IJID Regions 14 (2025) 100566

Contents lists available at ScienceDirect

IJID Regions

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

Mortality Associated with Surgical Site Infections Following Cardiac Surgery: Insights from the International ID-IRI Study

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https://doi.org/10.1016/j.ijregi.2025.100566
Received 26 December 2024; Received in revised form 2 January 2025; Accepted 3 January 2025

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ARTICLE INFO

Keywords:
Surgical
CABG
Cardiac
Infection
Mortality

ABSTRACT

Objectives: Surgical site infections (SSIs) after cardiac surgery increase morbidity and mortality rates. This multicenter study aimed to identify mortality risk factors associated with SSIs after heart surgery.

Methods: Conducted from January to March 2023, this prospective study included 167 patients aged >16 years with post-heart surgery SSIs. The primary focus was the 30-day mortality. Univariate analysis and multivariate logistic regression utilizing the backward elimination method were used to establish the final model.

Results: Several factors significantly correlated with mortality. These included urinary catheterization (odds ratio [OR] 14.197; 90% confidence interval [CI] 12.198-91.721]), emergent surgery (OR 8.470 [90% CI 2.028-35.379]), valvular replacement (OR 4.487 [90% CI 1.001-20.627]), higher quick Sequential Organ Failure Assessment scores (OR 3.147 [90% CI 1.450-6.827]), advanced age (OR 1.075 [90% CI 1.020-1.132]), and postoperative re-interventions within 30 days after SSI (OR 14.832 [90% CI 2.684-81.972]). No pathogens were isolated from the wound cultures of 53 (31.7%) patients. A total of 43.1% of SSIs (n = 72) were due to gram-positive microorganisms, whereas 27.5% of cases (n = 46) involved gram-negatives. Among the gram-positive bacteria, *Staphylococci* (n = 30, 17.9%) were the predominant microorganisms, whereas *Klebsiella* (n = 16, 9.6%), *Escherichia coli* (n = 9, 5.4%), and *Pseudomonas aeruginosa* (n = 7, 4.2%) were the most prevalent.

Conclusions: To mitigate mortality after heart surgery, stringent infection control measures and effective surgical antisepsis are crucial, particularly, in the elderly. The clinical progression of the disease is reflected by the quick Sequential Organ Failure Assessment score and patient re-intervention, and effective treatment is another essential component of SSI management.

Introduction

Cardiac surgery is a complex and invasive procedure that carries significant risks including mortality, morbidity, and surgical site infections (SSIs), which can have serious consequences for patients. Infections can lead to prolonged hospital stays, additional medical treatments, reoperations, increased morbidity and mortality, and raised costs [1]. In addition, patients who underwent cardiac surgery are often elderly with preexisting medical conditions, making them more vulnerable to complications from SSIs [2]. Therefore, infections can compromise the success of cardiac surgery.

Identifying the characteristics of patients with SSIs and exploring the factors predicting mortality are crucial for optimizing patient management. Thus, this prospective observational international study aimed to analyze patients with SSIs after cardiac surgery and investigate the factors leading to mortality.

Materials and methods

This multicenter study was conducted prospectively between January 1, 2023 and March 31, 2023.

Inclusion criteria

Adult patients (>16 years old) who developed SSIs after cardiac surgery after sternotomy were enrolled in the study.

Definitions

Multidrug resistant isolates

Multidrug resistant bacteria have been previously described [3].

Surgical site infection

Standardized definitions of superficial incisional, deep, and organ/space SSIs were used according to the Centers for Disease Control and Prevention criteria [4].

Outcome measure

The outcome was 30-day postoperative mortality [5].

Data collection

Data were collected from 29 centers across 12 countries (Afghanistan, Bosnia-Herzegovina, Croatia, Egypt, Iran, Italy, Poland, Saudi Arabia, Serbia, Pakistan, North Macedonia, and Türkiye) through the Infectious Diseases International Research Initiative (ID-IRI) using a web-based case report form. The parameters related to demographic, clinical, laboratory, and therapeutic parameters, previous prophylaxis, and 30-day mortality data were recorded.

Ethical consent

The ethical consent of the study was approved/registered by the Istanbul Medeniyet University, School of Medicine at 23.11.2022 (No: 20220672). The centers obtained local approval if deemed necessary, and informed patient consent was obtained.

Statistical analysis

The assumption of normality required for the parametric tests was evaluated using the Shapiro-Wilk test. The results indicated that the continuous variables did not follow a normal distribution. For the comparison of the survivors and those who died of SSI in terms of unadjusted effects of these variables, the Mann-Whitney U test was used. The association between categorical variables and mortality was investigated using Pearson's chi-square test. Candidate variables for estimating the risk of death in the multivariate model were selected based on univariate tests, with a P <0.10 [6].

A multiple binary logistic regression model was used to obtain the adjusted effects. The internal validity of the logistic regression model was assessed using a five-fold cross-validation method. Furthermore, model performance was evaluated using metrics such as area under the curve, false positives and false negatives, sensitivity, specificity, positive predictive value, and classification accuracy. Due to the small total number of deceased cases (n = 11) and the unbalanced distribution between survivors and patients who died, determining the significant effects of risk factors in multiple binary logistic regression could be challenging; for this reason, a statistical significance level of P <0.10 was accepted [7,8]. SPSS (ver. 23) and Orange (ver. 3.35.0) were used for the calculations.

Results

The data of 275 patients were obtained from the participating centers, but 108 of these patients were excluded from the study because they were ineligible or because of missing data. Surgical procedures were as follows: coronary artery bypass grafting (n = 131), valvular replacement (n = 50), surgery of the aorta (n = 7), atrial septal defect closure (n = 3), and heart transplantation (n = 1). A total of 11 patients died of SSIs, whereas an additional six patients who underwent coronary artery bypass grafting died due to causes unrelated to SSIs and were consequently excluded from the analysis. Hence, 161 patients were included and analyzed for SSI-related mortality.

Types and findings of surgical site infections

Patients with SSIs were categorized as superficial incisional (n = 115, 68.9%), deep incisional (n = 32, 20.9%), and organ/space SSIs (n = 20, 12%). Local findings were as follows:

(1) Localized swelling, redness, heat, or fever and the incision opened deliberately or spontaneously (n = 80, 47.9%);
(2) Purulent drainage was performed from the superficial fascia (n = 76, 45.5%), deep fascia (n = 40, 23.9%), muscles (n = 14, 8.3%), and organs or space components of the surgical site (n = 17, 10.2%);
(3) Abscess formation (n = 16, 9.6%); and
(4) Organ space infection ([n = 20, 12%], mediastinitis [n = 9], retrosternal infection [n = 6], endocardial infection of the prosthetic valves after surgery [n = 2], graft infection [n = 2], and transplanted heart infection after surgery [n = 1]).

Coexisting infections

Coexisting foci of hospital-acquired infections were identified in 37 patients, representing 22.2% of the total cases. These include pneumonia (n = 17, 10.2%), catheter-associated urinary tract infection (n = 14, 8.3%), central line–associated blood stream infections (n = 10, 6%), decubitus infection (n = 1, 0.6%), and endocarditis (n = 1, 0.6%).

Microbiological data

In 53 (31.7%) patients, no microorganism was isolated from wound cultures. Gram-negative bacteria were recovered from 46 (27.5%) patients, whereas gram-positive microorganisms were recovered from 72 (43.1 %) patients. In two patients, two microorganisms were recovered (*Pseudomonas aeruginosa* and *Staphylococcus aureus* in one patient and *Escherichia coli* and *Enterococcus faecium* in the other). The distribution of the isolated microorganisms is presented in Table 1.

Table 1
Distribution of the bacteria isolated from the cultures.

	N	%
Coagulase negative *Staphylococci*	30	17.9%
• *Staphylococcus epidermidis*	21	12.6%
• *Staphylococcus haemolyticus*	1	0.6%
• Untyped CoNS	8	4.8%
Klebsiella	16	9.6%
• *Klebsiella pneumoniae*	12	7.2%
• *Klebsiella aerogenes*	3	1.8%
• *Klebsiella oxytoca*	1	0.6%
E. coli	9	5.4%
P. aeruginosa	7	4.2%
Enterococci	5	3%
• *Enterococcus faecalis*	3	1.8%
• *E. faecium*	2	1.2%
Serratia marcescens	4	2.4%
Corynebacterium striatum	3	1.8%
Proteus spp	3	1.8%
• *P. mirabilis*	2	1.2%
• *P. vulgaris*	1	0.6%
Acinetobacter baumannii	2	1.2%
Streptococcus anginosus	1	0.6%
Cutibacterium acnes	1	0.6%
Morganella morganii	1	0.6%

Empirical antimicrobial treatment

Single-antibiotic regimens were used in 73 (43.7%) patients, double-antibiotic combinations were administered in 94 (56.3%) patients, and triple-antibiotic combinations were administered in two (1.2%) patients. The antibiotics used in the empirical treatment of SSIs in descending order were piperacillin-tazobactam (n = 33; 19.8%), imipenem/meropenem (n = 29; 17.4%), clindamycin/lincomycin (n = 29; 17.4%), ampicillin-sulbactam (n = 23; 13.8%), vancomycin (n = 23; 9%), cefazolin (n = 14; 8.4%), ceftriaxone/cefotaxime (n = 12; 7.2%), linezolid (n = 11; 6.6%), gentamicin (n = 10; 6%), ciprofloxacin (n = 8; 4.8%), metronidazole (n = 4; 2.4%), cefepime (n = 3; 1.8%), ceftazidime (n = 3; 1.8%), amikacin (n = 3; 1.8%), cefuroxime (n = 2; 1.2%), colistin/polymyxin-B (n = 2; 1.2%), daptomycin (n = 2; 1.2%), ertapenem (n = 1; 0.6%), meropenem-vaborbactam (n = 1; 0.6%), cloxacillin (n = 1; 0.6%), amoxicillin-clavulanic acid (n = 1; 0.6%), and micafungin (n = 1; 0.6%).

Therapeutic suitability

Appropriate treatment was empirically administered to 71 (42.5%) patients, whereas inappropriate treatment was administered to 43 patients (25.7%). In the remaining 53 (31.7%) patients, cultures were negative.

Antibiotic modification

Antibiotic modification was done in 76 (44.5%) patients. Treatment escalated in 52 (31.1%) patients and de-escalated in 24 (14.4%) patients.

Results of univariate analysis

For the 11 patients who died of SSI, the average survival time was 18.6 ± 16.15 days, with a median value of 11 (interquartile range 7-28). Table 2 illustrates the distribution of categorical features and presents descriptive statistics for the numerical characteristics of patients who died (n = 11, 6.6%) and those who survived (n = 150, 89.8%).

Results of multivariate logistic regression model

Significant variables with P <0.10 in Table 2 were examined using a multivariate logistic regression model with the backward elimination method. This model includes the adjusted effects of the variables and was used to predict the risk of death. The results of the final model are presented in Table 3. Upon evaluating the results, it was observed that in individuals undergoing emergency surgery, such as those with valvular replacement, as the quick Sequential Organ Failure Assessment (qSOFA) score increases, in individuals with a urinary catheter at the time of SSI and when postoperative re-intervention was performed within 30 days after SSI, there was a significant increase in the risk of death (P <0.10) (Table 3).

Table 2
Descriptive statistics of patients died of surgical site infection and the survivors.

Categorical variables Risk factors		Survived (n = 150)		Death (n = 11)		
		n	%	n	%	*P*[a]
Gender	Female	42	89.4	5	10.6	0.219
Surgery classification	Emergency	29	80.6	7	19.4	**0.001**
Diabetes mellitus	Absent	59	88.1	8	11.9	**0.030**
Acute renal failure	Present	8	80.0	2	20.0	0.088
Chronic renal failure	Present	11	91.7	1	8.3	0.830
Hypertension	Absent	32	88.9	4	11.1	0.248
Chronic respiratory disease	Present	16	84.2	3	15.8	0.099
Congestive Heart failure	Absent	129	92.8	10	7.2	0.647
Hyperlipidemia	Absent	140	92.7	11	7.3	0.386
Coronary arterial bypass grafting	Absent	31	88.6	4	11.4	0.223
Valvular replacement	Present	42	85.7	7	14.3	**0.013**
Surgery of the Aorta	Present	6	85.7	1	14.3	0.424
Rational antimicrobial treatment	No	37	90.2	4	9.8	0.218
	Yes	63	91.3	6	8.7	
	Unknown	50	98.0	1	2.0	
Use of antibiotic prophylaxis	Yes	148	93.1	11	6.9	0.700
The number of prophylactic regimens	Single-drug	86	92.5	7	7.5	0.683
Surgical prophylaxis with						
• Cefazolin	Yes	68	89.5	8	10.5	0.079
• Cefuroxime	No	118	91.5	11	8.5	0.087
• Cefotaxime/Ceftriaxone	No	114	91.2	11	8.8	0.065
• Ciprofloxacin/Levofloxacin	No	131	92.3	11	7.7	0.209
• Ampicillin-Sulbactam/Amoxicillin-Clavulanate	Yes	2	66.7	1	33.3	0.066
• Piperacillin Tazobactam	No	147	93.0	11	7.0	0.636
• Linezolid	No	149	93.1	11	6.9	0.783
• Clindamycin	No	148	93.1	11	6.9	0.700
• Vancomycin	Yes	9	81.8	2	18.2	0.122
• IMP/MER	Yes	4	80.0	1	20.0	0.236
• Gentamicin	No	139	92.7	11	7.3	0.352
• Azithromycin	No	131	92.3	11	7.7	0.209
Postoperative MV	Yes	112	91.8	10	8.2	0.225
Re-exploration after surgery for non-infectious causes like bleeding	Yes	14	82.4	3	17.6	0.062
Surgical site infection type						
• Organ space infection	Yes	15	78.4	4	21.7	**0.016**
• Deep incisional	Yes	28	90.3	3	9.7	
• Superficial	Yes	107	96.4	4	3.6	
Coexisting infections						
• Catheter associated urinary tract infection	No	136	92.5	11	7.5	0.289
• Pneumonia	Yes	11	78.6	3	21.4	**0.023**
• Blood stream infections	Yes	5	55.6	4	44.4	**0.001**
• Endocarditis	No	149	93.1	11	6.9	0.786
• Decubitus infection	No	149	93.1	11	6.9	0.786
Indwelling catheters						
• Central venous catheter	Yes	86	89.6	10	10.4	**0.049**
• Urinary catheter	Yes	74	89.2	9	10.8	**0.037**
• Arterial line	Yes	19	86.4	3	13.6	0.173
Postoperative re-intervention done within 30 days after surgical site infection	Yes	52	85.2	9	14.8	**0.003**
Re-intervention related to sternal incision. and the need for sternal bone debridement	Yes	11	78.6	3	21.4	**0.023**

Descriptive statistics	Survived						Died						
		Mean	SD	Percentiles				Mean	SD	Percentiles			
	N			25th	Median	75th				25th	Median	75th	
Age	150	60.58	13.60	55.00	63.00	68.25	11	66.73	8.27	64.00	66.00	74.0	0.118
Body mass index	150	29.01	5.90	24.70	27.90	32.53	11	30.74	8.03	25.80	27.50	33.0	0.743
Pre-op ejection fraction	150	51.57	10.73	45.00	55.00	60.0	11	49.27	12.41	36.00	50.0	60.0	0.480
qSOFA score	150	0.59	0.78	0	0	1.0	11	1.55	1.21	0	2.0	3.00	**0.005**
Duration of surgery in minutes	148	250.1	89.9	180.0	240.0	302.0	11	254.36	98.8	180.0	240.0	300.0	0.940
Total hospital stays (duration in days)	150	22.6	17.85	11.0	15.0	28.0	11	13.64	10.67	4.0	10.0	20.0	**0.025**
Preoperative stay in days	150	5.55	6.29	2.0	3.0	7.00	11	2.09	2.02	1.0	2.0	3.0	**0.013**
Duration of prophylaxis after surgery (days)	150	6.03	8.91	2.0	3.5	7.00	11	4.55	4.89	2.0	3.0	6.0	0.688

[a] Chi-square test[b]Mann-Whitney U test.

Table 3
Final predictive model for mortality in patients who underwent cardiac surgery with surgical site infections.

	90% Confidence interval for odds ratio			
	OR	Lower	Upper	P[a]
Surgery classification ***(Emergency vs Elective)***	8.470	2.028	35.379	0.014
qSOFA score	3.147	1.450	6.827	0.015
Valvular replacement ***(Present vs Absent)***	4.487	1.001	20.627	0.090
Urinary catheter ***(Yes vs No)***	14.197	2.198	91.721	0.019
Was postop re-intervention done within 30 days after SSI ***(Yes vs No)***?	14.832	2.684	81.972	0.009
Age	1.075	1.020	1.132	0.022
Constant	0.000001			<0.001

[a] Multiple binary logistic regression model.

Table 4
Classification results and metrics.

FINAL MODEL			Predicted from the model		
			Survived	**Died**	**Total**
Actual	***Survived***		135	15	150
	Dead		1	10	11
		Total	136	25	161
			Classification metrics		
Cut-off			0.10		
Area under the curve ±SE			0.957 ± 0.017		
Classification accuracy			90.1%		
Precision (positive predictive value)			40.0%		
Recall (sensitivity)			90.9%		
Specificity			90.0%		
False positive			10.0%		
False negative			9.1%		

FN, false negative; FP, false positive; PPV, positive predictive value.
Positive group is the group that died.
Negative group is the survivor group.

The prediction model

In this model, the predicted probabilities of individuals are between 0 and 1, and when those with a probability greater than 0.10 are classified as "dead" and those with a lower probability are classified as "survived," the diagnostic success criteria were obtained as shown in Table 4.

$$Pred.\ prob. = \frac{e^{(-13{,}6+2{,}137*X_1+1{,}146*\ X_2+2{,}653*\ X_3.+2{,}697*X_4+0{,}372*X_5+1{,}501*X_6)}}{\left(1+e^{(-13{,}6+2{,}137*X_1+1{,}146*\ X_2+2{,}653*\ X_3.+2{,}697*X_4+0{,}372*X_5+1{,}501*X_6)}\right)}$$

Where:

- X_1 = surgery classification is elective, otherwise this value equal is to "0;"
- X_2 = qSOFA score;
- X_3 = urinary catheter is yes, otherwise this value equal to "0;"
- X_4 = postop re-intervention done within 30 days of SSI is Yes, otherwise this value is equal to "0;"
- X_5 = age; and
- X_6 = valvular replacement is present, otherwise this value is equal to "0."

The nomogram of the logistic regression model makes it easier for researchers to calculate the risk of death in any individual (Figure 1). The receiver operating characteristic curve of the predicted probabilities from the logistic regression is shown in Figure 2. When the cut-off value of the predictions of death probabilities obtained from the final model was accepted as 0.10, owing to the unbalanced distribution in the number of survivors and deaths, the numbers of correctly and incorrectly classified patients; the model performance metrics are presented in Table 4. A total of 10 of the 11 (90.9%) patients who died were classified as dead according to the logistic regression model. Of the 150 patients who were alive, 15 (10%) were predicted to have died according to the logistic regression model.

Discussion

SSIs in cardiac surgery cases can lead to systemic infections, such as sepsis, and are associated with a high risk of mortality. In this prospective study, we found significant increases in mortality risk among patients with SSIs that developed after cardiac surgery, such as emergency surgery, valvular replacement, higher qSOFA scores, increased age, urinary catheterization at the time of SSI, and postoperative re-interventions within 30 days after SSI.

Although superficial SSIs are more common, organ/space SSIs are considered more serious [9]. In this study, although we found that organ/space infections were associated with significantly higher mortality in the univariate analysis, we could not establish such a correlation in the multivariate analyses, possibly because of the small number of patients in this group. Conversely, we found that postoperative re-intervention, identified as a predictor of mortality, often involves treating deep-seated infections, which typically require surgical drainage of the infected cavity [10]. In addition, patients who undergo valvular replacement have a higher likelihood of mortality when SSIs occur. Although data elucidating the higher mortality rates in SSIs among patients undergoing valvular replacement are lacking, it is noted that minimally invasive valve surgery can decrease the likelihood of deep wound infections compared with the standard thoracotomy procedure, which is the preferred approach in our patient cohort [11]. Thus, despite the absence of a direct correlation between deep wound infections and mortality, the use of valvular replacement and postoperative re-intervention as indicators of SSI mortality for SSIs were significant.

Hospitalized patients with bloodstream infections are known to be at an increased risk of complications and death [12,13]. Although the univariate analysis showed a notable connection, our final model did not reveal a clear association between mortality and bacteremia, which was likely influenced by variations in blood culture practices across surgical departments. In addition, although coexisting pneumonia was found to be significant in the initial analyses, its predictive power for mortality was limited, potentially because of the small number of cases involved.

Our study found that emergency surgery was associated with a higher risk of mortality than elective surgery. Previous studies have shown that preoperative optimization and adequate preparation are crucial for surgical outcomes [14]. Therefore, it is possible that disruptions in the antisepsis chain may have contributed to SSIs caused by aggressive and drug-resistant hospital-acquired pathogens rather than harmless skin colonizers. This, in turn, may have led to increased mortality rates. Consequently, the high mortality rate associated with emergency surgery may serve as an indicator of inadequate preoperative optimization, raising concerns regarding patient safety and ethics.

Patients with qSOFA score of 1 or lower were more likely to survive, indicating the urgency of optimized treatment. The recognized utility of qSOFA in predicting mortality in sepsis and critical infections aligns

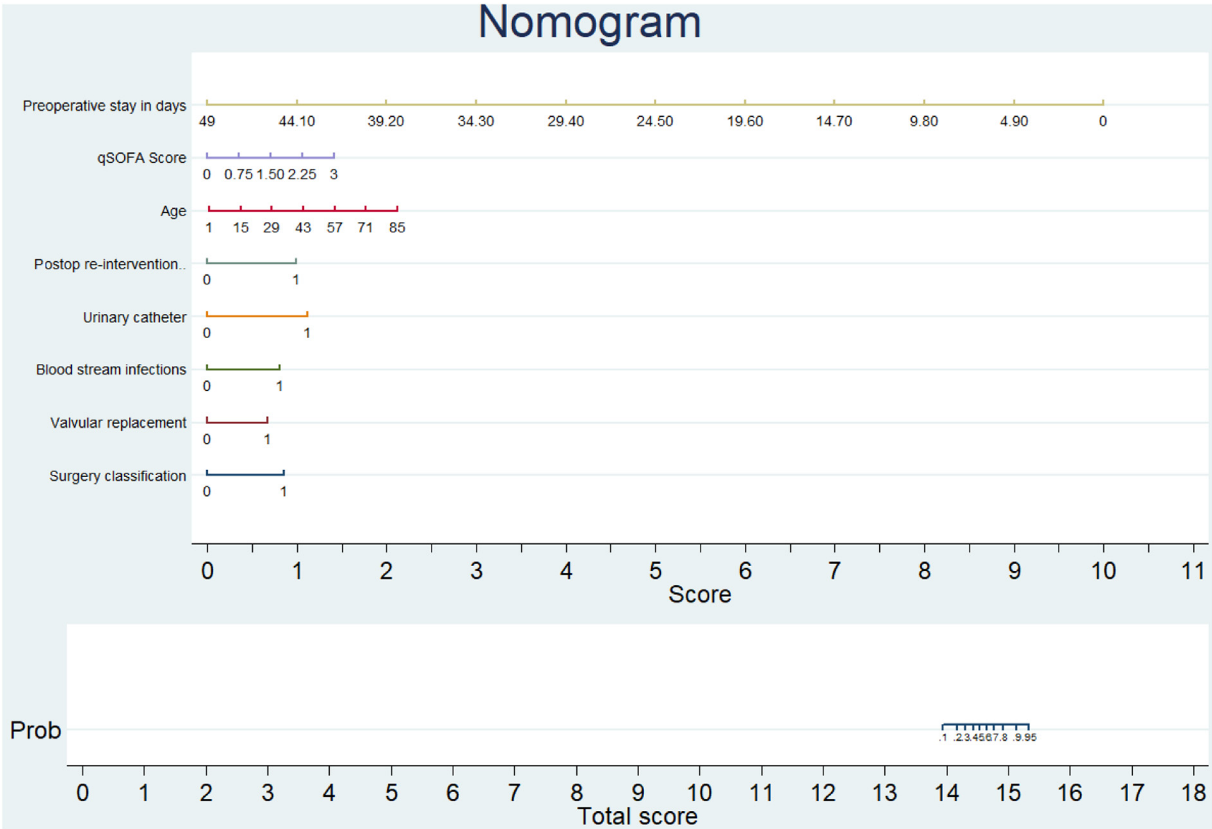

Figure 1. Nomogram to predict the risk of death.

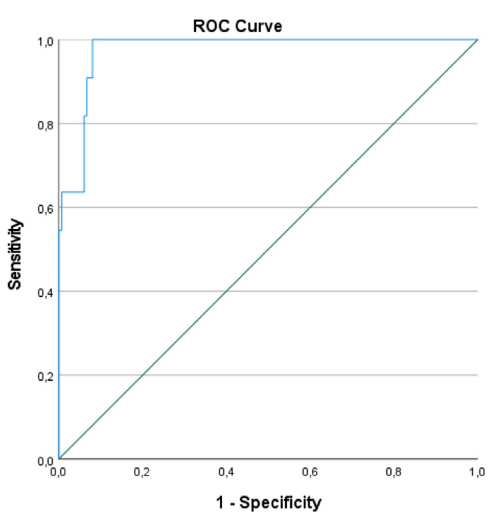

Figure 2. ROC curve for logistic regression model. ROC, receiver operating characteristic curve.

with the favorable prognosis associated with a qSOFA score of 1 or lower [15]. Accordingly, the development of SSIs after cardiac surgery is significantly associated with increased mortality, particularly, in older patients in this study. Increased age is linked to weakening of the immune system, rendering older patients more vulnerable to infections, especially when coupled with a high burden of comorbidities [16,17].

The findings of this study provide important information regarding the microbial makeup of SSIs after sternotomy. Gram-negative microorganisms were found in 27.5% of patients with SSIs, whereas gram-positive microorganisms were more prevalent, accounting for 43.1%. Other epidemiologic studies have reported a higher prevalence of gram-positive bacteria after major cardiac surgery in general and methicillin-resistant *Staphylococcus aureus* in particular [18–20]. Although Staphylococci were the dominant gram-positive bacteria, *K. pneumoniae, E. coli*, and *P. aeruginosa* were the dominant gram-negative bacteria in this study.

Managing SSIs, along with negative culture reports in routine medical practice, poses a formidable challenge, constituting over 30% of cases worldwide [21]. Accordingly, one-third of SSIs in this study had negative cultures, which could have been due to the early start of antimicrobial treatment before culturing. In addition, common colonizers, such as coagulase-negative staphylococci, Corynebacterium, and Acinetobacter spp. were identified in two-fifths of the cultures, further complicating the interpretation of the microbiological results for targeted therapy [22]. The lack of specific pathogen identification and their antibiotic susceptibility in a certain number of post-cardiac surgery SSI cases impeded our ability to evaluate the statistical effectiveness of targeted antimicrobial treatments in this study. Among the cases where antibiotic susceptibility data were ultimately available, only two-thirds received suitable initial empirical therapy, whereas the remaining one-third required adjustments to their antimicrobial treatments after obtaining the susceptibility data. Because rational antimicrobial therapy is the cornerstone for treating critical infections, identification of the pathogen alongside its antibiotic susceptibility data is pivotal in managing SSIs [23,24]. Overall, antibiotic modification was performed in 44.5% of patients, escalated in two-thirds, and de-escalated in one-third, emphasizing the importance of microbiological input in optimizing therapy.

Conclusion

There are a few of limitations in our study. First, although the study was multicenter, it was conducted over a relatively short time frame, which may have introduced regional or institutional biases. Second, this study focused on 30-day mortality, which can be regarded as a short-term outcome. Third, different centers may have varying protocols for infection control, surgical antisepsis, and postoperative care, which could introduce variability in patient outcomes and affect the generalizability of the results. On the other hand, the strengths of this study are its prospective design and inclusion of patients solely with major cardiac surgery and the exclusion of patients with missing data. In addition, our model successfully forecasted death using an easy-to-use nomogram (Figure 1). In summary, the results of this study provide key insights into the relationships between various risk factors and mortality. However, because this predictive model is a new analysis, no external validation using an independent data set could be performed.

Emergency surgery and qSOFA scores should be identified to help health care providers identify patients who are more likely to die. In an era marked by extensive antibiotic resistance, surgeons conducting cardiac surgery should utilize every possible means of obtaining microbiological data, especially before commencing antimicrobial treatment. In addition, SSIs after valvular replacement, the presence of a urinary catheter at the time of SSI, and the requirement of postoperative reinterventions should alert the treating surgeon to potential poor outcomes. Our study provides a core understanding of the effective prevention, early detection, and rational management of SSIs after major cardiac surgery.

Declarations of competing interest

The authors have no competing interests to declare.

Funding

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

Ethical approval statement

The ethical consent of the study was approved/registered by the Istanbul Medeniyet University, School of Medicine at 23.11.2022 (No: 20220672).

Author contributions

Conception and design: Hakan Erdem and Handan Ankarali. *Data acquisition:* all authors. *Data analysis:* Handan Ankarali. *Data interpretation:* all authors. *Drafting the article:* Hakan Erdem, Jaffar A. Al-Tawfiq, and Handan Ankarali. Critical revision of the article: all authors. *Final approval:* all authors. All authors agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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