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ANTIMICROBIAL RESISTANCE AND CLINICAL OUTCOMES OF BLOODSTREAM INFECTIONS IN A CARDIOVASCULAR SURGERY DEPARTMENT

KARDİYOVASKÜLER CERRAHİ KLİNİĞİNDE KAN DOLAŞIMI ENFEKSİYONLARINDA ANTİMİKROBİYAL DİRENÇ VE KLİNİK SONUÇLAR

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ABSTRACT

Objective: Bloodstream infections (BSIs) following cardiovascular surgery and cardiovascular interventions are major postoperative complications associated with substantial morbidity and mortality. Although antimicrobial resistance (AMR) has become an increasingly important global public health concern, this study aimed to clarify its impact on clinical outcomes in patients who develop postoperative BSIs.

Method: This retrospective study included 139 adult patients who developed BSIs after cardiovascular surgery or cardiovascular interventions at a tertiary referral center. The associations of multidrug resistance (MDR), carbapenem resistance (CR), methicillin resistance, and penicillin resistance with mortality, hospital length of stay (LOS), intensive care unit (ICU) stay, and mechanical ventilation duration were evaluated. Independent predictors of mortality were identified using multivariable logistic regression analysis.

Results: The overall mortality rate was 30.9%. Gram-negative pathogens accounted for 56.8% of BSIs and Gram-positive pathogens for 43.2%. *Staphylococcus* species were the most frequently isolated pathogens (33.8%), comprising other *Staphylococcus* species (26.6%) and *Staphylococcus aureus* (7.2%), followed by *Klebsiella pneumoniae* (21.6%) and *Acinetobacter baumannii* (12.9%). Neither MDR nor CR was significantly associated with mortality (p>0.05). However, among patients with Gram-negative BSIs, carbapenem-resistant isolates were associated with significantly longer hospital, and ICU stays than carbapenem-susceptible isolates (both p=0.006). Univariable analyses showed significant associations between mortality and Gram-negative BSIs, diabetes mellitus, hypertension, and surgical procedure type. Multivariable analysis identified prolonged cardiopulmonary bypass (CPB) duration (OR=1.015, 95% CI: 1.005–1.025; p=0.003) and Gram-negative BSI (OR=3.938, 95% CI: 1.225–12.659; p=0.021) as independent predictors of mortality.

Conclusion: AMR was associated with greater healthcare resource utilization, particularly prolonged hospital and ICU stays, but was not significantly associated with mortality in this cohort. In contrast, Gram-negative BSIs and prolonged CPB duration were independent predictors of mortality.

Key Words: Cardiovascular Surgery Procedures, Bacteremia, Drug Resistance, Carbapenem Resistance, Cardiopulmonary Bypass

ÖZ

Amaç: Kalp cerrahisi ve kardiyovasküler girişimler sonrasında ortaya çıkan kan dolaşımı enfeksiyonları (KDE), yüksek morbidite ve mortalite ile ilişkili önemli postoperatif komplikasyonlardır. Antimikrobiyal direnç (AMR) giderek artan küresel bir halk sağlığı sorunu haline gelmiş olsa da, bu çalışma postoperatif KDE gelişen hastalarda AMR'nin klinik sonuçlar üzerindeki etkisini ortaya koymayı amaçlamıştır.

Yöntem: Bu retrospektif çalışmaya, üçüncü basamak bir merkezde kardiyovasküler cerrahi veya kardiyovasküler girişimler sonrasında KDE gelişen 139 erişkin hasta dahil edildi. Çoklu ilaç direnci (MDR), karbapenem direnci (CR), metisilin direnci ve penisilin direncinin hastane içi mortalite, hastanede kalış süresi (LOS), yoğun bakım ünitesinde (YBÜ) kalış süresi ve mekanik ventilasyon süresi ile ilişkisi değerlendirildi. Hastane içi mortalitenin bağımsız belirleyicileri çok değişkenli lojistik regresyon analizi ile araştırıldı.

Bulgular: Genel hastane içi mortalite oranı %30.9 olarak bulundu. KDE'lerin %56.8'i Gram-negatif, %43.2'si ise Gram-pozitif patojenlerden kaynaklanmaktaydı. En sık izole edilen mikroorganizmalar *Staphylococcus* türleri (%33.8; diğer *Staphylococcus* türleri %26.6 ve *Staphylococcus aureus* %7.2), *Klebsiella pneumoniae* (%21.6) ve *Acinetobacter baumannii* (%12.9) idi. MDR ve CR ile hastane içi mortalite arasında anlamlı ilişki saptanmadı (p>0.05). Ancak Gram-negatif KDE bulunan hastalarda karbapenem dirençli izolatlar, karbapeneme duyarlı izolatlara kıyasla anlamlı derecede daha uzun hastane ve yoğun bakım yatış süreleri ile ilişkiliydi (her iki karşılaştırma için p=0.006). Tek değişkenli analizlerde Gram-negatif KDE, diyabetes mellitus, hipertansiyon ve cerrahi işlem tipi ile hastane içi mortalite arasında anlamlı ilişki bulundu. Çok değişkenli analizde ise uzamış kardiyopulmoner baypas (KPB) süresi (OR=1.015; %95 GA: 1.005–1.025; p=0.003) ve Gram-negatif KDE varlığı (OR=3.938; %95 GA: 1.225–12.659; p=0.021) hastane içi mortalitenin bağımsız belirleyicileri olarak saptandı.

Sonuç: Antimikrobiyal direnç, hastane içi mortaliteyi artırmaktan ziyade sağlık hizmeti kaynak kullanımını etkileyerek daha uzun hastane ve yoğun bakım yatış süreleri ile ilişkili bulundu. Buna karşılık mortalite, bağımsız olarak Gram-negatif kan dolaşımı enfeksiyonları ve uzamış kardiyopulmoner baypas süresi ile ilişkiliydi.

Anahtar Kelimeler: Kalp Damar Cerrahisi İşlemleri, Bakteriyemi, Ilaç Direnci, Karbapenem Direnci, Kardiyopulmoner Baypas

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INTRODUCTION

Bloodstream infections (BSIs) remain among the most serious infectious complications following cardiovascular surgery and cardiovascular interventions. Despite advances in perioperative care, surgical techniques, and infection control measures, BSIs continue to be associated with prolonged hospitalization, increased healthcare costs, organ dysfunction, and substantial mortality [1]. Patients undergoing cardiovascular surgery represent a particularly vulnerable population because of advanced age, multiple comorbidities, prolonged intensive care unit (ICU) stays, invasive monitoring, mechanical ventilation, and frequent exposure to broad-spectrum antimicrobial agents [1,2].

The global emergence of antimicrobial resistance has further complicated the management of postoperative infections. Multidrug-resistant (MDR) Gram-negative pathogens, carbapenem-resistant organisms, methicillin-resistant staphylococci, and other resistant microorganisms are increasingly encountered in cardiac surgical units [3]. These pathogens often limit therapeutic options and may delay the initiation of effective antimicrobial treatment [4]. Previous studies have suggested that antimicrobial resistance may contribute to adverse clinical outcomes, including prolonged hospitalization, increased ICU utilization, and higher mortality rates. However, reported findings remain inconsistent across patient populations and healthcare settings [5].

Among resistant pathogens, carbapenem-resistant Gram-negative bacteria are of particular concern because carbapenems are frequently considered last-line agents for severe infections. Similarly, resistance to methicillin and other commonly used antimicrobial agents among Gram-positive organisms may complicate treatment strategies. Although the epidemiology of resistant BSIs has been extensively studied in general intensive care and hospital populations, evidence focusing specifically on patients undergoing cardiovascular surgery remains limited. Furthermore, it remains unclear whether antimicrobial resistance independently contributes to adverse outcomes or primarily reflects greater illness severity and healthcare exposure [6-8].

Patients undergoing cardiovascular surgery may be particularly vulnerable to BSIs because of cardiopulmonary bypass (CPB), prolonged mechanical ventilation, invasive monitoring, and frequent exposure to healthcare-associated risk factors. Moreover, postoperative organ dysfunction and systemic inflammatory responses may increase susceptibility to severe infections and adverse clinical outcomes. Therefore, understanding the clinical impact of antimicrobial resistance in this population is of particular importance.

Therefore, the present study aimed to evaluate the impact of antimicrobial resistance patterns on clinical outcomes in patients who developed BSIs following cardiovascular surgery or cardiovascular interventions. Specifically, we investigated the associations of multidrug resistance (MDR), carbapenem resistance, methicillin resistance, and penicillin resistance with mortality, hospital length of stay, ICU length of stay, mechanical ventilation duration, and transfusion requirements. We additionally sought to identify independent predictors of mortality in this high-risk patient population.

METHOD

Study Design and Participants

This retrospective study was conducted at a tertiary cardiovascular surgery center. Patients who underwent cardiovascular surgical procedures between September 2018 and February 2026 and had at least one positive blood culture during hospitalization were identified through the institutional microbiology database.

Patients younger than 18 years of age and those with incomplete clinical or microbiological records were excluded. Demographic characteristics, comorbidities, operative variables, microbiological findings, antimicrobial resistance profiles, and clinical outcomes were retrieved from electronic medical records.

Outcome Measures

The following variables were recorded: age, sex, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, smoking status, type of surgery, CPB duration, aortic cross-clamp time, erythrocyte suspension transfusion requirement, hospital length of stay, ICU length of stay, duration of mechanical ventilation, and mortality.

Microbiological Evaluation: Blood culture results were retrieved from the institutional microbiology laboratory database. Isolates were identified by Gram staining and culture characteristics, as well as matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics, Bremen, Germany). Antimicrobial susceptibility was determined using the VITEK 2 system (Bio-Merieux, France).

MDR status was determined according to the international expert proposal jointly developed by the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention [9]. According to these criteria, MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Carbapenem resistance was defined as resistance to at least one carbapenem agent (meropenem, imipenem, or ertapenem). Resistance variables were analyzed as binary outcomes (susceptible/resistant) in the statistical analyses.

Primary and Secondary Outcomes

The primary outcome was mortality. Secondary outcomes included ICU length of stay, hospital length of stay, duration of mechanical ventilation, and erythrocyte suspension transfusion requirement.

Ethical Approval

This study was evaluated and approved by the Gülhane Scientific Research Ethics Committee (date: 12.05.2026, decision number: 2026-215). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments. Due to the retrospective nature of the study and the use of anonymized patient data, the requirement for written informed consent was waived by the Ethics Committee.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were evaluated for normality using visual methods and the Shapiro-Wilk test. Normally distributed variables were presented as mean ± standard deviation, whereas non-normally distributed variables were presented as median (interquartile range). Categorical variables were summarized as frequencies and percentages.

Comparisons between groups were performed using the independent-samples t test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Effect sizes were reported as Cramer's V or Phi coefficient for categorical variables and as r values for Mann-Whitney U test comparisons.

Variables with a p value <0.10 in univariable analyses were entered into a multivariable logistic regression model to identify independent predictors of mortality. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A two-sided p value <0.05 was considered statistically significant. Post-hoc power analysis was performed using G*Power version 3.1.9.7. Based on the primary multivariable logistic regression analysis evaluating the association between Gram-negative bloodstream infection and in-hospital mortality, a two-tailed α level of 0.05, a total sample size of 139 patients, an odds ratio of 3.938, a Gram-negative bloodstream infection prevalence of 56.8%, and an event probability under H0 of 0.22 were

used. The R^2 other X parameter was set to 0 according to the default recommendation of the software because no prior information regarding the correlation among covariates was available. The calculated post-hoc statistical power of the study was 95.9%.

RESULTS

Baseline Characteristics of the Study Population

A total of 139 patients with BSIs following cardiovascular surgery or cardiovascular interventions were included in the study. The cohort consisted predominantly of males (63.3%), and the overall mortality rate was 30.9% (Table 1). Among patients with available clinical data, diabetes mellitus was present in 46.6%, hypertension in 44.9%, chronic obstructive pulmonary disease in 16.9%, and chronic kidney disease in 4.2%. Smoking history was reported in 36.8% of patients.

Regarding procedural characteristics, most patients underwent CPB with aortic cross-clamping (95.6% of cases with available data). Coronary artery bypass grafting (CABG) was the most common surgical procedure (33.8%), followed by valve surgery (18.0%) and combined CABG plus valve surgery (7.9%). Gram-negative microorganisms accounted for 56.8% of BSIs, whereas Gram-positive microorganisms represented 43.2% of isolates (Table 1).

Table 1. Baseline demographic, clinical, and microbiological characteristics of the study population (n=139)

Variable		n (%)
Sex	Male	88 (63.3)
	Female	51 (36.7)
Diabetes Mellitus*	Present	55 (46.6)
	Absent	63 (53.4)
Hypertension	Present	53 (44.9)
	Absent	65 (55.1)
Chronic Obstructive Pulmonary Disease*	Present	20 (16.9)
	Absent	98 (83.1)
Chronic Kidney Disease*	Present	5 (4.2)
	Absent	113 (95.8)
Smoking*	Present	43 (36.8)
	Absent	74 (63.2)
CPB Status†	CPB + cross-clamp	86 (95.6)
	Off-pump	4 (4.4)
	CABG	47 (33.8)
Surgical Procedure	Valve surgery	25 (18.0)
	CABG + valve surgery	11 (7.9)
	Aortic surgery and other complex cardiac operations	7 (5.0)
	Non-surgical cardiac/vascular intervention or peripheral ECMO	49 (35.3)
Gram Stain Classification	Gram-positive	60 (43.2)
	Gram-negative	79 (56.8)
Mortality	Survived	96 (69.1)
	Died	43 (30.9)

*CPB:Cardiopulmonary bypass, CABG:Coronary artery bypass grafting, *Percentages were calculated among patients with available data. †Available in 90 patients. + Includes aortic surgical procedures, cardiac mass excisions, and aortic operations combined with concomitant coronary artery bypass grafting and/or valve surgery.*

Distribution of Bloodstream Infection Pathogens

The distribution of microorganisms isolated from positive blood cultures is summarized in Table 2. The most frequently identified pathogen was other *Staphylococcus* species (26.6%), followed by *Klebsiella pneumoniae* (21.6%) and *Acinetobacter baumannii* (12.9%). Among Gram-positive pathogens, *Staphylococcus aureus* accounted for 7.2% of isolates, whereas *Corynebacterium* spp. and *Enterococcus* spp. represented 4.3% and 2.9%, respectively. Among Gram-negative pathogens, *Stenotrophomonas maltophilia* (6.5%), *Escherichia coli* (4.3%), and *Enterobacter* spp. (2.9%) were also commonly identified. Less frequently isolated organisms included *Pseudomonas* spp., other *Streptococcus* spp., and *Burkholderia cepacia* (each 2.2%). A small proportion of isolates consisted of other Gram-negative bacilli, including *Delftia, Morganella, Serratia*, and *Citrobacter* species (4.3%) (Table 2).

Table 2. Distribution of microorganisms isolated from positive blood cultures (n=139)

Microorganism	n (%)
Other *Staphylococcus* spp.	37 (26.6)
Klebsiella pneumoniae	30 (21.6)
Acinetobacter baumannii	18 (12.9)
Staphylococcus aureus	10 (7.2)
Stenotrophomonas maltophilia	9 (6.5)
Corynebacterium spp.	6 (4.3)
Escherichia coli	6 (4.3)
Enterococcus spp.	4 (2.9)
Enterobacter spp.	4 (2.9)
Pseudomonas spp.	3 (2.2)
Other *Streptococcus* spp.	3 (2.2)
Burkholderia cepacia	3 (2.2)
Other Gram-negative bacilli*	6 (4.3)

**Includes Delftia spp., Morganella spp., Serratia spp., and Citrobacter spp.*

Association of Antimicrobial Resistance Patterns with Mortality in Gram-negative BSIs

Among patients with Gram-negative BSIs, mortality rates did not differ significantly according to carbapenem resistance status (Table 3). Mortality was observed in 38.1% of patients with carbapenem-susceptible isolates, 40.8% of those with carbapenem-resistant isolates, and 22.2% of patients with intrinsically resistant organisms. No significant association was found between carbapenem resistance status and mortality (Cramer's V=0.119, p=0.694). Similarly, MDR was not significantly associated with mortality (Table 3). Mortality occurred in 31.3% of patients infected with non-MDR organisms and in 42.6% of those infected with MDR organisms. Although mortality was numerically higher in the MDR group, the difference did not reach statistical significance (Cramer's V=0.114, p=0.352).

Clinical Outcomes according to Carbapenem Resistance Status

Clinical outcomes stratified by carbapenem resistance status are presented in Table 4. No significant differences were observed among carbapenem-susceptible, carbapenem-resistant, and intrinsically resistant groups with respect to age, CPB duration, cross-clamp duration, mechanical ventilation duration, or erythrocyte suspension transfusion requirements (all p>0.05; Table 4).

In contrast, significant differences were identified for both hospital length of stay (LOS) and ICU LOS. Patients with carbapenem-resistant BSIs had significantly longer hospital stays, and ICU stays compared with those infected by carbapenem-susceptible organisms (hospital LOS: p=0.006, r=0.346; ICU LOS: p=0.006, r =0.350; Table 4). The effect sizes for these comparisons were in the moderate range.

Table 3. Association of carbapenem resistance and MDR with mortality among patients with Gram-negative BSIs (n=79)

Variable		Alive n (%)	Dead n (%)	Total n (%)	Effect Size (Cramer's V)	p value
Carbapenem Resistance	Susceptible	13 (61.9)	8 (38.1)	21 (26.6)	0.119	0.694*
	Resistant	29 (59.2)	20 (40.8)	49 (62.0)		
	Intrinsic Resistance	7 (77.8)	2 (22.2)	9 (11.4)		
Resistance Phenotype	Non-MDR	22 (68.8)	10 (31.3)	32 (40.5)	0.114	0.352*
	MDR	27 (57.4)	20 (42.6)	47 (59.5)		

**Exact Pearson chi-square test*

Table 4. Clinical outcomes according to carbapenem resistance status among patients with Gram-negative BSIs

Variable	Carbapenem Susceptible Mean±SD (Median)	Carbapenem Resistant Mean±SD (Median)	Intrinsic Resistance Mean±SD (Median)	Effect Size (ε^2)	p value
Age (years)	59.32±12.58 (61.0)	63.12±9.85 (63.0)	61.14±15.05 (63.0)	<0.001	0.453
CPB time (min)	140.15±50.53 (140.0)	156.71±55.62 (151.0)	168.20±58.60 (180.0)	0.010	0.476
Cross-clamp time (min)	85.83±34.96 (80.0)	94.40±47.25 (82.0)	101.60±33.78 (107.0)	0.004	0.553
Hospital LOS (days)	18.17±9.73 (17.5)	44.17±62.02 (28.0)	28.40±16.04 (30.0)	0.087	0.021
ICU LOS (days)	9.39±8.64 (5.5)	35.39±64.54 (20.0)	23.60±16.95 (25.0)	0.099	0.016
VD (days)	6.50±8.80 (3.0)	22.18±64.21 (3.0)	16.60±21.15 (2.0)	<0.001	0.800
ES transfusion (mL)	533.33±287.10 (600)	1375.61±1921.56 (600)	600.00±200.00 (600)	0.004	0.330

VD:Ventilation duration, ES:Erythrocyte suspension, Kruskal–Wallis test. Effect size reported as epsilon-squared (ε^2).

Post-hoc analyses demonstrated no significant differences between carbapenem-susceptible and intrinsically resistant organisms or between carbapenem-resistant and intrinsically resistant organisms with respect to hospital LOS or ICU LOS (all p>0.05; Table 4). Similarly, age did not differ significantly between any pairwise comparison groups (all p>0.05; Table 4).

Association of Methicillin and Penicillin Resistance with Mortality in Gram-positive BSIs

No significant relationship was observed between penicillin resistance and mortality. Mortality occurred in 12.5% of patients with penicillin-susceptible isolates and 25.0% of patients with penicillin-resistant isolates; however, this difference was not statistically significant (Phi=0.104, p=0.665).

Similarly, methicillin resistance was not associated with mortality. Mortality rates were 27.3% among patients infected with methicillin-susceptible organisms and 22.2% among those infected with methicillin-resistant organisms. The strength of association was negligible (Phi=0.051), and no statistically significant difference was detected between the groups (p=1.000).

Clinical Outcomes according to Penicillin Resistance in Gram-positive BSIs

Patients with penicillin-resistant Gram-positive BSIs had significantly longer CPB durations compared with those infected by penicillin-susceptible organisms (152.55±80.66 vs. 83.25±29.47 minutes, p=0.048, r=0.346). In addition, ICU length of stay was significantly prolonged in the penicillin-resistant group (7.24±8.90 vs. 1.50±1.00 days, p=0.013, r=0.373), with both comparisons demonstrating moderate effect sizes.

No significant differences were observed between penicillin-susceptible and penicillin-resistant groups regarding age, cross-clamp duration, hospital length of stay, mechanical ventilation duration, or erythrocyte suspension transfusion requirements (all p>0.05). Although patients with penicillin-resistant isolates tended to have longer hospital stays and ventilation durations, these differences did not reach statistical significance.

Clinical Outcomes according to Methicillin resistance in Gram-positive BSIs

No statistically significant differences were observed between methicillin-susceptible and methicillin-resistant groups with respect to age, CPB duration, cross-clamp duration, hospital length of stay, ICU length of stay, mechanical ventilation duration, or erythrocyte suspension transfusion requirements (all p>0.05).

Although methicillin-resistant infections were associated with numerically higher values for several clinical parameters, including CPB duration (160.40±89.30 vs. 89.20±28.36 minutes), ICU length of stay (7.77±10.43 vs. 3.50±3.85 days), and erythrocyte suspension transfusion requirements (819.05±692.55 vs. 533.33±230.94 mL), these differences did not reach statistical significance. The largest effect sizes were observed for CPB duration (r=0.380) and ICU length of stay (r=0.323).

Factors associated with Mortality in Gram-positive BSIs

Patients who died during hospitalization had significantly longer CPB durations than survivors (214.63±102.95 vs. 123.71±53.47 minutes, p=0.006, r=0.464). Similarly, ICU length of stay was significantly greater among non-survivors (11.62±13.41 vs. 4.55±3.87 days, p=0.009, r=0.458).

The most pronounced difference was observed for mechanical ventilation duration. Non-survivors required substantially longer ventilatory support compared with survivors (9.92±13.34 vs. 1.87±2.03 days, p<0.001, r=0.785), representing a large effect size.

No significant differences were identified between survivors and non-survivors with respect to age, cross-clamp duration, hospital length of stay, or erythrocyte suspension transfusion requirements (all p>0.05). Although cross-clamp duration and hospital length of stay demonstrated moderate effect sizes (r =0.294 and r = 0.309, respectively), these associations did not reach statistical significance.

Overall, prolonged CPB duration, longer ICU stay, and extended mechanical ventilation were associated with mortality among patients with Gram-positive BSIs, with mechanical ventilation duration showing the strongest association.

Univariate Analysis of Factors associated with Mortality

The results of the univariate analyses for factors associated with mortality are presented in Table 5. Mortality was significantly more frequent among patients with Gram-negative BSIs compared with those with Gram-positive infections (38.0% [30/79] vs. 21.7% [13/60], p=0.044, Cramer's V=0.175). Among patients who died during hospitalization, 69.8% had Gram-negative bloodstream infections, whereas 30.2% had Gram-positive bloodstream infections.

Several patient-related factors were also associated with mortality. Diabetes mellitus was more common among non-survivors than survivors (61.0% vs. 39.0%, p=0.033, Cramer's V=0.210). Similarly, hypertension was observed more frequently in patients who died during hospitalization (58.5% vs. 37.7%, p=0.034, Cramer's V=0.200). Smoking status was also associated with mortality, with a lower proportion of smokers among non-survivors compared with survivors (22.5% vs. 44.2%, p=0.026, Cramer's V=0.213).

Surgical procedure type demonstrated the strongest association with mortality among the categorical variables examined (Cramer's V=0.334, p=0.003). The highest mortality rate was observed in patients undergoing combined CABG and valve surgery (72.7%), whereas the lowest mortality rates were seen in patients undergoing aortic surgery (14.3%) and non-surgical cardiac/vascular interventions or peripheral extracorporeal membrane oxygenation (ECMO) support (18.4%).

In contrast, no significant association was identified between sex and mortality (p=1.000). Overall, Gram-negative bloodstream infection, diabetes mellitus, hypertension, smoking status, and surgical procedure type were significantly associated with mortality in the univariate analysis (Table 5).

Table 5. Univariate analysis of factors associated with mortality

Variable		Alive n (%)	Dead n (%)	Effect Size	p value
Gram	Gram-positive infection	47 (49.0)	13 (30.2)	0.175	0.044
	Gram-negative infection	49 (51.0)	30 (69.8)		
Sex	Male	61 (63.5)	27 (62.8)	0.007	1.000
	Female	35 (36.5)	16 (37.2)		
Diabetes Mellitus	Present	30 (39.0)	25 (61.0)	0.210	0.033
	Absent	47 (61.0)	16 (39.0)		
Hypertension	Present	29 (37.7)	24 (58.5)	0.200	0.034
	Absent	48 (62.3)	17 (41.5)		
Smoking	Present	34 (44.2)	9 (22.5)	0.213	0.026
	Absent	43 (55.8)	31 (77.5)		
Surgery Type	CABG	33 (70.2)	14 (29.8)	0.334	0.003
	Valve	14 (56.0)	11 (44.0)		
	CABG + Valve	3 (27.3)	8 (72.7)		
	Aortic	6 (85.7)	1 (14.3)		
	Non-surgical/ECMO	40 (81.6)	9 (18.4)		

CABG:Coronary artery bypass grafting, ECMO:Extracorporeal membrane oxygenation.

Multivariable logistic regression analysis of factors associated with mortality

Variables found to be associated with mortality in the univariate analyses were entered into a multivariable logistic regression model. As shown in Table 6, prolonged CPB duration and Gram-negative bloodstream infection remained independent predictors of mortality after adjustment for potential confounding factors.

Each one-minute increase in CPB duration was associated with a 1.5% increase in the odds of mortality (OR=1.015, 95% CI:1.005–1.025, p=0.003). In addition, patients with Gram-negative BSIs had approximately four-fold higher odds of mortality compared with those with Gram-positive infections (OR=3.938, 95% CI:1.225–12.659, p=0.021).

Hypertension and smoking status also remained statistically significant in the final model. Absence of hypertension was associated with lower odds of mortality (OR=0.220, 95% CI: 0.076–0.638, p=0.005), whereas absence of a smoking history was associated with higher odds of mortality (OR=3.420, 95% CI: 1.059–11.049, p=0.040).

Overall, prolonged CPB duration and Gram-negative bloodstream infection emerged as the most clinically relevant independent predictors of mortality in the study cohort (Table 6).

Table 6. Multivariable logistic regression analysis for predictors of mortality

Variable	B	OR (Exp(B))	95% CI	p value
Hypertension (absence vs presence)	-1.513	0.220	0.076-0.638	0.005
Smoking (absence vs presence)	1.230	3.420	1.059-11.049	0.040
CPB time (per minute increase)	0.015	1.015	1.005-1.025	0.003
Gram-negative bloodstream infection	1.371	3.938	1.225-12.659	0.021
Constant	-3.664	0.026	-	0.001

CPB:Cardiopulmonary bypass.

Factors associated with mortality in Gram-negative BSIs

Patients who died during hospitalization had significantly longer hospital length of stay (55.68±76.56 vs. 22.98±14.84 days, p=0.006, r=0.328), ICU length of stay (50.54±77.23 vs. 11.00±9.90 days, p<0.001, r=0.557), and mechanical ventilation duration (36.18±78.07 vs. 4.05±7.68 days, p<0.001, r=0.469) compared with survivors.

No significant differences were observed between survivors and non-survivors regarding age, CPB duration, cross-clamp duration, or erythrocyte suspension transfusion requirements (all p>0.05).

DISCUSSION

BSIs following cardiovascular surgical procedures remain a major postoperative complication despite continuous advances in surgical techniques and perioperative management, as they are associated with prolonged hospital stays, increased healthcare costs, and, most importantly, higher mortality rates [10]. In the present study, we investigated the impact of antimicrobial resistance patterns on mortality and clinical outcomes among patients who developed BSIs following cardiovascular surgery and other cardiovascular interventions.

One of the most notable epidemiological findings of our study was that Gram-negative pathogens accounted for 56.8% of all isolated microorganisms, whereas Gram-positive pathogens represented 43.2%. Although Gram-positive organisms, particularly *Staphylococcus aureus* and coagulase-negative staphylococci, have historically been considered the predominant pathogens in post-cardiovascular surgery infections, especially surgical site infections (SSIs), our findings confirm the ongoing epidemiological shift in the global microbiological landscape toward Gram-negative predominance [11]. Indeed, in a multicenter retrospective study conducted by Wang et al. evaluating blood culture isolates from cardiovascular surgery centers, Gram-negative pathogens such as

Acinetobacter, Klebsiella, and *Pseudomonas* spp. were shown to account for an increasingly larger proportion of bloodstream infection episodes in ICUs [12]. Similarly, in a recent study by Ren et al. investigating multidrug-resistant organisms (MDROs) following cardiovascular surgery, *Acinetobacter baumannii, K. pneumoniae*, and *P. aeruginosa* were identified as the most frequently isolated pathogens [13]. This epidemiological shift necessitates a re-evaluation of prophylactic and empirical antibiotic strategies in cardiovascular surgery units, which have traditionally focused primarily on Gram-positive coverage. The increasing empirical use of broad-spectrum antimicrobial agents may contribute to the selection and hospital colonization of Gram-negative bacteria.

In the multivariable logistic regression analysis performed in our study, patients with Gram-negative bacteremia were found to have a statistically significantly higher risk of mortality compared with those with Gram-positive infections. This finding provides further evidence of the devastating impact that Gram-negative pathogens can have in the vulnerable postoperative cardiovascular surgery population. Our results are consistent with those reported by Massart et al. in a large cohort study evaluating healthcare-associated infections following cardiovascular surgery. In that study, mortality was significantly higher among patients who developed healthcare-associated infections (15.4%) compared with those who did not (5.7%). Furthermore, *P. aeruginosa* infections (HR 2.09) and BSIs overall (HR 2.08) were independently associated with increased mortality [1].

Another striking independent predictor of mortality identified in our study was CPB duration. In our multivariable analysis, each one-minute increase in CPB duration was associated with a 1.5% increase in the odds of mortality (OR=1.015, p=0.003). Moreover, even among patients with Gram-positive BSIs, those who died had substantially longer CPB durations than survivors. The strong association between prolonged CPB duration and mortality may reflect not only increased procedural complexity but also underlying pathophysiological mechanisms, including impairment of intestinal barrier function and subsequent bacterial translocation. In a large-scale study involving more than 6,500 patients, Mork et al. demonstrated that perfusion duration exceeding 120 minutes (OR 2.45) and prolonged aortic cross-clamp time (OR 2.31) were associated with a markedly increased risk of early primary bloodstream infection [14]. The authors postulated that prolonged CPB causes hypoperfusion and ischemia within the splanchnic circulation, particularly at the level of the intestinal mucosa, leading to disruption of the intestinal epithelial barrier. This process may facilitate the translocation of Gram-negative organisms, including members of the *Enterobacterales* that normally reside within the gut microbiota, directly into the bloodstream [14]. The predominance of Gram-negative pathogens among bloodstream infection cases in our cohort, together with the direct association between prolonged CPB duration and mortality, provides strong support for this hypothesis of gut-derived bacterial translocation. Furthermore, Yan et al. and Jahromi et al. reported findings indicating that prolonged CPB may impair immune function and increase susceptibility to postoperative infections [2,15]. Consequently, surgical strategies aimed at optimizing CPB duration, as well as innovative perioperative medical approaches designed to prevent or target bacterial translocation (such as agents that improve intestinal perfusion or targeted prophylactic interventions), may emerge as important determinants of not only surgical success but also patient survival in the future.

As antimicrobial resistance has become a major global health concern, resistant pathogens are generally assumed to be associated with worse clinical outcomes. However, the relationship between antimicrobial resistance and mortality is complex and may be influenced by multiple factors, including host characteristics, the severity of the underlying disease, the adequacy of source control, and the timing and appropriateness of antimicrobial therapy [10,16,17]. One of the most specific—and perhaps paradoxical—findings of our study is that, among Gram-negative pathogens, neither carbapenem resistance nor MDR was independently associated with mortality. In contrast, these resistance phenotypes were associated with significantly prolonged hospital and ICU stays. In other words, antimicrobial resistance did not appear to directly increase mortality, but rather substantially increased the complexity of clinical management and the consumption of healthcare resources [18].

Several studies in the literature evaluating MDRO infections in adult cardiovascular surgery patients have also supported our findings. Although MDRO infections were associated with a numerical increase in mortality, the most pronounced and statistically significant effects were observed in ICU length of stay and post-infection hospital length of stay [13,19]. This observation was not limited to Gram-negative bacteremia but was also evident in Gram-positive BSIs. Neither methicillin resistance nor penicillin resistance was associated with mortality. However, penicillin-resistant infections were associated with longer CPB durations and prolonged ICU stays. These findings may reflect the tendency of resistant Gram-positive infections to occur in patients undergoing more complex procedures or experiencing a more complicated postoperative course. Importantly, given the retrospective nature of the study, the observed associations should not be interpreted as causal relationships [20].

In our study, mortality rates varied considerably according to the type of surgical procedure performed. In particular, patients undergoing combined procedures involving both CABG and valve surgery exhibited a remarkably high mortality rate (72.7%). By their nature, combined operations represent some of the most complex cardiac surgical procedures, being associated with greater surgical trauma, increased risks of bleeding and re-exploration, and, most importantly, a substantially higher need for blood transfusion. In the study by Massart et al., combined procedures were identified as an independent risk factor for healthcare-associated infections (OR 1.64). Furthermore, blood transfusions may increase susceptibility to infections through their immunomodulatory effects, a phenomenon known as transfusion-related immunomodulation [1]. Longer CPB durations and more extensive tissue dissection may facilitate both exogenous microbial contamination and the establishment of persistent niches for biofilm-forming MDRO through the implantation of foreign materials such as prosthetic valves. Infection of these implanted materials, particularly in the form of infective endocarditis, may initiate a cascade of severe complications that often cannot be resolved with medical therapy alone, necessitate repeat surgical intervention, and are associated with substantial mortality [10].

In our univariable analysis, hypertension, diabetes mellitus, and smoking status emerged as factors associated with mortality. Diabetes mellitus may contribute to adverse outcomes through impaired leukocyte chemotaxis and phagocytic dysfunction, whereas hypertension may compromise end-organ perfusion and impair the physiological response to sepsis. However, these associations should be interpreted with caution, as the retrospective design of the study precludes causal inference and residual confounding cannot be excluded [21,22].

However, the more controversial issue, both in our study and in existing literature, is the seemingly paradoxical finding that smokers may appear to have lower mortality rates in certain analyses. Consistent with this observation, smokers in our cohort demonstrated significantly lower mortality than non-smokers. The so-called “Smoker’s Paradox,” which has frequently been reported in studies of acute coronary syndromes and cardiovascular surgical outcomes, was comprehensively examined in a systematic review conducted by Aune et al. [23]. In that review, the apparent protective effect observed among smokers in statistical analyses was shown to be largely attributable to the fact that smokers tend to experience major cardiovascular events -such as myocardial infarction or the need for cardiovascular surgery-approximately 10 to 15 years earlier than non-smokers. Consequently, smokers often present at a younger age and with a different comorbidity profile, creating the misleading

impression of a survival advantage in unadjusted or incompletely adjusted analyses.

In other words, smokers are often substantially younger at the time of surgery and are less likely to have age-related comorbidities that are themselves major predictors of mortality, such as diabetes mellitus and chronic kidney disease. The complex relationships among age, comorbidities, and smoking status observed in our cohort should therefore be interpreted within this context. Importantly, there is no biological evidence to suggest that smoking confers any protective effect on survival following surgery or infection. On the contrary, smoking impairs tissue oxygenation, delays wound healing, and disrupts ciliary clearance in the lower respiratory tract, thereby increasing susceptibility to ventilator-associated pneumonia (VAP) and secondary BSIs [10].

Limitations

Our study has several methodological limitations that should be considered when interpreting the findings and integrating them into clinical practice. First, the single-center and retrospective design limits the ability to establish causal relationships and may restrict the generalizability of the observed microbiological profiles and survival outcomes to other geographic regions and healthcare settings. Second, the relatively limited sample size may have reduced the statistical power of subgroup analyses, particularly those evaluating the impact of specific antimicrobial resistance phenotypes, such as MDR and carbapenem resistance, on mortality outcomes. Third, important clinical variables, including illness severity scores at the time of infection diagnosis (e.g., SOFA and APACHE II scores), the appropriateness of empirical antimicrobial therapy, and the timing of antibiotic initiation, were not included in the analytical model. This represents an important limitation, as it may have hindered the ability to fully distinguish the independent effect of resistant pathogens on mortality. Finally, the study included a heterogeneous patient population comprising patients undergoing cardiovascular surgery as well as those receiving non-surgical cardiovascular interventions or peripheral ECMO support. Differences in baseline characteristics, disease severity, infection risk, and prognosis among these groups may have influenced the observed outcomes.

CONCLUSION

In conclusion, BSIs following cardiovascular surgery remain a significant postoperative complication characterized by the predominance of Gram-negative pathogens and a substantial impact on patient prognosis. Our findings demonstrated that prolonged CPB duration was an independent factor associated with mortality, whereas carbapenem resistance and MDR among Gram-negative BSIs did not independently increase the risk of mortality. However, resistant infections were associated with longer hospital and ICU stays, imposing a considerable burden on healthcare resources.

Resistance phenotype was not significantly associated with mortality in this cohort; however, given the limited sample size, this finding should be interpreted with caution rather than as evidence of a true absence of effect. Therefore, successful management of infections in cardiac surgical patients depends not only on antimicrobial treatment strategies but also on optimizing surgical and perfusion times, carefully managing high-risk patients, and implementing effective infection prevention and control measures. Such a comprehensive approach may contribute to improved clinical outcomes in patients undergoing cardiovascular surgery.

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