VILNIUS UNIVERSITY

FACULTY OF MEDICINE

Medicine

Institute of Clinical Medicine – Clinic of Cardiovascular Diseases

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Integrated study master’s thesis

Surgical Treatment of Infective Endocarditis Results 2011-2022 in Vilnius University Hospital Santaros Klinikos

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Vilnius, 2024/05/10

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Abbreviations

Abbreviation	Definition
CABG	Coronary Artery Bypass Graft
CCS	Canadian Cardiovascular society
CI	Confidence interval
CC	Creatinine clearance
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
ECMO	Extracorporeal Membrane Oxygenation
ESPI	Elektroniczny System Przekazywania Informacji
GFR	Glomerular Filtration Rate
HR	Hazard ratio
IABP	Intra-aortic balloon pump
ICD-10-CM	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICU	Intensive care unit
IE	Infective endocarditis
IQR	Interquartile range
Leu	Leucocytes
LVEF	Left ventricular ejection fraction
MR	Multi-resistant
NYHA	New York Heart Association for stages of heart failure
OR	Odds Ratio
PPM	Permanent pacement maker
RRT	Renal replacement therapy
VU	Vilnius University

Abstract

Infective endocarditis (IE) is a rare disease with a worldwide incidence of 3-10/100,000/year and a prevalence of 5.6/100,000 in 2019 (1). It is related to high morbidity, connected to systemic complications and a generally high mortality rate, about 25%. (5) In summary, those numbers highlight the importance of identifying risk factors for mortality to improve these numbers, not only in Lithuania but also over the world.
The aim of this study was to evaluate the mid- and long-term survival, the freedom from reinfection and the incidence of IE patients undergoing open-heart surgery in Vilnius, Lithuania. In addition, factors for mortality in these cases were sought to be identified. The objective of this study was to conduct an international comparison and assessment of the operative outcomes for infective endocarditis, in line with similar studies conducted in various other countries.

A retrospective observational single-center study data collection between January 2011 and December 2022 was done, with 294 cases by reviewing medical records of the hospital database, using standardized forms. Patients under 18 years of age and cases without follow-up were excluded. Patients were followed up till the 2023/06/01. Primary outcome was mortality from any cause, secondary outcomes were absence of reinfection or postoperative complications.
A multivariate binary logistic regression analysis was performed to assess the independent risk factors for mortality. Significant factors were analyzed by univariant model of Cox regression.

294 cases were analyzed. The median incidence was 25 cases/year without significant trend in numbers. 9.0% died in first 30 days after operation. 1-year survival was 83.0%, 10-year survival 60.0%. Freedom of reinfection after 5-years was 95.3%, after 10 years 91.5%. Significant variables in the 1-year analysis are moderate impaired creatinine clearance (p 0.019, 95% CI 1.176-5.935, HR 2.642), preoperative dialysis (p 0.000, 95% CI 3.553-16.941, HR 7.758), and fungal infection (p 0.001, 95% CI 1.892-14.692, HR 5.272). Postoperatively factors were a therapy with extracorporeal membrane oxygenation (p 0.000, 95% CI 9.936-49.698, HR 22.222), renal replacement therapy (p = 0.000, 95% CI 5.429-16.999, HR 9.607), stroke (p 0.000, 95% CI 3.366-13.300, HR 6.691), tracheostomy (p 0.000, 95% CI 5.195-19.068, HR 9.953).

For the overall follow up time preoperative factors were dialysis (p 0.000, 95% CI 2.107-8.741, HR 4.291), left ventricular ejection fraction ≤ 20% (p 0.000, 95% CI 3.410-61.368, HR 14.465), pulmonary edema (p 0.000, 95% CI 1.401-3.123, HR 2.092), inotropic support (p 0.000, 95% CI 2.138-7.638, HR 4.041), and fungal infection (p 0.000, 95% CI 2.174-13.485, HR 5.414). Heterogeneity analysis of gender and age groups revealed no significance.

The incidence in Vilnius showed no significant over the past years. The mortality risk was in overall acceptable. Significant variables highlight the interference of mortality and the renal-cardiovascular system, leading to the conclusion of the implementation of better preoperative – renal focused - monitoring, and close surveillance of neurological deficits and alertness.

Keywords:
Infective endocarditis, open heart surgery, mortality, risk factors, freedom of reinfection

Introduction

The first mentioned medical data about infective endocarditis was in the 17th century, 1646, by Lazare Rivière a French physician who was the first one who described vegetations of endocarditis from the aortic valve (2). It almost took 200 years since the term ‘endocarditis’ was instituted in the medical world by Jean Baptiste Bouillaud, in 1835. "I have given the name of endocardium to the inner lining of this organ and that of endocarditis to its inflammation" (3).
The long history of infective endocarditis with the discovery of pathophysiology, diagnostic algorithm development, and the latest treatment plan, highlights the complex and ongoing process of understanding and handling the disease.

Infective endocarditis (IE) is a rare disease with a worldwide incidence of 3-10/100,000/year and a prevalence of 5.6/100,000 in 2019 (1). In Kaunas Arzanauskiene et al. calculated in 2002 an incidence of 0.0042% per year (4).
It’s not only a rare disease, but infective endocarditis is also related to high morbidity, a long and difficult treatment plan, and a generally high mortality rate, about 25%, not specified on the treatment (5). The age-standardized disability-adjusted life years rates (per 100 000) for both sexes combined in 2019 by the Institute of Global Health Metrics indicated for Lithuania of 14.6 - < 17.1. In between the years of 1990 to 2019 the mortality rate globally increased by 131%. (1)
Furthermore, infective endocarditis is connected to systemic complications, for example, cerebrovascular embolies, 65% of those affecting the CNS and over 90% of the supply area of A. cerebri media. Connecting with a median hospital stay time in Germany of 40 days (6), the treatment is complex. In summary, those numbers highlight the importance of identifying risk factors for mortality to improve these numbers, not only in Lithuania but also over the world.

The aim of this study was to evaluate the mid- and long-term survival, the freedom from reinfection and the incidence of IE patients undergoing open-heart surgery in Vilnius, Lithuania. In addition, risk factors for the mortality were sought to be identified. The objective of this study was to conduct an international comparison and assessment of the operative outcomes for infective endocarditis, in line with similar studies conducted in various other countries. Drawing on the theory, that the incidence is decreasing over the years, but that the mortality in Lithuania after endocarditis-surgery is acceptable.

Material and Methods

Data collection

In 11 years, between January 2011 and December 2022, 303 cases of operations were found that corresponded the diagnosis of infective endocarditis according to the International Statistical Classification of Diseases and Related Health Problems ICD-10-CM code I33.0 along together with the Duke's criteria in Santaros Klinikos in Vilnius. Every patient was included who met the diagnostic criteria. The data collection was based on a retrospective observational single-center study by reviewing the medical records of the hospital database, by using standardized forms. Missing's were 10.50% of the data, due to absent data in the medical files and the retrospective data collection study design.

Exclusion criteria were an age of under 18 years old and no possibility for a follow-up. If one patient was operated more than one time, the first operation was counted as the initial case.

Socioeconomic status, pre-, intra-, and postoperative factors were collected and taken from the patient's files. Details on the diverse factors can be seen in the results following. Time frames and durations were calculated by the records in the files by the person collecting the data.

The status of survival or mortality and cause of death were all obtained on 01.06.2023 using the Elektroniczny System Przekazywania Informacji (ESPI) and the status by the ministry of health.

Diagnostic algorithm

Clinical observations, serial blood sample testing, imaging, and Duke's criteria were used to make the diagnosis of active infective endocarditis.

Before and after surgery, laboratory tests were included measuring the serum levels of C-reactive protein and serum leucocyte count. Echocardiographic findings accounted for a considerable portion of the surgical indication. Both, transesophageal and transthoracic echocardiography were used.

A surgical procedure carried out fewer than 48 hours following admission was considered an urgent surgical treatment, whereas emergency procedures are required as immediately as possible. If a patient was operated on an open-heart surgery due to infective endocarditis more than one time, the patient was considered as one case.

Regardless of the afflicted valves, the surgical procedure involved total removal of the infected native tissue, thorough local debridement, and rebuilding of the impacted structures. As necessary, valve replacement or reconstruction was done.

Statistical Analysis

In this section, the statistical analysis methodology is explained further. The primary outcome was mortality due to any reason. Secondary outcomes were freedom of reinfection, postoperative complications.

Microsoft Excel (Version 16.79.2) was used, and SPSS Version 20.0 software (SPSS Inc, Chicago, IL) was used.

Continuous data are presented as median, interquartile range. Categorical data are given as proportions. Discrete data are given as counts and percentages. The percentages have been rounded for easy reading.

Overall survival and freedom from reinfection were calculated according to the method of Kaplan and Meier. A binary logistic regression model was used first, as a multivariate analysis, to assess the independent risk factors for 30-day mortality, 1-year mortality as well as the overall mortality till the end of follow-up. Due to a large amount of data and for a correct goodness-of-fit test, the binary logistic regression model was divided into two parts. First, the preoperative factors were analyzed, followed by a model of the intra- and postoperative factors. The results of the model are displayed using the odds ratio (OR) and a 95% confidence interval (CI). Every statistical test was exploratory, two-sided, and carried out at the significance level of 0.05.

The regression diagnostics and overall fit of the used model were performed using the standard procedures and following the assumptions of a binary logistic regression.

The factors that were displayed as significant in the logistic regression were analyzed by using an univariant model of Cox regression, repetitively by using the standardized methods and displaying the final outcome Hazard Ratio (HR) and Confidence interval (CI).

Results

Study Collective

A total of 294 patient were included. Mean age was 56.6 years (SD ±14.8), 77% were male (n = 227) and 23% (n = 68) female gender. The patient characteristics are presented in Table 1. Three patients were excluded because they were under 18 years of age and one adult was omitted due to loss of follow-up, as he was not a Lithuanian citizen.

Table 1. Patient characteristic

Patient characteristic	N (Total = 294)	%
Age, median (IQR)	56.5 (46-66)	
Male gender	226	77
Female gender	68	23
Follow-up time, median (IQR)	1512 (576-2724)	

Preoperative course

Apparent from Table 3, in the preoperative course values, each factor of the EuroSCORE II was included. The EuroSCORE was used to calculate the risk of mortality in the case of cardiac surgery.

Starting with the Creatinine Clearance (CC), the majority (n = 179, 61%) had a normal CC range of > 85 ml/min. 24% were classified within a moderate creatinine clearance between 50-85 ml/min. About 10% were initially administered to the hospital with severe renal impairment of < 50 ml/min CC. Every patient who received dialysis regardless of their CC rate was categorized into the "dialysis group", which was 5% in this study population.

17% (n = 49) had an extracardiac arteriopathy of various origins. 11% were diagnosed with any kind of chronic pulmonary disease, most often chronic obstructive pulmonary disease (COPD). Another 11% (n = 33) of the study collective had a previous cardiac surgery.

10% of the investigated people had a poor mobility. Poor mobility is defined as "severe impairment of mobility secondary to musculoskeletal or neurological dysfunction" (7). 4% (n = 12) were in a critical preoperative state, which includes preoperative cardiac massage, preoperative ventilation before entering the anesthesia room, preoperative inotropic support, preoperative intraaortic balloon pump (IABP), or preoperative acute renal failure (anuria or oliguria 10 ml/hr) (7). 4% (n = 11) had insulin-dependent diabetes.

By using a scale of four levels, the CCS angina categorization classifies symptoms experienced during physical exercise. It is used by the EuroSCORE II, by giving another point if patients do have CCS class IV. In the analyzed population at Santaros Klinikos, 3% (n = 10) were categorized into this class. The classification can be seen in Table 2.

Table 2. Classification of angina severity according to the Canadian Cardiovascular Society (8)

Canadian Cardiovascular Society	
Class I	Ordinary activity does not cause angina such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
Class II	Slight limitation of ordinary activity. Angina on walking or climbing stairs rapidly, walking or stair climbing after meals, or in cold, wind or under emotional stress, or only during the first few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity. Angina on walking one to two blocks on the level or one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort' - angina syndrome may be present at rest.

In evaluating the preoperative course, another aspect to consider was the ejection fraction of the heart, specifically the left ventricular ejection fraction (LVEF), which was categorized into four groups. Among the study population, over 50% of EF was reached by 55% (n = 161). An ejection fraction of 31-50 was in 41% (n = 120), and 21-30 was seen in 3% (n = 10) and 1% (n = 3) of the total population demonstrated an ejection fraction below 20%. Besides the pump function of the heart, the systolic pulmonary artery pressure is included as well. It was classified into three groups, under 31 mmHg 45% (n = 132 patients); between 31 and 55 mmHg 43% patients (n = 125). Severe pulmonary hypertension, a systolic pressure over 55 mmHg was seen in 13% of the selected patients (n = 37).

Furthermore, the NYHA (New Year Heart Association) for staging heart failure was selected for every patient. 1.7% (n = 5), were ordered into NYHA I, and 8.2% (n = 24) into NYHA Class II. The majority of the patients had NYHA Class III (n = 234, 79.6%). The most severe heart failure group according to symptoms were in 10.5% (n = 31). 3% (n = 8) had a recent myocardial infarction within the prior 90 days before the surgery.

At the end of the EuroSCORE, the operation is grouped into different categories. Another factor, if it's a thoracic aortic surgery, is given into account when calculating the risk of mortality. In this case, 4% (n = 13) accounted for this additional risk. The operation itself is divided into "Single Non-CABG" (coronary artery bypass graft), two or three procedures. As we investigated only patients receiving cardiac surgery due to infective endocarditis, the category of single CABG operation wasn't applied to any of these cases. The majority of the study collective (n = 167, 57%) had two procedures in the same operation. Followed by 30% (n = 87) for a single non-CABG and last with three procedures, 4% (n = 13) built the last category.

The EuroSCORE points of each patient weren't taken into the statistical model of binary logistic regression due to the high chance of bias, due to the selection of the variables by subjective interpretation, and older versions of the EuroSCORE.

16% of the study collective (n = 47) were preoperatively in the intensive care unit due to a variety of indications. All of the patients were intubated. 5% (n = 16) of the whole study collective received inotropic support. Pulmonary edema was determined in 43% of the cases (n =127).

Table 3. Preoperative characteristics

Preoperative characteristics	N (Total = 298)	%
Creatinine clearance – Renal impairment		
Normal (CC > 85 ml/min)	182	61
Moderate (CC 50-85 ml/min)	73	24
Severe (CC < 50 ml/min)	29	10
Dialysis (regardless of CC)	14	5
Extracardiac arteriopathy	49	16
Chronic Pulmonary disease	34	11
Poor mobility	31	10
Previous cardiac surgery	37	12
Critical preoperative state	13	4
Diabetes on insulin	11	4
CCS class 4 of angina	10	3
LVEF		
> 50%	163	55
31-50%	122	41
21-30%	10	3
≤ 20%	3	1

Recent myocardial infarct	8	3
Systolic PA pressure mmHg		
No (< 31 mmHg)	133	45
Moderate 31-55 mmHg	128	43
Severe > 55 mmHg	37	12
NYHA	5	2
NYHA I	5	1.7
NYHA II	24	8.2
NYHA III	237	79.6
NYHA IV	32	10.5
CRP on admission, median (IQR)	28 (11-76)	
Leu on admission, median (IQR)	21 (6-11)	
CRP before surgery, median (IQR)	21 (8-56)	
Leu before surgery, median (IQR)	8 (6-10)	
Taken from ICU	47	16
Taken from department	251	84
Intubated preop	47	16
Pulmonary edema preoperative	129	43
Inotropic support preop	17	6
Blood culture		
Positive	107	36
Negative	187	64
Source		
Unknown	146	49
Dental	49	16
Skin	2	1
Other	70	23
Drugs	10	3
Multiple	21	7
Fungal infection	6	2

LVEF = Left ventricular ejection fraction; NYHA = New York Heart Association for stages of heart failure.

Etiology of acute infective endocarditis

15% (n = 49) were identified with a dental offspring of infective endocarditis. The third most common category was patients with multiple sources of the infection with 7% (n = 21) of the study group. 3% (n = 10) of the study population were abusing intravenous drugs at the time of the operation. For 1% (n = 2) the source of infection was identified as bacteria from the skin area. The remaining patients couldn't be identified with some origin of the disease, which displayed the second largest part. An overview about these details can be seen in Table 3.

36% had a positive blood culture (n = 107). 2% (n = 7) were diagnosed with a fungal infection. For 7% (n = 22) of the 187 patients with a negative blood culture result, no blood culture at all could be found in perspective. The bacteria isolated in detail are shown in Table 4.

With 55%, the left side of the heart, including the mitral and/or aortic valve was most affected. At the same time, 5% (n = 14) had right-sided infective endocarditis.
In total 39% were diagnosed with an infection on both sides of the valve.
Single-valve infective endocarditis was the most often operated one with 62% of the cases (n = 183). Followed in order by two valves, and three valves that are affected (23% and 14%). One patient was operated on infective endocarditis with no focus on any valve. This patient had an operation indication due to an aortic aneurysm due to infective endocarditis.
The aortic valve was affected most often (n = 201), followed by the mitral valve (n = 131). With 110 patients, the tricuspid valve was the third place affected in this study population. A single patient had a single focus on the pulmonary valve.

Table 4. Distribution of Bacteriology

Groups of bacteriology	N
Staphylococcus epidermidis MR	21
Staphylococcus aureus	16
Enterococcus faecalis	11
Streptococcus mitis and oralis	9
Staphylococcus haemolyticus MR	4
Streptococcus gordonii	4
No bacterial growth (blood culture -)	167
No bacterial culture	22
Other	80

MR = multi-resistant

Antibiotic and antifungal regimen

The most used antibiotics are Penicillin and aminopenicillins, followed by the second-place antifungal medications, clear from Table 5. According to the guidelines, a combination of Aminopenicillin, Flucloxacillin, and Gentamycin is recommended in case of native valve infections in the first line. If the infective endocarditis is based on a prosthetic valve Vancomycin, Gentamycin, and Rifampicin are the first choices. Those antibiotics cover the most common causative agents. (9) Due to high resistance bacterial colonies and the adaption to the antibiogram further choices of different antibiotics can be seen in Table 5. A de-escalation of antibiotic therapy is recommended after the results of cultures and antibiogram. It should be noted that the number of used antibiotics exceeds the number of patients due to multiple use of different antibiotics in one superordinate. As fungal endocarditis infection has a worse outcome the early usage of antifungal medication is needed in case of positive results on fungal tests. In this patient collective, in 164 cases antifungal medication were administered.

Table 5. Distribution of Antibiotics

Groups of antibiotics	N
Penicillin, Aminopenicillin	315
Sulfonamides and Diaminopyrimidin	67
Cephalosporin	63
Carbapenems	53
Fluoroquinolones	52
Macrolides	19
Tetracycline	17
Rifamycin	12
Glycylcyclines	6
Polymyxin E	4
Aminoglycoides	4
Nitroimidazoles	1
Oxazolidinones	1

Surgical Procedure

Discernible from Table 6, most of the cases were operated as an elective procedure (93%, n = 272). 6% (n = 17) had an urgent procedure. Closed by 2% (n = 5), who were selected as emergent operations.

The surgical procedure was done following standardized methods, such as removing and debriding infective tissue. Suppose necessary destroyed structures were reconstructed, for example, the outflow tract. The valve was replaced by an artificial valve in 60% (n =176), and 61% (n = 107) of those were a biological valve. For 7% (n = 22) the affected valve was reconstructed or repaired. In nearly a third of the cases (29%), patients received multiple and different procedures.

The median operation time was about five hours and 19 minutes [IQR 1-3 4h 20min - 6h 35min)].

Table 6. Intraoperative characteristics

Intraoperative characteristics	N (Total = 298)	%
Type of surgery		
Emergency surgery	5	1.5
Urgent surgery	17	6
Elective surgery	276	92.5
Weight of operation		
Single non-CABG	88	30
2 procedures	170	57
3 procedures	40	13
Thoracic aortic surgery	13	45
Affected side of heart		
Left side	165	55.25
Right side	14	5.25
Both sides	117	39.5
Numbers of valve(s) involved		
One valve involved	186	62
Two valves involved	69	23
Three valves involved	42	14
Native valve endocarditis	259	87
Prosthetic valve endocarditis	37	12
Valve replacement	180	60
Valve implanted mechanical	69	23
Biological	110	37
Valve repair	22	7
Other	11	4
Multiple	85	29
OP duration, median (IQR)	5h20min (4h20min-6h35min)	

CABG = coronary-artery bypass-grafting; CCS = Canadian Cardiovascular Scoring for angina; CRP = C-Reactive Protein; Leu = Leucocytes; ICU = Intensive Care Unit.

Postoperative course

As visible in Table 7, 7% (n = 21), had an intraaortic balloon pump that had to be placed to maintain hemodynamic stability. 3% (n =10) of the patients were indicated to have an extracorporeal membrane oxygenation (ECMO) implanted in the intensive care unit.
17% (n = 49) received renal replacement therapy.

About the postoperative neurological injury and complications, 7% (n = 21) were diagnosed with a stroke by symptoms and neurologic imaging. No preoperative screening was performed. 1% (n = 3) of the study population had a stroke and peripheral neuropathy after the surgical procedure. No patient had signs of peripheral neuropathy exclusively. 5% (n = 16) had different neurological complications, such as post-hypoxic encephalopathy, meningitis, convulsive syndrome, or epilepsy. Multiple neurological complications have been described by 2% (n = 5).
Regarding the local surgical access point, the sternum complications such as mediastinitis, and resternotomy were calculated. 17% (n = 51) needed a resternotomy due to various reasons. For example, 3% of all patients received a reoperation due to repeated valve replacement (n = 10). In 6% (n = 17) of the cases, a tracheostomy was performed. Due to various arrhythmic conditions and conducting disorders in 11% (n = 33) a permanent pacemaker was implanted. For a median of five days (IQR 2-10), the patients had to stay in the intensive care unit postoperatively. In total 27 days was the median time of the hospital stay (IQR 18.75 - 39 days). For 3% (n = 9), a reinfection occurred, requiring a valve replacement. The median time till reinfection was about 4 years (IQR 563-1719 days) after initial surgery.

Table 7. Postoperative characteristics

Postoperative characteristics	N (Total = 298)	%
IABP	22	7
ECMO	10	3
Renal replacement therapy postoperative	51	17
Neurological complications		
Stroke	22	7
Peripheral neuropathy	0	0
Both	3	1
Other	16	5
Multiple	5	2
Resternotomy	51	17
Tracheostomy	17	6
Mediastinitis	2	1
PPM	33	11
ICU stay, median (IQR)	5 (2-10)	
Hospital stay, median (IQR)	27 (19-39)	
Valve prosthesis was replaced	9	3
Valve prosthesis replacement days after OP, median (IQR)	1460 (563-1719)	

IABP = Intra-Aortic Balloon Pump; ECMO = Extra-Corporeal Membranous Oxygenation; PPM = Permanent Pace Maker

Mortality data

9% of the study population died within thirty days after the operation. As a result of the underlying infectious process, cardiopulmonary failure claimed the lives of most of these patients. Three patients died due to dysrhythmic events.

17% died within one year afterwards. In most of the cases, the reason for death was not documented or known. For the cases with an identified reason for the death, was a septic shock or sepsis.

About half of the patients (46.5%), died in total till the end of follow-up, the 01st of June 2023, with a median follow-up time of 4.2 years (1549 days).

30-day and 1-year survival using the Kaplan-Meier-Survival was 91% and 83%, respectively (Figure 1-3) - 5-year survival was 69% and 10-year survival 60%. The overall survival till loss-of-follow-up was 53.5%. All mortality data in this section are unadjusted.

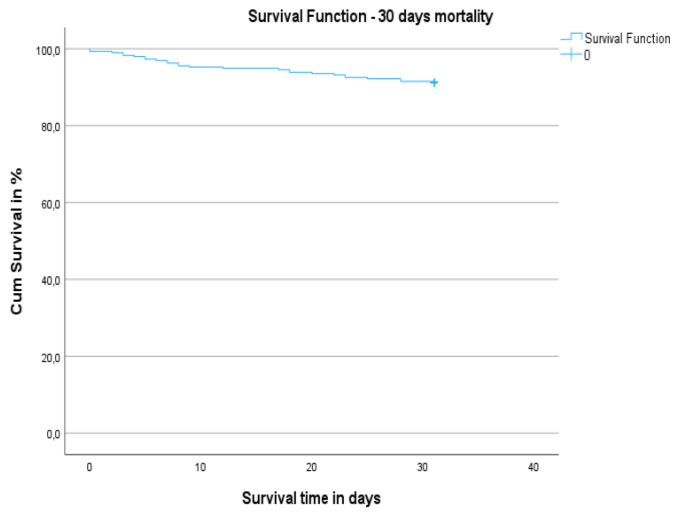

Figure 1. 30-days Survival (days)

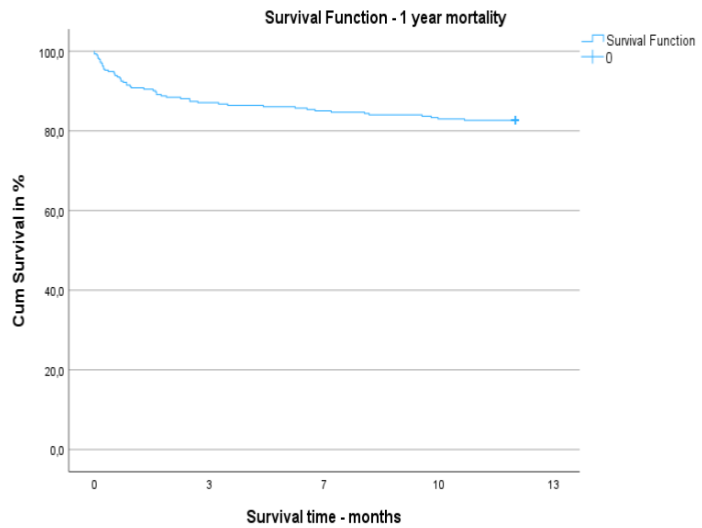

Figure 2. 1-year Survival (months)

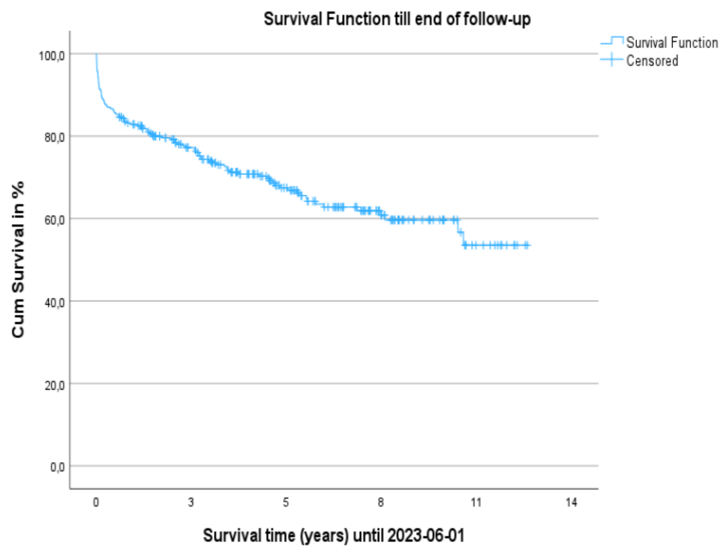

Figure 3. Overall Survival till end of follow up (years)

Freedom of reinfection

The actuarial freedom of reinfection was calculated by using the Kaplan-Meier analysis. The one-year actuarial freedom from reinfection was close to 100% with 99.6%, by looking at the 5-year actuarial freedom from reinfection the number entitled 95.3% respectively. The freedom of reinfection till the end of follow-up in this data set was 91.7% (Figure 4).

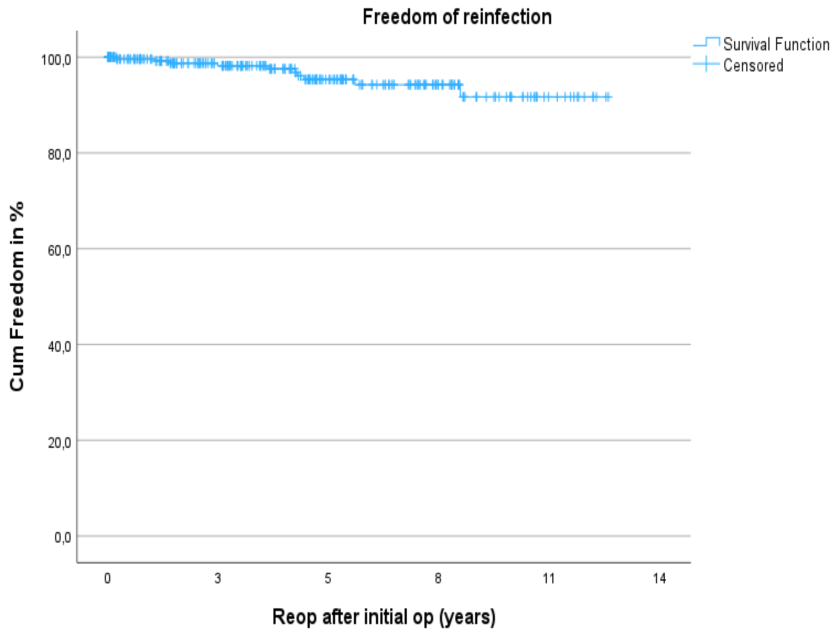

Figure 4. Freedom of reinfection

Risk factors for 30-day mortality after surgery

For statistic correct application, the model was fitting according to the Hosmer and Lemeshow test. The contingency table showed that all paired values are approximately equal, confirming a good model. Of the 295 cases in the study population, 282 were analyzed in the preoperative model and 280 in the second model using SPSS. Only significant values ($p < 0.05$) in the COX regression are valued. Details are shown in Table 8.

In the model of analyzing preoperative factors, a moderate creatinine clearance with 50-85 ml/min was displayed with an increase of three times in mortality risk ($p = 0.034$). Furthermore, in the COX regression of creatinine clearance preoperative a severe impairment < 50 ml/min is augmenting the risk by seven times ($p < 0.001$).

Another factor included in the EuroSCORE analysis is insulin-dependent diabetes, with a four-fold rise in mortality risk ($p = 0.023$).

A preoperative ICU stay was significant in the binary logistic regression ($p = 0.02$), but could not be established with the COX regression ($p = 0.08$).

Regarding the source of infection, a fungal infection plays a role raising the mortality risk about fivefold (p = 0.041). Multiple valve replacement displays first as a significant factor in the binary logistic regression (p = 0.007), but couldn't be shown in the univariant analysis (p = 0.948).

Following the second round of analysis, the postoperative factors, an ECMO with over 30 times increase in mortality and renal replacement therapy postoperatively with nine-fold increase are risk factors for mortality (ECMO p < 0.001, RRT p < 0.001).

Looking at the neurological complications, a postoperative stroke affected the 30-day mortality by four times higher (p = 0.023). In the COX regression, univariant analysis both, stroke and peripheral neuropathy escalating the mortality risk to nine times its baseline (p = 0.037), as well as other neurological complications by five times (p = 0.004) and multiple complications by ten times (p = 0.002).

To "other" neurological complications, in the study population a post-hypoxic encephalopathy, meningitis, epilepsy, and some further diseases; due to low numbers of patients with each of these complications, they were grouped into one category (4 – other), for easier statistic evaluation.

Finally, a postoperative tracheostomy significantly increased the mortality ninefold 30 days after the operation (p < 0.01).

Table 8. Significant covariates of 30-Days Mortality

Factor	Odds Ratio (OR) in binary logistic Hazard ratio (HR) in COX	95% CI	p value
Creatinine clearance			
Moderate - Binary	41.889	3.331-526.80	0.004
Moderate – COX	3.137	1.090-9.031	0.034
Severe - COX	7.718	2.852-20.888	0.000
Diabetes on Insulin			
Binary	29.163	2.366-359.505	0.008
COX	4.086	1.219-13.704	0.023
Fungal infection			
Binary	471.078	3.080-72052.514	0.016
COX	4.528	1.064-19.271	0.041
ECMO			
Binary	30.553	2.170-430.068	0.011
COX	34.955	14.198-86.058	0.000
RRT			
Binary	5.295	1.721-16.287	0.004

COX	9.407	4.113-21.515	0.000
Neurological complications			
Stroke Binary	6.185	1.501-25.488	0.012
Stroke COX	3.655	1.192-11.210	0.023
Stroke and peripheral neuropathy COX	8.747	1.143-66.915	0.037
"Other" COX	5.294	1.725-16.243	0.004
"Multiple" COX	10.275	2.316-45.582	0.002
Tracheostomy			
Binary	22.982	3.634-145.337	0.001
COX	8.953	3.825-20.959	0.000

Risk factors for 1-year mortality after discharge

The following stated factors exposed as significant ($p < 0.05$) with an associated increasing risk for one-year mortality. For the preoperative phase, the model revealed again an impaired creatinine clearance for moderate creatinine clearance ($p = 0.019$) and the necessity for dialysis ($p < 0.01$) as risk factors with increasing the mortality risk by about three-times and eight-times. Repetitive, insulin-dependent diabetes was in both models significant and amplifying the mortality risk by four times ($p = 0.007$). First confusing a systolic pulmonary artery pressure classified as severe with > 55 mmHg ($p = 0.033$, OR = 0.127), the weight of operation with three procedures ($p = 0.036$, OR = 0.124) would suggest a decrease in 1-year mortality rate. But in the univariant analysis of COX regression both those factors couldn't be confirmed as significant, and consequently as not either decreasing or increasing the chance of dying (COX Systolic PA pressure Severe $p = 0.398$; COX weight of operation – 3 procedures $p = 0.366$). Any condition requiring an ICU-monitoring preoperatively could not be confirmed in the univariant model ($p = 0.332$).

Similar to the model examining the risk factors for 30-day mortality, the source of the infection played a risk factor as well as some of the postoperative courses, and all were confirmed in the univariant study. A fungal infection showed an increase in mortality by five-times ($p = 0.001$). The same as already mentioned in the section above, ECMO and RRT postoperative, Tracheostomy, and stroke increased the mortality odds, all with $p < 0.01$. ECMO magnifying the risk by over 22-times, RRT by ten-times, tracheostomy as well with ten-times and stroke by seven-times. Additionally, in the univariant exploration of neurological complications, the category of "Other" besides stroke or peripheral neuropathy, with augmenting the risk by five times and "Multiple", with nine-times increase were proven to be significant ("Other" $p < 0.01$; "Multiple" $p < 0.01$).

Table 9. Significant covariates of 1-year Mortality after discharge

Factor	Odds Ratio (OR) in binary logistic Hazard ratio (HR) in COX	95% CI	p value
Creatinine clearance			
Moderate COX	2.642	1.176-5.935	0.019
Dialysis Binary	29.676	3.131-281.241	0.003
Dialysis COX	7.758	3.553-16.941	0.000
Diabetes on Insulin			
Binary	12.081	1.490-97.952	0.020
COX	3.596	1.425-9.073	0.007
Fungal infection			
Binary	281.657	4.869-16294.257	0.006
COX	5.272	1.892-14.692	0.001
ECMO			
Binary	19.229	1.084-340-992	0.044
COX	22.222	9.936-49.698	0.000
RRT			
Binary	6.154	41.993-19.004	0.002
COX	9.607	5.429-16.999	0.000
Neurological complications			
Stroke Binary	6.963	2.126-22.799	0.001
Stroke COX	6.691	3.366-13.300	0.000
"Other" COX	5.145	2.232-11.862	0.000
"Multiple" COX	9.029	2.728-29.881	0.000
Tracheostomy			
Binary	7.836	1.149-53.465	0.036
COX	9.953	5.195-19.068	0.000

Risk factors for the overall mortality after surgery till loss of follow-up

The same statistical pathway was done for the analysis of risk factors for overall mortality as mentioned before. Starting with a binary logistic regression model, several covariates were identified to have a significant value and then were checked again with the COX regression. First, a continuous variable – age – was significant, but couldn't be confirmed in the univariant analysis ($p = 0.07$). Second, creatinine clearance, a moderate renal impairment was displayed as significant ($p = 0.009$), but not in the second model ($p = 0.556$). Despite the moderate creatine clearance as non-significant in the COX regression, a severe impairment is linked to a four-fold rise in mortality risk ($p < 0.01$). Some other covariates were revealed as significant in the first multivariate investigation but could not be confirmed. To be more precise, poor mobility ($p = 0.199$), left ventricular ejection fraction of 31-50% ($p = 0.3$) as those factors.

In the case of LVEF, an ejection fraction of ≤ 20% was noteworthy ($p < 0.01$) with an elevated risk of 14 times.

Furthermore, pulmonary edema preoperative ($p < 0.001$) was confirmed a relevant variate.

The need for inotropic support preoperative was substantial with a four-fold increase in mortality risk ($p < 0.01$).

Closed with fungal infection, as it increased mortality risk by five-times ($p = 0.005$). No factor in the intra- and postoperative statistic for the overall mortality was revealed as noteworthy. An overview about the exact numbers is demonstrated in Table 10.

Table 10. Significant covariates of overall mortality

Factor	Odds Ratio (OR) in binary logistic Hazard ratio (HR) in COX	95% CI	p value
Creatinine clearance - Dialysis COX	4.291	2.107-8.741	0.000
LVEF ≤ 20% COX	14.465	3.410-61.368	0.000
Pulmonary oedema preop			
Binary	0.407	0.205-0.809	0.010
COX	2.092	1.401-3.123	0.000
Inotropic support preop			
Binary	0.025	0.001-0.631	0.025
COX	4.041	2.138-7.638	0.000
Fungal infection			
Binary	0.005	0.000-0.274	0.010
COX	5.414	2.174-13.485	0.000

Heterogeneity analysis

Since the gender factor was not significant in the Kaplan-Meier analysis with the log-rank test, the overall mortality to loss to follow-up (Figure 7) was close to each other with about 52% for men and 59% chance of survival for women, which emphasizes the results of the Cox regression analysis.

These similar values can be found during the 30-day and 1-year period as well (30 days: male 91% and female 93%; 1 year: male 83% and female 81%) (Figure 5-7).

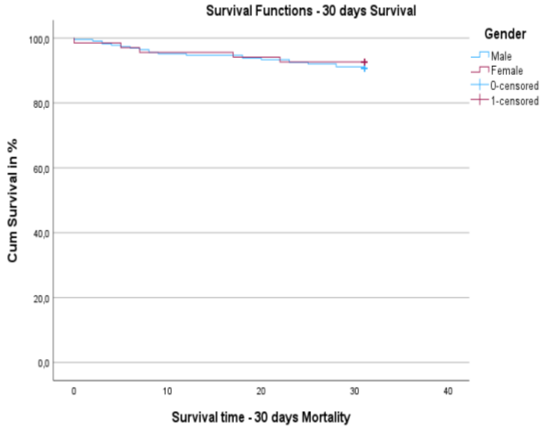

Figure 5. Survival 30-days by gender (log-rank test 0.637)

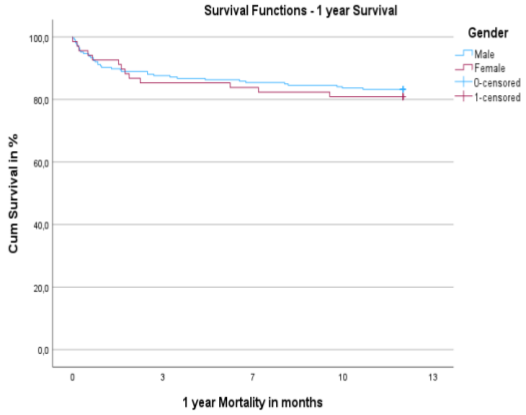

Figure 6. Survival 1-year by gender (log-rank test 0.673)

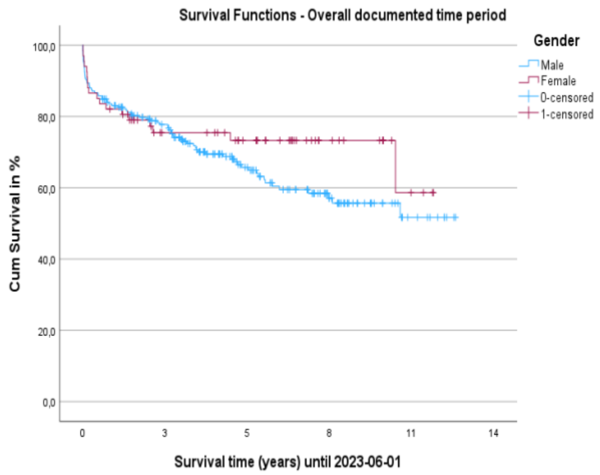

Figure 7. Survival till loss of follow-up by gender (log-rank test 0.237)

Focused research on the different age groups revealed no statistical significance. But visually with higher age groups the survival chance decreased throughout the different time spots evaluated. Except in the 61-70 age group, the survival rate was higher after 1 year and until loss to follow-up (51-60 years: 1-year 77.8% and till loss of follow-up 41%; 61-70 years: 1-year 87.3% and till loss of follow-up 64.5%; 71-80 years: 1-year 73% and till loss of follow-up 56.8%). (Figure 8-10).

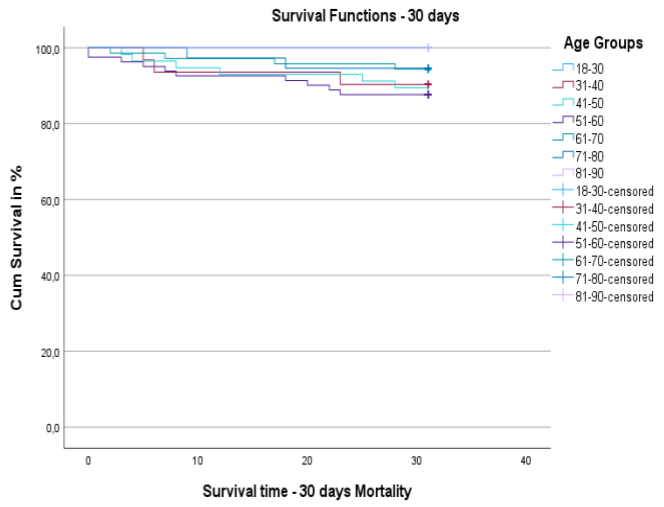

Figure 8. Survival 30-days by age groups (log-rank test 0.526)

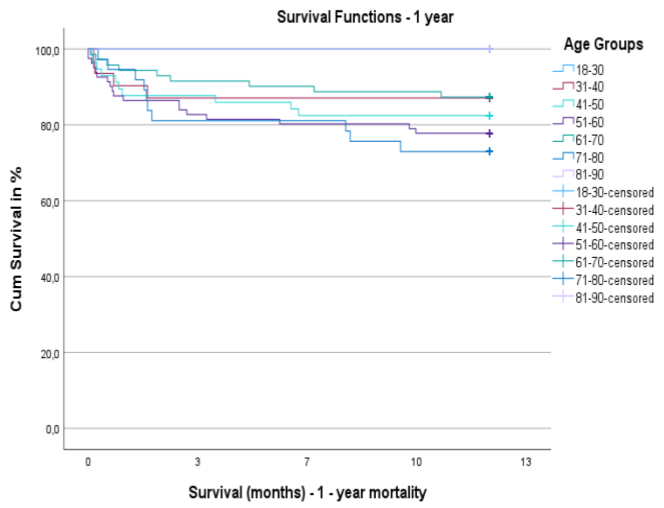

Figure 9. Survival 1-year by age groups (log-rank test 0.216)

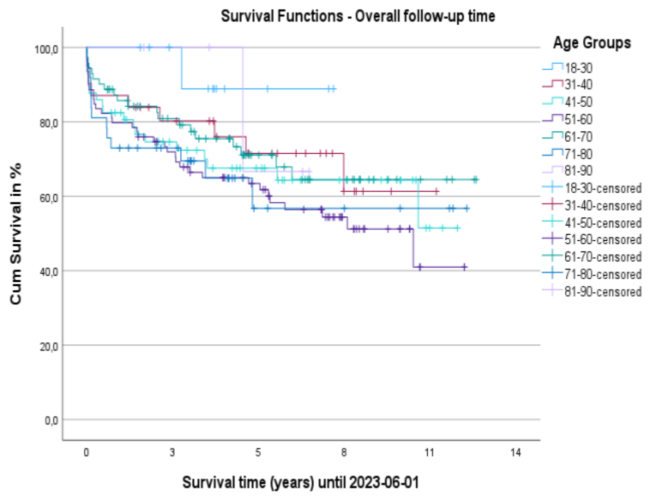

Figure 10. Survival till loss of follow-up by age groups (log-rank test 0.388)

Discussion

The incidence, with a median of about 25 cases/year of infective endocarditis requiring open-heart surgery in VU Santariškės maintained between the years of 2011-2022, without a significant trend to either increase or decrease. Without a significant decrease in absolute numbers, as visible in Figure 11.

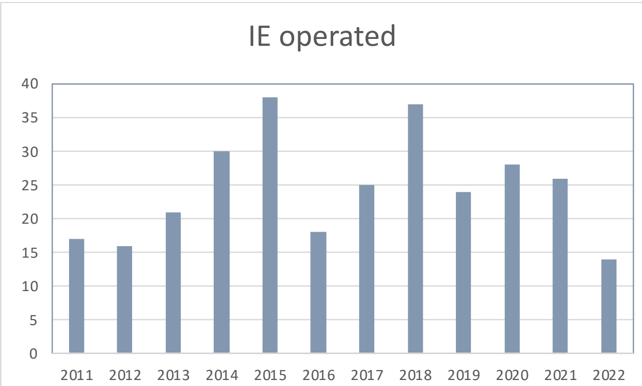

Figure 11. Incidence cases

Most of the patients were male (77%), but as the heterogeneity analysis has shown no significant difference in survival could be identified. The difference in prevalence between genders matches the literature research.(10, 11) The reasons for a higher prevalence of infective endocarditis in males are still unknown, but for example, Sevilla et al. described that the bacteria that causes IE may vary. Streptococcus viridans is more common in men, maybe because they are more likely to develop native valve endocarditis (12). Concerning the results of long-term survival, the above-mentioned literature supports the results of the conducted investigation. Although Weber et al. state that the female gender "was associated with more severe manifestations of IE and significantly higher 30-day and 1-year mortality" but clarifies that associated comorbidities are the reason, not the gender by itself (13).

In this study, the in-hospital mortality risk with a time frame of 30 days after the operation, was calculated at about 9%. Compared to other studies and countries and a general objective point of view, the mortality risks together with postoperative complications were comparable.
Regarding the long-term results, the one-year mortality risk of 17% and 10-year mortality risk of 35% underlined the relatively high risks of open-heart surgery due to infective endocarditis.

Evaluating the data concerning the mortality risk and survival rate in other countries, similar numbers can be identified in Table 11. It should be taken into account that direct comparisons are difficult due to different patient population and their characteristics.
Concerning the freedom of reinfection with about 95% at five years and about 92% freedom of reinfection till loss-of-follow the study showed favorable results.

Table 11. Overview of mortality risks in different countries

Country	30-days/In-hospital Mortality risk in %	1-year Mortality risk in %	5-year Mortality risk in %	10-year Mortality in %
Lithuania (this study)	9	17	31	40
Dutch (14)	10.9	15	26	29
Swiss (15)			26	
Iceland (16)	11		59	59
Spain (17)		14	32	
Portugal (18)		7	28 (6-years)	28 (9-years)
China (19)	4.1			
Canada (20)				56 (15-years)
Italy (21)	11.6			
Latvia (22)	11.16	21.7	28.7 (3-years)	
Morocco (23)	17.8		3	9
Sweden (24)	8.7	14	25	
England (25)	0	8	17 (3-years)	
Chile (26)			24.4	51.4
Germany (27)	8.5			42.8 (12-years)

Concerning the mortality risk the European Journal of Cardio-Thoracic Surgery just published in October 2023 that the EuroScore II is deemed since they do not take age-related risk factors into sufficient account. As a result, the multidisciplinary working group suggests that before undergoing TAVI or heart surgery, a thorough assessment of frailty be conducted. Measures including walking speed, psoas muscle measurement, the Short Physical Performance Battery, and preoperative mental and nutritional health are all included in this (28). They are underlining the need for the investigation of mortality risk factors.
The Staphylococcus epidermidis with multi-resistant antibiogram was the most commonly identified causative agent in this analysis (14.5%). Followed by Staphylococcus aureus with 11.6%. Matching the most common agents of the literature (29).

Still, within the topic of the source of the infection and causative agent, a fungal origin of the disease was identified as a significant predictor for early in-hospital mortality, as well as for 1-year and 10-year mortality risk, as described above. 2% of the 295 cases analyzed hereby were due to a fungal origin. Hoenigl at al wrote that “[f] ungal endocarditis accounts for 1% to 3% of all infective endocarditis cases, [and] is associated with high morbidity and mortality (> 70%)”, underlying these results. The treatment of fungal infective endocarditis usually requires surgery and extensive medical treatment together with a multimodal approach. (30)
As Michele Di Mauro et al. wrote in their publication about the predictors for early mortality in infective endocarditis, they identified Staphylococcus aureus and fungal species, together with a creatinine value above 2mg/dl as predictors, similar to this analysis (31).

Analogous, the intravenous abuse of drugs necessitates surgery (20).
In a similar report from Iceland, 13.9% (16) of the study population were identified as intravenous drug abusers requiring heart surgery due to infective endocarditis. In Boston, 17.9% (32), and in Prague, Czech Republic even 45.6% (33) could be stated. So, the number of 3% in the years in-between 2011 and 2022 in Vilnius, seemed relatively lower. The publication by the European Monitoring Centre for Drugs and Drug Addiction showed that the prevalence of people who inject drugs was lower in Lithuania than in Czech for example (34).
The dental offspring for infective endocarditis is highlighted frequently in the literature (35). In the above-investigated study group, in 17% of the cases, a dental issue was identified, emphasizing the relationship between dents, the oral environment to the heart. As well as the subsequently updated guidelines of the European Society of Cardiology from 2023 (36), underlining the preventive measures in contrast to the guidelines of 2009 (37), in which the antibiotic prophylaxis was not as clearly as nowadays recommended and already implemented in the modern clinical practice.

Regarding the descriptive exploration, the most common different categories within examining the characteristics of infective endocarditis requiring open-heart surgery were the native valve infection (88%), left-sided (55%) including the aortic valve (45%), with a valve replacement surgery (60%), using a biological prosthesis (60%). Similar numbers are observable in other studies (14–16).

Noticeable was the overlapping significance of the level of creatinine clearance – Moderate and dialysis – before the surgery, highlighting the importance of renal function and its effect on the

need for postoperative complications requiring dialysis and the connection of the cardiovascular system to the renal circuit. This variable could be identified for increasing the mortality risk in all three timeframes – 30 days, one year after a hospital stay, and mortality risk till loss-of-follow-up with remarkable numbers of about 45% chance of survival in case of the need of dialysis preoperative, and in case of the overall survival time a chance of about 10%. These numbers correlated with the presence of insulin-dependent diabetes with a survival rate of 65% in 30-days mortality versus about 90% if diabetes wasn't diagnosed, similar to one-year survival with 55% in case of diabetes, and over 80% without an insulin-dependent diabetes mellitus.
Kamalakannan et al. already researched the outcomes of infective endocarditis in patients requiring hemodialysis, publishing the result of a worse outcome for this group of patients (38). Probably, interfering and reflecting the 17% in this study of patients requiring renal replacement therapy after the surgery. And subsequently displaying the significant variable for 30-day mortality and 1-year mortality after the initial period for increasing the risk of dying. As the published article by Guiomar et al. referred as well, the need for renal replacement therapy is one of the predictors for early in-hospital mortality (39).

Another shared significant variable was preoperative insulin-dependent diabetes for 30 days and 1 year after hospital stay. As Yoshioka et al exposed: "The short- and mid-term outcome after valve surgery for active IE in patients with DM is worse because of the greater prevalence of infection-related death and IE recurrence" (40).
The renal creatinine clearance function is interfering with diabetes mellitus as the glomerular filtration rate (GFR) in diabetic individuals may be overestimated by creatinine clearance, especially in those with severe renal failure. This may be caused by things like inadequate urine collection, reduced serum creatinine linked to a higher risk of type 2 diabetes, and problems with patients' intact renal function that limit the applicability of estimated GFR equations (41). Moreover, the kidneys are important for the metabolism and clearance of circulating insulin. As chronic kidney disease advances, insulin clearance declines and a dosage reduction is required to prevent hypoglycemia (42). On the other hand, those two covariates can be a significant risk factor for any operation (43, 44).
The last part of interest examined in the different analyses was the postoperative period. The variables ECMO, RRT, Tracheostomy, and some subgroups of neurological complications increased 30-day mortality risk as well as 1-year after hospital stay. In general, 14% of the patients had neurological complications. Several publications in the years between 2008-2011

confirmed the associated worse outcome of patients with infective endocarditis and neurologic or cerebrovascular complications. Furthermore, the guidelines of the European Society of Cardiology recommend the preoperative use of a CT and/or MRI (36). And the publication of Ruttmann et al. from 2020 propagated the statement, that an IE-related stroke is not a contraindication for early surgery on infective endocarditis, even neurologists recommend (45).

Limitations

Reflecting on the study, some limitations need to be addressed. First, the study population size was in absolute numbers too small for the general conclusion. Even if, the absolute number and the investigated time frame were relatively in a normal size range, compared to other studies, the results should be analyzed with a bigger population. Together with the restriction on the Santaros Klinikos in Vilnius, Lithuania, these boundaries could have been lifted by including Kaunas Hospital or other big hospitals in Lithuania as well.

Furthermore, there will be an intrinsic selection bias as well as further bias with the assortment of only open-heart surgery cases as infective endocarditis and open-heart surgery are related to multiple risk factors and pathophysiological processes. Moreover, the reason for death in some patients couldn’t be identified, which may influence further conclusion about endocarditis-related causes.

Conclusion

The hypothesis of decreasing cases requiring open-heart surgery for infective endocarditis is not supported by trends over the past decade. Mortality rates post-surgery show acceptable early postoperative outcomes, with 1-year survival at 83% and 5-year at 69%, aligning with global statistics. The study's aim, accepting and explaining its hypothesis, finds a tolerable 5-year reinfection rate of 4.7% and identifies significant mortality risk factors, notably impaired renal function and preoperative variables like reduced left-ventricular ejection fraction. Specific risks include pulmonary edema, inotropic support preoperative, and fungal infections. Preoperative factors outweigh postoperative ones in mortality risk, emphasizing the need for enhanced preoperative monitoring, particularly renal function. Early mortality concerns necessitate close neurological surveillance, aligning with literature recommendations. The study prompts further investigation into strategies for improving preoperative care, hospital stays, and comprehensive neurological monitoring alongside surgical outcomes.

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Appendix

30-days mortality risk factors

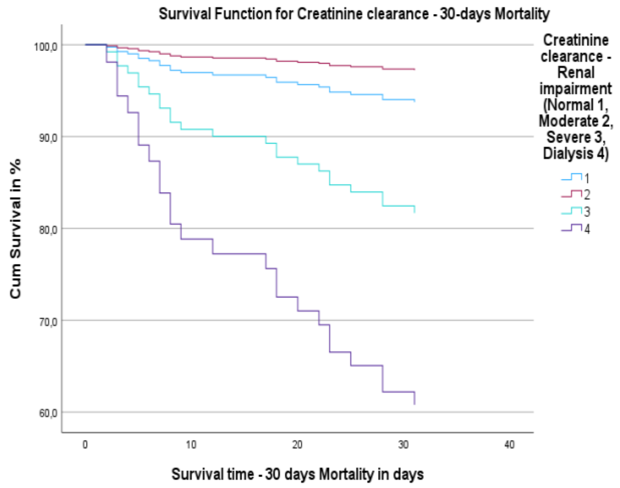

Figure 12. Creatinine clearance - 30-day mortality

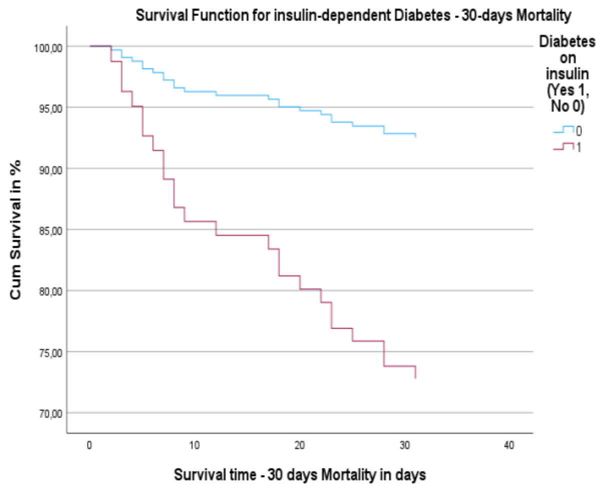

Figure 13. Diabetes on insulin - 30-day mortality

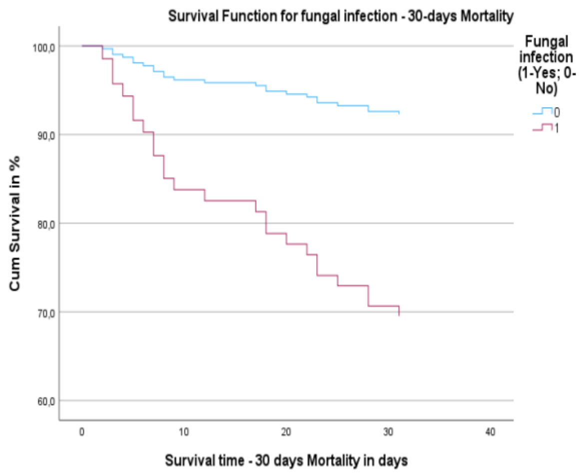

Figure 14. Fungal infection - 30-day mortality

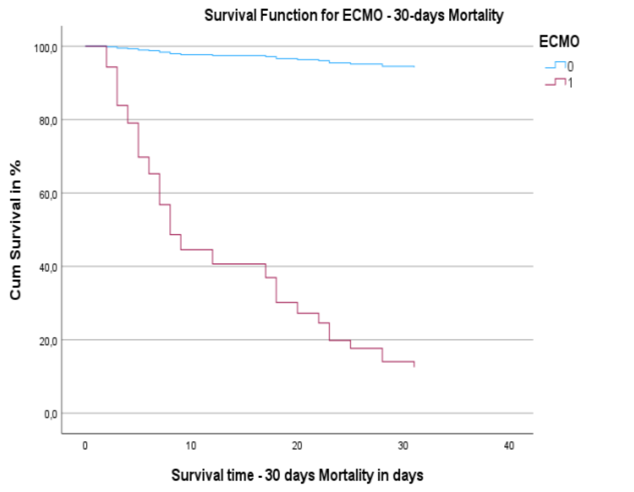

Figure 15. ECMO- 30-day mortality

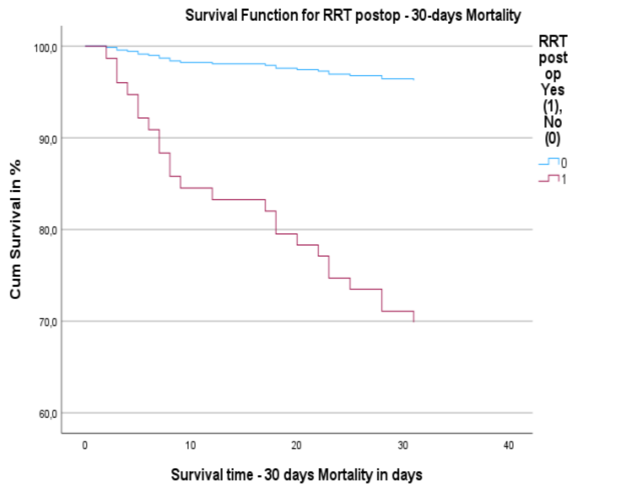

Figure 16. Renal replacement therapy postoperative - 30-day mortality

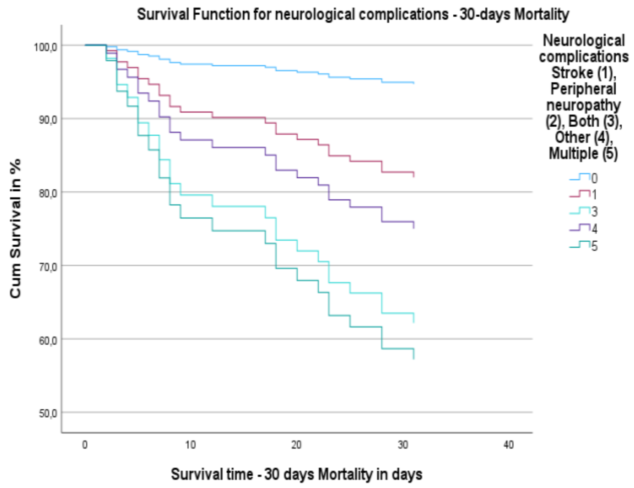

Figure 17. Neurological complications postoperative - 30-day mortality

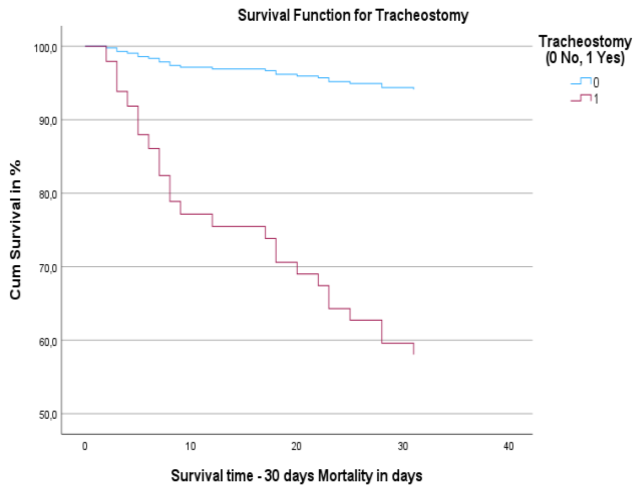

Figure 18. Tracheostomy - 30-day mortality

1-year mortality risk factors

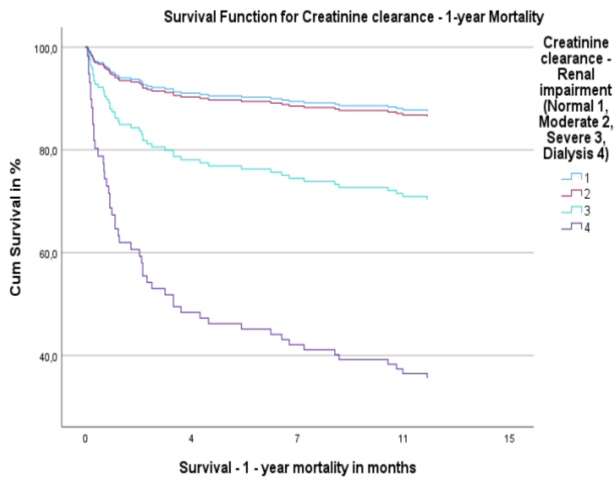

Figure 19. Creatinine clearance – 1-year mortality

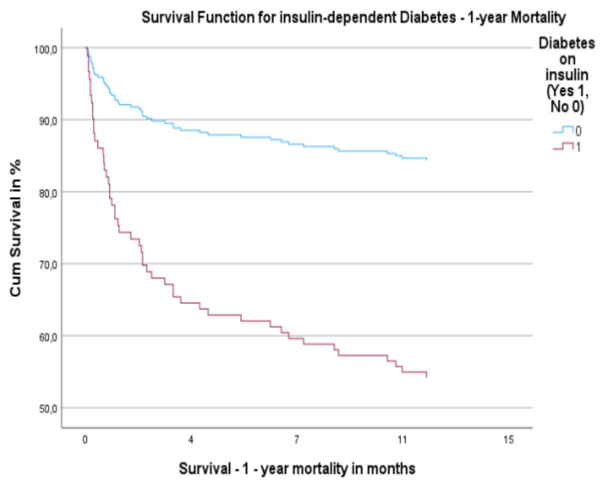

Figure 20. Diabetes on insulin – 1-year mortality

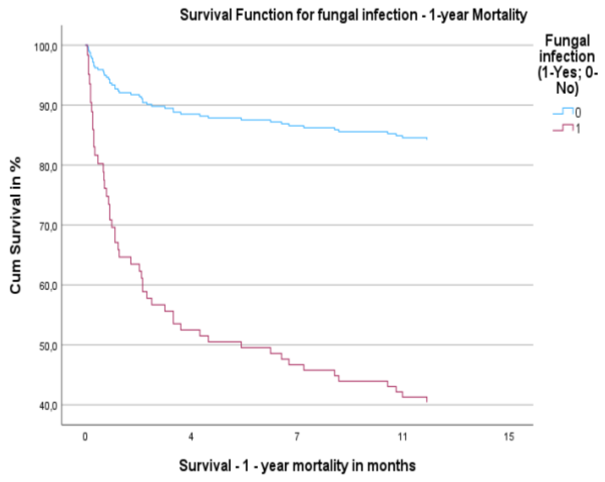

Figure 21. Fungal infection – 1-year mortality

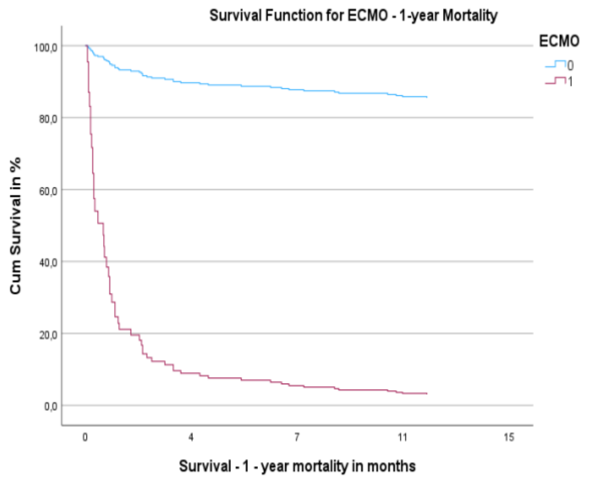

Figure 22. ECMO – 1-year mortality

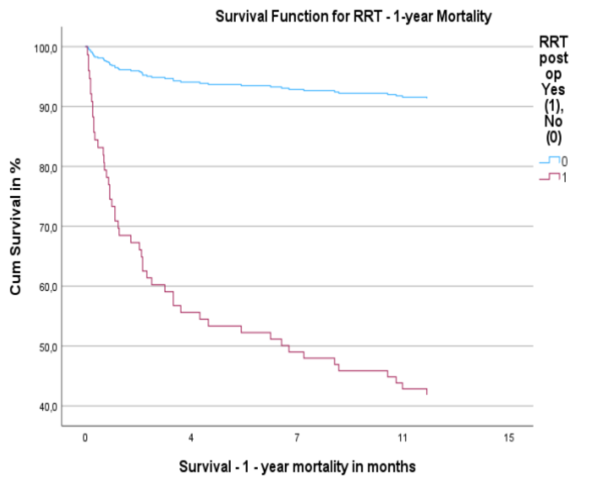

Figure 23. Renal replacement therapy postoperative – 1-year mortality

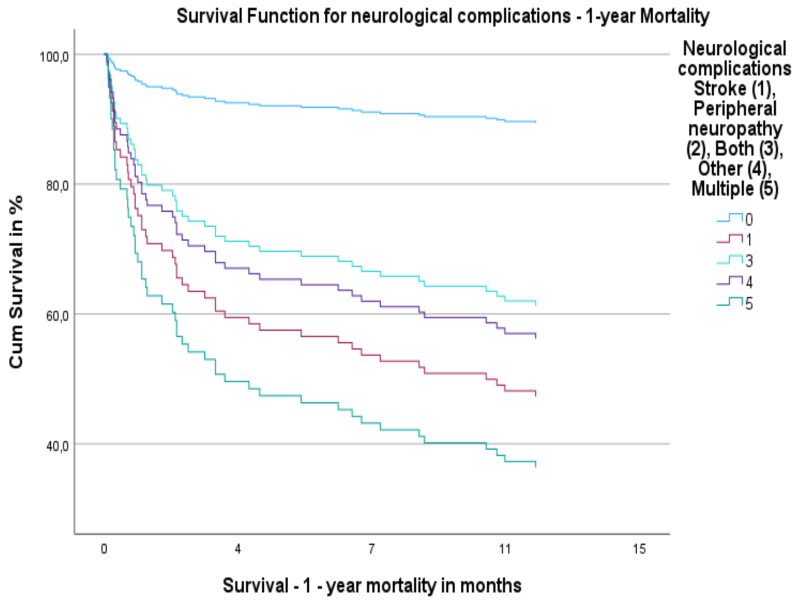

Figure 24. Neurological complications postoperative – 1-year mortality

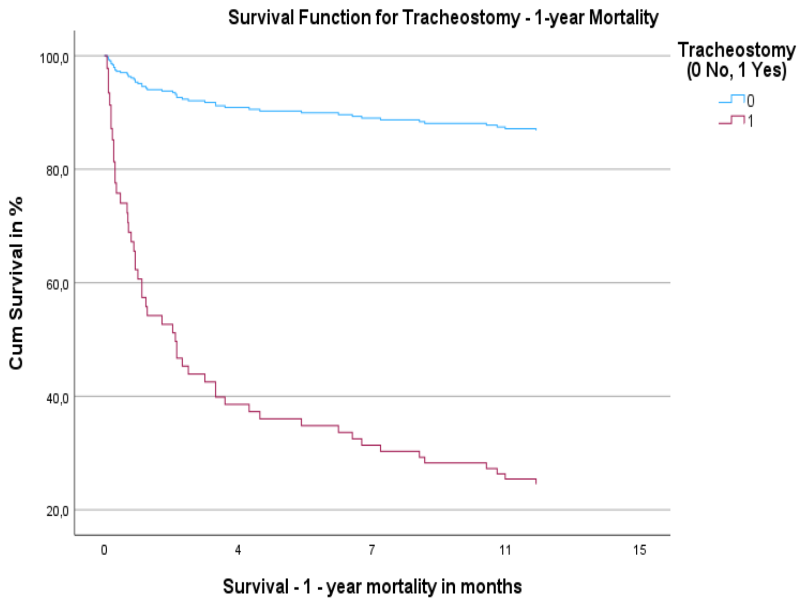

Figure 25. Tracheostomy – 1-year mortality

Till loss-of-follow-up risk factors

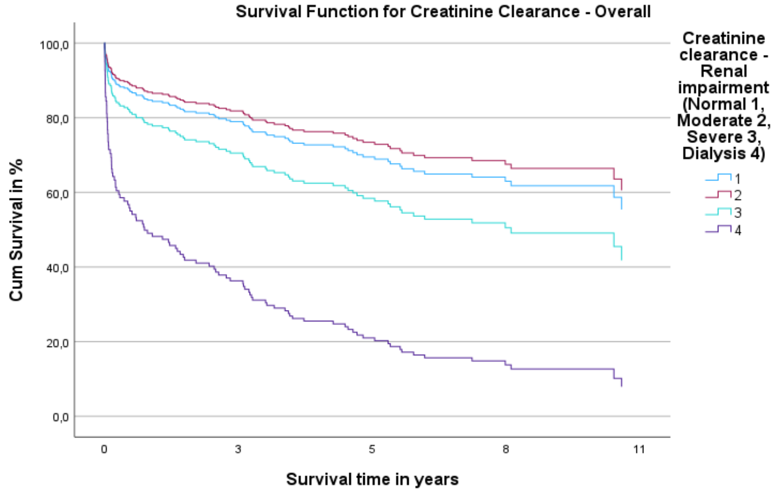

Figure 26. Creatinine clearance preoperative – till loss of follow-up

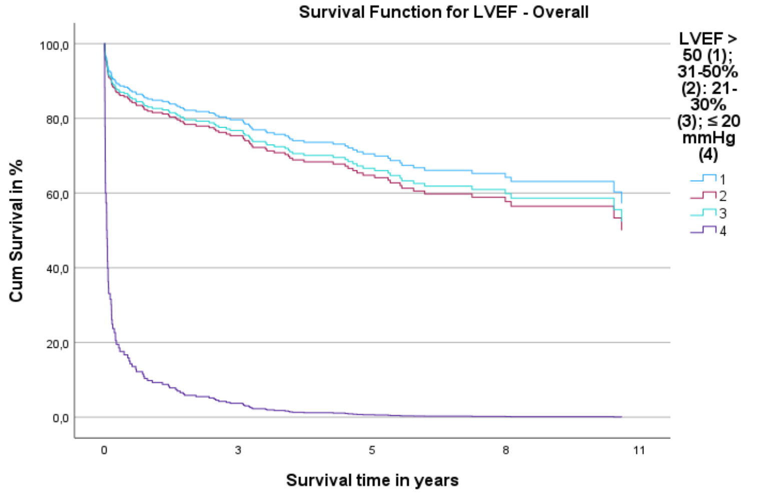

Figure 27. LVEF preoperative – till loss of follow-up

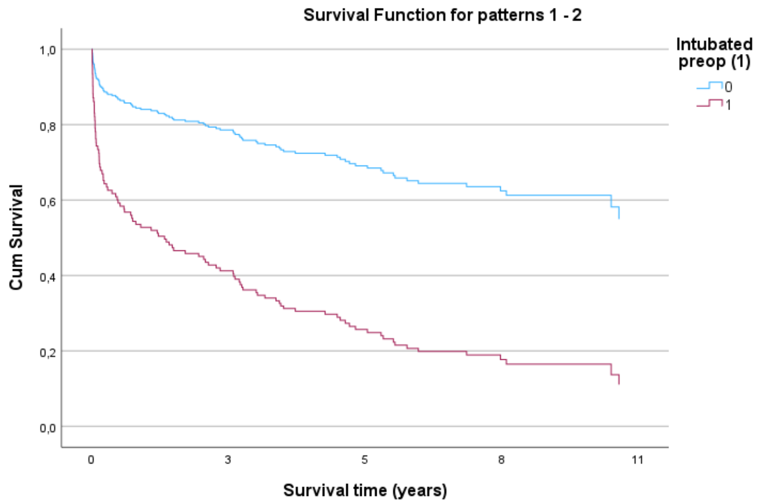

Figure 28. Intubated preoperative – till loss of follow-up

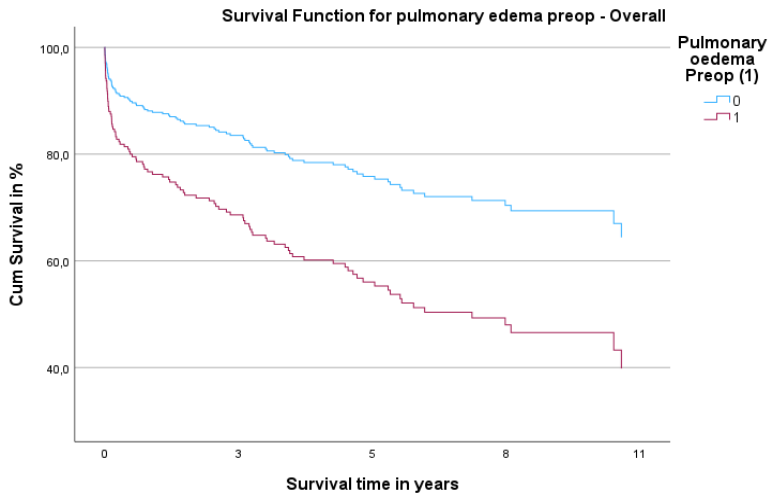

Figure 29. Pulmonary edema preoperative – till loss of follow-up

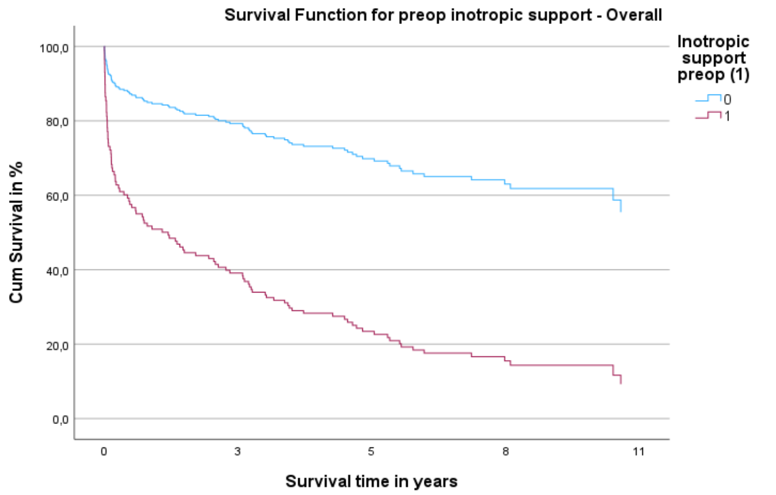

Figure 30. Inotropic support preoperative – till loss of follow-up

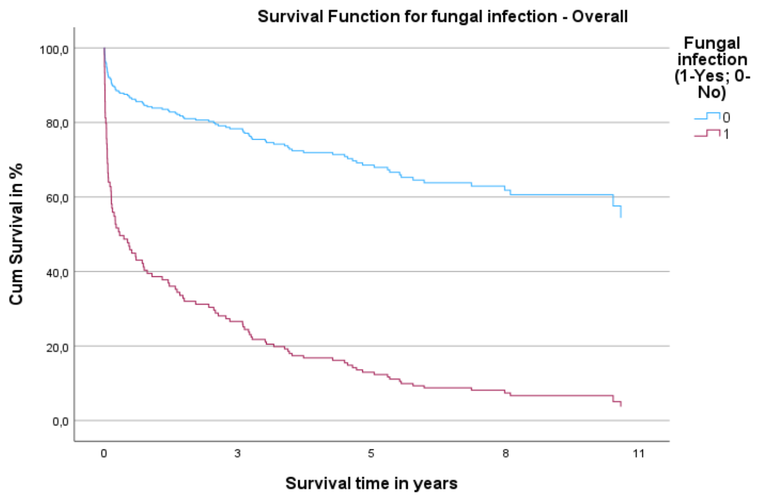

Figure 31. Fungal infection – till loss of follow-up