		
Delayed-onset (>100 days posttransplant)	5.32 (4.62 – 6.12)	<0.001		
Without septic shock	4.44 (3.89-5.06)	<0.001	3.71 (3.23-4.26)	<0.001
With septic shock	12.98 (11.11-15.16)	<0.001	10.96 (9.31-12.90)	<0.001
Transplant failure or rejection	2.31 (2.03-2.62)	<0.001	1.41 (1.23-1.61)	<0.001
Posttransplant laparotomy	2.20 (1.93-2.51)	<0.001	1.40 (1.22-1.61)	<0.001
Increasing age at time of transplantation per decade	1.12 (1.05-1.19)	<0.001	1.15 (1.06-1.35)	<0.001
Female sex	1.19 (1.05-1.34)	0.005		
Possible reasons for liver transplant				
Hepatitis C cirrhosis	1.26 (1.12-1.41)	<0.001	1.20 (1.06-1.35)	0.003
Hepatocellular carcinoma	1.00 (0.89-1.13)	1.000		
Alcoholic cirrhosis	1.02 (0.91-1.16)	0.684		
Cirrhosis, no viral etiology identified	0.90 (0.77-1.06)	0.194		
Hepatitis B cirrhosis	0.94 (0.77-1.15)	0.570		
Nonalcoholic steatohepatitis	0.97 (0.79-1.20)	0.808		
Biliary cirrhosis	0.76 (0.56-1.02)	0.065		
Prior solid-organ transplant	1.93 (1.44-2.59)	<0.001	1.48 (1.10-1.99)	0.011
Other comorbidities				
Diabetes mellitus	1.13 (1.00-1.27)	0.044		
Renal failure	1.29 (1.12-1.48)	<0.001		
Chronic pulmonary disease	1.24 (1.06-1.45)	0.001		
Obese	0.98 (0.81-1.18)	0.815		
Congestive heart failure	1.55 (1.26-1.89)	<0.001		
Transplant center-level variables				
Transplant center size by volume				
Small (<25 transplants/y)	1.00			
Medium (26 to 75 transplants/y)	1.26 (1.05-1.51)	0.012		
Large (>75 transplants/y)	1.08 (0.90-1.29)	0.423		
Transplant center size by bed number				
Small (<250)	1.00			
Medium (251-500)	0.92 (0.83-1.01)	0.081		
Large (>500)	1.08 (0.98-1.20)	0.121		
Teaching hospital	1.33 (1.03-1.72)	0.029		

central venous catheters. We therefore could not precisely identify causative microorganisms, antibiotic susceptibilities, antimicrobials administered, or whether bloodstream infections were catheter-related. Although classes of microorganisms were identified in the majority of cases, a significant proportion of microorganisms were unspecified (eg, "bacteremia"). However, Cox regression analyses showed that unspecified microorganisms were similarly associated with death as specific microorganisms, indicating comparably morbid conditions. Despite its limitations, our study provides population-level information regarding the epidemiology of bloodstream infections after liver transplantation in the current era, identifies variability in the incidence and risk of developing bloodstream infections and death across transplant centers after accounting for many patient-level factors, and highlights the need for further research regarding better prevention and management strategies for bloodstream infections across transplant centers nationally.

In summary, we showed that bloodstream infections after liver transplantation were common and costly complications that were associated with a markedly increased risk of death. The incidence and risk of developing bloodstream infections may vary across transplant centers. Better prevention and management strategies should be subjects of future research.

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