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Characterization and outcome analysis of cardiac valve surgery for infective endocarditis

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ABSTRACT

Introduction and objectives: Evaluating the effect of cardiac valve surgery in the context of infective endocarditis (IE), an uncommon and still deadly disease, can be particularly advantageous in whole-nation population-based studies. It allows a high-volume database analysis with a reduction in the impact of selection bias inherent to single center-based observational studies. The objective was to characterize the profile of patients hospitalized with IE and submitted to cardiac valve surgery, and identify factors associated with in-hospital mortality using a populational-based database.
Methods: A retrospective nationwide observational study of patients hospitalized with IE based on hospital admissions data between 2010 and 2018 in Portugal.
Results: A total of 7574 patients were analyzed (56.9% male; 68.3 ± 17.3 years old). Of these, 937 patients underwent cardiac valve surgery (75.2% men; mean age 61.1 ± 14.7 years old). Single valve intervention was predominant in nearly three quarters of cases. Surgery on the aortic valve was more frequent. Mitral valve repair occurred in 30% of cases. The in-hospital all-cause postoperative mortality rate was 15.6%. Factors associated with in-hospital mortality were female sex, liver, kidney and coronary disease, valve prosthesis, *Staphylococcus* spp, acute renal failure and sepsis.
Conclusions: This analysis identified factors associated with worse outcome in surgically managed patients with IE in Portugal. Appropriate early identification of surgical stratification markers that may influence the overall prognosis in IE is crucial in the real world clinical setting.

Abbreviations: ICD, International Classification of Diseases; IE, infective endocarditis.

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Caracterización y análisis de resultados de la cirugía valvular cardiaca por endocarditis infecciosa

Palabras clave:
Endocarditis infecciosa
Cirugía cardiaca
Mortalidad
Pronóstico

RESUMEN

Introdución y objetivos: Evaluar el efecto de la cirugía valvular cardiaca en el contexto de la endocarditis infecciosa (EI), una enfermedad poco común y aún mortal, puede ser particularmente ventajoso en estudios poblacionales. Permite un análisis de base de datos de gran volumen con una reducción en el impacto del sesgo de selección inherente a los estudios observacionales basados en un solo centro. El objetivo fue caracterizar el perfil de los pacientes hospitalizados por EI tratados con cirugía valvular cardiaca e identificar los factores asociados a la mortalidad intrahospitalaria mediante una base de datos poblacional.

Métodos: Estudio observacional retrospectivo nacional de pacientes hospitalizados con EI basado en datos de ingresos hospitalarios entre 2010 y 2018 en Portugal.

Resultados: Se analizó a 7.574 pacientes (56,9% varones; 68,3 ± 17,3 años). De estos, 937 pacientes se trataron con cirugía valvular cardiaca (75,2% varones; edad media 61,1 ± 14,7 años). La intervención valvular única fue predominante en casi tres cuartas partes de los casos. La cirugía de la válvula aórtica fue más frecuente. La reparación de la válvula mitral ocurrió en el 30% de los casos. La tasa de mortalidad posoperatoria intrahospitalaria por cualquier causa fue del 15,6%. Factores asociados a la mortalidad hospitalaria: sexo femenino, enfermedad hepática, renal y coronaria, prótesis valvulares, *Staphylococcus* spp., insuficiencia renal aguda y sepsis.

Conclusiones: Este análisis identificó factores asociados con un peor resultado en pacientes con EI tratados quirúrgicamente en Portugal. La identificación temprana adecuada de marcadores de estratificación quirúrgica que pueden influir en el pronóstico general de la EI es crucial en el entorno clínico del mundo real.

Introduction

The 2009 and 2015 ESC guidelines[1,2] introduced a contemporary approach to the role of surgery during the active phase of infective endocarditis (IE) and nowadays early surgical intervention is standardized. Complementary surgical intervention occurs in 15–50% of overall cohorts -in registries such as EURO-ENDO[3] or ICE,[4] almost half the patients had surgery, being higher in Europe than in the rest of the world.[5]

Additionally, it is estimated that less than half of the patients who have an indication for surgery during IE treatment are submitted to surgery.[6,7]

Retrospective unicenter observational studies and expert input constitute the majority of worldwide published evidence[3] on surgery in the context of IE. In fact, randomized clinical trials and metanalyses are scarce in the field of IE. In a multicentric registry in Spain, Revilla et al.[8] have identified heart failure and uncontrolled infection as the main reasons to undergo urgent surgery, with the latter and renal failure as important predictors of a fatal outcome.

Information derived from nationwide studies is crucial to understand the full impact of surgical intervention on the outcome of such an uncommon disease, avoiding the selection bias inherent to all published observational studies from tertiary hospital centers.

Therefore, using populational-based data, we aimed to characterize the clinical profile of patients hospitalized with IE and submitted to cardiac valve surgery and to identify factors associated with in-hospital mortality.

Methods

Study design

A nationwide retrospective observational study on the surgical management of IE was performed.

Data source and patient selection

Data source and patient selection have been addressed elsewhere.[9] In brief, we retrospectively identified all patients with a discharge diagnosis of incident IE (ICD-9-CM codes 421.0, 421.1, 421.9, and 424.9; ICD-10-CM I33.0, I33.9, I38, and I39) hospitalized in public hospitals between 1st January 2010 and 31st December 2018 (Table 1 of the supplementary data). Patients admitted in 2009 with a diagnosis of IE were removed as well as day case episodes. Episodes of patients transferred between hospitals were consolidated in a single episode.

Data derived from coded information included in the patient hospital discharge report. The database was assigned from Administração Central Sistemas Saúde (ACSS) from the Portuguese Ministry of Health. These reports include demographic information, a list of clinical diagnoses and procedures (up to twenty), using the International Classification of Diseases (ICD) 9th (until 2016) and 10th version (from 2016 on).

We identified patients that underwent cardiac valve surgery (repair or replacement) using procedure codes ICD9 – 35.1x and 35.2x, and ICD10 – 02RFx, 02RGx, 02RHx, 02RJ4x, 02QFx, 02QGx, 02QHx, 02QJx (Table 2 of the supplementary data).

Variables

For each index IE hospitalization with associated valvular surgery, we identified the year of hospitalization, hospitals of admission with Cardiothoracic Surgery Unit on-site, date of surgery (when available), clinical information (sex, age, year of discharge, length of hospitalization), previous heart history and comorbidities, microorganisms, IE compatible complications, type of valve procedure, and in-hospital death were collected using the ICD-9 and ICD-10 codes (Tables 1 and 2 of the supplementary data).

Analyses

The following analyses were performed: (a) comparison between patients submitted to cardiac surgery ("medical–surgical patients") and patients that did not undergo cardiac valve surgery during the index hospitalization with IE ("non-surgical patients"); (b) comparison between patients submitted to cardiac surgery having into account the hospital level of complexity at admission (with or without cardiac surgery onsite); (c) in-hospital mortality outcome defined as all-cause mortality between the hospital admission and the hospital discharge in patients submitted to cardiac valve surgery.

Statistical methods

Continuous variables were presented as mean ± standard deviation, and categorical variables were expressed as frequencies and percentages. For continuous variables, comparisons were made through the Student *t* test or Mann–Whitney's *U* test. For categorical variables, comparisons were made using the chi-squared test or Fisher's exact test. Linear by Linear association was performed to test for a linear trend during the analyzed period.

The inferential analysis was performed using binary logistic regression to assess the factors associated with in-hospital surgical intervention and in-hospital mortality (a generalized linear model using Poisson distribution and the logit link function). The Stepwise (Forward) method based on the Akaike Information Criteria minimization was used to select variables included in the model. The adjusted odds ratio and the 95% confidence interval were estimated for each variable included in the regression model.

Receiver operating characteristic curves were used to evaluate the discrimination of our logistic model for the prediction of in-hospital surgical management and mortality (considered outcomes). Precision was quantified by the Hosmer–Lemeshow goodness-of-fit statistic for each of the specified models.

All tests were 2-sided. The level of significance was set as a $P = .05$.

The data were analyzed using IBM SPSS Statistics for Windows version 24 software (IBM Corp., USA).

Ethics

A cooperation protocol between the School of Medicine of Lisbon and ACSS allowed the access to anonymized data that allows the evaluation of performance data of the National Health System.

This study was submitted and approved by the Scientific Council of University of Lisbon Academic Centre in September 2019 and by the Ethics Committee (reference number 349/19), the need of informed consent was waived and was according to the Declaration of Helsinki.

Results

Comparison between patients who underwent surgery versus no surgery

During the study period, 937 (12,4% of the overall cohort) patients underwent cardiac valve surgery in the context of incident IE (Table 1).

IE patients who underwent surgery were younger (61.1 ± 14.7 versus 69.3 ± 17.4 years old; $P < .001$), predominantly male (75.2%), with a higher prevalence of rheumatic and non-rheumatic valve disease or valve prosthesis, with a lower prevalence of comorbidities such as diabetes mellitus (22.8% versus 27.2%; $P = .005$) and chronic renal or hepatic disease, cancer, or chronic lung disease. A higher proportion of patients with *Staphylococcus*, *Streptococcus*, or *Enterococcus* infection underwent surgery. The medical-surgical patients' mortality rate was lower than the mortality rate from non-surgical patients (15.6% versus 20.6%; $P < .001$), with a more prolonged hospital stay (9 days longer on average; $P < .001$). The rate of surgically managed patients first admitted to a tertiary hospital was higher than medically managed patients (65.7% versus 40.5%; $P < .001$).

In-hospital surgical management

The logistic regression performed to depict which variables were associated with in-hospital surgical management of IE hospitalized patients is presented in Table 2.

Factors associated with in-hospital heart valve surgery in IE were: age (patients younger than 60 years old were most likely to undergo surgery), previous heart valve disease, congenital heart disease, infectious agent *Streptococcus spp*, the presence of complications such as heart failure, systemic embolism, or acute renal failure.

On the other hand, female patients, older than 60 years old and the presence of other comorbidities (such as cancer, chronic renal, lung, or hepatic disease) were associated with lower odds of surgery.

Our logistic regression model produced an receiver operating characteristic area of 0.874 (Fig. 1A). The Hosmer–Lemeshow test revealed good fit ($P = .289$).

Table 1 – Baseline characteristics and bivariate analysis of patients hospitalized with incident IE and submitted to surgery in Portugal between 2010 and 2018.

	Overall	Non-surgical	Medical-surgical	P
Number of patients	7574	6637 (87.6)	937 (12.4)	
Cardiothoracic surgery unit on site on first admission	3302 (43.6)	2686 (40.5)	616 (65.7)	< .001
Male	4308 (56.9)	3606 (54.3)	705 (75.2)	< .001
Age, years	68.3 ± 17.3	69.3 ± 17.4	61.1 ± 14.7	< .001
Age groups				
< 18	91 (1.2)	85 (1.3)	6 (0.6)	< .001
18–39	503 (6.6)	414 (6.2)	89 (9.5)	
40–59	1253 (16.5)	990 (14.9)	263 (28.1)	
60–79	3565 (47.1)	3031 (45.7)	534 (57.0)	
≥ 80	2162 (28.5)	2117 (31.9)	45 (4.8)	
Length of hospital stay, days - average (median)	29.3 (21)	26.1 (17)	34.9 (26)	< .001
*Days between admission and surgery - average, median**	–		12.9; 5	
Medical background				
Diabetes mellitus	2016 (26.6)	1802 (27.2)	214 (22.8)	.005
Arterial hypertension	2828 (37.3)	2442 (36.8)	386 (41.2)	.009
Atrial fibrillation	1876 (24.8)	1650 (24.9)	226 (24.1)	.66
HIV	133 (1.8)	124 (1.9)	9 (1)	.05
CRF	887 (11.7)	810 (12.2)	77 (8.2)	< .001
CRF on hemodialisis	324 (4.3)	297 (4.5)	27 (2.9)	.02
Non rheumatic cardiac valve disease	1590 (21)	1062 (16)	528 (56.4)	< .001
Rheumatic valve disease	709 (9.4)	520 (7.8)	189 (20.2)	< .001
Mitral valve disease	914 (12.1)	622 (9.4)	292 (31.2)	< .001
Aortic valve disease	904 (11.9)	585 (8.8)	319 (34)	< .001
Aortic and mitral valve disease	405 (5.3)	275 (4.1)	130 (13.9)	< .001
Tricuspid and pulmonary valve disease	448 (5.9)	335 (5)	113 (12.1)	< .001
Cardiac valve prosthesis	914 (12.1)	776 (11.7)	139 (14.8)	.006
Cardiac implantable electronic devices	649 (8.6)	602 (9.1)	47 (5)	< .001
Coronary artery disease	970 (12.8)	846 (12.7)	124 (13.2)	.68
Previous PCI	108 (1.4)	92 (1.4)	16 (1.7)	.46
Previous CABG	183 (2.4)	168 (2.5)	15 (1.6)	.09
Congenital heart disease	42 (1)	26 (0.4)	15 (1.6)	< .001
Cancer	1018 (13.4)	930 (14)	88 (9.4)	< .001
COPD	702 (9.3)	639 (9.6)	63 (6.7)	.004
Opioid consumption	103 (1.4)	89 (1.3)	14 (1.5)	.65
Chronic hepatic disease	366 (4.8)	336 (5.1)	30 (3.2)	.01
Infectious agents				
Staphylococcus	1242 (16.4)	1040 (15.7)	202 (21.6)	< .001
Streptococcus	1030 (13.6)	767 (11.6)	263 (28.1)	< .001
Enterococcus	535 (7.1)	403 (6.1)	132 (14.1)	< .001
Gram negative	898 (11.9)	910 (12.2)	88 (9.4)	.01
Anaerobes	20 (0.3)	17 (0.3)	3 (0.3)	.73
Fungi	10 (0.1)	9 (0.1)	1 (0.1)	.99
Brucella	9 (0.1)	6 (0.1)	3 (0.3)	.09
In-hospital complications/outcomes				
Heart failure	2232 (29.5)	1861 (28)	371 (39.6)	< .001
Sepsis	937 (12.4)	830 (12.5)	138 (14.7)	.06
Ischemic CNS event	743 (9.8)	598 (9)	108 (11.5)	.01
Hemorrhagic CNS event	204 (2.7)	185 (2.8)	19 (2)	.2
Non-neurological systemic embolism	97 (1.3)	60 (1)	37 (3.9)	< .001
Splenic abscess	73 (1)	51 (1)	22 (2.3)	< .001
CNS abscess/meningitis	91 (1.2)	69 (1)	22 (2.3)	.001
Acute renal failure	819 (10.8)	658 (9.9)	161 (17.2)	< .001
Acute myocardial infarct	220 (2.9)	196 (3)	24 (2.6)	.6
In-hospital death, incident episode	1513 (20)	1367 (20.6)	146 (15.6)	< .001

Data are expressed as no. (%) or mean ± standard deviation. CABG, coronary artery bypass grafting; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; HIV, human imunodeficiency virus; IE, infectious endocarditis; PCI, percutaneous coronary intervention

* Date of surgery available in 609 patients.

Data are expressed as no. (%) or mean ± standard deviation.

Table 2 – Logistic regression analysis of in-hospital surgical management of IE patients in Portugal, from 2010 to 2018.

	Adjusted OR	95%CI	P
Sex			
Female	0.47	0.39–0.56	< .001
Male	1		
Group age			
< 18 yrs old	4.42	1.66–11.60	< .001
18–39 yrs old	4.22	1.64–10.85	.003
40–59 yrs old	2.72	1.06–6.96	.003
60–79 yrs old	0.35	0.13–0.93	.037
≥ 80 yrs old	1		.035
Previous cardiac valve disease			
Yes	7.51	6.34–8.89	< .001
No	1		
CRF			
Yes	0.73	0.56–0.97	.03
No	1		
Cardiac devices			
Yes	0.63	0.44–0.89	.009
No			
Arterial hypertension			
Yes	1.45	1.22–1.73	< .001
No			
First admission in hospital with cardiothoracic unit onsite			
Yes	4.12	3.47–4.89	< .001
No			
Cancer			
Yes	0.61	0.47–0.80	< .001
No	1		
COPD			
Yes	0.63	0.46–0.87	.005
No	1		
Congenital heart disease			
Yes	3.4	1.50–7.55	.003
No	1		
Chronic hepatic disease			
Yes	0.31	0.20–0.47	< .001
No	1		
Infectious agents/Streptococcus spp			
Yes	1.99	1.64–2.42	< .001
No	1		
Heart failure			
Yes	2.04	1.71–2.43	< .001
No	1		
Systemic embolism			
Yes	3.46	2.06–5.83	< .001
No	1		
Acute renal failure			
Yes	1.60	1.28–2.01	< .001
No	1		

95%CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; CRF: chronic renal failure; IE, infectious endocarditis; OR, odds ratio.
Dependent variable: Surgical management. *Reference categories*: female (sex); 80+ years (age-group); *Streptococcus* spp agent (infectious agents). No (for remaining factors). Previous cardiac heart valve disease include rheumatic and non-rheumatic valve disease. Neurological events include ischemic or hemorrhagic stroke, transient ischemic accident, central nervous system abscess/meningitis.

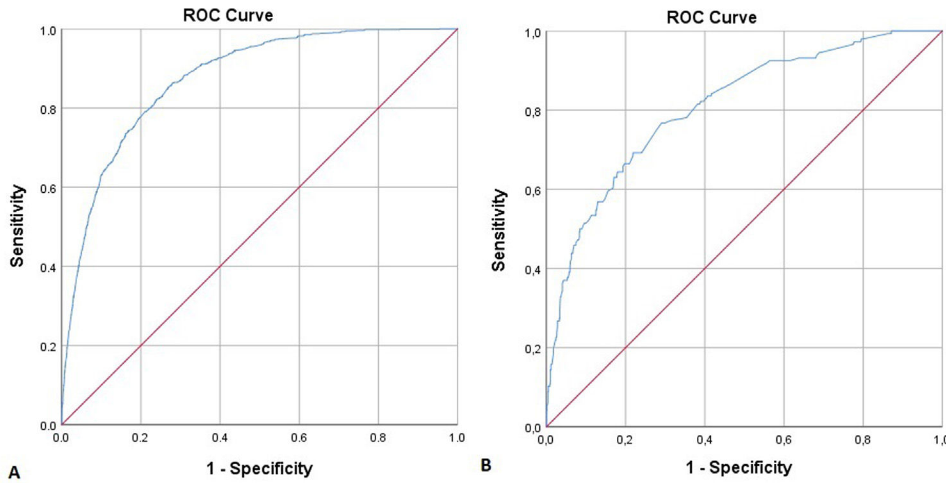

Fig. 1 – Receiver operating characteristic (ROC) curves for in-hospital surgical management logistic regression model (A) and for in-hospital post surgical mortality (B).

Impact of the admission in a tertiary hospital with cardiothoracic surgery unit on-site

In patients hospitalized with IE, the proportion of patients firstly admitted in a hospital with a cardiothoracic surgery unit on-site undergoing surgery was substantially higher compared to only medical management patients (Table 1).

Additionally, this variable was also associated with the performance of cardiac valve surgery in the context of active IE (OR, 4.12, 95% confidence interval, 3.37–4.89; $P<.001$) (Table 2).

Operated patients admitted through a hospital with a cardiac surgical unit presented lower proportions of cardiac valve disease (rheumatic and non-rheumatic), of a prosthetic valve, of infection with *Staphylococcus* and *Enterococcus,* and of other complications such as acute heart or renal failure, ischemic stroke, and systemic embolism when compared with those that were admitted in a non-tertiary institution (Table 2 of the supplementary data). No significant differences were noted regarding sex, age, or mortality rate.

Type of valvular surgical procedure

During the index hospitalization for IE, most patients underwent single valve intervention (73.9%). A total of 102 patients (10.9%) presented combined procedures with repair and replacement techniques during the same surgery.

The aortic valve was the most frequently involved, replacement being essentially always performed (repair was performed in 2% of aortic valve interventions) (Table 3). On the other hand, 30% of interventions on the mitral valve consisted of repair.

In-hospital mortality among surgical patients

A total of 15.6% of patients who underwent surgery during the index hospitalization died, and the estimated annual rate was stable throughout the 9 years ($P=.12$).

The logistic regression results depicting which variables were associated with in-hospital mortality among surgical patients hospitalized with IE are presented in Table 4. The following variables were included: female sex, age, diabetes mellitus, arterial hypertension, previous cardiac valve disease, left heart valve disease, atrial fibrillation, chronic renal failure, chronic obstructive pulmonary disease, previous coronary artery disease, congenital heart disease, chronic hepatic disease, cardiac valve prosthesis, cardiac intra electronic device, isolation of *Streptococcus* spp, *Staphylococcus* spp or *Enterococcus* spp, heart failure, acute renal failure, sepsis and systemic emboli. Factors associated with in-hospital mortality in IE patients submitted to surgery were female sex, previous coronary, renal or liver disease, acute renal failure, and the presence of sepsis. Conversely, *Streptococcus* spp infection and being less than 80 years old conferred a protective effect in this group of patients.

This logistic regression model produced an area under the curve of 0.809 (Fig. 1B). The Hosmer-Lemeshow test indicated a good-fit model ($P=.556$).

Discussion

This contemporary nationwide analysis of 937 patients hospitalized with IE and submitted to cardiac surgery in the public hospital network in Portugal assessed demographics, medical background, microbiology and clinically relevant outcomes such as all cause in hospital mortality. Three quarters of patients were men, most in the 4th to 7th decade of life, with a significant prevalence of structural valve disease. Factors associated with in-hospital surgical management included male sex, age younger than 60 years old, with few comorbidities, the presence of previous cardiac valve disease, *Streptococcus* spp infection, heart failure, acute renal failure, and systemic embolism. Finally, 85% of patients survived until hospital discharge. Female patients, patients with previous coronary, renal, or liver chronic disease, cardiac valve prosthesis, infection with *Staphylococcus* spp, acute renal failure, and the presence of sepsis had higher odds of in-hospital mortality.

Table 3 – Surgical procedures (absolute value) in IE patients during the index hospitalization ($n = 937$ patients).

Procedure	2010–2012	2013–2015	2016–2018	Total
Aortic valve repair	3	3	8	14
Aortic valve replacement	166	234	213	613
Mitral valve repair	37	62	46	145
Mitral valve replacement	114	111	107	332
Pulmonary valve replacement	0	4	0	4
Tricuspid valve replacement	6	8	0	14
Tricuspid valve repair	14	22	20	56

Table 4 – Logistic regression analysis of in-hospital mortality in patients that underwent surgery.

	Adjusted OR	95%CI	*P*
Group age			
18–39 yrs old	0.02	0.01–0.12	< .001
40–59 yrs old	0.12	0.05–0.28	< .001
60–79 yrs old	0.24	0.12–0.49	< .001
≥ 80 yrs old	1		< .001
Sex			
Female	2.11	1.36–3.26	.001
Male	1		
Cardiac valve prosthesis			
Yes	1.72	1.03–2.85	.037
No	1		
Chronic hepatic disease			
Yes	3.88	1.52–9.86	.004
No	1		
Chronic renal failure			
Yes	2.68	1.47–4.88	.001
No	1		
Previous CAD			
Yes	1.85	1.08–3.18	.026
No	1		
Staphylococcus spp			
Yes	1.73	1.09–2.73	.019
No	1		
Streptococcus spp			
Yes	0.34	0.19–0.59	< .001
No	1		
Acute renal failure			
Yes	2.04	1.29–3.22	.002
No	1		
Sepsis			
Yes	4.52	2.79–7.32	< .001
No	1		

95%CI, 95% confidence interval; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; HIV, human immunodeficiency virus; IE, infectious endocarditis; OR, odds ratio.
Dependent variable: Surgical management. Reference categories: female (sex); 80+ years (age-group). No (for remaining factors). Previous cardiac heart valve disease include rheumatic and non-rheumatic valve disease. Neurological events include ischemic or hemorrhagic stroke, transient ischemic accident, central nervous system abscess/meningitis.

In our study, patients that underwent cardiac surgery had a similar profile to other international series.[10,11] The average age of surgically managed patients was 61.1 years old, and 85.1% were between 40 and 79 years old. Elderly patients (≥ 80) rarely underwent surgery in the context of IE which is comparable to the findings in the recently published Swedish registry by Ragnarsson et al.[12] Advanced age is related to worse outcomes in cardiac surgery even though the threshold for intervention is shifting towards sicker and more elderly patients, particularly in the elective field. In IE, the frequent indication for urgent surgery and patient's clinical instability makes this assessment more challenging. Aging is also linked to a higher rate of comorbidities. Even though our data did not allow for the estimation of the Charlson score, a score that evaluates the 10 year prognosis in patients with multiple comorbidities, we can appreciate that the burden of comorbidities was lesser in the surgically managed cohort. This is also a common finding in other registries such as the Euro-Heart Survey.[13] Heart valve disease was also a predominant finding in our study, as was the case for the large multicentric registry GAMES.[14]

Patients treated with surgery were predominantly men. In fact, gender impact in the access to cardiac surgery overall is still quite controversial. Varela et al.[15] also concluded that women were less likely to undergo cardiac surgery in the context of IE. Female gender is a current variable predicting increased risk in most stratification risk scores for cardiac surgery such as EUROSCORE I[16] and II[17] or the specifically IE related PALSUSE[14] risk score which may therefore lead to a selection bias in the access to cardiac surgery in the context of IE.

The surgical rate presented in this analysis was lower than reported by Portuguese cross-sectional single-center institutions[18] (29.8% on average), matching other European populational series such as Sunder et al.[19] (in France) or Shah et al.[20] (in Scotland) nonetheless. Reasons explaining this discrepancy between populational and registries/single-center observational series may lie on national global access to cardiac surgery (tertiary versus community hospital differences, the formers with a higher number of cross-sectional studies published), physicians' awareness, and selection bias. In addition, postponing surgery in IE patients to the ambulatory settings was not assessed in our analysis, which could also have contributed to a lower than the expected surgical rate in this analysis.

Worldwide, access to cardiac surgery is not homogeneous between different regions.[21] Cabell et al.[22] were the first to acknowledge that geographical location was a strong predictor of IE outcome, even after adjusting for other patient-specific variables. Health care access, different practices, and referral pathways were identified as relevant factors. The EURO-endo registry[23] concluded that patients hospitalized with IE in European centers were more likely to undergo surgery. In Portugal, the National Health System delivers global health care and access to all Portuguese citizens. Still, the distribution of health care and human resources is diverse.[24] Araújo et al.[25] have shown existing inequalities in coronary heart disease mortality in different Portuguese regions. Healthcare-related factors such as distribution and access to services and patterns of use/referral could significantly impact coronary heart disease's outcome. Probably these aspects are also relevant regarding IE surgical management. There are 6 Portuguese public centers of cardiac surgery – 2 in the Oporto area, 1 in Coimbra, and 3 in Lisbon, the most industrial and crowded regions.[26] In our study, less than half the patients were admitted to the previously mentioned tertiary hospitals firsthand. Still, being first admitted in a hospital with cardiac surgery on-site was associated with surgical management, even after correction for other clinical variables. Additionally, patients presented fewer comorbidities and had a lower rate of complications than those from non-surgical hospitals. Inadequate referral pathways and physician's noncompliance to scientific guidelines are among the reasons that can partially explain these findings.

In our study, nearly three quarters of the total cohort underwent single valve surgical intervention as in most other surgical series.[27] The aortic valve was the most frequently involved, with replacement being performed in nearly all situations. Regarding mitral valve repair, it was performed in 30% of cases. In fact, the more recent guidelines[2,28] have been defending mitral repair as the first option whenever feasible. In this context, published series have evaluated mitral valve intervention in this context report repair ranging between 21–80% of cases.[29–35] Populational series, namely Lee et al.[34] (from Taiwan) and Toyoda et al.[35] (USA), report values inferior to our findings (21.2% and 22%, respectively). Overall, significant heterogeneity among centers and series is noted, probably related to the individual complexity of cases and the technical expertise in relation to the volume of cases.[2] Our study is focused on immediate postoperative outcomes, not providing data on the clinical and imagiological follow-up of patients. Nevertheless, we acknowledge that assessing the effectiveness of these interventions in IE through lifelong surveillance is indeed of paramount importance.

Patients submitted to cardiac surgery presented a lower in-hospital mortality rate when compared to exclusively medically managed patients. The protective role of cardiac surgery has been acknowledged in several cross-sectional studies,[36–39] in registries such as the International Collaboration on Endocarditis – Prospective Cohort Study (ICE-PCS)[39] and in a metanalysis published in 2011.[40] Additionally, high risk patients are the ones that benefit the most from surgical intervention.[41] Nevertheless, a better clinical profile of the patients submitted to surgery is noted in our study which can be a translation of an inherent selection bias ultimately contributing to a more favorable outcome.

The all-cause mortality rate among surgically managed patients was similar to that observed in cross-sectional observational single centers[18] in Portugal (ranging from 13% to 16%). After stepwise logistic regression, 7 factors were associated with a fatal outcome: female gender, cardiac valve prosthesis, previous chronic coronary, kidney, or liver disease, and the presence of acute renal failure or sepsis. Apart from liver disease, all the remaining factors are included in the general surgical risk stratification scores previously mentioned, particularly EuroSCORE I and II, already validated in a Portuguese surgical center.[42] In fact, those are non specific prognostic markers in surgically managed patients. We identified 4 variables included in the PALSUSE score[41] such as age, female gender, prothesis heart valve and *Staphylococcus* spp infection. An Italian registry published by De Feo et al.[43] also identified renal failure as a significant prognostic marker. The presence of previous liver disease usually puts patients at the highest risk, being denied surgery globally. Our data does not allow for the analysis of IE specific markers such as physical signs at presentation, intracardiac destruction or vegetation size which could also play a relevant role in the final outcome of these patients as was documented in a recent brasilian cohort analysis[44] or in the IE specific risk score PALSUSE.[14]

Our analysis provides an exceptional insight into the characterization and prognosis of patients hospitalized with IE and submitted to cardiac surgery assembling data from most public hospitals of the National Health System in Portugal, regardless of their complexity level. Future research may rely on prospective assessment of patient risk stratification

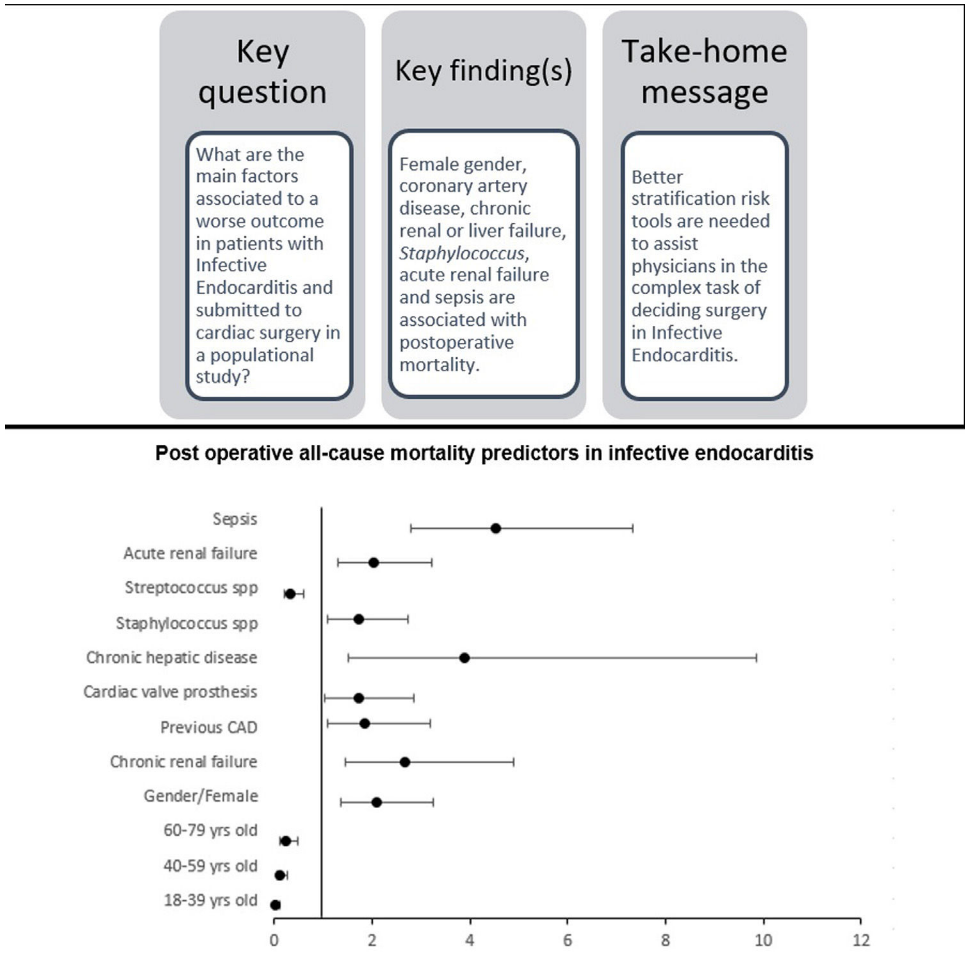

Fig. 2 – Main findings and take-home message of the current study.

considering IE specific markers, impact of negative blood cultures, geographical location, timing to intervention, effectiveness of valve repair in IE, and the need to reintervention.

Limitations

First, it is an analysis based on administrative data originated from discharge medical reports. Confirmation of the data, diagnosis, and ICD coding was not possible. Nevertheless, well-trained physicians are responsible for the discharge medical report and its coding, which can reduce the impact of errors. Additionally, high volume administrative databases allow the analysis of large sample sizes obtained over time and robust power even for very rare events.[45] In healthcare, it can be especially useful when the object of study is a specific event like hospitalization for IE or a procedure such as cardiac valve surgery,[46] as was our case.

Second, identifying the patients with a precise surgical indication not submitted to surgery was not accessible, and therefore an inherent selection bias may be present in this analysis.

Third, a complete analysis of patients operated after discharge in an elective setting was not accessible, possibly leading to underestimating patients submitted to surgery. Therefore, our study is limited to in-hospital surgical intervention in the index hospitalization.

Fourth, as this is based on discharge medical report information, no data were obtained regarding surgery's timing, the urgency, and technical details regarding the surgery, which could also influence these patients' outcomes.

Finally, confounders not evaluated in the database cannot be excluded.

Conclusions

Cardiac surgery in IE was performed in younger patients, mostly men with few comorbidities. Clinical complications, namely heart failure and systemic embolism, were also associated with cardiac surgery. Finally, female sex, chronic diseases, valve prosthesis, and a clinical course complicated by acute renal failure and sepsis were associated with a fatal outcome (Fig. 2), factors considered in conventional general surgical risk scores such as EuroSCORE. Early identification of stratification markers that may influence the overall prognosis in IE is crucial in the real world clinical setting.

What is known about the subject?

Cardiac surgery has a protective impact on the management of patients with infective endocarditis. Populational based studies on the impact of cardiac surgery in infective endocarditis are infrequent.

Does it contribute anything new?

We found that women, valve prosthesis, chronic illnesses, infection by *Staphylococcus* spp, the presence of sepsis or acute renal failure were associated with higher post-operative mortality in a populational based study. Early identification of surgical stratification markers in IE is crucial to recognize those that benefit the most from intervention.

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Authors' contributions

Conceptualization: C. Sousa; F.J. Pinto. Data curation: C. Sousa; P.J. Nogueira. Formal analysis: C. Sousa; P.J. Nogueira. Funding acquisition: A. Nobre. Investigation: C. Sousa; P.J. Nogueira; RF; A. Nobre; F.J. Pinto. Methodology: C. Sousa; P.J. Nogueira. Project administration: C. Sousa; F.J. Pinto. Resources: C. Sousa; P.J. Nogueira. Software: C. Sousa; P.J. Nogueira. Supervision: P.J. Nogueira; A. Nobre; F.J. Pinto. Validation: P.J. Nogueira; R. Ferreira; A. Nobre; F.J. Pinto. Visualization: C. Sousa. Writing – original draft: C. Sousa. Writing, review, and editing: P.J. Nogueira; R. Ferreira; A. Nobre; F.J. Pinto.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rccl.2022.02.008.

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