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Original Article

Risk factors and crucial prognostic indicators of mortality in liver transplant recipients with bloodstream infections: A comprehensives study of 1049 consecutive liver transplants over an 11-year period

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Abstract *Background:* Liver transplantation (LT) is a pivotal treatment for end-stage liver disease. However, bloodstream infections (BSI) in the post-operative period present a significant threat to patient survival. This study aims to identify risk factors for post-LT BSI and crucial prognostic indicators for mortality among affected patients.
Methods: We conducted a retrospective study of adults diagnosed with end-stage liver disease who underwent their initial LT between 2010 and 2021. Those who developed BSI post-LT during the same hospital admission were classified into the BSI group.
Results: In this cohort of 1049 patients, 89 (8.4%) developed BSI post-LT, while 960 (91.5%) did not contract any infection. Among the BSI cases, 17 (19.1%) patients died. The average time to BSI onset was 48 days, with 46% occurring within the first month post-LT. Of the 123 isolated microorganisms, 97 (78.8%) were gram-negative bacteria. BSI patients had significantly longer stays in the intensive care unit and hospital compared to non-infected patients. The 90-day

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and in-hospital mortality rates for recipients with BSI were significantly higher than those without infections. Multivariate analysis indicated heightened BSI risk in patients with blood loss >3000 mL during LT (odds ratio [OR] 2.128), re-operation within 30 days (OR 2.341), post-LT bile leakage (OR 3.536), and graft rejection (OR 2.194). Additionally, chronic kidney disease (OR 6.288), each 1000 mL increase in intraoperative blood loss (OR 1.147) significantly raised mortality risk in BSI patients, whereas each 0.1 mg/dL increase in albumin levels correlated with a lower risk of death from BSI (OR 0.810).

Conclusions: This study underscores the need for careful monitoring and management in the post-LT period, especially for patients at higher risk of BSI. It also suggests that serum albumin levels could serve as a valuable prognostic indicator for outcomes in LT recipients experiencing BSI.

Introduction

Liver transplantation (LT) stands as a pivotal therapeutic intervention for patients with end-stage liver disease, offering a conduit to improved survival and quality of life in scenarios where other treatments have been rendered futile.[1] The global burden of end-stage liver disease, propelled by etiological factors such as viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, and hepatocellular carcinoma underscores the indispensable role of LT in contemporary hepatology.[2] However, the journey post-LT is punctuated with numerous challenges, among which bloodstream infections (BSI) emerge as a formidable adversary, wielding substantial clinical impact. BSI, particularly in the immunocompromised post-LT population, are notorious for their propensity to trigger a cascade of complications, including graft dysfunction, and in severe instances, mortality.[3] The risk factors attributing to BSI post-LT are multifaceted, intertwining recipient, donor, and procedural variables, such as recipient comorbidities, donor organ quality, surgical technique, and the intensity and duration of immunosuppressive therapy.[4] Moreover, the outcomes following BSI are not merely confined to the biomedical realm but also permeate dimensions of prolonged hospitalization, escalated healthcare expenditures, and compromised quality of life.[5]

This study investigates the risk factors associated with the development of BSI in patients' post-LT and evaluates the clinical outcomes during the same hospital admission for transplantation. Moreover, we examine the factors linked to mortality in post-LT patients who developed BSI during the same admission. Early identification and understanding of these determinants can aid clinicians in enhancing care strategies and improving the overall prognosis of patients after LT.

Methods

Ethics statement

This study was conducted with the approval of the Institutional Review Board at Kaohsiung Chang Gung Memorial Hospital in Taiwan (Approval Document No. 202300332B0). The requirement for informed consent was waived due to the anonymous nature of the data analysis. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

Study design

The study was conducted at Kaohsiung Chang Gung Memorial Hospital, a 2634-bed primary medical care and tertiary referral center in Taiwan. We conducted a retrospective study involving 1049 adult individuals (≥20 years of age) diagnosed with end-stage liver disease who underwent their initial LT between 2010 and 2021.

Patients who developed BSI after undergoing LT during the same admission were categorized into the BSI group. To minimize potential bias stemming from repetitive assessments of bacteremia, only the initial episode of BSI for each patient was included in the analysis. Patients who did not experience any infection episodes, including both BSI and other types of infections, after receiving LT during the same admission were referred to as the non-infection group.

To assess the risk factors associated with post-LT BSI acquisition, we conducted a comparative analysis of patient characteristics between the BSI group and the non-infection group. Additionally, we examined clinical outcomes for both groups, including their durations of stay in the intensive care unit and hospital, as well as mortality rates. Further analyses were undertaken to explore the mortality risk within the BSI group, distinguishing between survivors and non-survivors.

Post-LT care protocol

All LT recipients were administered post-operative prophylactic antibiotics, specifically ceftazidime and teicoplanin, for a period of 7 days following the LT procedure. To prevent *Pneumocystis jirovecii* infection, recipients received trimethoprim-sulfamethoxazole, in the form of a single-strength tablet administered once daily, in the post-LT period. Antifungal prophylaxis with fluconazole was administered for one week following LT. Cytomegalovirus prophylaxis was provided to all patients who were cytomegalovirus-donor positive and recipient-negative. Complete blood count, C-reactive protein levels, kidney and liver function tests, and routine ascites evaluations were performed daily during the initial two weeks post-LT.

Blood cultures were obtained upon clinical suspicion of infection, as indicated by fever, elevated C-reactive protein levels, or an increase in white blood cell counts. The standard immunosuppression protocol consisted of tacrolimus, mycophenolate mofetil and steroids. Briefly, the target blood trough level for tacrolimus was initially maintained at 8—12 ng/mL during the first two weeks post-transplantation, and subsequently adjusted to a range of 5—8 ng/mL thereafter.

Data collection

We created a standardized form for the documentation of clinical data, primarily extracted from the hospital's electronic medical records, with supplementary data obtained through a secondary manual search. This comprehensive dataset included patient demographics, the charlson comorbidity index, American Society of Anesthesiologists score, Model for End-Stage Liver Disease (MELD) score, comorbidities beyond liver disease, microbiological findings, factors contributing to liver disease etiology, complications stemming from liver disease, laboratory test results, operative details, antibiotic therapy and post-LT outcomes. These outcomes involved the duration of stay in the intensive care unit, in-hospital stays, as well as mortality rates.

Definitions

BSI is defined as the detection of a microorganism in a blood culture specimen, along with supporting laboratory, radiological, and clinical evidence indicative of an infection. BSI attributed to common skin contaminants such as *Micrococcus*, *Brevibacillus*, *and Corynebacterium species* were deemed significant only if the microorganism was identified in two distinct blood cultures and associated with clinical signs of infection, including fever, elevated C-reactive protein, or increased white blood cell counts. The source of infection was determined when the same microorganism was isolated from both the blood and the site of infection during the same time period. Primary bacteremia was defined as significant BSI occurring in a patient in whom no obvious source or site of infection could be identified. The microbiology laboratory employs standard microbiology techniques in accordance with the guidelines set forth by the Clinical and Laboratory Standards Institute for the identification of microorganisms in blood cultures and for conducting in vitro antimicrobial susceptibility testing.[6] Inappropriate empirical antibiotic therapy is defined as the administration of empirical treatment within the initial 48 h following the onset of bacteremia, to which the isolated microorganism exhibits resistance. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 of body surface area, sustained for a duration of more than 3 months.

Statistical analysis

Comparisons were made between patients with BSI and those without infection, as well as between fatal and non-fatal cases among patients with BSI. Statistical analyses were conducted using the Student's t-test (or Mann—Whitney U test) for continuous variables, and the Chi-square test (or Fisher's exact test) for categorical variables to assess their statistical significance. Variables that demonstrated statistical significance in univariate analysis ($p < 0.05$) were further analyzed through multivariate logistic regression to identify independent risk factors. The Kaplan—Meier method is utilized for outcome analysis. All data analyses were performed using the Statistical Package for the Social Sciences software, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Out of the 1049 adult patients who underwent LT, 89 (8.4%) experienced BSI. Among these 89 BSI patients, the mean age was 54.7 years, and 82 of them received living donor transplantation, accounting for 92.1% of the BSI group. In contrast, among the 960 patients who did not experience any infection episodes following LT, the mean age was 53.7 years, with 883 of them undergoing living donor transplantation, constituting 94.2% of the non-infection group. Table 1 provides a summary of the clinical characteristics of the study population.

Among the 89 patients with BSI, the causes of liver disease were as follows: hepatocellular carcinoma (53.9%), hepatitis C (44.9%), alcoholic liver disease (22.5%), hepatitis B (19.1%), autoimmune hepatitis (2.3%), primary biliary cirrhosis (1.1%), and biliary atresia (1.1%). The mean MELD score was 14.7 before LT. The average duration of the transplantation procedure was 11.9 h, with a mean blood loss of 5989.3 mL, and 52 patients (58.4%) experienced blood loss exceeding 3000 mL during the surgical procedure. Re-operation after transplantation during the same admission was required for 47 patients (52.8%). Intra-abdominal bleeding, bile leakage, and graft rejection occurred in 14 patients (15.7%), 6 patients (6.7%), and 23 patients (25.8%), respectively. Among the 89 patients, the average duration from LT to the onset of BSI was 48 days, occurring during the same hospital admission for the transplantation. Furthermore, 41 patients, accounting for 46% of the total cases, developed BSI within one-month post-LT, and 17 patients, representing 19.1% of the total cases, developed BSI within 14 days after LT. Patients with BSI had a mean length of intensive care unit stay of 53.5 days and an in-hospital stay of 113.5 days. Among the 89 patients with BSI, 17 patients died, accounting for a 19.1% in-hospital mortality rate.

Microbiology and sources of infection

A total of 89 patients experienced BSI, resulting in the isolation of 123 microorganisms. Among these cases, 13 (14.6%) were identified as polymicrobial infections. Of the isolated bacterial strains, gram-negative bacteria were the most prevalent (78.8%), followed by gram-positive bacteria (17.8%), and *Candida species* (3.2%). The predominant gram-negative bacterium was *Klebsiella pneumoniae*, accounting for 17 isolates (13.8%), followed by *Escherichia coli* with 14 isolates (11.3%), and *Enterobacter species* with 13 isolates (10.5%). Of the 17 *K. pneumoniae* isolates, five (29.4%)

Table 1 Characteristics of patients who experienced BSI and those without any infection after receiving LT.

Variable	BSI group (N = 89)	Non-infection group (N = 960)	P
Demographic			
Age, mean (±SD)	54.7 (8.3)	53.7 (8.8)	0.313
Age ≧65 years	8 (9.0)	77 (8.0)	0.748
Male	59 (66.3)	665 (69.3)	0.561
CCI score ≧3	52 (58.4)	501 (52.2)	0.259
MELD score, mean (±SD)	14.7 (7.4)	13.9 (7.3)	0.345
Underlying diseases			
Ischemic heart disease	0	3 (0.3)	1.000
Congestive heart failure	2 (2.3)	5 (0.5)	0.113
COPD	7 (7.9)	60 (6.3)	0.551
Type 2 diabetes mellitus	29 (32.6)	259 (27.0)	0.257
CKD	10 (11.2)	60 (6.3)	0.071
Liver cirrhosis	83 (93.3)	855 (89.1)	0.218
Child pugh C	9 (10.1)	129 (13.4)	0.374
Liver disease-induced complications			
Ascites	54 (60.7)	445 (46.4)	0.009
Esophageal variceal bleeding	18 (20.2)	130 (13.5)	0.083
Gastrointestinal bleeding	0	9 (0.9)	1.000
Encephalopathy	1 (1.1)	8 (0.8)	0.551
Cause of liver disease			
Alcoholic liver disease	20 (22.5)	250 (26.0)	0.461
Primary biliary cirrhosis	1 (1.1)	33 (3.4)	0.353
Biliary atresia	1 (1.1)	9 (0.9)	0.589
Autoimmune liver disease	2 (2.3)	23 (2.4)	1.000
Hepatitis B	17 (19.1)	239 (24.9)	0.223
Hepatitis C	40 (44.9)	282 (29.4)	0.002
Hepatocellular carcinoma	48 (53.9)	485 (50.5)	0.538
Mean interval between LT and BSI (±SD), days	48.0 (45.3)	—	—
Occurrence of BSI within first month post-LT	41 (46)	—	—
Operative factors			
ASA score ≥3	84 (94.4)	911 (97.2)	0.180
Surgical wound classification ≥3	10 (11.2)	56 (6.0)	0.053
Received living donor LT	82 (92.1)	883 (94.2)	0.422
Mean duration of the transplantation procedure (±SD) (hours)	11.9 ± 1.9	11.7 ± 1.7	0.232
Mean blood loss during LT (±SD), mL	5989.3 ± 7149.9	3718.5 ± 5319.9	0.004
>1500 mL	68 (76.4)	611 (63.7)	0.016
>3000 mL	52 (58.4)	340 (35.4)	<0.001
Re-operation after LT	47 (52.8)	179 (19.1)	<0.001
<7 days after LT	31 (34.8)	121 (12.9)	<0.001
<30 days after LT	36 (40.5)	150 (16.0)	<0.001
Intraabdominal bleeding	14 (15.7)	56 (5.8)	0.001
Bile leakage	6 (6.7)	8 (0.8)	<0.001
Graft rejection	23 (25.8)	108 (11.3)	<0.001
Laboratory data[a]			
Mean creatinine (±SD), mg/dL	0.98 (0.90)	0.83 (0.72)	0.111
Mean total bilirubin (±SD), mg/dL	6.06 (10.03)	5.82 (9.70)	0.823
Mean aspartate transaminase (±SD), U/L	57.3 (45.6)	64.7 (80.9)	0.179
Mean alanine aminotransferase (±SD), U/L	38.6 (45.3)	49.1 (90.6)	0.063
Mean albumin (±SD), g/dL	3.03 (0.57)	3.18 (0.62)	0.024
Mean white blood cell count (±SD), $\times 10^9$/L	4.17 (2.57)	4.10 (2.47)	0.802
Mean hemoglobin (±SD), g/dL	9.83 (2.10)	10.45 (2.27)	0.013
Mean platelet count (±SD), $\times 10^9$/L	66.6 (49.2)	79.7 (50.1)	0.018
Mean C-reactive protein (±SD), mg/dL	10.08 (11.20)	8.11 (12.40)	0.157
Mean international normalized ratio for prothrombin time (±SD)	1.36 (0.37)	1.38 (0.43)	0.645

[a] Laboratory data for BSI cases were collected within one week after the onset of BSI. For the non-infection group, laboratory data were obtained within one week post-LT.

Data are no (%) unless otherwise indicated.
Abbreviations: ASA, American Society of Anesthesiologists; BSI, bloodstream infections; CCI, charlson comorbidity index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; SD, standard deviation.

exhibited resistance to 3rd and 4th generation cephalosporins, and five isolates (29.4%) were resistant to carbapenems. Out of 14 *E. coli* isolates, 10 (71.4%) were resistant to 3rd and 4th generation cephalosporins, and 2 isolates (14.2%) were carbapenem-resistant. The most frequently isolated gram-positive bacterium was *Enterococcus faecium*, accounting for 10 isolates (8.1%), with six of these (60%) being vancomycin-resistant strains. Throughout the study period, there was no significant trend indicating an increase in antimicrobial resistance among either gram-positive or gram-negative organisms. Table 2 provides a summary of the microorganisms that were isolated from patients who developed BSI and the antibiotic resistance patterns.

In our study of 89 patients with BSI, 95 infection sources were identified. Intrabdominal infections were the most common, occurring in 55 cases (58%), followed by primary bacteremia in 18 cases (19%), catheter-related infections in 13 cases (14%), pneumonia in 7 cases (7%), and urinary tract infections in 2 cases (2%) as shown in Fig. 1. It is noteworthy that among these 89 BSI patients, 4 had multiple simultaneous infections: two patients presented with intrabdominal infection, catheter-related infection, and pneumonia concurrently; one had both intrabdominal and catheter-related infections; and another experienced catheter-related infection along with a urinary tract infection.

Comparison between patients with BSI and those did not encounter any infection following LT (Table 1)

Patients with BSI exhibited a significantly higher prevalence of hepatitis C, as well as liver disease-induced ascites compared to the non-infection group (44.9% vs. 29.4%, $P = 0.002$; and 60.7% vs. 46.4%, $P = 0.009$, respectively). In terms of operative factors, patients with BSI experienced significantly greater blood loss during operation, including incidences of blood loss >1500 mL and >3000 mL, and a

Table 2 The microorganisms isolated from blood samples and antibiotic resistance patterns.

Organism[a]	No. (%)	Vanco-R strain, no./No. (%)	3rd cephalo-R strain, no./No (%)	4th cephalo-R strain, no./No. (%)	Carba-R strain, no./No. (%)
Gram negative bacteria					
Klebsiella pneumoniae	17 (13.8)		5/17 (29.4)	5/17 (29.4)	5/17 (29.4)
Escherichia coli	14 (11.3)		10/14 (71.4)	10/14 (71.4)	2/14 (14.2)
Enterobacter spp.	13 (10.5)		2/13 (15.3)	2/13 (15.3)	
Acinetobacter spp.	11 (8.9)			3/11 (27.2)	2/11 (18.1)
Stenotrophomonas maltophilia	10 (8.1)				
Pseudomonas aeruginosa	8 (6.5)			5/8 (62.5)	3/8 (37.5)
Acinetobacter baumannii	7 (5.6)				
Pseudomonas spp.	5 (4)			1/5 (20)	1/5 (20)
Chryseobacterium spp.	4 (3.2)			3/4 (75)	3/4 (75)
Klebseilla oxytoca	3 (2.4)		1/3 (33.3)		
Aeromonas spp.	2 (1.6)		1/2 (50)		
Bacteroides spp.	1 (0.8)				
Gram negative bacilli-glucose nonfermenting group	1 (0.8)			1/1 (100)	1/1 (100)
Serratia spp.	1 (0.8)		1/1 (100)	1/1 (100)	
Gram positive bacteria					
Enterococcus faecium	10 (8.1)	6/10 (60)			
Gram-positive bacilli	4 (3.2)				
Enterococcus faecalis	2 (1.6)				
Streptococcus spp.	2 (1.6)				
Micrococcus spp.	1 (0.8)				
Brevibacillus spp.	1 (0.8)				
Corynebacterium spp.	1 (0.8)				
Staphylococcus aureus	1 (0.8)				
Fungal					
Candida spp.	4 (3.2)				
Total	123 (100)				

[a] Polymicrobial bacteremia (N = 13).
Abbreviations: Carba-R, carbapenem-resistant; cephalo-R, cephalosporins-resistant; no./No., number of isolates/total number of isolates; Vanco-R, Vancomycin-resistant.

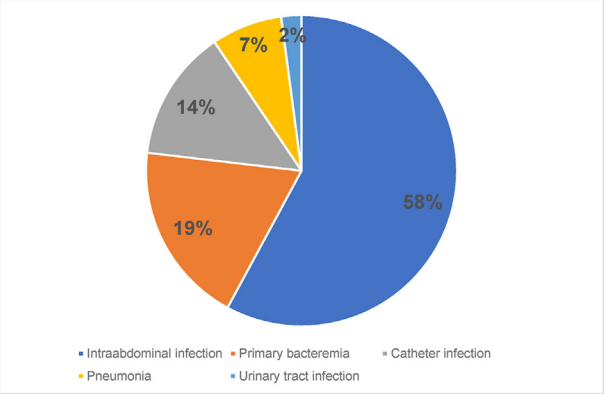

Fig. 1. The source of bacteremia in 89 patients undergoing LT.

higher frequency of re-operation after transplantation, including re-surgery within both 7 and 30 days after transplantation, when compared to the non-infection group (mean blood loss, 5989.3 mL vs. 3718.5 mL, P = 0.004; 76.4% vs. 63.7%, P = 0.016; 58.4% vs. 35.4%, P < 0.001; 52.8% vs. 19.1%, P < 0.001; 34.8% vs. 12.9%, P < 0.001; and 40.5% vs. 16%, P < 0.001, respectively). Patients with BSI also significantly experienced bile leakage, and graft rejection compared to the non-infection group (6.7% vs. 0.8%, P < 0.001; and 25.8% vs. 11.3%, P < 0.001, respectively). Furthermore, significantly lower serum albumin, hemoglobin, and platelet count levels were observed in the BSI group compared with the non-infection group (mean 3.03 g/dL vs. 3.18 g/dL, P = 0.024; mean 9.83 g/dL vs. 10.45 g/dL, P = 0.013; and mean 66.6 $\times$ 10^9/L vs. 79.7 $\times$ 10^9/L, P = 0.018, respectively).

Risk factors for acquiring BSI following LT (Table 3)

Multivariable analysis revealed that patients who experienced blood loss exceeding 3000 mL during transplantation (odds ratio [OR] 2.128, 95% confidence interval [CI] 1.341–3.375, P = 0.001), those who underwent re-operation within 30 days post-LT (OR 2.341, 95% CI 1.420–3.860, P < 0.001), patients encountering bile leakage (OR 3.536, 95% CI 1.102–11.351, P = 0.033), and those suffering graft rejection (OR 2.194, 95% CI 1.268–3.793, P = 0.004) were identified as having independent risk factors for the acquisition of BSI after LT.

Comparison of outcomes between patients with BSI and the non-infection group following LT

Patients with BSI experienced significantly prolonged stays in the intensive care unit and overall hospitalization compared to the non-infection group, with mean (±standard deviation) durations of 53.5 (±53.2) days vs. 17.1 (±7.9) days (P < 0.001) and 113.5 (±87.7) days vs. 45.0 (±17.6) days (P < 0.001), respectively. The BSI group also exhibited higher 90-day and in-hospital mortality rates compared to the non-infection group, at 5 (5.6%) cases vs. 18 (1.9%) cases (P = 0.042) and 17 (19.1%) cases vs. 18 (1.9%) cases (P < 0.001), respectively. Fig. 2 displays a Kaplan–Meier curve analysis comparing outcomes between LT recipients with BSI and those without infections.

Comparative analysis of survivors versus non-survivors among LT recipients who developed BSI (Table 4)

Non-survivors among LT recipients who developed BSI demonstrated a significantly higher prevalence of CKD, and substantial blood loss during the transplant surgery, and a greater rate of intraabdominal bleeding compared to their surviving counterparts (29.4% vs 6.9%, P = 0.019; mean blood loss, 11776.5 mL vs 4622.9 mL, P = 0.024; and 35.3% vs 11.1%, P = 0.023, respectively). Furthermore, non-survivors exhibited significantly elevated creatinine levels and decreased albumin levels compared to survivors (1.62 mg/dL vs 1.01 mg/dL, P = 0.028; and 2.82 g/dL vs 3.11 g/dL, P = 0.003, respectively).

Risk factor for mortality among LT recipients with BSI (Table 5)

The multivariable analysis identified patients with CKD (OR 6.255, 95% CI 1.314–30.091, P = 0.021) and every additional 1000 mL of blood loss incurred during the transplantation procedures (OR 1.147, 95% CI 1.046–1.258,

Table 3 Independent risk factors for developing BSI post-LT.

Variable	BSI group[a] (N = 89)	Non-infection group[a] (N = 960)	Odds ratio	95% CI	P
Ascites	54 (60.7)	445 (46.4)	1.446	0.876–2.387	0.149
Mean albumin (±SD), g/dL	3.03 ± 0.57	3.18 ± 0.62	0.993	0.949–1.040	0.779
Mean hemoglobin (±SD), g/dL	9.83 ± 2.10	10.45 ± 2.27	0.999	0.987–1.012	0.881
Blood loss during LT > 3000 mL	52 (58.4)	340 (35.4)	2.128	1.341–3.375	**0.001**
Re-operation within 30 days after LT	36 (40.5)	155 (16.2)	2.341	1.420–3.860	**<0.001**
Intraabdominal bleeding	14 (15.7)	56 (5.8)	1.147	0.518–2.542	0.735
Bile leakage	6 (6.7)	8 (0.8)	3.536	1.102–11.351	**0.033**
Graft rejection	23 (25.8)	108 (11.3)	2.194	1.268–3.793	**0.004**

[a] Data are no (%), unless otherwise indicated.
The bold text indicates the significance of the independent risk factors for the acquisition of bloodstream infections after liver transplantation.
Abbreviations: BSI, bloodstream infections; CI, confidence interval; LT, liver transplantation; OR, odds ratio; SD, standard deviation.

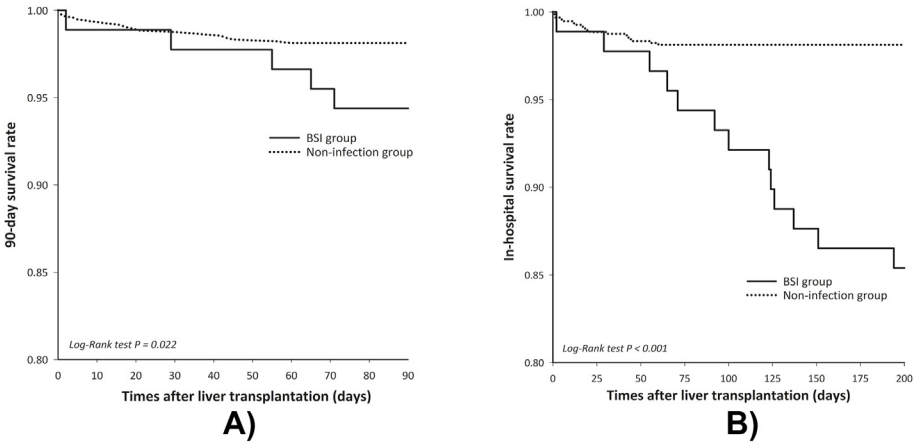

Fig. 2. Kaplan—Meier curve analysis for LT recipients with BSI versus those without infections. (A) The 90-day survival rate; and (B) the in-hospital survival rate.

P = 0.007) as independent factors escalating mortality risks among LT patients who developed BSI. Conversely, each incremental 0.1 mg/dL rise in albumin levels was associated with a reduced mortality risk from BSI (OR 0.810, 95% CI 0.676—0.970, P = 0.018).

Discussion

In this study, we examined 1049 LT recipients over an 11-year period, uncovering several key insights into post-LT BSI. Firstly, we observed that the incidence of BSI following LT stood at 8.4%. The median time to the onset of BSI was 48 days post-LT, with nearly half (46%) of these infections manifesting within the first 30 days. The predominant causative agents were gram-negative bacteria. Secondly, patients who suffered from blood loss exceeding 3000 mL during the LT, underwent re-operation within 30 days, or experienced post-LT bile leakage and graft rejection, were at a heightened risk for developing BSI. Thirdly, our data indicate that BSI-affected patients had significantly longer intensive care and overall hospital stays and faced higher mortality rates within 90 days and during hospitalization when compared to patients without infections. Fourthly, our analysis suggests that CKD, and each additional 1000 mL of blood loss during surgery substantially increased mortality risk for patients with BSI. Conversely, each increment of 0.1 mg/dL in albumin levels was associated with a decreased risk of death from BSI.

In our study, gram-negative bacteria accounted for 78.8% of BSI cases, with *K. pneumoniae* being the predominant pathogen. This observation is in line with the findings of Singh et al., which indicated an increase in gram-negative bacteremia among LT recipients from 25% in 1989—1993 to 51.8% in 1998—2003.[7] Additionally, a separate study reported that 56% of gram-negative bacterial infections following LT were due to multi-drug resistant organisms.[8] On the other hand, gram-positive bacteria were found to be the culprits in 78% of infections in LT recipients in another study, with methicillin-resistant coagulase-negative staphylococci representing 42% of such infections.[9] In the context of escalating drug-resistant infections, our data align with prior research, revealing that 35.2% of *K. pneumoniae* isolates were carbapenem-resistant and 60% of *E. faecium* isolates were vancomycin-resistant strains. The discrepancies in microbial distribution and antimicrobial resistance patterns across studies can be attributed to a variety of factors, including the level of hospital resources, the sophistication of surgical methods, the regimen of immunosuppressive management, and the efficacy of infection prevention protocols. This vigilant surveillance is essential for devising targeted infection control strategies and enhancing patient care for this vulnerable group.

Prior research has highlighted those factors such as prolonged surgical duration, increased procedural complexity, significant intraoperative blood loss, subsequent reoperations, aggressive immunosuppression, and extended intensive care unit stays are independent risk factors for BSI following LT.[10,11] Our investigation has revealed that two specific operative factors—considerable blood loss during LT and reoperation within 30 days—markedly elevate the risk of BSI post-LT. Intraoperative blood loss, often a result of preoperative hemostatic abnormalities, portal hypertension, portal vein thrombosis, and splenomegaly, is a known complication of LT. The correlation between significant blood loss and an increased risk of postoperative complications, including mortality, is well-documented. Our study further quantifies the risk, showing that blood loss exceeding 3000 mL doubles the likelihood of BSI compared to patients with lesser blood loss. Significant hemorrhage may cause hemodynamic instability, diminish oxygen delivery, and tissue perfusion, resulting in cellular hypoxia. This condition can adversely affect graft function and may lead to vital organ ischemia,[12,13] as well as vascular thrombosis,[14] evidenced by increased instances of graft loss and postoperative infections.[15,16] Remarkably, 19.1% of BSI cases developed bacteremia within 14 days post-LT, despite receiving post-operative prophylactic antibiotics. Hypoperfusion, combined with hepato-biliary and gastrointestinal mucosal damage from ischemic or thrombotic events, might facilitate bacterial translocation, leading to BSI, even with the use of post-operative prophylactic antibiotics. This understanding has prompted a call for reevaluation of preoperative and intraoperative variables contributing to blood

Table 4 Comparison between survivors and non-survivors who experienced BSI after LT.

Variable	Non-survivors (N = 17)	Survivors (N = 72)	P
Characteristics			
Age, mean (±SD)	56.0 (7.3)	54.4 (8.6)	0.473
Age ≧65 years	1 (5.9)	7 (9.7)	1.000
Male	10 (58.8)	49 (68.1)	0.468
CCI ≧3	11 (64.7)	41 (56.9)	0.559
MELD score, mean (±SD)	18.3 (9.8)	13.8 (6.5)	0.090
Underlying diseases			
Ischemic heart disease	0 (0)	0 (0)	.
Congestive heart failure	0 (0)	2 (2.8)	1.000
COPD	0 (0)	7 (9.7)	0.338
Type 2 diabetes mellitus	7 (41.2)	22 (30.6)	0.400
CKD	5 (29.4)	5 (6.9)	0.019
Liver cirrhosis	14 (82.4)	69 (95.8)	0.081
Child pugh C	4 (23.5)	5 (6.9)	0.063
Liver disease-induced complications			
Ascites	11 (64.7)	43 (59.7)	0.705
Esophageal variceal bleeding	3 (17.7)	15 (20.8)	1.000
Gastrointestinal bleeding	0 (0)	0 (0)	.
Encephalopathy	1 (5.9)	0 (0)	0.191
Cause of liver disease			
Alcoholic liver disease	5 (29.4)	15 (20.8)	0.520
Primary biliary cirrhosis	0 (0)	1 (1.4)	1.000
Biliary atresia	0 (0)	1 (1.4)	1.000
Autoimmune liver disease	1 (5.9)	1 (1.4)	0.347
Hepatitis B	4 (23.5)	13 (18.1)	0.731
Hepatitis C	7 (41.2)	33 (45.8)	0.728
Hepatocellular carcinoma	10 (58.8)	38 (52.8)	0.652
Inappropriate empirical antibiotic therapy	7 (41.2)	21 (29.2)	0.337
Polymicrobial infection	3 (17.7)	8 (11.1)	0.433
Operative factor			
ASA score ≥3	16 (94.1)	69 (94.4)	1.000
Surgical wound classification ≥3	2 (11.8)	8 (11.1)	1.000
Received living donor LT	14 (82.3)	68 (94.4)	0.124
Mean duration of the transplantation procedure (±SD) (hours)	12.1 ± 1.8	11.9 ± 1.9	0.741
Mean blood loss during LT (±SD), mL	11776.5 (11760)	4622.9 (4720.4)	0.024
>1500 mL	15 (88.2)	53 (73.6)	0.340
>3000 mL	13 (76.5)	39 (54.2)	0.093
Re-operation <7 days after LT	8 (47.1)	23 (31.9)	0.239
Re-operation <30 days after LT	10 (58.8)	26 (36.1)	0.086
Intraabdominal bleeding	6 (35.3)	8 (11.1)	0.023
Bile leakage	3 (17.7)	3 (4.2)	0.081
Graft rejection	7 (41.2)	16 (22.2)	0.129
Laboratory data			
Positive of CMV IgG	16 (94.1)	72 (100)	0.191
Positive of CMV IgM	1 (5.9)	5 (6.9)	1.000
Mean creatinine (±SD), mg/dL	1.62 (1.01)	1.01 (0.62)	0.028
Mean total bilirubin (±SD), mg/dL	8.06 (4.83)	7.63 (4.74)	0.743
Mean aspartate transaminase (±SD), U/L	1339.0 (3021.3)	275.5 (231.0)	0.166
Mean alanine aminotransferase (±SD), U/L	555.6 (950.9)	246.6 (200.0)	0.200
Mean albumin (±SD), g/dL	2.82 (0.44)	3.11 (0.35)	0.003
Mean white blood cell count (±SD), $\times 10^9$/L	6.72 (2.02)	7.80 (4.58)	0.143
Mean hemoglobin (±SD), g.dL	9.13 (1.23)	9.06 (1.37)	0.846
Mean platelet count (±SD), $\times 10^9$/L	52.5 (24.5)	51.0 (33.0)	0.854
Mean C-reactive protein (±SD), mg/dL	18.9 (9.0)	24.0 (10.2)	0.057
Mean international normalized ratio for prothrombin time (±SD)	1.84 (0.47)	1.82 (0.33)	0.922
Mean tacrolimus level, (±SD), ng/mL	4.55 (2.29)	6.03 (3.17)	0.110

Data are no (%) unless otherwise indicated.
Abbreviations: ASA, American Society of Anesthesiologists; BSI, bloodstream infections; CCI, charlson comorbidity index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; SD, standard deviation.

Table 5 Multivariable analysis of risk factors for mortality in LT patients with BSI.

	Non-survivors (N = 17)[a]	Survivors (N = 72)[a]	Odds ratio	95%CI	P
CKD	5 (29.4)	5 (6.9)	6.288	1.314—30.091	**0.021**
Intrabdominal bleeding	6 (35.3)	8 (11.1)	2.617	0.430—15.936	0.296
Each additional 1000 mL of blood loss during LT	Mean blood loss, 11776.5 mL	Mean blood loss, 4622.9 mL	1.147	1.046—1.258	**0.007**
Each increase of 0.1 mg/dL in albumin levels	Mean albumin, 2.82 mg/dL	Mean albumin, 3.11 mg/dL	0.810	0.676—0.9970	**0.018**

[a] Data are no (%), unless otherwise indicated.
The bold text indicates the significance of the independent risk factors for mortality in liver transplant patients with bloodstream infections.
Abbreviations: BSI, bloodstream infections; CI, confidence interval; CKD, chronic kidney disease; LT, liver transplantation; OR, odds ratio.

loss, as well as the refinement of anesthesiological and surgical techniques to mitigate this risk and subsequent post-transplant complications. Additionally, our findings emphasize the augmented risk of BSI associated with reoperation within 30 days post-LT. Common causes for such reoperations include hemorrhage, vascular thrombosis, biliary leakage, and intra-abdominal infections,[17,18] with reported reoperation rates of 29.3% and 17.3%.[18,19] In our cohort, the 30-day post-LT reoperation prevalence was 16.8% among the non-infection group, consistent with prior studies. However, this rate escalated to 40.5% among patients with BSI, with intrabdominal bleeding (15.7%) and bile leakage (6.7%) being the principal reasons. Significantly, reoperation was associated with an increased incidence of BSI. These insights reinforce the necessity for heightened awareness and meticulous management of operative factors to decrease the incidence of BSI and improve patient outcomes post-LT.

In our study, we identified bile leakage and graft rejection as independent predictors for the development of BSI post-LT, with bile leakage notably emerging as a primary cause for reoperation. Biliary complications, including bile leaks, are frequently observed after LT, with incidences reported between 2% and 25%.[20] Gondolesi et al. have highlighted the connection between bile leaks and increased risks of graft failure and mortality.[21] In our cohort, the incidence of bile leaks was 6.7% in patients with BSI, compared to only 0.8% in those without infection. Bile leaks can exacerbate the risk of biliary tract and extrahepatic infections by inducing inflammation due to biliary and peritoneal bile.[22,23] Additionally, our study underscores the relationship between graft rejection and BSI post-LT. Immunosuppression, necessary to prevent organ rejection, concurrently elevates the risk of infections.[24] The interplay between infection and graft rejection is complex, and while a direct cause-and-effect relationship remains unclear, several studies have suggested that infections can influence both acute and chronic allograft rejection.[25] The findings from our study highlight the delicate balance required in managing transplant patients — minimizing allograft rejection, optimizing immunosuppression, and reducing infection risks.

Our research identifies 3 critical predictors of mortality in LT recipients who develop BSI. Notably, we found that for each additional 1000 mL of blood loss during LT, the fatality rate increased by a factor of 1.147. Excessive blood loss often indicates more prolonged and challenging surgeries, typically involving extensive transfusions and complications related to the operative site. In our study, a significant volume of blood loss exceeding 3000 mL was associated with an increased risk of BSI. Moreover, substantial intraoperative blood loss can lead to decreased intravascular volume, resulting in hypoperfusion of critical organs, especially the transplanted liver. This compromised perfusion can trigger organ dysfunction and further elevate the mortality risk when a BSI is acquired.[26,27] In contrast, each incremental rise of 0.1 mg/dL in albumin levels is associated with a 0.810-fold decrease in the risk of mortality from BSI after LT. Albumin, synthesized by the liver, is crucial for establishing colloid-osmotic pressure. Current literature recognizes serum albumin concentration as a significant predictive biomarker for mortality in septic patients within intensive care settings.[28] Hypoalbuminemia, indicative of a compromised hepatic functional reserve, not only leads to ascites but also extends hospital stays post-liver resection for hepatocellular carcinoma.[29] Moreover, hypoalbuminemia has been linked to an increased likelihood of late mortality among patients on the LT waiting list.[30] It is well-documented that LT recipients often experience hypoalbuminemia postoperatively, which correlates with higher mortality rates and acute kidney injury.[31,32] A recent study further elucidates that the cumulative change in serum albumin levels until postoperative day 5 can serve as an indicator for predicting organ failure in patients undergoing living-donor LT.[33] Our findings underscore the prognostic significance of postoperative serum albumin levels, suggesting their utility as a guiding parameter for assessing the prognosis of LT recipients who suffer from BSI.

CKD is a common and serious complication following LT, significantly increasing the mortality risk.[34,35] In our study, CKD emerged as a key predictor of mortality in LT recipients who developed BSI, with an odds ratio of 6.288 compared to

those without CKD. Mansur et al. highlighted that patients with CKD face the highest 90-day mortality risk in the context of sepsis, especially when compared to patients without CKD or with other chronic conditions.[36] Infections can exacerbate pre-existing renal impairment. Additionally, CKD often coexists with other comorbidities, notably heart conditions and diabetes, which are known to further worsen sepsis outcomes.

The study's conclusions are subject to certain limitations. Its retrospective design may introduce inherent biases typical of such studies. Being a single-center study, the applicability of its findings across varied healthcare settings may be limited. Furthermore, the focus on adult recipients means the results may not be relevant to the pediatric population.

In summary, our study determined that LT recipients who developed post-LT BSI had longer hospitalizations and intensive care unit stays, as well as elevated rates of in-hospital mortality and mortality within 90 days post-LT, compared to those without infections. Significant risk factors for developing BSI included substantial intraoperative blood loss >3000 mL, the necessity for reoperation within 30 days, and complications such as bile leakage and graft rejection. Furthermore, CKD, greater blood loss was associated with higher mortality rates in patients with BSI, whereas elevated albumin levels were correlated with reduced mortality risk. These findings underscore the critical importance of careful monitoring and management in the post-LT period to minimize BSI risks and suggest that serum albumin levels may serve as a valuable prognostic indicator for outcomes in these patients.

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CRediT authorship contribution statement

Ing-Kit Lee: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing — original draft, Writing — review & editing. **Po-Hsun Chang:** Data curation, Formal analysis, Methodology, Validation. **Cheng-Hsi Yeh:** Conceptualization, Data curation, Formal analysis, Methodology, Validation. **Wei-Feng Li:** Conceptualization, Data curation, Validation. **Shih-Min Yin:** Data curation, Validation. **Yu-Cheng Lin:** Data curation, Validation. **Wei-Juo Tzeng:** Data curation, Validation. **Chao-Long Chen:** Data curation, Validation. **Chih-Che Lin:** Data curation, Validation. **Chih-Chi Wang:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation.

Declaration of competing interest

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