

Impact of Enterococcus infection in HSCT recipients: a national analysis

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SUMMARY

Background: Enterococci are the third most common cause of healthcare-associated infections in the United States, affecting 10-12% of all transplant recipients worldwide. Enterococcal bacteremia complicates the post-transplant recovery and raises mortality to 18%. This study aims to identify factors linked to mortality in hematopoietic stem cell transplant (HSCT) recipients with Enterococcus infection.

Methods: We conducted a retrospective analysis using the National Inpatient Sample Database (2018-2021). Adults treated with HSCT and admitted for Enterococcus infection were identified using ICD-10 codes. The analysis utilized descriptive statistics and multivariate regression, with significance at a p-value ≤ 0.05 .

Results: A total of 40,462 HSCT patients, 1.3% were admitted with Enterococcus infection. The crude mortality rate was higher in the Enterococcus cohort than in the non-Enterococcus cohort (10.4% vs. 4.6%);

however, the mortality risk was substantially lower in the Enterococcus cohort ($p < 0.001$). In the Enterococcus cohort, patients with fungal infections, sepsis, acute respiratory failure, and those with invasive ventilation had a high mortality risk ($p < 0.05$). In leukemia patients treated with HSCT, the Enterococcus cohort had higher mortality than the non-Enterococcus cohort (12.5% vs. 5.0%; aOR 1.8, 95% CI 1.9-2.6, $p = 0.005$).

Conclusions: In HSCT recipients, Enterococcus infection is a clinical marker for poor prognosis. Early broad-spectrum antibiotic therapy is essential for patients with sepsis, respiratory compromise, and fungal co-infections. Additionally, a multidisciplinary team is crucial for managing respiratory and renal failure.

Keywords: Enterococcus, Hematopoietic Stem Cell Transplant, mortality, Leukemia, infections.

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■ INTRODUCTION

Bacteremia is the most common cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) recipients. Both Gram-positive and Gram-negative bacteremia have been found to occur in HSCT recipients, typically in the early post-transplant phase [1]. Enterococci are the third most common cause of healthcare-associated infections in the United States and affect 10-12% of all transplant recipients worldwide [2-4]. Among the 58 recognized species of enterococci, the most common are *E. faecalis* and *E. faecium* [5].

There has also been a noticeable increase in the prevalence of *E. faecium*, constituting 40% of bloodstream isolates in liver and stem cell transplant recipients [6, 7]. Septic shock, urinary tract infections, meningitis, intra-abdominal and biliary tract infections, and endocarditis are common presentations of bacteremia [8-11]. Immunocompromised patients, those with prolonged neutropenia and gastrointestinal mucositis, are at increased risk for sepsis because of gut translocation into the bloodstream [1, 12]. Risk factors for bacteremia include age over 60 years at the time of transplantation, use of central venous and urinary catheters, prior antibiotic use, underlying acute lymphocytic leukemia, and previous hospitalizations [3, 8]. The risk of mortality also rises in HSCT recipients from 18% on day 7 to as high as 31% on day 30 [11, 13, 14].

However, distinguishing the impact of various risk factors that may co-occur or occur at different times following HSCT is challenging [15]. Studies focusing on the epidemiology and mortality of multidrug-resistant pathogens affecting the HSCT population are limited [16, 17]. The literature has not addressed the effects of bone marrow dysfunction such as anemia, neutropenia, and thrombocytopenia [18-21]. There is a dire need to identify effective strategies for preventing infections and sepsis during HSCT [22].

Our study focused on identifying the risk factors associated with inpatient mortality in HSCT recipients who develop Enterococcus infections, including those presenting with severe sepsis. Additionally, we sought to determine the impact of enterococci on solid organ transplant recipients and leukemia patients who received HSCT.

■ METHODS

Design and data source

We queried the 2018-2021 National Inpatient Sample (NIS) database for a retrospective cross-sectional study. The NIS was developed by the Healthcare Cost and Utilization Project (HCUP) and was sponsored by the Agency for Healthcare Research and Quality (AHRQ) [23]. The objective of this project was to produce comprehensive data on the utilization, costs, and outcomes of inpatient care at both the regional and national levels in the United States. The document consists of several elements, including patient demographics (such as age, sex, and race), diagnosis and procedure codes obtained from the International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS), indicators of severity and comorbidity, hospital characteristics, and discharge status.

Ethical Consideration, Sample Size, and Study Population

The NIS is a de-identified, publicly accessible database. A predetermined sample size was not calculated. Adults aged 18 years or older who were admitted with an ICD10-CM code for Hematopoietic Stem Cell Transplant and Enterococcus infection were included. Our study focused on Enterococcus infections, including those presenting with sepsis and other presentations. The ICD-10-CM/PCS codes were used to identify patients and are provided in Supplementary File Table 1. Before accessing the NIS databases, we adhered to AHRQ's data user agreement. The databases utilized adhere to the HIPAA (Health Insurance Portability and Accountability Act) Privacy Rule's definition of limited datasets. These databases do not contain any explicit identifiers of patients. Ethics consent is not required for our study as this is a publicly available repository.

Variables Assessed

Gender was delineated as male or female. The patient's race was defined as White (referent), African American, Hispanic, Asian or Pacific Islander, or Native American. The ICD-10 codes encompass acute kidney injury, myocardial infarction, invasive ventilation, severe sepsis, acute respiratory failure, acute respiratory distress syndrome, acute heart failure, and vasopressor usage.

Table 1 - Prevalence, sepsis, mortality, and palliative care rates in different Solid Organ Transplant (SOT) recipients with enterococcal infection.

Population	Factors Studied	Crude Analysis of Enterococcus Infection			Univariate Regression of Enterococcus Infection			
		No (%)	Yes (%)	p-value	Unadjusted Odds Ratio	Lower Limit	Upper Limit	p-value
Heart transplant	Prevalence of Enterococcus	99.0	1.0	0.0154	1.2	1.0	1.5	0.016
	Severe Sepsis	4.9	14.2	<0.0001	3.2	1.9	5.3	<0.001
	All-cause-mortality	2.6	2.5	0.9482	–	–	–	–
	Utilization of Palliative Care	3.1	4.2	0.4856	–	–	–	–
Lung transplant	Prevalence of Enterococcus	98.9	1.1	0.0001	1.5	1.2	1.8	<0.001
	Severe Sepsis	4.3	15.8	<0.0001	4.2	2.3	7.4	<0.001
	All-cause-mortality	2.4	3.2	0.6291	–	–	–	–
	Utilization of Palliative Care	3.1	5.3	0.2388	–	–	–	–
Liver transplant	Prevalence of Enterococcus	98.5	1.5	<0.0001	2.0	1.9	2.2	<0.001
	Severe Sepsis	5.5	16.8	<0.0001	3.4	2.7	4.4	<0.001
	All-cause-mortality	2.5	2.6	0.8734	–	–	–	–
	Utilization of Palliative Care	2.8	3.2	0.6109	–	–	–	–
Kidney transplant	Prevalence of Enterococcus	98.3	1.7	<0.0001	2.2	2.1	2.3	<0.001
	Severe Sepsis	5.4	11.3	<0.0001	2.2	1.9	2.7	<0.001
	All-cause-mortality	2.7	3.4	0.1319	–	–	–	–
	Utilization of Palliative Care	2.5	3.0	0.2263	–	–	–	–
Pancreas transplant	Prevalence of Enterococcus	97.9	2.1	<0.0001	2.8	2.5	3.3	<0.001
	Severe Sepsis	5.5	8.4	0.0689	–	–	–	–
	All-cause-mortality	2.6	4.0	0.2396	–	–	–	–
	Utilization of Palliative Care	2.4	4.0	0.1376	–	–	–	–

Statistical Methods

We analyzed continuous variables using means and t-tests, while qualitative variables were analyzed using the chi-square test. We established a threshold of statistical significance at $p \leq 0.05$. The analysis was conducted using Stata v18. In our analysis, we employed two distinct techniques to account for confounding variables: Propensity score matching and multivariate regression analysis. Propensity scores were employed to pair HSCT recipients with Enterococcus infection with those without. A multivariate logistic regression model was created to calculate the propensity score for mortality utilizing the variables of age, gender, race, and the number of comorbidities. The researchers employed the double robust approach to calculate treatment weights. They then utilized the inverse likelihood of treatment weight-

ing to match cases with controls using generalized linear models, as described by Dugoff *et al.* [24]. The second analysis employed multivariable regression models to control for potential confounding factors. Multiple regression models were constructed by incorporating all confounding variables that were significantly associated with the outcome in the univariate analysis, with a threshold p-value of 0.2. The models included variables that were identified as significant determinants of the outcomes according to the literature. The Crude Mortality is an unadjusted rate reported as percentages (%). Adjusted mortality risks were calculated using multivariable logistic regression, controlling for confounders like age, gender, race, and number of co-morbidities. Results were reported as adjusted odds ratios (aOR) with 95% confidence intervals.

Outcomes

The primary aim of our study was to evaluate mortality in enterococcal-infected HSCT patients. The secondary aim of our study was to identify the impact of Enterococcus infection in solid organ transplant recipients. The tertiary aim was to assess the impact of Enterococcus in leukemia patients who were treated with HSCT.

■ RESULTS

Among the 198,045 patients who received organ, tissue, and stem cell transplantation (all transplants), 1.6% (n=3,175) of the admissions had Enterococcus infection. In comparison, 0.8% (n=173,813) of 23 million non-transplant patients had Enterococcus ($p \leq 0.001$). In the all-transplant group, individuals aged 61 to 75 years had the highest rate of Enterococcus infections (45.2%, $p=0.4742$) and experienced higher mortality rates (51.3%, $p=0.2698$). Overall, those over the age of 60 had a higher risk of mortality compared to younger patients (63.3%

vs. 55.7%, $p=0.0672$). Additionally, males had a higher prevalence of Enterococcus infections than females (55.6% vs. 44.4%) and experienced greater mortality (64.7% vs. 35.3%, $p=0.0215$); however, these differences were not statistically significant. Patients with Enterococcus infections had a prevalence of peritoneal abscess of 1.5% and urinary tract infection of 54.9%. In terms of bone marrow dysfunction or immunosuppression, the prevalence of anemia was 54.2%, that of thrombocytopenia was 12.2%, that of neutropenia was 5.4%, and that of pancytopenia was 13.5%. Supplementary file Table 2 depicts the Source of infection, bone marrow dysfunction, co-morbidities, interventions, and outcomes of all transplant recipients with and without enterococcal infection. The prevalence of Enterococcus infection in patients with pancreatic transplants was 2.1%, that in kidney transplants was 1.7%, that in hematopoietic stem cell transplantation was 1.3%, that in liver transplants was 1.5%, that in lung transplants was 1.1%, and that in heart transplants was 1.0%. Table 1

Table 2 - Mortality predictors in all-transplants with enterococcal infection.

Factors Studied in all types of Transplantation	Adjusted Odds Ratio	Lower Limit	Upper Limit	p-value
<i>Demographic factors</i>				
Female gender	0.8	0.5	1.2	0.318
<i>Hematologic factors</i>				
Pancytopenia	1.9	1.2	3.0	0.011
<i>Infections</i>				
Severe Sepsis	3.8	2.4	5.8	<0.001
Fungal Infections	2.3	1.2	4.6	0.017
<i>Respiratory and cardiovascular factors</i>				
Acute respiratory Failure	6.4	4.2	9.7	<0.001
Acute Heart Failure	0.8	0.5	1.4	0.457
Arrhythmia	1.6	1.0	2.7	0.052
Vasopressor Usage	4.2	2.1	8.2	<0.001
Invasive Ventilation	8.1	3.2	20.3	<0.001
Stroke	2.3	0.6	9.6	0.236
<i>Renal and metabolic factors</i>				
Acidosis	2.2	1.4	3.3	<0.001
Metabolic Encephalopathy	1.6	0.9	2.9	0.112
<i>Others</i>				
Diabetes	0.8	0.5	1.3	0.374

*Arrhythmia included atrial fibrillation, atrial flutter, ventricular fibrillation, and ventricular tachycardia.

shows the prevalence, sepsis, mortality, and palliative care rates in different solid organ transplant recipients with enterococcal infection. For all-transplants, the mortality rate of the Enterococcus cohort was 4.7% (95% CI 4.0%-5.5%), whereas that of the non-Enterococcus cohort was 3.1% (95% CI 3.0% to 3.1%). Patients who faced mortality tended to be over the age of 60 years ($p=0.0672$), male ($p=0.0215$), belonged to the White race ($p=0.6726$), and had three or more co-morbidities ($p=0.0526$). Supplementary file Table 3 shows the socio-demographic factors and number of co-morbidities in all transplant recipients with and without enterococcal infection. Crude analysis revealed the prevalence of comorbidities such as severe sepsis, pancytopenia, diabetes, fungal infections, acute respiratory failure, acute heart failure, life-threatening arrhythmias, stroke, acidosis, and metabolic encephalopathy was significantly higher in the patients who faced mortality compared to those who survived ($p<0.01$). However, the mortality risk of Enterococcus infection did not differ from the non-Enterococcus infection (aOR 1.1; 95% CI 0.9 to 1.4; $p=0.351$) when adjusted for age over 60 years, gender, comorbidities, and interventions (invasive ventilation and vasopressors). We also identified

the predictors of mortality via regression analysis. The risk factors for mortality, showing high odds with a $p\leq 0.05$, included severe sepsis, pancytopenia, fungal infections, acute respiratory failure, arrhythmia, invasive ventilation, and vasopressor usage. Table 2 depicts the mortality predictors in all transplants with enterococcal infection. Compared with the non-Enterococcus cohort, the Enterococcus cohort required more palliative care (4.9% vs. 3.6%, $p=0.0001$) as shown in Table 3. Among the 198,045 patients who received transplants, 20.4% ($n=40,462$) received hematopoietic stem cell transplantation (HSCT). In the HSCT group, 1.3% ($n=531$) were admitted for Enterococcus infection. In the HSCT population, individuals aged 61-75 years were most frequently affected by Enterococcus infections (49.2%). Compared with male patients, female patients had more Enterococcus admissions (51.0% vs. 49.0%, $p<0.0001$). The race did not differ between the Enterococcus and non-Enterococcus cohorts ($p=0.0612$). Supplementary file Table 4 shows the socio-demographic factors and number of co-morbidities in HSCT recipients with and without enterococcal infection. Among the patients with Enterococcus infection, 0.6% had peritoneal abscesses and 39.0% had

Table 3 - All transplantation and HSCT transplantation.

Population	Factors Studied	Crude Analysis of Enterococcus Infection			Univariate Regression of Enterococcus Infection			
		No (%)	Yes (%)	p-value	Unadjusted Odds Ratio	Lower Limit	Upper Limit	p-value
No transplantation	Prevalence of Enterococcus	99.3	0.8	<0.0001	-	-	-	-
All transplantation	Prevalence of Enterococcus	98.4	1.6	<0.0001	2.0	1.9	2.0	<0.001
	Severe Sepsis	6.0	15.3	<0.0001	2.8	2.5	3.1	<0.001
	All-cause-mortality	3.1	4.7	<0.0001	1.6	1.4	1.9	<0.001
	Utilization of Palliative Care	3.6	4.9	0.0001	1.4	1.2	1.7	<0.001
Population	Factors Studied	Crude Analysis of Enterococcus Infection			Univariate Regression of Enterococcus Infection			
		No (%)	Yes (%)	p-value	Unadjusted Odds Ratio	Lower Limit	Upper Limit	p-value
No HSCT	Prevalence of Enterococcus	99.2	0.8	<0.0001	-	-	-	-
HSCT	Prevalence of Enterococcus	98.7	1.3	<0.0001	1.7	1.6	1.9	<0.001
	Severe Sepsis	7.8	20.2	<0.0001	3.0	2.4	3.7	<0.001
	All-cause-mortality	4.6	10.4	<0.0001	2.4	1.8	3.2	<0.001
	Utilization of Palliative Care	6.9	11.1	0.0001	1.7	1.3	2.3	<0.001

Table 4 - Mortality predictors in HSCT recipients with enterococcal infection.

<i>Factors studied in HSCT recipients</i>	<i>Adjusted Odds Ratio</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>p-value</i>
<i>Demographics</i>				
Age over 60 years	0.7	0.3	1.4	0.333
Female gender	0.5	0.3	1.1	0.079
<i>Hematological factors</i>				
Thrombocytopenia	0.5	0.2	1.3	0.147
Pancytopenia	1.0	0.5	2.2	0.915
<i>Infections</i>				
Acute Urinary Tract Infection	0.7	0.3	1.6	0.424
Fungal Infections	4.2	1.7	10.7	0.002
Severe Sepsis	3.0	1.5	5.9	0.002
<i>Respiratory and Cardiovascular factors</i>				
Acute respiratory Failure	4.3	2.1	8.8	<0.001
Invasive Ventilation	9.7	1.0	89.8	0.046
Vasopressor Usage	2.4	0.8	7.5	0.129
<i>Renal and metabolic factors</i>				
Acute Kidney Injury	1.9	0.9	4.0	0.073
Acidosis	2.9	1.4	6.0	0.003

acute urinary tract infections. Severe sepsis was seen in 20.2% of the patients. The factors associated with bone marrow dysfunction or immunosuppression were anemia (68.4%), thrombocytopenia (21.3%), neutropenia (18.6%), and pancytopenia (46.3%) in the Enterococcus cohort. Supplementary file Table 5 depicts the sources of infection, bone marrow dysfunction, co-morbidities, interventions, and outcomes of HSCT recipients with and without enterococcal infection. On crude analysis, the mortality rate of the Enterococcus cohort was higher than the non-Enterococcus cohort by 10.4% (95% CI 8.1-13.2%) vs. 4.6% (95% CI 4.4% to 4.8%). However, after matching and adjusting for age over 60 years, gender, comorbidities mentioned above, and interventions (invasive ventilation and vasopressor usage), patients with Enterococcus infection had a lower mortality risk than did those without Enterococcus infection (aOR 0.1, 95% CI 0.0 to 0.3, $p < 0.001$). We also identified risk factors for mortality in the Enterococcus cohort. These factors, including severe sepsis, fungal infections, acute respiratory failure, acidosis, and invasive ventilation, had high odds of mortality, with a p -value of ≤ 0.05 . Table 4 illustrates the mortality predictors in HSCT recipients with enterococcal infec-

tion. The Enterococcus cohort required more palliative care than the non-Enterococcus cohort did (11.1% vs. 6.9%, $p = 0.0001$). The total hospital charges (Coefficient \$94,629, 95% CI \$-113,069 to \$302,327, $p = 0.372$) and the duration of hospital stay (Coefficient 7.6 days, 95% CI -2.8 to 18.1, $p = 0.152$) did not differ between the two cohorts. We also identified the prevalence of post-transplant complications in HSCT patients (2.7%; $n = 1091$). Among these patients, 2.0% had Enterococcus infection.

The HSCT population was stratified based on the underlying disease. Among the HSCT recipients, Enterococcus infection was found in 344 (1.4%) of 23,930 leukemia patients and 134 (2.4%) of 5,693 AML (Acute Myeloid Leukemia) patients. Among the 23,930 leukemia patients, 344 (1.4%) had Enterococcus infection. This proportion was higher than that in the non-leukemic population ($n = 187$, 1.1%, $p = 0.008$). In those with leukemia, age over 60 years and race did not differ between the Enterococcus and non-Enterococcus cohorts. Compared to males, females had higher Enterococcus infection (50.3% vs. 49.7%, $p = 0.0046$). Additionally, the Enterococcus cohort had a higher prevalence of urinary tract infections, fungal infections,

acute respiratory failure, acute kidney injury, and acidosis. Enterococcus infection was common among patients with signs of bone marrow dysfunction such as neutropenia, anemia, and pancytopenia. Enterococcus infection was also associated with increased rates of severe sepsis and vasopressor usage. In the crude analysis, the mortality

rate in the Enterococcus cohort was again higher than that in the non-Enterococcus cohort (12.5% vs. 5.0%, $p < 0.0001$). However, after adjusting for age over 60 years, gender, comorbidities (severe sepsis, acute respiratory failure, acute kidney injury, and acidosis), and vasopressor usage, the mortality risk was found to be higher than that in

Table 5 - Socio-demographic factors, Bone marrow dysfunction, Comorbidities and Interventions in HSCT-Leukemia and HSCT-AML: With and without Enterococcus infection.

	HSCT-Leukemia			HSCT-Acute Myeloid Leukemia		
	Non-Enterococcus %	Enterococcus %	p-value	Non- Enterococcus %	Enterococcus %	p-value
<i>Socio-Demographic Factors</i>						
Age over 60 years	58.2	54.1	0.1236	48.9	42.5	0.1481
Gender			0.0046			0.0856
Male	57.3	49.7		55.2	47.8	
Female	42.7	50.3		44.8	52.2	
Race			0.3711			0.9761
White	68.8	71.6		74.9	74.6	
Black	14.2	11.4		8.1	8.5	
Hispanic	10.2	9.9		8.5	9.2	
Asian or Pacific Islander	3.3	2.7		4.7	3.9	
Native American	0.4	0.0		0.4	0.0	
Other	3.2	4.5		3.5	3.9	
Palliative Care	7.7	13.1	0.0002	9.8	12.7	0.2723
<i>Bone Marrow Dysfunction</i>						
Anemia	60.1	75.0	<0.0001	57.6	79.9	<0.0001
Neutropenia	14.7	25.0	<0.0001	22.7	19.4	0.3696
Thrombocytopenia	21.7	23.3	0.4797	20.9	33.6	0.0004
Pancytopenia	36.7	55.2	<0.0001	42.7	61.9	<0.0001
<i>Other Infections/ Presentations</i>						
Acute Urinary Tract Infection	6.2	37.5	<0.0001	5.2	28.4	<0.0001
Fungal Infections	4.8	10.5	<0.0001	8.6	13.4	0.0489
<i>Comorbidities</i>						
Severe Sepsis	8.0	21.5	<0.0001	9.4	22.4	<0.0001
Acute Respiratory Failure	14.1	20.9	0.0003	15.5	26.1	0.0009
Acute Kidney Injury	26.0	38.1	<0.0001	24.4	34.3	0.0086
Acidosis	11.9	19.8	<0.0001	10.0	18.7	0.001
<i>Interventions</i>						
Invasive Ventilation	1.2	0.9	0.5495	1.6	0.8	0.4331
Vasopressor usage	2.3	5.2	0.0003	3.0	6.7	0.0142

the non-Enterococcus cohort (aOR 1.8, 95% CI 1.9 to 2.6, $p=0.005$). The impact of Enterococcus could be understood through the utilization of palliative care services. Patients with Enterococcus infection had a significantly greater need for palliative care than did those without Enterococcus (13.1% vs. 7.7%, $p=0.0002$). Table 5 outlines the socio-demographic factors, bone marrow dysfunction, comorbidities, and interventions in HSCT-Leukemia and HSCT-AML- with and without Enterococcus infection.

In the AML population, there were no significant differences in socio-demographic factors such as age over 60 years, gender, or race between those with and without Enterococcus infection ($p>0.5$). Additionally, the Enterococcus cohort had a higher prevalence of urinary tract infections, fungal infections, and acute respiratory failure. Enterococcus infection is common among patients with signs of bone marrow dysfunction such as neutropenia, anemia, and pancytopenia. Enterococcus infection was also associated with increased rates of severe sepsis and increased vasopressor usage. Crude analysis revealed a higher mortality rate in the Enterococcus cohort compared to the non-Enterococcus cohort (16.1% vs. 8.8%, $p=0.032$). However, after adjusting for age over 60 years, severe sepsis, co-morbidities (fungal infections, acute respiratory failure), and vasopressor usage, the mortality risk did not significantly differ between the two cohorts (aOR 0.9, 95% CI 0.4-1.7, $p=0.67$). Similarly, the utilization of palliative care services did not differ between the two cohorts (12.7% vs. 9.8%, $p=0.2723$).

■ DISCUSSION

To our knowledge, our study is the first to exclusively focus on Enterococcus-related mortality and associated risk factors in a large population of HSCT recipients with enterococcal infections. Additionally, propensity matching and multivariate regression aid in understanding the severity of Enterococcus infection in the transplant population. In the HSCT population, Gram-positive bacteremia is a common cause (41.2%) of infection [25]. Our findings revealed that 1.3% of HSCT recipients had enterococcal infections, in contrast to the higher prevalence of Methicillin-resistant *Staphylococcus aureus* (2.9%) and gram-negative infections such as *Escherichia coli* (13%) and *Klebsiella*

pneumoniae (7.2%) [25, 26]. Males and females had the same prevalence of enterococcal infections, despite males facing a higher mortality risk in our study. Urinary tract infection was one of the most common presentations of enterococcal infection [9, 27]. In line with this, in our study, one-third of HSCT recipients with enterococcal infections had a urinary tract infection, and a quarter of this population faced mortality. Additionally, half of all HSCT recipients with enterococcal infections had pancytopenia. We found that one-tenth of the HSCT recipients with enterococcal infections experienced mortality and required palliative care. The crude mortality rates were higher in enterococcal-infected patients, but after adjusting for confounders, the mortality risk was lower compared to uninfected patients. This suggests that the HSCT population is at risk of death from other causes. Similarly, registry studies from the U.S., Australia, and Europe in HSCT cohorts report that infections contribute only marginally (0.3-10%) to mortality, with other factors such as relapse of the primary malignancy (>50%), subsequent secondary malignancies (7.5-25%), and graft versus host disease (25%) having a more substantial impact [28-30]. Similar to these findings, Tavazde *et al.* and Avery *et al.* reported that enterococcal bacteremia was a sign of a rapidly deteriorating clinical course and poor overall survival [31, 32]. The risk of mortality increases in patients who need invasive ventilation or concurrently have pancytopenia, severe sepsis, fungal infections, respiratory distress, and acidosis. Avery *et al.* also reported that fungal infections, multiorgan failure, and ARDS contributed to death [31]. We observed that Enterococcus infections are linked to higher rates of sepsis and vasopressor support. The closer hemodynamic monitoring and managing metabolic disturbances often require ICU level of care. HSCT patients require broad-spectrum antibiotics, respiratory support, and multidisciplinary care to reduce mortality.

With respect to the underlying disease in HSCT recipients, we observed that the mortality risk among those with leukemia caused by enterococci was greater than that among those without enterococcal infection (aOR 1.75, 95% CI 1.18 to 2.58, $p=0.005$). However, for HSCT recipients with AML, the mortality risk did not differ between those infected with enterococci and those who were not (aOR 0.86, 95% CI 0.4-1.7, $p=0.67$). Fer-

reira *et al.* reported that HSCT patients aged more than 62 years were at a higher risk of enterococcal infections [33]. However, in our study, we noted that age and race were not determinants of Enterococcus infection in either the leukemia or the AML group. Peng *et al.* reported thrombocytopenia as a risk factor for Enterococcus infection in the pediatric population [34]. We identified similar findings in our study, which included adult patients over 18 years of age. We found that patients with anemia, thrombocytopenia, and pancytopenia were more likely to develop enterococcal infections. In leukemia patients, anemia ($p < 0.001$) and pancytopenia ($p < 0.001$) were significant factors, while in AML patients, anemia ($p < 0.0001$), thrombocytopenia ($p = 0.0004$), and pancytopenia ($p < 0.0001$) were found to be significantly associated with Enterococcus-related admissions.

In patients with Enterococcus infection, severe sepsis, urinary tract infection, or respiratory failure necessitate aggressive treatment with broad-spectrum antibiotics that need to be switched to appropriate antibiotics after resistance patterns are identified. Broad-spectrum antibiotics are implicated in this condition for several reasons, including the multidrug-resistant nature of Enterococcus, the tendency of enterococci to coexist and present as polymicrobial infections, and the vulnerability of HSCT patients [5, 35]. Owing to the high crude mortality rate (10.4%), providing multidisciplinary care is essential to reduce hemodynamic compromise, ensure close monitoring, and manage other comorbidities. Enterococcus should be considered a differential diagnosis for any Leukemia patient with HSCT who presents with a urinary tract infection or respiratory failure.

We found that patients who underwent pancreas, kidney, liver, or renal transplantation presented a slightly greater prevalence of Enterococcus infection (1.5-2.0%) than did those who underwent heart or lung transplantation (1.0-1.1%). Newell *et al.* reported that among liver transplant recipients, Enterococcus-related sepsis significantly contributed to mortality. This was influenced by factors such as coinfection with multidrug-resistant bacteria, additional laparotomies, and prior vancomycin use [36]. Gotur *et al.* also reported high sepsis rates in heart and lung transplant recipients [37]. Consistent with these findings, our study revealed high severe sepsis rates in liver (16.8%) and lung (15.8%) transplant recipients. Additionally,

we found that among heart transplant recipients, despite the lower prevalence of Enterococcus, there was a higher rate of severe sepsis (14.2%), indicating that these patients are more prone to Enterococcus-associated complications. Furthermore, we observed that mortality rates were particularly high among pancreas (4.0%) and kidney transplant recipients (3.4%). Similarly, Linares *et al.* reported increased mortality among kidney transplant recipients infected with multidrug-resistant bacteria, with 9.5% of these infections attributed to enterococci [38]. Farges *et al.* reported high mortality in organ transplant patients with invasive fungal infections despite measures such as early ICU admission, the use of vasopressors, and mechanical ventilation [39]. Similarly, our study revealed a mortality rate of 23.6% for fungal infections in the HSCT Enterococcus cohort. These findings underscore the critical need for early detection and aggressive management of infections in transplant recipients to improve patient outcomes.

Limitations in our study include the inability to gather detailed information regarding the relapse of leukemia, transplant rejection rates, other solid organ transplants, transplant complications, and the number of transplants. Additionally, evidence regarding the patients' code status, initiation and duration of antibiotic and immunosuppressant therapies, laboratory values, the exact cause of mortality, and the persistence and severity of complications is limited. We also lacked detailed outcome data, such as death at 30 days, follow-up information, and whether patients recovered from illness. Our study could not investigate the antimicrobial resistance patterns in this population. The primary data source was from clinical registries, from which retrospective chart abstractions were made using billing codes, discharge diagnosis codes, and similar identifiers, introducing the possibility of coding errors. Another notable limitation of our analysis is the failure to stratify data by enterococcal species, specifically *E. faecium* and *E. faecalis*. Owing to the retrospective design of the research, we could not control for unidentified confounding variables.

Future research should focus on developing predictive models that integrate prognostic factors—such as infection severity, immune profile, and patient demographics—to enhance mortality risk assessment in HSCT recipients with enterococcal

infections. In high-risk populations the role of antimicrobial stewardship programs that optimize antimicrobial use, reduce antimicrobial resistance, and improve overall outcomes are critical but could not be studied due to the limitations of the study design. Longitudinal studies examining immediate and late post-transplant complications and optimizing antimicrobial stewardship are necessary to improve survival.

■ CONCLUSIONS

Our goal of this study was to draw attention to the significance of enterococcal infections in transplant recipients among adults in the United States. Enterococcus infection is a clinical marker for poor prognosis, as evidenced by the high mortality rate. Early broad-spectrum antibiotic therapy that covers Enterococcus is essential for patients with sepsis, respiratory compromise, and fungal co-infections. Additionally, a multidisciplinary team is crucial for managing respiratory and renal failure to improve outcomes.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Authors' contributions

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Supplementary file Table 1 - ICD 10 codes.

<i>Patient characteristics</i>	<i>Codes</i>
All transplantation	T8613 T8603 T8623 T8633 T8643 T86892 T86852 T86842 T86832 T86822 T86812 T8693 Z9481 Z9482 Z9483 Z9484 Z9489 Z949 Z940 Z941 Z942 Z943 Z944 Z945 Z946 Z947 Z9481 Z9482 Z9483 Z9484 Z9489 Z949 Z940 Z941 Z942 Z943 Z944 Z945 Z946 Z947
HSCT	T8603 T8600 T8601 T8602 T8603 T8609 T865
AML	C9200 C9201 C9202 C9252 C9240 C9260 C9261 C9262 C92A0 C92A1 C92A2 C9250 C9251 C9252 C9240 C9241 C9242 C9300 C9301 C9302 C9330 C9331 C9332
Leukemia	C9100 C9101 C9102 C9110 C9111 C9112 C9130 C9131 C9132 C9140 C9141 C9142 C9150 C9151 C9152 C9160 C9161 C9162 C9190 C9191 C9192 C91A0 C91A1 C91A2 C91Z0 C91Z1 C91Z2 C9200 C9201 C9202 C9210 C9211 C9212 C9220 C9221 C9222 C9230 C9231 C9232 C9240 C9241 C9242 C9250 C9251 C9252 C9260 C9261 C9262 C9290 C9291 C9292 C92A0 C92A1 C92A2 C92Z0 C92Z1 C92Z2 C9300 C9301 C9302 C9310 C9311 C9312 C9330 C9331 C9332 C9390 C9391 C9392 C93Z0 C93Z1 C93Z2 C9400 C9401 C9402 C9420 C9421 C9422 C9430 C9431 C9432 C9440 C9441 C9442 C946 C9480 C9481 C9482 C9500 C9501 C9502 C9510 C9511 C9512 C9590 C9591 C9592 D7581 2386 2030 20300 20301 20302 2038 20380 20381 20382 2731 2733 E8581 D473 C9000 C9001 C9002 C9010 C9011 C9012 C9020 C9021 C9022 C9030 C9031 C9032 C880
Acute UTI	N390 N10 N3000 N3001 N340 N341 N342 N390
Acute Kidney Injury	N170;N171;N172;N178;N179
Blood Transfusion	30233N1;30243N;30243P0;30233P0
Vasopressor	3E050XZ;3E063XZ;3E060XZ;3E053XZ;3E043XZ;3E040XZ;3E033XZ;3E030XZ
Respiratory Failure	J9620;J9621;J9622;J9600;J9601;J9602
ARDS	J80
Severe Sepsis	R6520;R6521
Arrhythmias	I4901;I472;I480;I481;I482;I483;I484;I491;I492
Cardiogenic Shock	R570
Acute Heart Failure	I5040;I5041;I5043;I509;I5030;I5031;I5033;I5023;I5020;I5021; I501; J810
Acute Heart Failure	I5040;I5041;I5043;I509;I5030;I5031;I5033;I5023;I5020;I5021; I501; J810
Stroke	I63;I6050;I6051;I6052;I606;I607;I608;I609;I6030;I6031;I6032;I604;I6010;I6011;I6012;I602;I600;I601;I602;I61 0.x;I618;I619;I6200;I6201;I6202;I6203;I621;I629;I6300;I6301;I6302;I6303;I631;I629;I6300;I6301;I6302;I6303; I6309;I6310;I6311;I6312;I6313;I6319;I6320;I6321;I6322;I6323;I6329;I6330;I6331;I6332;I6333;I6339;I6340;I63 41;I6342;I6343;I6349;I6350;I6351;I6352;I6353;I6359;I6360;I6361;I6362;I6363;I6369;I6370;I6371;I6372;I6373 ;I6379;I6380;I6381;I6382;I6383;I6389;I6390;I6391;I6392;I6393;I6399;I640;I641;I6411;I6412;I6413;I6419;I642 ;I6421;I6422;I6423;I6429;I643;I6431;I6432;I6433;I6439;I644;I6441;I6442;I6443;I6449;I645;I6451;I6452;I6453 ;I6459;I646;I6461;I6462;I6463;I6469;I647;I648;I6481;I6482;I6483;I6489;I649;I6491;I6492;I6493;I6499;I650;I6 51;I652;I660;I670;I680;I690

Supplementary file Table 2 - Sources of infection, bone marrow dysfunction, comorbidities, interventions and outcomes of all-transplant recipients with and without enterococcal infection.

Factors	All Transplant			All Transplant with Enterococcus Infection		
	Non-Enterococcus %	Enterococcus %	p-value	Survival %	Mortality %	p-value
<i>Source of infection</i>						
Peritoneal Abscess	0.3	1.5	<0.0001	1.4	4.0	0.0124
Acute Urinary Tract Infection	88.8	54.9	<0.0001	45.7	34.0	0.0051
Severe Sepsis	94.0	84.7	<0.0001	12.9	62.7	<0.0001
<i>Bone marrow dysfunction</i>						
Anemia	43.9	54.2	<0.0001	53.8	61.3	0.0714
Thrombocytopenia	10.7	12.2	<0.0001	11.9	16.7	0.0834
Neutropenia	4.0	5.4	<0.0001	5.5	4.7	0.6773
Pancytopenia	9.8	13.5	<0.0001	12.7	29.3	<0.0001
<i>Comorbidities</i>						
Diabetes	45.7	49.3	0.0001	49.8	38.0	0.0047
Hypertension	12.4	11.0	0.0181	11.0	10.7	0.8961
Fungal Infections	3.6	5.4	<0.0001	4.9	15.3	<0.0001
Acute Respiratory Failure	12.9	12.4	0.4521	9.9	63.3	<0.0001
Acute Respiratory Distress Syndrome	0.5	1.0	<0.0001	0.5	12.7	<0.0001
Acute Heart Failure	13.4	10.8	<0.0001	10.4	19.3	0.0005
Arrhythmia	10.8	10.9	0.8336	10.5	19.3	0.0007
Cardiogenic Shock	0.6	0.5	0.5131	0.3	5.3	<0.0001
Sudden Cardiac Arrest	0.8	0.7	0.6549			
Stroke	1.2	1.4	0.2456	1.1	8.7	<0.0001
Pressure Sores	2.3	6.7	<0.0001	6.5	11.3	0.0204
Bleeding from Any Source	4.5	4.9	0.288	4.8	6.0	0.5019
Acute Kidney Injury	31.8	42.0	<0.0001	41.0	62.0	<0.0001
Acidosis	13.9	19.0	<0.0001	17.7	45.3	<0.0001
Metabolic Encephalopathy	3.8	7.2	<0.0001	6.7	18.0	<0.0001
Hyperkalemia	11.8	12.3	0.3946	12.1	16.0	0.1515
<i>Interventions or procedures</i>						
Inpatient Hemodialysis	10.6	8.6	0.0003	8.5	10.7	0.3465
Blood Transfusion	6.8	10.2	<0.0001	10.0	14.0	0.1122
Invasive Ventilation	1.0	0.9	0.2951	0.4	9.3	<0.0001
Vasopressor	1.6	3.2	<0.0001	2.1	26.0	<0.0001

*Arrhythmia included atrial fibrillation, atrial flutter, ventricular fibrillation, and ventricular tachycardia.

Supplementary file Table 3 - Socio-demographic factors, number of comorbidities in all-transplant recipients with and without enterococcal infection.

<i>Factors</i>	<i>All Transplant</i>			<i>All Transplant with Enterococcus Infection</i>		
	<i>Non-Enterococcus %</i>	<i>Enterococcus %</i>	<i>p-value</i>	<i>Survival %</i>	<i>Mortality %</i>	<i>p-value</i>
<i>Age Groups</i>			0.4742			0.2698
18-30 years	5.2	5.6		5.6	5.3	
31-45 years	11.9	11.8		12.0	6.7	
46-60 years	27.8	26.6		26.6	24.7	
61-75 years	44.3	45.2		44.9	51.3	
>75 years	10.8	10.9		10.8	12.0	
<i>Age over 60 years</i>				55.7	63.3	0.0672
<i>Gender</i>			0.1058			0.0215
Male	57.0	55.6		55.1	64.7	
Female	43.0	44.4		44.9	35.3	
<i>Race</i>			0.5099			0.6726
White	63.2	63.2		63.1	65.1	
Black	17.4	16.9		16.9	16.8	
Hispanic	12.7	12.4		12.5	10.1	
Asian or Pacific Islander	3.4	4.0		4.1	2.7	
Native American	0.7	0.7		0.7	1.3	
Other	2.7	2.7		2.7	4.0	
<i>Charlson Comorbidity Index</i>			0.0588			0.0526
0 comorbidities	4.9	4.4		4.4	3.3	
1 comorbidity	7.0	6.4		6.6	1.3	
2 comorbidities	21.0	20.0		20.1	19.3	
≥3 comorbidities	67.1	69.3		68.9	76.0	

Supplementary file Table 4 - Socio-demographic factors, number of comorbidities in HSCT recipients with and without enterococcal infection.

<i>Factors</i>	<i>HSCT recipients</i>			<i>HSCT with Enterococcus Infection</i>		
	<i>Non-Enterococcus %</i>	<i>Enterococcus %</i>	<i>p-value</i>	<i>Survival %</i>	<i>Mortality %</i>	<i>p-value</i>
<i>Age Groups</i>			0.7991			0.3821
18-30 years	7.2	8.1		7.8	10.9	
31-45 years	10.6	10.9		10.9	10.9	
46-60 years	26.7	24.7		24.0	30.9	
61-75 years	48.1	49.2		49.6	45.5	
>75 years	7.5	7.2		7.8	1.8	
<i>Age over 60 years</i>				57.4	47.3	0.1536
<i>Gender</i>			<0.0001			0.0041
Male	57.7	49.0		46.9	67.3	
Female	42.3	51.0		53.2	32.7	
<i>Race</i>			0.0612			0.7594
White	71.2	72.8		73.2	69.1	
Black	12.4	10.2		9.7	14.6	
Hispanic	9.9	7.9		8.2	5.5	
Asian or Pacific Islander	3.2	4.1		4.1	3.6	
Native American	0.4	0.2		0.2	0.0	
Other	3.1	4.8		4.5	7.3	
<i>Charlson Comorbidity Index</i>			0.009			0.1027
0 comorbidities	7.7	4.5		4.6	3.6	
1 comorbidity	5.5	3.8		4.2	0.0	
2 comorbidities	32.1	33.2		34.2	23.6	
≥3 comorbidities	54.6	58.6		56.9	72.7	

Supplementary file Table 5 - Sources of infection, bone marrow dysfunction, comorbidities, interventions, and outcomes of HSCT recipients with and without enterococcal infection.

<i>Factors</i>	<i>HSCT recipients</i>			<i>HSCT with Enterococcus Infection</i>		
	<i>Non-Enterococcus %</i>	<i>Enterococcus %</i>	<i>p-value</i>	<i>Survival %</i>	<i>Mortality %</i>	<i>p-value</i>
<i>Source of Infection</i>						
Peritoneal Abscess	0.2	0.6	0.0583	0.6	0.0	0.5549
Acute Urinary Tract Infection	6.4	39.0	<0.0001	40.6	25.5	0.0298
<i>Bone Marrow Dysfunction</i>						
Anemia	53.2	68.4	<0.0001	67.7	74.6	0.2976
Thrombocytopenia	19.5	21.3	0.2923	22.3	12.7	0.1016
Neutropenia	11.9	18.6	<0.0001	19.3	12.7	0.234
Pancytopenia	29.5	46.3	<0.0001	44.3	63.6	0.0065
<i>Other Comorbidities</i>						
Severe Sepsis	7.8	20.2	<0.0001	15.8	58.2	<0.0001
Diabetes	23.4	27.7	0.0192	28.4	21.8	0.3045
Hypertension	6.1	6.0	0.9739	5.9	7.3	0.6816
Fungal Infections	4.3	8.1	<0.0001	6.3	23.6	<0.0001
Acute Respiratory Failure	14.2	18.5	0.0056	13.7	60.0	<0.0001
Acute Respiratory Distress Syndrome	0.6	1.1	0.1144	0.0	10.9	<0.0001
Acute Heart Failure	9.4	10.0	0.6537	9.5	14.6	0.233
Arrhythmia	9.3	9.6	0.8032	9.7	9.1	0.8914
Cardiogenic Shock	0.8	0.6	0.573	0.4	1.8	0.1903
Sudden Cardiac Arrest	0.8	0.4	0.3071	–	–	–
Stroke	1.5	3.2	0.0009	2.1	12.7	<0.0001
Pressure Sores	1.8	7.2	<0.0001	6.9	9.1	0.5566
Bleeding from Any Source	5.4	9.0	0.0002	8.6	12.7	0.3138
Acute Kidney Injury	24.8	37.7	<0.0001	34.5	65.5	<0.0001
Acidosis	11.2	19.4	<0.0001	16.2	47.3	<0.0001
Metabolic Encephalopathy	3.4	6.0	0.0007	5.5	10.9	0.108
Hyperkalemia	5.1	6.2	0.2438	5.5	12.7	0.0346
<i>Interventions</i>						
Inpatient Hemodialysis	3.3	3.6	0.6677	3.8	1.8	0.458
Blood Transfusion	10.7	15.4	0.0004	15.3	16.4	0.8417
Invasive Ventilation	1.3	0.8	0.2993	0.2	5.5	<0.0001
Vasopressor Usage	2.3	5.7	<0.0001	3.6	23.6	<0.0001

*Arrhythmia included atrial fibrillation, atrial flutter, ventricular fibrillation, and ventricular tachycardia.