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Research Article

The Influence of Preoperative Neurological Complications on Outcomes after Surgery for Infective Endocarditis

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Background. Infective endocarditis (IE) is considered a life-threatening cardiac infection with a predilection to involve heart valves. One of the most feared complications of IE is the development of new-onset neurological complications (NCs). The aim of this study is to compare the short- and long-term outcomes of surgery in patients with IE presenting with vs. without NCs. *Methods*. We retrospectively reviewed patient records which were regularly collected in our institutional database. Between January 2002 and August 2020, 438 consecutive patients who underwent open cardiac surgery in our university hospital due to IE were included in the retrospective study. *Results*. Of the total cohort, 89 patients (20.3%) had preoperative NCs. Patients in the NC group were more likely to be female (33.7% vs. 23.5%; $P = 0.049$), had more acute kindly injury at presentation (22.5% vs. 10.0%; $P = 0.002$), were more likely to be admitted to ICU (36.0% vs. 18.3%; $P < 0.001$), and had significantly more vegetations (84.3% vs. 69.8%; $P = 0.006$) and overall higher preoperative embolization (92.1% vs. 11.7%; $P < 0.001$). *Staphylococcus aureus* as causative organism of IE was significantly higher in the NC group (35.2% vs. 16.1%; $P < 0.001$). Patients in the NC group had significantly higher affection of the mitral valve. There was no difference in postoperative outcomes between the two groups. The long-term survival was also similar in both groups. Preoperative atrial fibrillation (adjusted odds ratio (aOR): 2.03; 95% CI [1.04–3.93]; $P = 0.037$) and *Staphylococcus aureus* IE (aOR: 2.60; 95% CI [1.4–4.8]; $P = 0.002$) were independent risk factors of developing NCs, while previous endocarditis was a protective factor (aOR: 0.33; 95% CI [0.11–0.99]; $P = 0.048$). *Conclusion*. Our study emphasizes the shared risk factors between mortality and developing NCs. NCs are critical in IE's clinical presentation, but they do not independently predict short- or long-term survival following surgery for IE.

1. Introduction

Infective endocarditis (IE) is considered a life-threatening cardiac infection with a predilection to involve heart valves [1]. In 2019, the global incidence of IE accounted for approximately 1.1 million cases with an annual mortality exceeding 66,300 deaths. This burden showed a steep increase in the past three decades. Results from the global burden of disease study showed an annual percentage increase of 1.2% for IE incidence and 0.7% for its associated mortality [2]. Interestingly, an annual percentage increase of 4.1% was reported for Europe during the last two decades [3].

Cardiac surgery is indicated in around 40–60% of cases [4, 5]. In patients where cardiac surgery is indicated but not performed, the thirty-day and one-year mortality rates were as high as 60% and 75%, respectively [4]. Surgery is indicated in cases of IE for conditions like heart failure, uncontrolled infection, large vegetation, and as a preventive measure against embolic complications [6, 7]. Several factors can prohibit or delay indicated surgery in patients with IE including advanced age, female gender [8–10], affection of the mitral valve, high surgical risk, and neurological complications (NCs). However, the current guidelines recommend early surgery during initial admission and before antibiotic completion for indicated patients [6, 7]. Several reports

concluded that IE patients presenting with neurological complications (NCs) would have significantly higher in-hospital and long-term mortality [11–15]. In this article, we evaluate a large cohort of IE patients who underwent surgical repair in our tertiary hospital. The aim of this study is to compare the short- and long-term outcomes in patients who underwent cardiac surgery for IE based on the presence of preoperative NCs.

2. Methods

2.1. Patient Population and Study Design. We retrospectively reviewed patient records which were regularly collected in our institutional database. Between January 2002 and August 2020, 438 consecutive patients who underwent open cardiac surgery in our university hospital due to IE were included in the retrospective study. Patients presented with neurological complications were 89, while 349 patients underwent surgery with no evidence of NCs. NCs were defined as preoperative stroke, transient ischemic attack, or the presence of silent cerebral embolization.

We review and compare baseline characteristics and outcomes of patients who presented with NCs in contrast to those who had no NCs. The 30-day mortality rate was the primary endpoint outcome. Long-term survival, intraoperative details, and postoperative clinical outcomes such as redo surgery, blood loss, ventilation time, acute renal failure, and NCs were secondary endpoints. Patients with active IE required ongoing antibiotic therapy.

2.2. In-Hospital Patient Management. All patients were discussed among a multidisciplinary team. Diagnosis of IE was confirmed using the modified Duke criteria. Blood cultures were obtained from all patients in order to aid diagnosis and identify organisms based on species and sensitivities. All patients had a transthoracic or transesophageal echocardiography to determine the location and size of vegetation, the presence of valve destruction or abscess, and the left ventricular ejection fraction. Antibiotic treatment began as soon as IE was suspected. If the patient's condition was stable, coronary angiography and additional computed tomography (CT) scans were performed, including brain CT, thoracic CT, and pan CT scans, especially in high-risk patients or those who required redo surgery. Then, patients were referred to our surgical department and scheduled for surgery. If intraoperative evidence of endocarditis was identified, an intravenous antibiotic regimen was continued for 4–6 weeks postoperatively. All patients with NCs were evaluated by a consultant neurologist, as well as a CT scan of the brain to assess bleeding risks and prognosis. Perioperative risk factors, intraoperative details, and predictors of mortality were all analyzed and reviewed.

2.3. Surgical Technique. The surgical technique used in our university hospital has been previously described [16, 17].

All patients underwent curative surgery performed by senior faculty surgeons and experienced assistants. Direct cannulation of the ascending aorta was used to establish cardiopulmonary bypass (CPB). Venous drainage was performed either by direct cannulation of the right atrium in situations of aortic valve endocarditis or with double cannulation of the superior and inferior vena cava followed by cross-clamping of the ascending aorta in cases of mitral or tricuspid valve infection. The choice of biological, mechanical prosthesis, or valve repair was made on an individual basis considering patients' age, preferences, and their compliance with long-term anticoagulation, as well as intraoperative details and the degree of macroscopic valve damage. The diseased areas were extensively debrided and thoroughly irrigated. In situations of significant damage or the presence of abscesses, the defective regions were restored via isolated valve replacement or aortic root reconstruction with or without autologous or bovine pericardium. The standard technique for cardiac de-airing was continuous CO_2 insufflation. Transesophageal echo was used for postoperative evaluation and to assess for any residual air during rewarming.

2.4. Statistical Analysis. We employed descriptive statistics to summarize patient baseline characteristics, operative details, and postoperative outcomes throughout the study. The normality of continuous variables was assessed by the Kolmogorov–Smirnov test. We used median and interquartile ranges (IQRs) to depict normally and nonnormally distributed continuous data. Categorical variables are shown as frequency distributions (n) and percentages (%). We used Student's t-test to test for group difference when the data were normally distributed. For nonnormally distributed data, we used the Mann–Whitney U test. For categorical variables, the chi-square and Fisher's exact tests were used to provide a univariate comparison between groups. All tests were two-tailed, and P values less than 0.05 were deemed statistically significant. IBM SPSS Statistics for Windows (version 29.0) was used to examine the data. Variables associated with 30-day mortality ($P \leq 0.1$) were selected according to clinical relevance and included in multivariable logistic regression analysis to assess for their adjusted impact on developing NCs. We used adjusted odds ratio (OR) as the effect measure. In multivariable logistic regression, we controlled for age, female gender, BMI >30, arterial hypertension, atrial fibrillation, acute renal insufficiency, combined valve surgery, previous endocarditis, diagnosis on day of surgery, *Staphylococcus aureus*, mitral valve affection, and vegetation. Survival of the NC and non-NC groups was estimated on right censored data by Kaplan–Meier curves and was compared for differences by the log-rank test.

3. Results

3.1. Preoperative Data and Baseline Characteristics. A total of 438 patients underwent surgery for IE in our institution. Of these patients, 112 were females (25.6%), who were observed more frequently in the NC group (33.7 vs. 23.5%; $P = 0.049$). Patients in the NC group had a higher incidence of AKI at presentation (22.5% vs. 10.0%; $P = 0.002$), a higher likelihood of being indicated for acute dialysis (12.4% vs. 4.6%; $P = 0.006$), suffered more often from acute myocardial

infarction preoperatively (6.8% vs. 2.3%; $P = 0.042$), and received immunosuppressive therapy more frequently (6.7% vs. 2.0%; $P = 0.030$).

In contrast, patients in the non-NC group had a higher rate of previous cardiac surgery (45.0% vs. 27.0%; $P = 0.002$) and were more likely to have a history of combined valve surgery (22.8% vs. 9.3%; $P = 0.005$). They also had a higher incidence of previous endocarditis episodes (16.6% vs. 5.6%; $P = 0.008$) and more often arterial hypertension (61.0% vs. 49.4%; $P = 0.047$).

Patients in the NC group were more likely to be admitted to ICU at presentation (36.0% vs. 18.3%; $P < 0.001$) and had a higher rate of preoperative embolization (92.1% vs. 11.7%; $P < 0.001$). *Staphylococcus aureus* was the causative organism of IE more frequently in the NC group (35.2% vs. 16.1%; $P < 0.001$).

Regarding valvular involvement, patients in the NC group were more likely to have isolated mitral valve involvement (33.7% vs. 19.8%; $P = 0.005$) or combined mitral valve involvement (43.8% vs. 28.1%; $P = 0.004$) at admission, while isolated and combined prosthetic valve involvement occurred more frequently in the non-NC group (41.3% vs. 24.7%; $P = 0.004$). Furthermore, patients in the NC group had a higher incidence of vegetations (84.3% vs. 69.8%; $P = 0.006$) and tended to have larger vegetation sizes (15 [IQR: 10; 20] vs. 13 [IQR: 8; 19] mm; $P = 0.12$). Tables 1(a)–1(d) summarize preoperative data and baseline characteristics of patients.

3.2. Operative Details. Regarding intraoperative data, patients without NCs had a longer duration of surgery compared to those with NCs (median: 280 [IQR: 230–360] min vs. 254 [IQR: 208–329] min; $P = 0.022$) and were more likely to undergo aortic valve surgery (75.6% vs. 64.0%; $P = 0.028$). On the other hand, patients with NCs were more likely to undergo mitral valve surgery (50.6% vs. 35.6%; $P = 0.01$) (Table 2).

3.3. Postoperative Outcomes. In the postoperative period, intensive care unit stay (3 [IQR: 1–7] vs. 3 [IQR: 1–7] days; $P = 0.33$) was similar between both groups, but in-hospital length of stay was longer in the non-NC group (10 [7; 16] vs. 8 [5; 16] days; $P = 0.034$). Patients with no NCs experienced more new-onset neurological deficit (7.1% vs. 3.6%; $P = 0.24$), however, with no significant difference. In-hospital mortality (19.1% vs. 15.9%; $P = 0.46$) was similar between groups, but 30-day mortality (23.6% vs. 15.8%; $P = 0.081$) was slightly higher in the NC group; however, the result did not reach statistical significance. Postoperative outcomes are summarized in Table 3.

3.4. Follow-Up. Follow-up data were available for 326 patients in the non-NC group (93.4%) and for 83 patients in the NC group (93.3%). For patients who survived thirty days following the indexed operation, follow-up data were available for 273 patients with no NCs (92.9%) and for 63 patients in the NC group (92.6%). Survival probabilities were similar between both groups at one (90% vs. 93%), five (73% vs. 78%), and ten (56% vs. 62%) years of follow-up in the 30-day survivor cohort. Figures 1 and 2 illustrate the Kaplan–Meier curves for the total cohort and for patients who survived 30 days following the indexed procedure.

3.5. Risk Analysis for NCs. A multivariate logistic regression analysis for NCs in the overall cohort showed that patients with preoperative atrial fibrillation (adjusted odds ratio (aOR): 2.03; 95% CI [1.04–3.93]; $P = 0.037$) and *Staphylococcus aureus* IE (aOR: 2.60; 95% CI [1.4–4.8]; $P = 0.002$) were independent risk factors for developing NCs. Furthermore, patients who have experienced previous IE attacks (aOR: 0.33; 95% CI [0.11–0.99]; $P = 0.048$) and those who had previous combined valve surgery (aOR: 0.38; 95% CI [0.15–0.99]; $P = 0.047$) were less likely to develop NCs (Table 4).

4. Discussion

Infective endocarditis remains a serious and potentially life-threatening condition. One of the most feared complications of IE is the development of new-onset NCs, with embolic events being the most likely cause. In our study, we aimed to evaluate the impact of NCs on clinical outcomes in patients who underwent surgery for IE. Our results showed that approximately one-fifth of the patients who underwent surgery for IE at our institution had NCs. Patients with NCs were more often female, had a higher incidence of AKI, required more acute dialysis, and were more likely to be admitted to ICU at presentation. Furthermore, NCs were associated with multiple organ embolization as well as *Staphylococcus aureus* as IE causative organism and more often presented with affection of the mitral valve. Consequently, mitral valve surgery was performed more often in the NC group. Patients with no NCs were more likely to have undergone previous cardiac surgery, received combined valve surgery, experienced previous endocarditis episodes, and presented more frequently with prosthetic valve endocarditis. However, there was no significant difference in postoperative length of ICU; moreover, hospital stay was shorter in the non-NC group. In-hospital mortality rate was similar, but 30-day mortality was slightly higher in the NC group.

In a majority of studies, the incidence of NCs in patients with IE who are referred to surgery is reported to range from 20% to 30% [12, 18–21], with some studies reporting rates as high as 63% [14]. Additionally, ischemic events have been identified as the most common presenting complication [18–22]. Similarly, 20.3% of our patients have experienced preoperative NCs. Multiple studies [12, 13, 21–23] have concluded that developing preoperative NCs in patients with IE was consistently associated with higher mortality rates. In our study, we focus on NCs in patients who were indicated and underwent surgery for IE. In this subgroup of patients, we did not observe a significant difference in postoperative mortality. Interestingly, studies have also reported that mitral valve affection, large vegetations, and infection with

Table 1: (a) Demographic characteristics of the study population. (b) Clinical presentation data. (c) Specific endocarditis data. (d) Preoperative laboratory parameters.

(a)

	All patients ($n = 438$)	No neurological complications preoperative ($n = 349$, 79.7%)	Neurological complications preoperative ($n = 89$, 20.3%)	p value
Age, years	61.0 ± 14.9 64 (52; 73)	61.0 ± 14.9 64 (52; 73)	61.1 ± 15.0 64 (53; 74)	0.964
Female gender	112 (25.6%)	82 (23.5%)	30 (33.7%)	**0.049***
Body mass index (kg/m^2)	25.9 (23.0; 29.4)	26.1 (23.2; 29.8)	24.7 (22.6; 28.7)	0.122
Logistic EuroSCORE I	25.0 (11.0; 45.7)	24.2 (9.2; 44.9)	26.8 (15.9; 51.6)	**0.042***
EuroSCORE II	11.5 (4.5; 25.5)	11.8 (4.8; 26.0)	8.7 (3.9; 25.2)	0.353
COPD	55 (12.6%)	43 (12.3%)	12 (13.5%)	0.768
Arterial hypertension	257 (58.7%)	213 (61.0%)	44 (49.4%)	**0.047***
Ejection fraction (%)	55 (50; 56)	55 (48; 56)	55 (50; 60)	0.263
LVEF poor (<30)	40 (9.3%)	34 (10.0%)	6 (6.8%)	0.365
Atrial fibrillation	83 (18.9%)	61 (17.5%)	22 (24.7%)	0.120
Peripheral vascular disease	38 (8.7%)	30 (8.6%)	8 (9.0%)	0.906
Drug abuse	24 (5.5%)	18 (5.2%)	6 (6.7%)	0.601
Type 2 diabetes mellitus	88 (20.1%)	73 (20.9%)	15 (16.9%)	0.393
IDDM	51 (11.6%)	41 (11.7%)	10 (11.2%)	0.893
Immunosuppressive therapy	13 (3.0%)	7 (2.0%)	6 (6.7%)	**0.030***
Acute renal insufficiency	55 (12.6%)	35 (10.0%)	20 (22.5%)	**0.002***
Acute dialysis preoperative	27 (6.2%)	16 (4.6%)	11 (12.4%)	**0.006***
Chronic dialysis preoperative	19 (4.3%)	15 (4.3%)	4 (4.5%)	1.000
Chronic renal insufficiency	123 (28.1%)	101 (28.9%)	22 (24.7%)	0.429
NYHA stages	2 (2; 3)	2 (2; 3)	2 (2; 3)	0.340
NYHA IV	88 (20.2%)	71 (20.5%)	17 (19.1%)	0.785
Coronary heart disease	186 (42.5%)	151 (43.3%)	35 (39.3%)	0.502
State after PCI	39 (8.9%)	31 (8.9%)	8 (9.0%)	0.975
Previous cardiac surgery	181 (41.3%)	157 (45.0%)	24 (27.0%)	**0.002***
CABG	11 (2.6%)	10 (3.0%)	1 (1.2%)	0.474
Aortic valve replacement	70 (16.7%)	57 (17.1%)	13 (15.1%)	0.665
Mitral valve replacement/ reconstruction	8 (1.9%)	7 (2.1%)	1 (1.2%)	1.000
Combined valve surgery	84 (20.0%)	76 (22.8%)	8 (9.3%)	0.005*
TAVI	2 (0.5%)	2 (0.6%)	0 (0.0%)	1.000
Tumor	55 (12.6%)	41 (11.7%)	14 (15.7%)	0.311

(b)

	All patients ($n = 438$)	No neurological complications preoperative ($n = 349$, 79.7%)	Neurological complications preoperative ($n = 89$, 20.3%)	p value
Acute myocardial infarction (≤48 h)	14 (3.2%)	8 (2.3%)	6 (6.8%)	**0.042***
Cardiogenic shock	21 (4.8%)	19 (5.4%)	2 (2.2%)	0.274
CPR (≤48 h)	9 (2.1%)	8 (2.3%)	1 (1.1%)	0.694
Inotropic therapy	84 (19.2%)	61 (17.5%)	23 (25.8%)	0.074
Emergency	96 (21.9%)	74 (21.2%)	22 (24.7%)	0.474
Intensive care patient	96 (21.9%)	64 (18.3%)	32 (36.0%)	**<0.001***
Intubated at admission	38 (8.7%)	27 (7.7%)	11 (12.4%)	0.167
Neurological complications	85 (19.4%)	0 (0.0%)	85 (95.5%)	<0.001
Stroke	78 (17.8%)	0 (0.0%)	78 (87.6%)	<0.001
TIA	7 (1.6%)	0 (0.0%)	7 (7.9%)	<0.001
Silent cerebral embolization	4 (0.9%)	0 (0.0%)	4 (4.5%)	0.841
Preoperative embolization	123 (28.1%)	41 (11.7%)	82 (92.1%)	**<0.001***
Cerebral	61 (13.9%)	0 (0.0%)	61 (68.5%)	**<0.001***
Spleen	17 (3.9%)	17 (4.9%)	0 (0.0%)	**0.030***
Several organs	34 (7.8%)	14 (4.0%)	20 (22.5%)	**<0.001***
Fever (≥38°C) before surgery	88 (20.1%)	72 (20.6%)	16 (18.0%)	0.577
Tumor	55 (12.6%)	41 (11.7%)	14 (15.7%)	0.311
Endocarditis experienced	63 (14.4%)	58 (16.6%)	5 (5.6%)	**0.008***
Time from diagnosis to surgery (days)	7 (2; 17)	8 (2; 17)	7 (3; 17)	0.851
Time from antibiotic start to surgery (days)	10 (3; 21)	10 (3; 21)	9 (4; 18)	0.826

Table 1: Continued.

(c)

	All patients ($n = 438$)	No neurological complications preoperative ($n = 349$, 79.7%)	Neurological complications preoperative ($n = 89$, 20.3%)	p value
Pathogens				
Staphylococcus aureus	87 (20.0%)	56 (16.1%)	31 (35.2%)	**<0.001***
Enterococcus	64 (14.7%)	56 (16.1%)	8 (9.0%)	0.089
Viridans streptococci	47 (10.8%)	40 (11.5%)	7 (7.9%)	0.320
Gram-positive streptococcus	39 (8.9%)	30 (8.6%)	9 (10.1%)	0.665
HACEK group	1 (0.2%)	1 (0.3%)	0 (0.0%)	0.612
Mycosis	6 (1.4%)	5 (1.4%)	1 (1.1%)	1.000
Culture negative	117 (26.8%)	94 (27.1%)	23 (25.8%)	0.813
Staphylococcus epidermidis	30 (6.9%)	26 (7.5%)	4 (4.5%)	0.319
MRSA	15 (3.4%)	10 (2.9%)	5 (5.6%)	0.201
Unknown	44 (10.1%)	38 (11.0%)	6 (6.7%)	0.240
Valve affection				
Number of affected valves	1 (1–3)	1 (1–3)	1 (1-2)	0.262
AV isolated	132 (30.1%)	102 (29.2%)	30 (33.7%)	0.411
AV combined	178 (40.6%)	138 (39.5%)	40 (44.9%)	0.354
AV + MV	38 (8.7%)	30 (8.6%)	8 (9.0%)	0.906
MV isolated	99 (22.6%)	69 (19.8%)	30 (33.7%)	**0.005***
MV + TV	2 (0.5%)	0 (0.0%)	2 (2.2%)	**0.041***
MV combined	137 (31.3%)	98 (28.1%)	39 (43.8%)	**0.004***
AV + TV	5 (1.1%)	4 (1.1%)	1 (1.1%)	1.000
AV + TV + MV	2 (0.5%)	2 (0.6%)	0 (0.0%)	1.000
TV isolated	9 (2.1%)	9 (2.6%)	0 (0.0%)	0.215
TV combined	18 (4.1%)	15 (4.3%)	3 (3.4%)	1.000
Prosthetic endocarditis isolated	149 (34.0%)	131 (37.5%)	18 (20.2%)	**0.002***
Prosthetic endocarditis combined	166 (37.9%)	144 (41.3%)	22 (24.7%)	**0.004***
TAVI	1 (0.2%)	1 (0.3%)	0 (0.0%)	1.000
Prosthetic endocarditis isolated	71 (16.2%)	61 (17.5%)	10 (11.2%)	0.154
Abscess	121 (27.6%)	101 (28.9%)	20 (22.5%)	0.223
Vegetation	315 (72.7%)	240 (69.8%)	75 (84.3%)	**0.006***
Vegetation size (mm)	13 (9; 19)	13 (8; 19)	15 (10; 20)	0.128

(d)

	All patients ($n = 438$)	No neurological complications preoperative ($n = 349$, 79.7%)	Neurological complications preoperative ($n = 89$, 20.3%)	p value
Hemoglobin (g/dL)	10.3 (9.2; 11.7)	10.3 (9.2; 11.8)	10.0 (8.7; 11.5)	0.066
Hematocrit (%)	30.8 (27.6; 35.0)	31.0 (28.0; 35.0)	29.2 (26.7; 34.0)	0.007
Lactate (mmol/L)	0.8 (0.6; 1.1)	0.8 (0.6; 1.2)	0.7 (0.5; 0.9)	0.006
Potassium (mmol/L)	3.9 (3.6; 4.3)	3.9 (3.6; 4.3)	4.9 (4.5; 5.4)	0.768
CRP (mg/L)	40.9 (15.8; 86.8)	39.7 (16.5; 82.4)	47.5 (13.6; 94.2)	0.539
PCT (ng/mL)	0.24 (0.11; 0.67)	0.21 (0.10; 0.65)	0.28 (0.14; 0.83)	0.375
Creatinine (μmol/L)	102 (76; 143)	103 (77; 141)	097 (71; 149)	0.782
GFR (ml/min)	61 (42; 68)	61 (42; 69)	61 (39; 64)	0.802
Leukocytes (10^9/L)	8.70 (6.64; 11.36)	8.60 (6.64; 11.16)	9.29 (6.61; 12.69)	0.509
Platelets (10^9/L)	238 (170; 313)	240 (171; 319)	219 (152; 301)	0.104
Urea (mmol/L)	5.8 (4.0; 10.0)	5.8 (3.9; 9.5)	6.0 (4.5; 11.4)	0.318
CK (U/L)	40 (26; 79)	41 (27; 81)	36 (23; 68)	0.143
CK-MB (U/L)	11.6 (7.8; 18.5)	11.5 (7.9; 17.1)	12.4 (7.4; 22.9)	0.793
AST/GOT (U/L)	29.1 (20.5; 48.0)	28.8 (20.0; 49.7)	30.6 (23.0; 42.8)	0.740
ALT/GPT (U/L)	22.1 (13.2; 37.8)	22.0 (13.2; 38.3)	23.0 (12.7; 37.0)	0.638
Bilirubin (μmol/L)	9.4 (6.3; 15.0)	9.7 (6.6; 16.0)	8.0 (4.9; 13.4)	0.037
INR	1.16 (1.07; 1.30)	1.16 (1.06; 1.30)	1.17 (1.10; 1.31)	0.392

EuroSCORE, European System for Cardiac Operative Risk Evaluation; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; IDDM, insulin-dependent diabetes mellitus; NYHA IV, New York Heart Association heart failure stage IV; CABG, coronary artery bypass grafting; TAVI, transcatheter aortic valve implantation. CPR, cardiopulmonary resuscitation; TIA, transient ischemic attack. HACEK, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*; MRSA, methicillin-resistant *Staphylococcus aureus*; AV, aortic valve; MV, mitral valve; TV, tricuspid valve; TAVI, transcatheter aortic valve implantation. CRP, C-reactive protein; GFR, glomerular filtration rate; CK, creatine kinase; INR, international normalized ratio.

Table 2: Operative data.

	All patients ($n = 438$)	No neurological complications preoperative ($n = 349$, 79.7%)	Neurological complications preoperative ($n = 89$, 20.3%)	p value
Length of surgery (min)	274 (220; 352)	280 (230; 360)	254 (208; 329)	**0.022***
Cardiopulmonary bypass time (min)	166 (125; 210)	171 (126; 216)	156 (122; 192)	0.105
Cross-clamp time (min)	116 (86; 156)	119 (86; 157)	110 (86; 142)	0.257
Circulatory arrest (min)	0 (0–36)	0 (0–32)	0 (0–36)	**0.049***
Number of packed red blood cells, unit	3 (0–27)	3 (0–27)	3 (0–14)	0.688
Number of fresh frozen plasma, unit	0 (0–13)	0 (0–13)	0 (0–10)	0.637
Number of platelets, unit	1 (0–6)	1 (0–6)	1 (0–6)	0.615
Aortic valve surgery	320 (73.2%)	263 (75.6%)	57 (64.0%)	**0.028***
Mitral valve surgery	169 (38.7%)	124 (35.6%)	45 (50.6%)	**0.010***
Tricuspid valve surgery	18 (4.1%)	14 (4.0%)	4 (4.5%)	0.770
Combined valve surgery	201 (46.0%)	161 (46.3%)	40 (44.9%)	0.823
Additional CABG	50 (11.4%)	40 (11.5%)	10 (11.2%)	0.946

Table 3: Postoperative data and outcomes.

	All patients ($n = 438$)	No neurological complications preoperative ($n = 349$, 79.7%)	Neurological complications preoperative ($n = 89$, 20.3%)	p value
AKI KDIGO stages	3 (1; 3)	3 (1; 3)	3 (1; 3)	0.686
1	46 (38.0%)	39 (38.6%)	7 (35.0%)	
2	8 (6.6%)	7 (6.9%)	1 (5.0%)	
3	67 (55.4%)	55 (54.5%)	12 (60.0%)	
24 h-drainage loss (ml)	650 (350; 1166)	600 (300; 1166)	650 (363; 1250)	0.090
Re-thoracotomy due to bleeding/tamponade	52 (12.1%)	42 (12.3%)	10 (11.2%)	0.781
24 h-number of packed red blood cells, unit	2 (0–27)	2 (0–27)	2 (0–21)	0.540
24 h-number of fresh frozen plasma, unit	0 (0–29)	0 (0–29)	0 (0–10)	0.958
24 h-number of platelets, unit	0 (0–8)	0 (0–8)	0 (0–5)	0.420
Reintubation	51 (12.0%)	39 (11.5%)	12 (13.8%)	0.557
Tracheotomy	59 (14.1%)	47 (14.2%)	12 (14.1%)	0.993
ICU time (d)	3 (1; 7)	3 (1; 7)	3 (1; 7)	0.331
Postoperative days	10 (7; 16)	10 (7; 16)	8 (5; 16)	**0.034**
Readmission to the intensive care unit	35 (8.3%)	27 (8.0%)	8 (9.3%)	0.693
Postoperative day of readmission	10 (5; 16)	9 (5; 15)	14 (4; 17)	0.851
Postoperative delirium	68 (16.1%)	58 (17.2%)	10 (11.8%)	0.226
Neurological deficit	27 (6.4%)	24 (7.1%)	3 (3.6%)	0.237
CPR	23 (5.4%)	21 (6.2%)	2 (2.3%)	0.190
Atrial fibrillation (postoperative new)	18 (4.9%)	16 (5.4%)	2 (2.8%)	0.544
Pacemaker patient new post-op	51 (11.6%)	39 (11.2%)	12 (13.5%)	0.544
Postoperative myocardial infarction	5 (1.2%)	4 (1.2%)	1 (1.2%)	1.000
Bronchopulmonary infection	44 (10.2%)	35 (10.2%)	9 (10.3%)	0.969
Sepsis	56 (13.0%)	44 (12.8%)	12 (13.8%)	0.804
Sternal wound infection	10 (2.5%)	8 (2.5%)	2 (2.6%)	1.000
Hospital mortality	72 (16.5%)	55 (15.9%)	17 (19.1%)	0.461
Cardiac death	11 (15.3%)	9 (16.4%)	2 (11.8%)	1.000
Cerebral death	1 (1.4%)	1 (1.8%)	0 (0.0%)	1.000
Sepsis	10 (13.9%)	8 (14.5%)	2 (11.8%)	1.000
MOF	50 (69.4%)	37 (67.3%)	13 (76.5%)	0.472
7 d-mortality	52 (11.9%)	40 (11.5%)	12 (13.5%)	0.599
30-day mortality	76 (17.4%)	55 (15.8%)	21 (23.6%)	0.081
Survival/FU-time (years)	2.8 (0.1; 7.0)	2.9 (0.2; 7.0)	1.5 (0.1; 6.9)	0.225

AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; ICU, intensive care unit; CPR, cardiopulmonary resuscitation; MOF, multiple organ failure.

Staphylococcus aureus were independent predictors of NCs. Furthermore, *Staphylococcus aureus*, large vegetations, and mitral involvement were associated with a markedly increased risk of mortality [21–24]. In an earlier analysis of patients in our cohort, the presence of valvular abscess, older age (>70 years), preoperative neurological deficits, and female gender were independent risk factors for mortality [17]. In this updated analysis, although present, the difference in 30-day mortality between patients with NCs and those without did not reach statistical significance (23.6% vs. 15.8%; $P = 0.08$). In this analysis, focusing on NCs in patients who underwent surgery for IE, we noted that infection

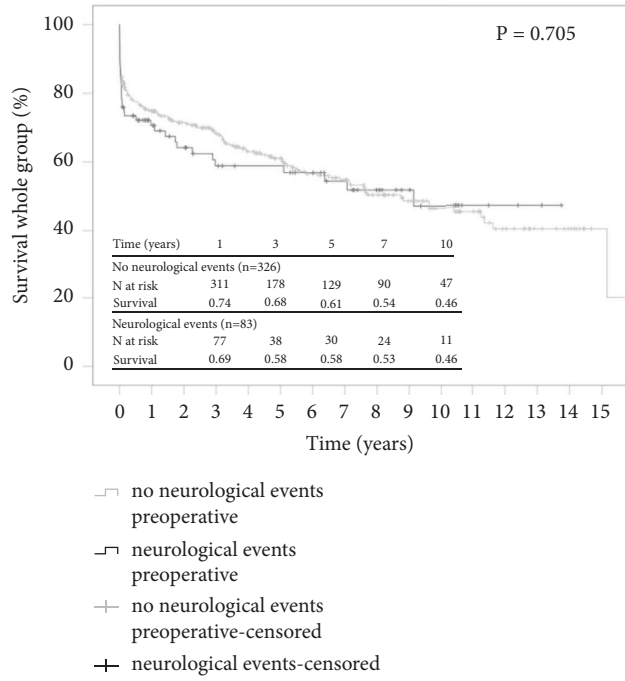

Figure 1: Kaplan–Meier curves for the whole group.

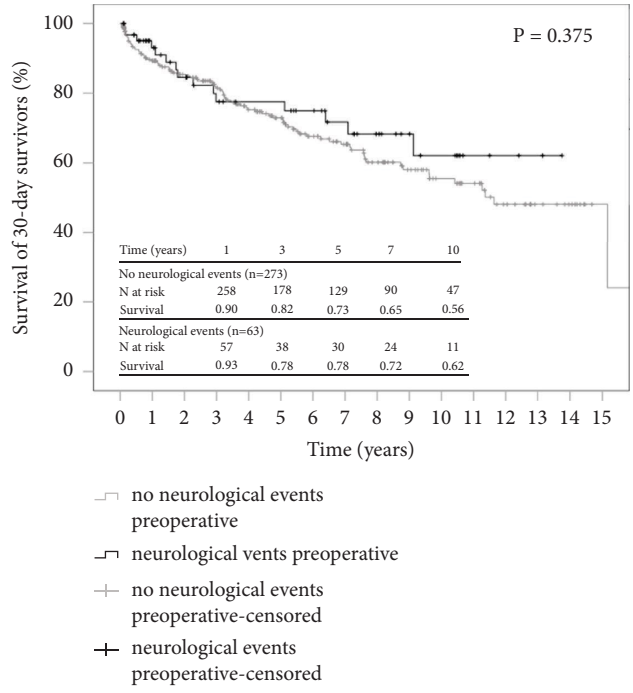

Figure 2: Kaplan–Meier curves for the 30-day survivor group.

with *Staphylococcus aureus* and preoperative atrial fibrillation were independently associated with increased risk for NCs, while previous endocarditis was a protective factor from developing NCs.

An earlier study by Diab and colleagues [24] concluded that NCs do not independently influence outcomes after surgery and that patients presenting with NCs already have high-risk profile. We assume that factors such as mitral affection, larger vegetations, and *Staphylococcus aureus* infection represent key risks that contribute to both increased incidence of NCs and higher mortality. However, it should be noted that all patients in our study were indicated and underwent surgery.

Previous results showed that earlier antimicrobial therapy can substantially decrease the risk of embolization [12, 25]. This highlights that the early recognition and

Table 4: Logistic regression analysis.

Variable	Odds ratio	Confidence interval	p value
Age	0.998	0.978–1.018	0.813
Female gender	1.276	0.698–2.332	0.428
Pre-op atrial fibrillation	2.026	1.044–3.933	**0.037**
Previous endocarditis	0.333	0.112–0.990	**0.048**
Staphylococcus aureus	2.602	1.404–4.820	**0.002**
Previous combined valve surgery	0.386	0.150–0.989	**0.047**

management of high-risk patients can significantly decrease both NCs and mortality rates.

Traditionally, NCs were considered as a major cause of surgery delay in indicated patients. This is mainly to avoid the risk of further exacerbation of NCs during heparinization and CPB, which may transform ischemic stroke into hemorrhage or exacerbate baseline hemorrhage [26]. However, this is reversed in the contemporary practice, encouraging earlier surgery especially for patients with nonhemorrhagic NCs. Patients who did not receive surgery when indicated had significantly worse outcomes [20–23]. Contemporary evidence has established that the most important prognostic factor in those patients is undergoing cardiac surgery when indicated [6, 7, 20–23]. The frequency of female patients was higher in the NC group compared to the non-NC group in our study and, as we had reported previously, there are indications of a delay in the presentation of female patients in our endocarditis cohort [27] and in general [8, 9, 28]. The higher mortality in female patients [27] has probably contributed to the slightly higher mortality in the NC group in our mixed cohort. However, female gender was not an independent predictor of NCs in our multivariable analysis.

The aortic valve is most commonly afflicted in IE followed by the mitral valve. Our analysis showed a significant association between mitral valve involvement and increased risk of NCs. Although patients with prosthetic valve IE present more commonly with intracardiac abscess [16], we observed that patients with native valve IE were at a significantly higher risk of NCs.

These findings highlight the importance of considering the location and type of valve affected in IE complicated by NCs.

While a considerable number of patients with IE can have silent brain embolization [26, 29], we did not perform routine brain CT scans in all patients, which could have precluded detection of silent NCs and might lead to misclassifying them as patients with no NCs. In our cohort, four patients exhibited radiological evidence of NCs, while lacking any clinical manifestations. This small number of patients posed a challenge in predicting outcomes in this subset of patients. Still, Cooper et al. [29] showed that early surgery for those patients was associated with significant reduction in three-month mortality (OR: 0.1; 95% CI [0.03–0.6]; $P = 0.008$).

Interestingly, we noted that previous endocarditis was protective from developing NCs. The protective effect of a previous IE on NCs in subsequent episodes is not fully understood. We hypothesize that initial exposure to infective endocarditis may trigger immune responses or adaptive changes, which may enhance the immune system's ability to defend against or restrict the formation and embolization of vegetations. However, future research might fully elucidate such observation.

It is imperative to consider several limitations when interpreting our results. Firstly, our study is a retrospective observational study, which introduces the possibility of inherent confounding bias and may limit the generalizability of our findings. Secondly, our cohort only includes IE patients who were indicated for and underwent surgery, limiting the generalizability of our conclusions to a broader population of IE patients. Moreover, the complex and varied nature of patient pathology in IE poses challenges in definitively assessing the specific impact of NCs on outcomes. It is crucial to take into account these limitations when interpreting our results.

Our findings provide insights into the risk factors and outcomes associated with NCs in our subset of patients who underwent surgery for IE. Moreover, we highlight that postoperative outcomes are influenced by a range of factors and not solely—rather indirectly—dependent on the presence of NCs.

Further research, including prospective studies, is warranted to better understand the influence of NCs on the outcomes of surgery in IE patients.

5. Conclusion

In conclusion, our study highlights the risk factors associated with NCs and their impact on the outcomes of surgery for patients with IE. We have identified multiple risk factors, such as organism type and preoperative AF, which are associated with the development of NCs. Furthermore, these risk factors also serve as predictors of mortality. However, we note that NCs alone do not independently predict short- or long-term survival following surgery for IE.

Data Availability

The data analyzed in this study are subject to the following licenses/restrictions: institutional dataset. Reasonable requests to access these datasets should be directed to the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Mohammed Al-Tawil and Christine Friedrich contributed equally to this work.

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Supplementary Materials

Graphical abstract showing the main risk factors associated with neurological complications in infective endocarditis. (*Supplementary Materials*)

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