Clinical Epidemiology and Global Health 16 (2022) 101104

Contents lists available at ScienceDirect

Clinical Epidemiology and Global Health

journal homepage: www.elsevier.com/locate/cegh

Prevalence, mortality, and resource utilization of *Staphylococcus aureus* bacteremia in liver transplant recipients: A 2012–2016 nationwide analysis

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ARTICLE INFO

Keywords:
Liver transplantation
S. aureus
Bacteremia
MSSA
MRSA

ABSTRACT

Background: Bacteremia due to *Staphylococcus aureus* is a known, serious complication of liver transplantation (LT).
Objectives: The purpose of our study was to evaluate the national impact of *S. aureus* bacteremia (SAB) in LT recipients in terms of mortality rates and the economic impact on an institution.
Methods: This retrospective cohort study used 2012–2016 National Inpatient Sample data, the largest public inpatient database in the United States, to separate LT recipients with SAB during index LT admission from those unaffected by SAB. The SAB cohorts are further defined by speciation, methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA). The primary outcome was the odds of inpatient mortality. Secondary outcomes included inpatient morbidity, resource utilization, hospital length of stay, and inflation-adjusted total hospital costs and charges.
Results: During the study period, 26,415 patients underwent LT. SAB was found in 340 patients (MSSA n = 180 [52.9%], MRSA n = 160 [47.1%]), while 26,075 LT patients had no SAB episode during the index admission. Patients with MSSA and MRSA bacteremias displayed higher inpatient mortality rates (11.1% and 9.4%, respectively) compared to the non-SAB cohort (3.4%, $p < 0.01$).
Conclusions: During the index LT hospitalization, SAB was directly correlated with increased mortality rates, sepsis occurrence, and shock. More extended hospital stays, higher healthcare costs and charges were found in the SAB cohort. SAB occurring during the index hospitalization of LT-recipients have higher mortality rates than LT-recipients without SAB. More healthcare resources as determined by inflation-adjusted total hospital costs and charges were spent on LT-recipients with SAB compared to those without SAB.

1. Introduction

Bacteremia is a significant concern in the early post-liver transplantation (LT) period and is the most frequent infectious complication. Bloodstream infections (BSI) account for up to 40% of all significant infections after LT and constitute a substantial cause of morbidity and mortality.[1,2] In that context, *S. aureus* remains one of the leading etiologies of BSI in the United States despite trends of increasing gram-negative bacteremias. Studies have shown that hospitalizations in general associated with *S. aureus* infections have higher death rates and steeper medical costs.[1]

More than any other solid organ transplant (SOT) recipients, LT recipients are predisposed to *S. aureus* infections complicated by bacteremia due to the implications of liver function compromise, the magnitude of the operation itself, and the significantly higher proportion of LT recipients hospitalized before the time of transplantation.[1] Bacteremia accounts for up to 30% of major infections post-LT and is often an early event. Karvellas et al. reported a median time to first BSI post-LT was 11 days with a 3–16-day range.[3] The early onset of SABs post-LT implies that these recipients' susceptibility to infection is due to (i) decreased hepatic complement productions, (ii) impaired phagocytosis due to compromised Kupffer cells, (iii) altered neutrophil

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https://doi.org/10.1016/j.cegh.2022.101104
Received 22 February 2022; Received in revised form 11 June 2022; Accepted 26 June 2022
Available online 3 July 2022

chemotaxis, and (iv) reduced cytokine clearance.[3–5]

Although several reports have stressed the burden of *S. aureus* bacteremia (SAB) in LT recipients, no large-scale systematic analysis of *S. aureus* infections complicated with bacteremia has been conducted. Insight into the outcomes and financial burden faced by LT recipients affected by SAB is crucial to improve their quality of care and improve resource allocations by establishing prophylactic and treatment standards that benefit this patient population. The purpose of our study was to evaluate the national impact of SAB in LT recipients during their index hospitalization period compared to a control group of patients without *S. aureus* bacteremia.

2. Materials and methods

2.1. Study design and data source

The 2012–2016 National Inpatient Sample (NIS) was used to conduct this retrospective cohort study. The NIS is the most extensive publicly available, inpatient, all-payer database in the United States. This database was developed by the Agency for Healthcare Research and Quality as part of its Healthcare Cost and Utilization Project (HCUP). Each yearly published dataset contained more than 7 million hospitalizations, a 20% stratified sample of over 4000 non-federal acute care hospitals in 44 states of the United States and is representative of 95% of hospitalizations nationwide.[6] This dataset included codes for principal and secondary diagnosis and codes for procedures performed during the hospitalization.

2.2. Study population

All adult patients with International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9/10 CM) procedural code for LT were included representing the index admission for a liver transplant. Patients under 18 years of age were excluded. We stratified the patient population into two cohorts: those without SAB and those with SAB. *Staphylococcus aureus* bacteremia was defined as growth of *S. aureus* in a blood culture while hospitalized, after which a provider coded the presence of bacteremia. We were unable to determine if a patient was asymptomatic or symptomatic for manifestations of the infection. Exact time of SAB detection could not be determined as ICD codes do not delineate sequence of events during hospitalization. Patients in which SAB was identified were separated into two groups based on speciation, i.e., MSSA or MRSA infection with bacteremia using the respective ICD codes (Supplementary Table 1).

2.3. Variable definition

Patient characteristics included age, gender, ethnicity, median income in patients' zip code, and insurance type. Hospital characteristics included hospital region, teaching status, hospital bed number (Supplementary Table 2), urban location, and weekend admission. The HCUP divides the US into four census regions based on geographical location: Northeast, Midwest, South, and West.[7] The vital status at the end of hospitalization, length of hospital stays, and total hospitalization charges were abstracted from the database. The Deyo adaptation of the Charlson Comorbidity Index was used to account for patient comorbidities validated for a comprehensive database analysis.[8]

2.4. Outcomes

The primary outcome was the adjusted odds of inpatient mortality during the index admission for LT, comparing patients with and without associated MSSA or MRSA infection with bacteremias. Patients diagnosed with MSSA or MRSA bacteremias (not just those with infections) were compared to those without *S. aureus* infections. Secondary outcomes included odds of specific infectious-related events, such as sepsis, central venous catheter (CVC) bacteremia, and endocarditis; inpatient morbidity, as measured by odds of shock, multiorgan failure (MOF), and intensive care unit (ICU) use; resource utilization, hospital length of stay (LOS), and expenditures. Since five different years of data were used to determine these financial measurements, data were adjusted for inflation using the Consumer-Price Index. Expenditures included total hospitalization charges and hospitalization costs. Total hospitalization charges represented the number of financial resources that each hospital billed to provide its service for each patient. In contrast, hospitalization costs represented the amount of money spent by each hospital in providing patient care. Hospitalization costs were calculated by multiplying the cost-to-charge ratios for the respective hospitals with the total hospitalization charges. The HCUP supplied Cost-to-charge rates for each hospitalization in the database to enable this calculation.

2.5. Statistical analysis

Discharge-level weights published by the HCUP were used to estimate the total number of liver transplantation recipients. Descriptive statistics were used to describe patient characteristics. Fisher's exact test was used to compare proportions. Analysis of variance was used to compare means. A hybrid multivariate logistic regression model was built by first conducting a univariate regression analysis on variables identified from other studies as relevant to the outcome. If these variables impacted the outcome in any direction with a p-value of ≤ 0.1, they were included in the multivariate logistic regression model. In multivariate logistic regression, odds ratios and means were adjusted for age, gender, ethnicity, Charlson Comorbidity Index, insurance type, the median income in the patients' zip code, hospital region, urban location, number of hospital beds, and teaching status. All statistical analyses were conducted using STATA, Version 14 (StataCorp LP, College Station, TX, USA).

3. Results

Of 26,415 new LT recipients documented in the study period, 340 patients had associated SAB events. After obtaining an organism-specific classification, the SAB cohort was further divided into 53% MSSA (n = 180) and 47% MRSA (n = 160) based on the resistance pattern of *S. aureus*.

Table 1 summarizes unadjusted patient and hospital characteristics. Patients affected by SAB were younger in age ($P < 0.01$). The cohorts did not display statistically significant differences in terms of gender ($P = 0.34$), ethnicity ($P = 0.77$), type of insurance ($P = 0.87$), stated income ($P = 0.61$), CCI ($P = 0.73$), day of the week of admission ($P = 0.69$), hospital geographic location ($P = 0.73$), teaching status ($P = 0.85$) or hospital size ($P = 0.16$).

3.1. Etiology

The different potential etiologies of SAB were categorized using the respective ICD-9/10-CM codes. The sub-stratification of MRSA and MSSA SAB etiologies are presented in Fig. 1. We found associations between MRSA SAB and CVC infections (N = 5) ($P = 0.02$) and endocarditis (N = 5) ($P < 0.01$). No patients with MSSA SAB were reported to have associated CVC infection or endocarditis.

3.2. Mortality and morbidity

Table 2 demonstrates that the adjusted in-hospital mortality was higher in the MSSA (OR, 4.45; 95% CI, 1.52–13.06; $P < 0.01$) and MRSA infected populations with bacteremias (OR, 3.10; 95% CI, 0.74–12.91; $P = 0.12$) compared to the non-infected LT recipients. Patients with MSSA infections with bacteremias displayed significantly higher odds of sepsis-associated mortality (OR, 9.92; 95% CI, 2.73–36.01; $P < 0.01$) and septic shock (OR, 11.82; 95% CI, 3.63–38.41; $P < 0.01$) compared to

Table 1
Baseline unadjusted patient and hospital characteristics[a,b].

	No MSSA/ MRSA Infection	MSSA Infection with SAB	MRSA Infection with SAB	P-value
Age (years)	51.6	47.6	42.6	<0.01
Female proportion	35.5%	38.9%	46.9%	0.34
Ethnicity (%)				
Caucasian	66.7	62.5	61.5	
African American	9.4	6.3	19.2	
Hispanic	16.3	25.0	11.5	0.77
Asian	4.5	3.1	3.9	
Other	3.1	3.1	3.9	
Insurance (%)				
Medicare	28.9	27.8	34.4	
Medicaid	14.7	16.7	18.8	0.87
Private	50.6	50.0	43.8	
Other	5.9	5.6	3.1	
Income in zip code (%)				
$1 - $37,999	23.7	25.0	29.0	
$38K–47,999	24.3	25.0	16.1	0.61
$48K–63,999	26.3	33.0	35.5	
> $64,000	25.7	16.7	19.4	
Charlson Comorbidity Index				
1	9.6	8.3	3.1	
2	4.5	2.8	6.3	0.73
3	3.5	0.0	3.1	
4 or above	82.4	88.9	87.5	
Hospital division				
New England	4.4	2.8	0	
Middle Atlantic	12.4	16.7	12.5	
East North Central	14.5	2.2	12.5	
West North Central	7.7	16.7	6.3	
South Atlantic	21.7	16.7	28.1	0.73
East South Central	6.3	2.8	12.5	
West South Central	13.5	8.3	12.5	
Mountain	5.3	5.6	0	
Pacific	14.2	8.3	15.6	
Weekend Admission (%)	23.4	19.4	28.1	0.69
Urban Hospital (%)	99.9	100	100	0.99
Teaching Hospital	99.3	100	100	0.85
Bedsize				
Small	4.3	5.6	6.3	
Medium	14.5	25.0	25.0	0.16
Large	81.21	69.4	68.8	

[a] MSSA = methicillin sensitive-*S. aureus*.
[b] MRSA = methicillin-resistant *S. aureus*.

LT recipients who did not experience *S. aureus* infection. Patients with MRSA infections with bacteremias displayed significantly higher odds of sepsis-associated mortality (OR, 5.70; 95% CI1.18–27.46; P < 0.01), septic shock (OR, 5.30; 95% CI, 1.59–17.67; P < 0.01) and sepsis-related MOF (OR, 9.46; 95% CI, 1.19–75.08; P = 0.03) compared to the non-*S. aureus* infected cohort. LT recipients with SAB (both MSSA and MRSA) had comparable odds of MOF and ICU stay to the general studied LT population.

3.3. Economic burden

The average total costs, hospitalization charges, and hospital stay durations in patients undergoing LT and the different SAB cohorts are presented in Table 3. Total costs, fees, and length of stay were all considerably higher in patients with MSSA and MRSA SAB than in the non-SAB cohort. Prolonged ICU stay of the SAB cohort is likely to have significantly contributed to the financial burden.

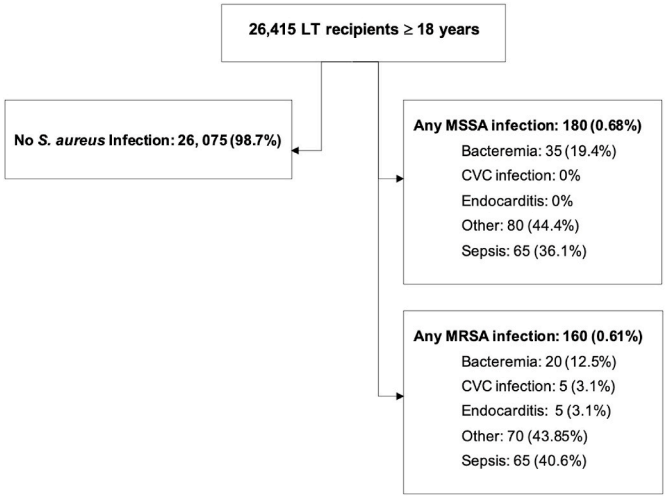

Fig. 1. Sub-stratification of all index admission liver transplantation recipients recorded in the National Inpatient Sample data bank from 2012 to 2016. LT, liver transplantation; MSSA, Methicillin-sensitive *S. aureus*; MRSA, Methicillin-resistant *S. aureus*; CVC, central venous catheter.

Table 2
Adjusted ORs for Inpatient Mortality of LT recipients with SAB Compared to LT Recipients Without SAB[a,b].

Variable	Adjusted OR (95% CI), P-value	
	MSSA SAB (n = 180)	MRSA SAB (n = 160)
Mortality		
All-Cause Mortality	4.45 (1.52–13.06), P < 0.01	3.10 (0.74–12.91), P = 0.12
Sepsis-Associated Mortality	9.92 (2.73–36.01), P < 0.01	5.70, (1.18–27.46), P < 0.01
Septic Shock	11.82 (3.63–38.41), P < 0.01	5.30, (1.59–17.67), P < 0.01
Multiorgan failure (MOF)	0.97 (0.49–1.93), P = 0.94	1.65 (0.66–4.10), P = 0.28
MOF with associated Sepsis	2.43 (0.62–9.51), P = 0.20	9.46 (1.19–75.08), P = 0.03
ICU stay associated with SAB	1.50 (0.71–3.18), P = 0.28	1.10 (0.43–2.80), P = 0.84

[a] MSSA = methicillin-sensitive S. *aureus*.
[b] MRSA = methicillin-resistant S. *aureus*.

Table 3
Inflation-Adjusted Economic Burden of LT recipients With and Without SAB[a,b].

Variable	No MSSA/MRSA	MSSA	MRSA	P-value
Total Hospital Costs	$140,345	$178,506	$274,418	<0.01
Total Hospital Charges	$495,213	$636,187	$857,776	<0.01
LOS (Days)	21.4	36.0	42.6	<0.01

[a] MSSA = methicillin-sensitive *S. aureus*.
[b] MRSA = methicillin-resistant *S. aureus*.

4. Discussion

This research is the first population-based study investigating SAB outcomes, specifically in patients undergoing LT. A total of 340 LT recipients were affected by SAB during their index transplant admission, representing the most significant literature reported cases per our knowledge. We note a statistically significantly increased risk of death, sepsis, and shock in the SAB cohort compared with controls. Also, the MRSA SAB cohort group had 5 cases each of CVC infection and endocarditis whereas the MSSA group had none highlighting that infection prevention guidance specifically for SAB in LT may be needed. This

study further reports that SAB in the LT population directly correlates with increased resource utilization rates compared to patients with non-SAB infections. LT patients with MSSA and MRSA were hospitalized for 14.6 and 21.2 more days, respectively, compared to LT recipients unaffected by SAB. While SAB may not solely account for this higher morbidity, mortality, and resource utilization given the granularity of using the NIS database, this study's value lies in providing an overview or a topographic perspective of SAB in LT recipients during their index admission. Data points, such as patients' pre-LT MELD-Na score, could not be accounted for since NIS does not include laboratory data. Validation of exposure classification was taken into account with the measurement approach used. Considering that the objective of this study was to frame the economic burden of SAB in LT recipients, the NIS database contains the element most pertinent to the exposures and outcomes considered.[9]

A total of 26,415 LT recipients from 2012 to 2016 were identified. The inpatient prevalence of SAB among this LT population was 1.3% (180 MSSA, 160 MRSA). Our data are lower than the range of reported incidence rates, which vary from 2.3% to 46.3%, as determined by Liu et al.[10] This low prevalence rate could in part be explained by the global shift in gram-negative BSIs in transplant recipients and the increasing awareness of prophylaxis management to prevent *S. aureus* infections. Most importantly, we show the impact that SAB has on the adjusted in-hospital mortality, regardless of *S. aureus* species compared to the non-infected LT recipient. MSSA (OR, 4.45; 95% CI, 1.52–13.06; $P < 0.01$) and MRSA infected populations with bacteremias (OR, 3.10; 95% CI, 0.74–12.91; $P = 0.12$) compared to the non-infected LT recipients had higher adjusted in-hospital mortality. In most series MRSA infections were associated with higher mortality compared to MSSA infections as Klein et al. reported in their study of *S. aureus* infections in the general inpatient population from 2010 to 2014 using NIS. This goes to show that MRSA infections are a problem for general and higher risk patient populations alike.[11]

SAB-cohort mortality rates (11.1% MSSA, 9.4% MRSA) were significantly higher than the non-SAB cohort (3.4%), as noted in Table 2. The higher mortality rate reflects the virulence of *S. aureus* in the significantly immunocompromised, post-operative LT recipient population. Karvellas et al. reported that patients who developed an infection in the ICU post-LT had increasing graft failure rates that required re-transplant.[3] Therefore, the presence of SAB may lead to death from the infection itself or its downstream impact on the graft. Our study's findings are consistent with the association that an LT recipient with an early bacterial infection post-transplantation has a more prolonged hospital stay and increased mortality than those who are not infected.[12]

This study's mortality rates were lower than previously published data in the same population, previously reported as ranging from 20% to 46% for SAB and 15–60% for MRSA.[10] These results may be because our study's sample size is significantly larger than other studies. Others, as do we, have attributed such differences in rates to sample sizes, with rates between 30-day mortality rate due to MRSA of 60% and from Singh et al. of 21%.[13–15] Our significantly lower mortality rates are due to large denominators limiting bias from single-center studies.

Interestingly, the MSSA SAB mortality rate was higher than that of MRSA SAB. One plausible reason for this finding is the preemptive prophylactic use of vancomycin in patients undergoing LT due to the MRSA prevalence in most communities. Glycopeptides like vancomycin are intrinsically less effective against MSSA than semi-synthetic penicillins.[16] In a study of over 3000 patients with MSSA bacteremia McDanel et al. found that the use of cefazolin was associated with lower mortality than treatment with oxacillin or nafcillin.[17]

Due to the potentially nephrotoxic effect of vancomycin, slow bactericidal activity, and poor tissue penetration, pre-speciation empiric treatment with vancomycin and a beta lactam appear preferable to de-escalation from vancomycin to a beta lactam.[18]

It is also likely that the MSSA bacteremia patients in our study were first treated with vancomycin on an empiric basis while awaiting speciation, a process that, in years past, took 24–48 h to complete. Currently, molecular and nonmolecular assays accurately identify MRSA and MSSA in a matter of hours, allowing prompt initiation of appropriate, directed antimicrobial therapy.[19] We also note the presence of catheter-related (CVC) infections being more prevalent in this population. These *S. aureus* hospital-acquired infections among LT recipients highlight the importance and need of having vital antimicrobial stewardship programs, infection preventionists, and infectious disease providers who are proficient in managing such patients at high-volume transplant centers.

Lastly, this study draws attention to the significant economic implications of SAB in LT recipients for institutions. The approximate total difference in costs and charges between SAB (MSSA and MRSA) and non-*S. aureus*-infected patients are shown in Table 4. As expected, patients undergoing LT with SAB had associated longer and costlier hospitalizations when compared to patients undergoing LT without *S. aureus* infections. These differences represent the higher cost of managing patients with bacteremia (i.e., duration of antibiotics, drug monitoring, and prolonged ICU stay). By preventing SAB in LT recipients, a more excellent value could be offered to patients by improving quality and lowering costs. Institutional buy-in for developing more strategic infection control monitoring and antimicrobial stewardship initiatives focused on SOT recipients is indicated. Early infectious disease consultation has been found to result in lower mortality and reduced rehospitalization rates in SOT recipients as well as decreased gross healthcare resource utilization.[20] Also, inappropriate antibacterial therapy of SAB is associated with worsened outcomes. Evidence exists that non-commercial insurance, discharging without assistance, and failure to consult with an Infectious Disease specialist are risks factors for inappropriate discharge antimicrobial therapy. Specifically, increase odds of receiving inappropriate antimicrobials was detected with the level of insurance coverage. The level of inappropriate antimicrobial prescribing is the lowest for commercial insurance and the highest for the uninsured, with Medicare and Medicaid recipients ranked between the other two. McHale et al. found that patients with *S. aureus* bacteremia and no insurance had four times the odds of being prescribed inappropriate therapy in univariate analysis.[21] The size of these dollar metrics should impact how a given transplant center allocates resources to optimize SOT outcomes and cost containment.

Table 4: This table outlines the costs and charges difference between each SAB cohorts and the non-SAB cohort, using the costs and charges associated with the non-SAB cohort as the baseline.

There are many limitations to this study. Maximizing granularity given the construct of NIS has already been discussed above. As a retrospective observational study, selection bias may exist. However, the large number of geographic regions and patients covered by NIS likely reduces the odds of selection bias occurring. *S. aureus* infections with bacteremia and comorbidities of interest were identified using ICD-9/10 codes; therefore, the results depended on the sensitivity and specificity of identifying *S. aureus* infection/bacteremias using ICD coding in the NIS database. Coding errors may affect outcomes, but these data sources cannot be validated by other means. While the ICD codes relevant to this study are consistent through the transition from ICD-9 to ICD-10, variation in coding practices across hospitals and financial

Table 4
Differences in costs and charges between patients with LT with and without SAB[a,b].

Variable	Value Difference Between SAB and non-SAB cohorts		P-value
	MSSA	MRSA	
Total Hospital Costs	$38,161	$134,073	<0.01
Total Hospital Charges	$140,974	$362,563	<0.01

[a] MSSA = methicillin-sensitive *S. aureus*.
[b] MRSA = methicillin-resistant *S. aureus*.

incentives for hospitals may influence the accuracy of coding. Local coding practices directly influence the accuracy of diagnostic coding, and bias may be factored in. While variability across local coding practices can exist, ICD coding is done by professional medical coders who adhere to US government standards by training, thereby should limit the impact of local practices in large datasets. The precedent for using this methodology in nationwide estimates despite these limitations has been set in previous studies showing dependable outcomes.[22]

By design, NIS remains the most significant data source for national population-based trends in the patient burden of *S. aureus* infections as it covers patients on Medicaid, Medicare, private insurance, and uninsured. The NIS is a 20-percent stratified sample further limited by its representation of health care utilization during a single hospital event. The health status and quality of care pre-discharge or post-discharge, including readmission, transfer, or complications due to *S. aureus* following discharge, could not be assessed in this study. The mortality rates found may not be infection-related mortality.[23] Because time-specific mortality (limited to the duration of index admission, but not specific to point or cause during admission) was used, the resulting mortality rates could have been affected by several factors other than SAB itself, as previously noted. Despite these limitations, this study maximizes the large NIS data sets to derive estimates while controlling for confounding variables (e.g., patient demographics, comorbidities, hospital, and payer-mix).

Preventing and aggressively treating *S. aureus* infections without SAB in the immediate post-LT setting is key to reducing mortality and morbidity, and consequently, resource utilization. A survey of global abdominal transplant centers conducted in 2015 by the American Society of Transplantation Infectious Diseases Community of Practice Control revealed no established standard of care for infection prevention and control in patients undergoing liver transplants.[24] Care providers need to be proactive in implementing pre-transplant infection screening and maintaining excellent hospital hand and contact hygiene measures. Russell et al. found that active surveillance cultures in all patients admitted to transplant care units to detect MRSA colonization helped identify patients who were more at risk of developing SAB post--transplantation.[25] Prospective studies evaluating factors such as the impact of time of onset of SAB post-LT procedure, the timing of prophylactic anti-staphylococcal therapy pre-operatively, the removal of central lines, and antibiotic therapy's appropriateness could shed light on preventing SAB in the LT recipient population. Development and implementation of care protocols targeting early identification of *S. aureus* colonization and subsequent infection prevention may lower the number of patient deaths by mitigating the risk of SAB.

5. Conclusion

This study highlights the significant implications of SAB on patients undergoing LT and the institutional costs to the current healthcare system. Due to MSSA and MRSA, infections with bacteremias are strongly associated with high mortality rates in the LT-recipient population. Given the considerable mortality associated with *S. aureus* bacteremia in LT recipients and institutional costs, further research is warranted to identify patient risk factors and develop a standard of infection prevention at transplant centers.

Funding disclosures

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

The data that support the findings of this study are available in the National Inpatient Database as a part of the Healthcare Cost and Utilization Project. These data were derived from the following resources available in the public domain: https://www.hcup-us.ahrq.gov/db/nation/nis/nisfilespecs.jsp.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

No acknowledgements.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cegh.2022.101104.

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