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Risk Factor Analysis for 30-day Mortality After Surgery for Infective Endocarditis

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Abstract

Background Infective endocarditis (IE) remains a challenging disease associated with high mortality. Several scores have been suggested to assess surgical risk. None was sufficiently adequate. We therefore analyzed risk factors for 30-day mortality.

Methods A total of 438 consecutive patients had surgery for IE in our department between 2002 and 2020. Patients were divided into two groups, one consisting of 30-day survivors (362 patients; 82.6%) and one of nonsurvivors (76 patients; 17.4%). Logistic regression analysis on pre- and intraoperative risk factors was performed and the groups were compared by univariable analyses.

Results Patients in mortality group were older (69 [58, 77] vs. 63 [50, 72] years; $p < 0.001$), EuroSCORE II was higher (24.5 [12.1, 49.0] vs. 8.95 [3.7, 21.2]; $p < 0.001$) and there were more females. More frequently left ventricular function (below 30%), preoperative acute renal insufficiency, chronic dialysis, insulin-dependent diabetes mellitus, NYHA-class IV (New York Heart Association heart failure class IV), and cardiogenic shock occurred. Patients in the mortality group were often intensive care unit patients (40.8 vs. 22.4%; $p < 0.001$) or had a preoperative stroke (26.3 vs. 16.0%; $p = 0.033$). In the nonsurvivor group *Staphylococcus aureus* was prevalent. *Streptococcus viridans* was common in the survivor group as was isolated aortic valve endocarditis (32.9 vs. 17.1%; $p = 0.006$). Prosthetic valve endocarditis (PVE) and abscesses occurred more often in nonsurvivors. In the logistic regression analysis, female gender, chronic dialysis, cardiogenic shock, and NYHA IV and from intra-operative variables PVE, cardiopulmonary bypass time, and mitral valve surgery were the strongest predictors for 30-day mortality.

Keywords
- endocarditis
- heart valve surgery
- infection
- outcomes (mortality morbidity)

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Conclusion This study indeed clearly indicates that significant risk factors for 30-day mortality cannot be changed. Nevertheless, they should be taken into account for preoperative counselling, and they will alert the surgical team for an even more careful management.

Introduction

Infective endocarditis (IE) remains one of the most challenging diseases of modern times. It is associated with high mortality and morbidity, although diagnostic and surgical skills as well as antibiotic pretreatment have substantially improved.[1]

Every study contributes to the knowledge of this frequently lethal disease, but one of the challenging questions remains which patients are likely to survive and how survival in general may be increased. At the current time between 52.9 and 58.9% of patients with IE have a theoretical indication for surgery. Yet, only in about 40% of the cases valve surgery is actually performed.[2] Several scores such as EuroScore I and II, PALSUSE, Risk-E, Costa, De Feo-Cotrufo, AEPEI, STS-risk, STS-IE, APORTEI, and ICE-PCS have been evaluated to approach the question of the operability of a given patient, yet the utility of these scores remains questionable.[3]

Although 30-day mortality seems an old tool for the evaluation of surgical quality and it was even suggested to abandon this concept, as mortality seems to increase after 30-days, we decided to use it nonetheless as none of the mentioned scores is sufficiently conclusive. To evaluate its justification for this study, all-hospital death was also included in the analysis. Thus, a retrospective analysis of our endocarditis registry was performed to evaluate risk factors for 30-day mortality and henceforth to approach the question of operability and benefit of surgical intervention for these critically ill patients.

Methods

Patients

Between the years 2002 and 2020 altogether 438 consecutive patients had surgery for IE at our department. All patients operated on IE were enrolled in our endocarditis registry. Patients treated with medication only were excluded. Data were retrospectively collected in a specially created database and retrieved from medical records. IE was located at least on one valve or valve prosthesis. This diagnosis was ensured intraoperatively and microbiologically. In this retrospective cohort study risk factors for 30-day mortality were analyzed and a comprehensive risk factor analysis performed. Patients were subsequently divided into two groups. One group consisted of 30-day survivors (362 patients; 82.6%) and one of nonsurvivors (76 patients; 17.4%). The local institutional ethics committee approved the study protocol and authorized its conduct (file number D 458/20). Individual patient's written informed consent for study participation was obtained.

Patient Management

Antibiotic treatment was usually started as soon as endocarditis was plausible according to the modified Duke criteria. All patients had blood cultures taken to identify organisms according to species and sensitivities. The location and the size of vegetation, presence of valve insufficiencies or abscesses, and left ventricular ejection fraction (LVEF) were analyzed using a transthoracic or transesophageal echocardiogram. Coronary angiography and additional computed tomography (CT) including cerebral CT, thoracic CT, and whole-body CT scans were performed in high-risk or redo patients. Patients were referred to our department and scheduled for near-term surgery as soon as surgical treatment was indicated. Intravenous antibiotic treatment regime was maintained for 4 to 6 weeks postoperatively, if diagnosis was intraoperatively reaffirmed. All patients with neurological complications had an evaluation of neurological status by a consultant neurologist and a CT scan of the brain to estimate risks of bleeding and prognoses if patients were intubated.

Surgical Technique

All patients had a routine general anesthesia. As standard access median sternotomy was performed. Few patients with mitral valve endocarditis had minimally invasive anterolateral thoracotomy. Extracorporeal circulation with heart–lung machine with mild hypothermia (34°C) was installed. Usually, arterial cannulation of the aorta and a single venous cannulation of the right atrial appendage was installed. Double cannulation of superior and inferior vena cava was used if tricuspid valve or mitral valve were operated on. This was followed by cross-clamping. Antegrade and retrograde application of cold blood cardioplegic solution was used to achieve myocardial protection. The surgical method was depending on macroscopic degree of valve destructions and clinical judgement of the surgical team based on universally applicable guidelines. Depending on the individual patient's situation and the intracardiac findings, additional procedures were performed. Choice of prothesis (biological or mechanical) was left to patient's preference.

Data Collection

Data collection was prospective in our internal endocarditis registry, yet evaluation of 30-day mortality was performed in a retrospective manner. Pre-, intra-, and postoperative variables were taken from medical records. All data collected were documented in anonymized form in an Excel spreadsheet.

Statistical Analyses

Statistical analysis was done using the IBM SPSS Statistics software (version 26.0). Normality of continuous variables

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was assessed by Lilliefors test/Kolmogorov–Smirnov test. Values of continuous data are presented as median with interquartile range or range as appropriate. Categorical variables are displayed as frequency distributions (n) and simple percentages (%). Categorical variables of the groups were compared by χ^2 and the Fisher's exact test as appropriate. Normally distributed quantitative variables were compared by t-test and Mann–Whitney U test was used for non-normally distributed variables. Statistical significance was considered when $p \leq 0.05$. Clinically relevant variables with at least eight events and less than 5.5% missing values except for LVEF (8.9% missing values) associated with 30-day mortality at $p < 0.1$ were included into multivariable logistic regression analysis. Further variable selection was based on clinical relevance and stepwise selection. Model 1 included preoperative parameters, model 2 included intraoperative parameters, and model 3 combined pre- and intraoperative variables with a p-value ≤ 0.1 in models 1and 2, with a goodness of fit, described by Cox's and Snell's R-squared of 0.235, 0.123, and 0.283, respectively. The results of models 1 and 2 are shown as ►**Supplementary Tables S1** and **S2** (available in the online version). Model 1 is visualised in ►**Fig. 1**, Model 2 is shown in ►**Fig. 2**. The results of model 3 are presented in ►**Table 6** and graphically demonstrated in ►**Fig. 3**.

Results

Out of our endocarditis registry all 438 patients having had surgery due to IE were retrieved. They were divided into two groups: the group of survivors ($n = 362$) and the group of nonsurvivors ($n = 76$).

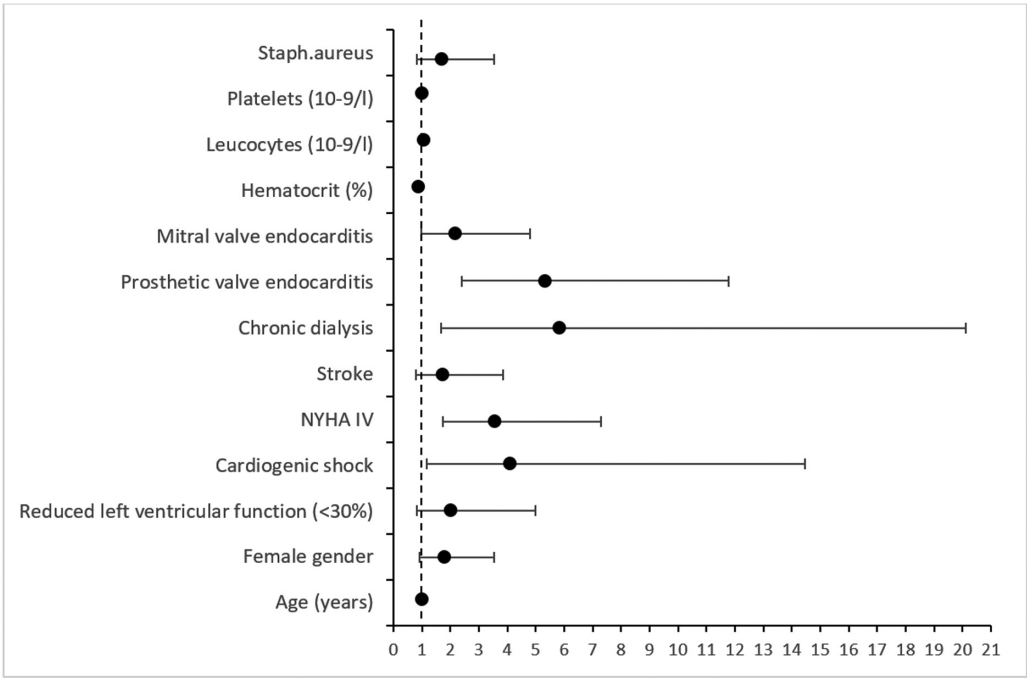

Fig. 1 Forest plot for risk factor analysis for preoperative conditions.

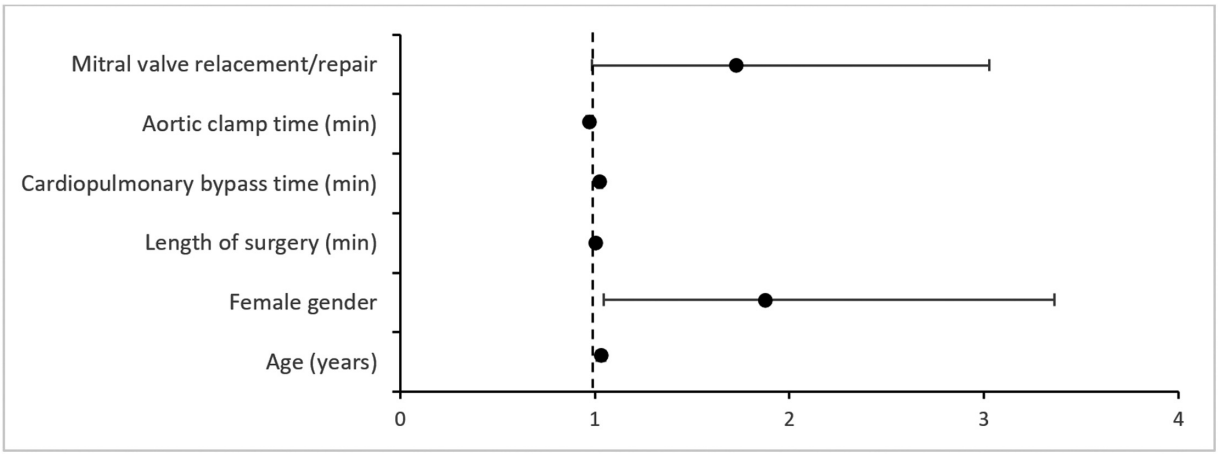

Fig. 2 Forest plot for risk factor analysis for intraoperative conditions.

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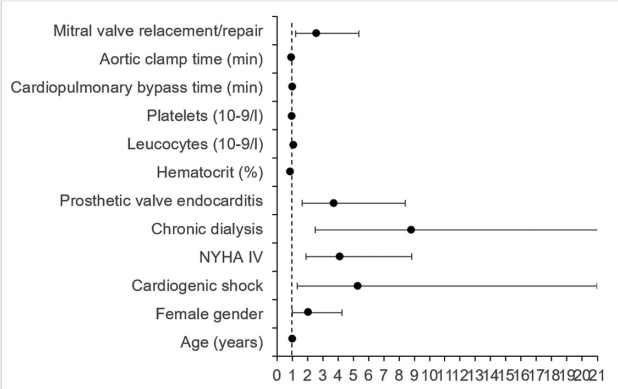

Fig. 3 Forest plot for risk factor analysis for combined pre- and intraoperative conditions.

Patients' Baseline Characteristics and Clinical Presentation

Patients in the nonsurvivor group were significantly older (69 vs. 63 years; $p < 0.001$), had a higher proportion of female patients ($p = 0.006$), and a higher logistic EuroSCORE (45.2 vs. 21.3; $p < 0.001$) and EuroSCORE II (24.52 vs. 8.95; $p < 0.001$). In the study group reduced left ventricular function below 30% (22.2 vs. 7.3%; $p < 0.001$) was significantly more frequent as was diabetes type II (28.8 vs. 18.2%; $p = 0.034$) and insulin-dependent diabetes (21.1 vs. 9.7%; $p = 0.005$).

Also, significantly different were preoperative acute and chronic renal insufficiency and chronic dialysis and NYHA-class IV (New York Heart Association heart failure class IV). Patients who were not likely to survive were in a worse preoperative state: they were often transferred from intensive care unit (ICU; 40.8 vs. 22.4%; $p < 0.001$) and had more often a cardiogenic shock (14.5 vs. 2.8%; $p < 0.001$), were in a more critical preoperative state (32.9 vs. 16.3%; $p < 0.001$), and had more often emergency surgery (32.9 vs. 19.6%; $p = 0.011$). They had more likely a preoperative stroke (26.3 vs.16.0%; $p = 0.033$). Yet, preoperative embolization either cerebral or into other organs did not differ significantly. Patients of the 30-day mortality group had a shorter time from diagnosis to surgery (5 [1, 12] vs. 8 [3, 18] days) and more often a time period from diagnosis to surgery $\leq$1 day. Nonsurvivors had a median of 6 days of fever prior to surgery compared with 5 days in the group of 30-day survivors ($p = 0.05$). No differences were noted concerning commencement of antibiotic treatment. Differences could be seen concerning pathogen spectrum. *Staphylococcus aureus* was the most common proven germ and more frequent in the 30-day mortality group ($p = 0.032$), whereas viridans streptococci or gram-positive streptococci were mainly present in the survivor group ($p = 0.003$ and 0.010, respectively). No differences concerning any other germ was noted. Especially methicillin-resistant *S. aureus* was not significantly higher in any group. Affected valves were mainly the aortic valve (highly significant for the survivor group) and the mitral valve (dominant in the non-surviving group), but the latter without reaching significance. Isolated prosthesis endocarditis occurred slightly more frequently in the 30-day nonsurvivor group (43.4 vs. 32.0%, $p = 0.057$). Isolated at least moderate valve insufficiency of the aortic valve was more common in the survivor group (28.2 vs. 11.8%, $p = 0.003$). Abscesses occurred more often in the nonsurvivor group (47.4 vs. 23.5%, $p < 0.001$).

In the 30-day nonsurvivor group preoperative laboratory parameters were significantly lower for hemoglobin, hematocrit, platelets, and glomerular filtration rate (GFR), whereas C-reactive protein, potassium, creatinine, leukocytes, urea, CK/CK-MB (creatine kinase/myocardial band), bilirubin, and international normalized ratio (INR) were significantly higher. An overview on demographic and preoperative clinical characteristics of the study population is outlined in ►**Tables 1**, **2** and **3**.

Operative Data

Length of surgery differed significantly between the groups ($p = 0.001$) as did cardiopulmonary bypass time ($p < 0.001$). Cross-clamp time tended to be longer in the nonsurvivor group. The nonsurvivors received on average more red blood cell units, fresh-frozen plasma units ($p < 0.001$), and a higher number of platelet units ($p < 0.001$). The survivor group received more often biological aortic valve replacements (48.1 vs. 37.3%; $p = 0.09$). The nonsurvivor group had more often biological composite aortic root replacements (30.7 vs. 16.3%; $p = 0.004$). Mitral valve surgery was more common in the 30-day mortality group but did not reach significance nor did tricuspid valve surgery, which was more common in the survivor group. Valve surgery with pacemaker implantation was more common in the nonsurvivor group, yet not significant. Operative data are summarized in ►**Table 4**.

Postoperative Data

Postoperative laboratory and clinical data and outcomes are summarized in ►**Table 5**. Differences in early and late postoperative complications were noticeable for both groups. Especially, laboratory parameters were significantly different after surgery. Hemoglobin and hematocrit (lowest values) after surgery were significantly different. Urea, lactate, sodium, potassium, creatinine, GFR, CK/CK-MB, aspartate transferase, alanine aminotransferase, bilirubin, leukocytes, and platelets differed significantly between the two groups. Not significantly different were C-reactive protein and INR until first postoperative day.

Moreover, acute kidney injury based on KDIGO (Kidney Disease: Improving Global Outcomes) stages was significantly different (60.6% nonsurvivors vs. 23.3% survivors; $p < 0.001$). Stage 3 occurred mainly in the 30-day mortality group (80 vs. 43.2%; $p < 0.001$). New onset on hemodialysis was more common in the nonsurvivor group (52.4 vs. 8.5%; $p < 0.001$). The reexploration rates due to profuse postoperative bleeding or cardiac tamponade within 3 days postoperative were higher in the 30-day mortality group (22.1 vs. 10.2%; $p = 0.006$). Twenty-four-hour drainage loss had the tendency to be more in the 30-day mortality group (600 [300–1,100] vs. 800 mL [450–1,350]; $p < 0.09$). Also, 24 and 48-hour numbers of packed red blood cells, fresh-frozen plasma units, as well as platelet units showed highly significant differences ($p < 0.001$ for all). Ventilation time was significantly longer in the nonsurvivor group (41 [19, 116] vs. 14 [8, 36] hours; $p < 0.001$).

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Table 1 Patients' baseline characteristics and clinical presentation

Patients baseline characteristics	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
Age (y)	64 (52, 73)	63 (50, 72)	69 (58, 77)	<0.001
Female gender	112 (25.6%)	83 (22.9%)	29 (38.2%)	0.006
Body mass index (kg/m^2)	25.9 (23.0, 29.4)	25.7 (22.6, 29.3)	27.3 (23.4, 29.3)	0.106
Logistic EuroSCORE I	25.0 (11.0, 45.7)	21.3 (9.6, 41.0)	45.2 (24.6, 70.6)	<0.001
EuroSCORE II	11.5 (4.5, 25.5)	8.95 (3.65, 21.2)	24.5 (12.1, 49.0)	<0.001
COPD	55 (12.6%)	45 (12.4%)	10 (13.2%)	0.862
Arterial hypertension	257 (58.7%)	209 (57.7%)	48 (63.2%)	0.383
Pulmonary hypertension (>25 mm Hg)	33 (7.5%)	24 (6.6%)	9 (11.8%)	0.118
Ejection fraction (%)	55 (50, 56)	55 (50, 57.3)	55 (40, 55)	0.001
LVEF poor (<30)	40 (10.0%)	24 (7.3%)	16 (22.2%)	<0.001
Atrial fibrillation	83 (18.9%)	69 (19.1%)	14 (18,4)	0.897
Peripheral vascular disease	38 (8.7%)	28 (7.7%)	10 (13.2%)	0.127
Drug abuse	24 (5.5%)	21 (5.8%)	3 (3.9%)	0.781
Type 2 diabetes mellitus	88 (20.1%)	66 (18.2%)	22 (28.9%)	0.034
IDDM	51 (11.6%)	35 (9.7%)	16 (21.1%)	0.005
Hyperlipoproteinemia	125 (28.5%)	102 (28.2%)	23 (30.3%)	0.714
Smoking	110 (27.7%)	94 (28.2%)	16 (25.0%)	0.597
Immunosuppressive therapy	13 (3.0%)	12 (3.3%)	1 (1.3%)	0.708
Coronary heart disease	186 (42.5%)	150 (41%)	36 (47.4%)	0.342
State after PCI ± DES	39 (8.9%)	33 (9.1%)	6 (7.9%)	0.734
Previous cardiac surgery	181 (41.3%)	137 (37.8%)	44 (57.9%)	0.001
CABG	11 (2.6%)	7 (2.0%)	4 (5.3%)	0.119
Aortic valve replacement	70 (16.7%)	56 (16.3%)	14 (18.4%)	0.650
Mitral valve replacement/reconstruction	8 (1.9%)	7 (2.0%)	1 (1.3%)	1.000
Combined valve surgery	84 (20.0%)	62 (18.0%)	22 (28.9%)	0.031
TAVI	2 (0.5%)	1 (0.3%)	1 (1.3%)	0.330

Abbreviations: CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DES, drug eluting stent; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IDDM, insulin-dependent diabetes mellitus; LVEF, left ventricular ejection fraction; NYHA IV, New York Heart Association heart failure stage IV; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.

Table 2 Patients' preoperative status

Patients preoperative status	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
Acute renal insufficiency	55 (12.6%)	39 (10.8%)	16 (21.1%)	0.014
Acute dialysis preoperative	27 (6.2%)	20 (5.5%)	7 (9.2%)	0.290
Chronic dialysis preoperative	19 (4.3%)	9 (2.5%)	10 (13.2%)	<0.001
Chronic renal insufficiency	123 (28.1%)	95 (26.2%)	28 (26.8%)	0.062
NYHA stages	2 (2, 3)	2 (2, 3)	3 (2, 4)	<0.001
NYHA IV	88 (20.1%)	58 (16.1%)	30 (39.5%)	<0.001
Clinical presentation				
Acute myocardial infarction (≤48 h)	14 (3.2%)	11 (3.0%)	3 (3.9%)	0.719
Cardiogenic shock	21 (4.8%)	10 (2.8%)	11 (14.5%)	<0.001
CPR (≤48 h)	9 (2.1%)	5 (1.4%)	4 (5.3%)	0.053

(*Continued*)

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Table 2 (*Continued*)

Patients preoperative status	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
Preoperative inotropic therapy	48 (11.0%)	31 (8.6%)	17 (22.4%)	<0.001
Emergency	96 (21.9%)	71 (19.6%)	25 (32.9%)	0.011
Transfer from intensive care unit	112 (25.6%)	81 (22.4%)	31 (40.8%)	<0.001
Intubated at admission	38 (8.7%)	28 (7.7%)	10 (13.2%)	0.127
Neurological deficits	85 (19.4%)	64 (17.7%)	21 (27.6%)	0.046
Preoperative embolization	123 (28.1%)	98 (27.1%)	25 (32.9%)	0.304
Cerebral	60 (13.7%)	47 (13%)	13 (17.1%)	0.347
Several organs	34 (7.8%)	25 (6.9%)	9 (11.8%)	0.144
Fever (≥38°C) before surgery	88 (20.1%)	73 (20.2%)	15 (19.7%)	0.932
Fever (d)	5 (2, 6)	5 (2, 9)	6 (3, 11)	0.050
Fever ≤ 1 d	15 (3.4%)	13 (3.6%)	2 (2.6%)	1.000
Fever ≤ 72 h	13 (3.0%)	10 (2.8%)	3 (3.9%)	0.479
Fever ≤ 7 d	28 (6.4%)	24 (6.6%)	4 (5.3%)	0.800
Fever > 7 d	32 (7.3%)	26 (7.2%)	6 (7.9%)	0.828
Tumor	55 (12.6%)	46 (12.7%)	9 (11.8%)	0.836
Rheumatic disease	25 (5.7%)	20 (5.5%)	5 (6.6%)	0.785
Endocarditis experienced	63 (14.4%)	52 (14.4%)	11 (14.5%)	0.980
History of liver disease	57 (13.0%)	46 (12.7%)	11 (14.5%)	0.677
History of hepatitis	22 (5.0%)	18 (5.0%)	4 (5.3%)	1.000
Liver cirrhosis	9 (2.1%)	5 (1.4%)	4 (5.3%)	0.053
Time from diagnosis to surgery (d)	7 (2, 17)	8 (3, 18)	5 (1, 12)	0.050
Time from antibiotic start to surgery (d)	10 (3, 21)	10 (4.0, 23.3)	9.5 (2.0, 14.8)	0.104
Pathogens				
Staphylococcus aureus	87 (20.0%)	65 (18.1%)	22 (28.9%)	0.032
Enterococcus	64 (14.7%)	54 (15%)	10 (13.2%)	0.680
Viridans streptococci	47 (10.8%)	46 (12.8%)	1 (1.3%)	0.003
Gram-positive streptococcus	39 (8.9%)	38 (10.6%)	1 (1.3%)	0.010
HACEK group	1 (0.2%)	1 (0.3%)	0 (0.0%)	0.646
Mycosis	6 (1.4%)	5 (1.4%)	1 (1.3%)	0.960
Culture negative	117 (26.8%)	91 (25.3%)	26 (34.2%)	0.110
Staphylococcus epidermidis	30 (6.9%)	22 (6.1%)	8 (10.5%)	0.167
MRSA	15 (3.4%)	12 (3.3%)	3 (3.9%)	0.732
Number of affected valves	1 (1–3)	1 (1–3)	1 (1–2)	0.829
Affected valves				
AV isolated	132 (30.1%)	119 (32.9%)	13 (17.1%)	0.006
AV + MV	38 (8.7%)	32 (8.9%)	6 (7.9%)	0.785
MV isolated	99 (22.6%)	77 (21.3%)	22 (28.9%)	0.146
AV + TV	5 (1.1%)	4 (1.1%)	1 (1.3%)	1.000
TV isolated	9 (2.1%)	9 (2.5%)	0 (0.0%)	0.370
Prosthetic endocarditis isolated	149 (34.0%)	116 (32%)	33 (43.4%)	0.057
Prosthetic endocarditis isolated	71 (16.2%)	58 (16.0%)	13 (17.1%)	0.816

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Table 2 (*Continued*)

Patients preoperative status	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
Abscess	121 (27.6%)	85 (23.5%)	36 (47.4%)	<0.001
Vegetation	315 (72.7%)	258 (72.3%)	57 (75.0%)	0.627
Vegetation size (mm)	13 (9, 19)	13 (9, 20)	13 (10, 17)	0.907

Abbreviations: AV, aortic valve; CPR, cardiopulmonary resuscitation; HACEK, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*; MRSA, methicillin-resistant *Staphylococcus aureus*; MV, mitral valve; NYHA IV, New York Heart Association heart failure stage IV; TIA, transient ischemic attack; TV, tricuspid valve.

Table 3 Patients' preoperative laboratory status

Preoperative laboratory parameters	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
Hemoglobin (g/dL)	10.3 (9.2, 11.7)	10.4 (9.3, 11.9)	9.5 (8,7, 10.6)	<0.001
Hematocrit (%)	30.8 (27.6, 35.0)	31.05 (28, 35,42)	28 (26, 31.9)	<0.001
Lactate (mmol/L), 18.7% missing values	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.05 (0.7, 1.47)	0.001
Sodium (mmol/L), 5.7% missing values	136 (133, 138)	136 (134, 138)	136 (132, 138)	0.450
Potassium (mmol/L)	3.9 (3.6, 4.3)	3.8 (3.6, 4.26)	4.1 (3.6, 4.6)	0.040
CRP (mg/L)	40.9 (15.8, 86.8)	34,85 (14, 75.52)	73.9 (42.4, 135.3)	<0.001
Creatinine (μmol/L)	102 (76, 143)	97 (74.2, 135.0)	128 (83.2, 182.2)	<0.001
GFR (mL/min)	61 (42, 68)	61 (45, 69)	48.5 (29, 66.25)	<0.001
Leukocytes (10^9/L)	8.70 (6.64, 11.36)	8.4 (6.5, 10.8)	10.16 (7.5, 15.19)	<0.001
Platelets (10^9/L)	238 (170, 313)	248 (181, 320.5)	192 (130, 272)	<0.001
Urea (mmol/L)	5.8 (4.0, 10.0)	5.45 (3.8, 8.2)	10.1 (5.5, 15.19)	<0.001
CK (U/L)	40 (26, 79)	38 (26, 70)	42 (29, 94)	0.083
CK-MB (U/L),	11.6 (7.8, 18.5)	10.1 (7.35, 16)	18.1 (13.3, 35)	<0.001
ALT/GPT (U/L), 9.4% missing values	22.1 (13.2, 37.8)	21.5 (13.3, 36.0)	25.0 (12.8, 52.8)	0.180
Bilirubin (μmol/L), 34.0% missing values	9.4 (6.3, 15.0)	9.06 (6.15, 13.59)	13.3 (7.52, 22.22)	0.007
INR	1.16 (1.07, 1.30)	1.15 (1.06, 1.29)	1.26 (1.11, 1.37)	<0.001

Abbreviations: ALT/GPT, alanine aminotransferase/glutamic pyruvic transaminase; CK/CK-MB, creatine kinase/myocardial band; CRP, C-reactive protein; GFR, glomerular filtration rate; INR, international normalized ratio.

Table 4 Operative data

Operative	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
Length of surgery (min)	274 (220, 352)	269 (216, 341.2)	310 (247.5, 425.25)	0.001
Cardiopulmonary bypass time (min)	166 (125, 210)	163 (120.7, 204.2)	187.5 (145.5, 265.2)	<0.001
Cross-clamp time (min)	116 (86, 156)	114 (86, 156)	127 (86.25, 170.75)	0.055
Circulatory arrest (min)	0 (0-36)	0 (0, 0)	0 (0, 0)	0.624
Number of packed red blood cells (unit)	3 (1, 5)	2 (1, 4)	4 (2, 8)	<0.001
Number of fresh-frozen plasma (unit)	0 (0, 2)	0 (0, 0)	0 (0, 6)	<0.001
Number of platelets (unit)	1 (0, 2)	1 (0, 2)	1 (1, 2)	<0.001
Aortic valve surgery	320 (73.2%)	268 (74%)	52 (69.3%)	0.403
Aortic valve replacement, bio	202 (46.2%)	174 (48.1%)	28 (37.3%)	0.090
Aortic valve replacement, mech	28 (6.4%)	28 (7.7%)	0 (0.0%)	0.008
Composite aortic root replacement, bio	82 (18.8%)	59 (16.3%)	23 (30.7%)	0.004

(*Continued*)

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Table 4 (*Continued*)

Operative	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
Composite aortic root replacement, mech	5 (1.1%)	4 (1.1%)	1 (1.4%)	1.000
Aortic valve reconstruction	3 (0.7%)	3 (0.8%)	0 (0.0%)	1.000
Mitral valve surgery	169 (38.7%)	133 (36.7%)	36 (48%)	0.068
Mitral valve replacement, bio	122 (27.9%)	93 (25.7%)	29 (38.7%)	0.023
Mitral valve replacement, mech	14 (3.2%)	13 (3.6%)	1 (1.3%)	0.481
Mitral valve reconstruction	32 (7.3%)	27 (7.5%)	5 (6.8%)	0.833
Tricuspid valve surgery	18 (4.1%)	17 (4.7%)	1 (1.3%)	0.334
Thoracic aortic surgery	58 (13.3%)	46 (12.7%)	12 (16.0%)	0.450
Valve surgery with ACB	50 (11.4%)	44 (12.2%)	6 (8.0%)	0.304
Valve surgery with pacemaker implantation	12 (2.7%)	9 (2.5%)	3 (4.0%)	0.441

Abbreviations: ACB, aortocoronary bypass; bio, biological; mech, mechanical.

Table 5 Postoperative laboratory and clinical data and outcomes

Postoperative laboratory parameters	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
Hemoglobin (g/dL)				
First value postop	10.25 (9.18, 11.73)	10.1 (9.3, 11)	10.4 (9.45, 11.4)	0.111
1st POD	9.6 (8.9, 10.6)	9.65 (8.93, 10.6)	9.6 (8.9, 10.6)	0.644
8th POD, 19.9% missing values	10.1 (9.3, 11.0)	10.2 (9.3, 11.1)	9.4 (8.7, 10.4)	0.003
Lowest value postop	8.2 (7.6, 8.8)	8.3 (7.7, 8.9)	7.9 (7.3, 8.6)	0.004
Hematocrit (%)				
First value postop	30.0 (27.53, 33.0)	30 (33, 27.43)	31.15 (34, 28)	0.125
1st POD	28.4 (26.0, 31.0)	28.7 (26, 31)	27.5 (25.4, 31)	0.284
8th POD, 19.9% missing values	30.2 (27.5, 33.0)	30.4 (27.97, 33)	27.7 (25.7, 30.65)	0.001
Lowest value postop	24.9 (22.8, 26.0)	25 (23, 26.5)	23.4 (22.1, 25.6)	0.006
Urea (mmol/L)				
First value postop	5.5 (3.9, 9.2)	5.2 (3.7, 7.9)	8.9 (5.7, 11.7)	<0.001
1st POD	5.7 (3.8, 8.7)	5.3 (3.8, 8.2)	7.8 (5.1, 10.5)	<0.001
3rd POD, 12.1% missing values	5.7 (3.8, 8.8)	5.8 (3.9, 58.7)	5.5 (3.7, 10.5)	0.764
Lactate (mmol/L)				
First value postop, 11.6% missing values	2.0 (1.4, 3.5)	1.9 (1.3, 2.79)	5.2 (2.2, 10.9)	<0.001
1st POD, 14.2% missing values	1.2 (0.9, 1.9)	1.1 (0.9, 1.6)	3.3 (1.4, 11.7)	<0.001
3rd POD, 12.3% missing values	96.0 (70.0, 144.8)	95.0 (68, 144.1)	109 (82, 167.2)	0.031
GFR (mL/min)				
First value postop	61 (42, 69)	61 (48, 69)	41 (32, 61)	<0.001
1st POD	59 (39, 61)	61 (43, 62)	40 (30, 60)	<0.001
3rd POD, 12.1% missing values	61 (43, 73)	61 (43.94)	61 (32, 66)	0.284
CK (U/L)				
First value postop	307 (203, 485)	295 (199, 451)	422 (250, 742.75)	<0.001
1st POD	314 (184, 619)	303 (183, 524)	527 (191, 1368)	0.002
CK-MB (U/L)				
First value postop, 8.7% missing data	56.7 (39.5, 79.9)	52.7 (37.1, 72.4)	83.4 (56.1, 147.0)	<0.001

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Table 5 (*Continued*)

Postoperative laboratory parameters	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
1st POD, 17.6% missing values	34.0 (24.5, 49.3)	33.4 (24.1, 44.3)	79.6 (33.6, 285.8)	<0.001
AST/GOT (U/L)				
First value postop	54.5 (40.0, 86.8)	51 (37.7, 75.5)	96 (62.7, 167)	<0.001
1st POD, 17.6% missing values	59.4 (41.3, 101.0)	55 (39.7, 81.2)	156.5 (61.9, 1391.8)	<0.001
ALT/GPT (U/L)				
First value postop, 6.4% missing values	19.7 (13.5, 32.1)	19.0 (13.0, 30.2)	28.0 (15.7, 56)	0.004
1st POD, 8.7% missing values	23.4 (15.6, 42.8)	22.2 (15.0, 35.5)	71.0 (19.8, 460.9)	<0.001
Bilirubin (μmol/L)				
First value postop, 7.5% missing values	18.1 (9.9, 35.8)	16.7 (9.3, 31.0)	43.3 (22.2, 62.1)	<0.001
1st POD, 12.6% missing values	18.0 (9.6, 39.3)	16.3 (9.0, 34.1	34.3 (21.9, 67.4)	<0.001
INR				
First value postop	1.24 (1.12, 1.37)	1.25 (1.14, 1.37)	1.22 (1.10, 1.14)	0.518
1st POD	1.18 (1.10, 1.28)	1.17 (1.09, 1.27)	1.24 (1.15, 1.14)	<0.001
3rd POD, 10.7% missing values	1.18 (1.09, 1.29)	1.17 (1.09, 1.29)	1.24 (1.11, 1.398)	0.051
CRP (mg/L)				
3rd POD	154 (110, 216)	155 (112, 216)	151 (86, 225)	0.544
4th POD	111 (78, 162)	112(78, 162)	103 (61, 188)	0.699
Leukocytes (10^9/L)				
First value postop	16.4 (10.8, 22.5)	15.7 (10.6, 22.0)	19.4 (12.6, 28.0)	0.002
1st POD	10.8 (8.2, 14.2)	10.6 (8.1, 14.0)	12.1 (9.9, 17.0)	0.007
3rd POD, 11.4% missing values	9.7 (7.6, 12.6)	9.4 (7.5, 12.2)	12.8 (9.80, 17.0)	<0.001
Platelets (10^9/L)				
First value postop	158 (117, 213)	159 (123, 217)	149 (99, 187)	0.009
1st POD	145 (111, 184)	150 (119, 190)	107 (82.75, 152.25)	<0.001
3rd POD, 11.4% missing values	148 (107, 199)	152 (115, 206)	84 (71, 131)	<0.001
AKI KDIGO	122 (29.2%)	82 (23.3%)	40 (60.6%)	<0.001
1	46 (38.0%)	40 (49.4%)	6 (15%)	
2	8 (6.6%)	6 (7.4%)	2 (5%)	
3	67 (55.4%)	35 (43.2%)	32 (80%)	
New-onset of hemodialysis	63 (15.1%)	30 (8.5%)	33 (52.4%)	<0.001
24-h drainage loss (mL)	650 (350, 1166)	600 (300, 1100)	800 (450, 1350)	0.090
Rethoracotomy due to bleeding/tamponade	52 (12.1%)	37 (10,2%)	15 (22,1%)	0.006
24-h number of packed red blood cells, unit	2 (0–27)	2 (0, 2)	3 (0, 5)	<0.001
24-h number of fresh-frozen plasma, unit	0 (0–29)	0 (0, 4)	6 (3, 9)	<0.001
24-h number of platelets, unit	0 (0–8)	0 (0, 0)	0 (0, 2)	<0.001
Ventilation time (h)	16 (9, 43)	14 (8, 36)	41 (19, 116)	<0.001
Reintubation	51 (12.0%)	37 (10.2%)	14 (21.9%)	0.008
Tracheotomy	59 (14.1%)	50 (14.1%)	9 (14.3)	0.973
ICU time (d)	3 (1, 7)	3(1, 7)	3 (1, 8.25)	0.208
Postoperative delirium	68 (16.1%)	60 (16.6%)	8 (13.1%)	0.496
Stroke	18 (4.3%)	14 (3.9%)	4 (6.6%)	0.311
CPR	23 (5.4%)	11 (3.0%)	12 (18.8%)	<0.001
Pacemaker patient, preop	45 (10.3%)	35 (9.7%)	10 (13.2%)	0.362

(*Continued*)

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Table 5 (*Continued*)

Postoperative laboratory parameters	All patients ($n = 438$)	Survivors ($n = 362$, 82.6%)	Nonsurvivors ($n = 76$, 17.4%)	*p*-Value
Pacemaker patient, new postop	21 (4.8%)	18 (5.0%)	3 (3.9%)	1.000
Defibrillator patient	3 (0.7%)	3 (0.8%)	0 (0.0%)	1.000
Postoperative myocardial infarction	5 (1.2%)	2 (0.6%)	3 (4.8%)	0.025
Bronchopulmonary infection	44 (10.2%)	27 (7.5%)	17 (24.6%)	<0.001
Sepsis	56 (13.0%)	16 (4.4%)	40 (57.1%)	<0.001
Sternal wound infection, 11.1% missing	10 (2.5%)	10 (2.8%)	0 (0.0%)	1.000
Hospital mortality	72 (16.5%)	5 (1.4%)	67 (88.2%)	<0.001
Cardiac death	11 (15.3%)	0 (0.0%)	11 (16.4%)	1.000
Cerebral death	1 (1.4%)	0 (0.0%)	1 (1.5%)	1.000
Sepsis	10 (13.9%)	1 (20.0%)	9 (13.4%)	0.538
MOF	50 (69.4%)	4 (80.0%)	46 (68.7%)	1.000
7-d mortality	51 (11.6%)	0 (0.0%)	51 (67.1%)	<0.001

Abbreviations: AKI, acute kidney injury; ALT/GPT, alanine aminotransferase/glutamic pyruvic transaminase; AST/GOT, aspartate transferase/glutamic oxaloacetic transaminase; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; INR, international normalized ratio; KDIGO, Kidney Disease: Improving Global Outcomes; MOF, multiple organ failure; postop, postoperative; preop, preoperative.

Table 6 Risk factor analysis for combined pre- and intraoperative conditions

Pre- and intraoperative combined	Odds ratio	95% CI	*p*-Value
Age (y)	1.026	0.998–1.055	0.072
Female gender	2.070	1.008–4.249	0.047
Cardiogenic shock	5.325	1.351–20.998	0.017
NYHA IV	4.110	1.913–8.829	<0.001
Chronic dialysis	8.797	2.511–30.812	<0.001
Prosthetic valve endocarditis	3.724	1.651–8.401	0.002
Hematocrit (%)	0.879	0.819–0.945	<0.001
Leukocytes (10^{-9}/L)	1.095	1.021–1.175	0.011
Platelets (10^{-9}/L)	0.995	0.991–0.998	0.003
Cardiopulmonary bypass time (min)	1.030	1.016–1.044	<0.001
Aortic clamp time (min)	0.970	0.954–0.988	<0.001
Mitral valve replacement/repair	2.571	1.234–5.356	0.012

Abbreviation: NYHA IV, New York Heart Association heart failure stage IV.

Reintubation was also significantly higher (21.9 vs. 10.2%; $p = 0.008$) and rate of bronchopulmonary infection (survivor 7.5 vs. nonsurvivor 24.6%, $p < 0.001$). Neither tracheostomy nor ICU stay in days was significantly different. Postoperative delirium did not show a significance. More nonsurviving patients developed a sepsis (57.1 vs. 4.4%; $p < 0.001$) and had to be resuscitated (18.8 vs. 3.0%; $p < 0.001$).

There were highly significant differences concerning 7-day mortality, which was 67.1% for the nonsurvivor group and due to study design 0% for the survivors $p < 0.001$). In-hospital mortality was 1.4% for the 30-day survivors and 85.5% for the nonsurvivors ($p < 0.001$).

In the final logistic regression analysis female gender (odds ratio [OR]: 2.070; 95% confidence interval [CI]: 1.008–4.249), chronic dialysis (OR: 8.797; 95% CI: 2.511–30.812; $p < 0.001$), cardiogenic shock (OR: 5.325; 95% CI: 1.351–20.998; $p = 0.017$), and NYHA class IV (OR: 4.110; 95% CI: 1.913–8.829; $p < 0.001$) were the strongest predictors for 30-day mortality. From the intraoperative variables prosthetic valve endocarditis (OR: 3.724; 95% CI: 1.651–8.401; $p = 0.002$), longer cardiopulmonary bypass time (OR: 1.030; 95% CI: 1.016–1.044; $p < 0.001$), and mitral valve replacement or repair (OR: 2.571; 95% CI: 1.234–5.356; $p = 0.012$) were risk factors for 30-day mortality.

Taking the laboratory parameters into account high hematocrit had rather a protective effect (OR: 0.879; 95% CI: 0.819–0.945; $p < 0.001$), as had high platelet count (OR: 0.995; 95% CI: 0.991–0.998; $p = 0.003$), whereas high leukocytes were a risk factor for 30-day mortality (OR: 1.095; 95% CI: 1.021–1.175; $p = 0.011$). See ►**Table 6** for logistic regression analysis.

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Discussion

IE is one of the most challenging surgical diseases.[4] Although treatment options have improved, disease burden is generally increasing.[5,6] Especially, since the modification of the endocarditis prophylaxis guidelines in 2002 patient numbers are continually rising.[7] Given scarce resources, it is eminent to evaluate which patients benefit mostly from early surgery and how survival might generally be improved.

Patients baseline characteristics differed significantly. As already known from other studies, patients in the nonsurvivor group were significantly older, yet age with an OR of 1.029 was not the strongest predictor for 30-day mortality looking at logistic regression analysis. Female gender has been shown to be an independent predictor for 30-day mortality in our previous study.[8] EuroScore II was significantly higher in our study group and was a good indicator for 30-day mortality. The EuroScore II in general is controversially discussed. While some researchers think it underestimates the mortality in cardiac surgery,[9,10] others believe it to be an appropriate tool for estimating perioperative risks even in IE patients.[11] Our study supports this assessment.

As previously reported reduced left ventricular function below 30% is an exceptionally high-risk factor for perioperative death. In our study group significant more patients of the 30-day mortality group had reduced left ventricular functions. It becomes more and more obvious that chronic dialysis has an impact on left ventricular function and cardiovascular events.[12] The exact pathways are not yet fully understood. Not surprisingly in our 30-day mortality group more patients had a preoperative acute renal insufficiency and chronic dialysis. Taking our logistic regression analysis into account, chronic dialysis is the most eminent risk factor for 30-day mortality. It is followed by cardiogenic shock, which is defined by low blood pressure caused by low cardiac output. NYHA class IV as the highest clinical parameter of heart failure was a strong predictor for 30-day mortality in our study as well.

Diabetes type II and insulin-depending diabetes were more frequent in the 30-day mortality group. Obesity and diabetes are widely known as risk factor for mortality in cardiac surgery.[13]

Surgical timing is not yet fully understood and thus a question of debate. The American College of Cardiology/American Heart Association endocarditis guidelines and the European Society for Cardiology endocarditis guidelines recommend specific parameters to be met for performing early valve surgery.[14,15] The time from diagnosis to surgery was significantly shorter in the nonsurvivor group. Also, significantly more patients had surgeries in less than 1 day from diagnosis in 30-day mortality group. The decision to perform early surgery is challenging, as there are numerable associated complications and the patient's response to antibiotic therapy is not predictable.[16] Bearing this in mind, it is also reasonable to understand that patients of the nonsurvivor group were in a worse preoperative state: they were often transferred from ICU and had more often emergency surgery. Thus, early surgery was in our analysis rather a necessity than a choice. In our study group, we could not demonstrate a survival benefit for early surgery in contrast to other groups.[16]

There were huge differences concerning pathogen spectrum. *Staphylococcus aureus*, which is deemed to be a predictor of late death and is discussed to increase risk of in-hospital mortality in the presence of decreased left ventricular function,[17] was significantly more common in the nonsurvivor group. Methicillin-resistant *S. aureus*, however, was not significantly higher. Streptococci (either viridans or gram-positive) were more common in the survivor group. In other centers Streptococci are the most common (up to 50%); we could not verify this finding.

Significantly more often affected was the aortic valve alone in the survivor group, whereas prosthetic valve endocarditis occurred only marginally more frequently in the nonsurvivor group. Yet, prosthetic valve endocarditis was an independent risk factor for 30-day mortality. Taking preoperative laboratory parameters into account higher hematocrit and higher platelet counts seem to have a protective effect against mortality. Higher leukocytes and C-reactive protein values seem to be an expression of worse clinical status. In combination with the higher appearance of *S. aureus*, this might hint that conventional antibiotic therapy is not sufficient in these critically ill patients and a therapeutic attempt with Exebacase, an antistaphylococcal lysin, could be a good choice for this group.[18]

According to the higher complexity of surgeries performed in the 30-day mortality group and the higher degree of destruction around the concerned valves length of surgery differed significantly between the groups as did cardiopulmonary bypass time. In logistic regression analysis cardiopulmonary bypass time was not a strong predictor for 30-day mortality. Yet, prosthesis endocarditis and mitral valve reconstruction or replacement could be determined as risk factors for 30-day mortality, thus supporting the hypothesis that more complex surgeries account for higher rates of 30-day mortality. Nonsurvivors received on average more red blood cell units, fresh-frozen plasma units, and a higher number of platelet units probably as a necessity due to their worse preoperative state. Most likely every blood transfusion itself is a risk factor for mortality as other studies also suggest.[19]

Postoperative data support the hypothesis that nonsurvivors were in a worse pre- and postoperative state. As retention values and transaminases were eminently higher, organ damage was ubiquitous more present in the 30-day mortality group. Reinforcing this impression were anytime higher lactate values. Nonrecovering from acute kidney injury is known to be associated with higher lactate levels.[20] In line with this, KDIGO stage 3 occurred mainly in the 30-day mortality group. Other organ damages like higher ventilation time, bronchopulmonary infection, cardiopulmonary resuscitation, myocardial infarction, and sepsis were much more likely to occur in the 30-day mortality group. Thus, helping to explain the reasons for hospital mortality, which were mainly multiorgan failure, cardiac death, and sepsis.

There were highly significant differences concerning 7-day mortality for the nonsurvivor group, which was 67.1% already. Thus, leading to the assumption that most factors leading to death were already determined at this early stage. In-hospital mortality rates vary from 15 to 30%.[16,21] In our study in-

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hospital mortality was 16.1% for all patients. This is comparable to other centers. In summary, this study indeed clearly indicates that significant risk factors for 30-day mortality cannot be changed. Nevertheless, they should be taken into account for preoperative counselling, and they will alert the surgical team for an even more careful management.

Limitations

Our results should be interpreted with caution and viewed as hypothesis generated in light of the retrospective study design from a single center. While treatment was performed according to guideline recommendations, it was still based on clinical judgment of the referring physicians and of the surgical team at our center.

Conclusion

In this study, several risk factors for 30-day mortality such as female gender, chronic dialysis, cardiogenic shock, prosthetic valve endocarditis, and NYHA class IV could be detected. They were partly depending not only on preoperative clinical status and pathogen spectrum, but also on surgical findings and variables. The strongest risk factors for 30-day mortality, which we found are not modifiable. However, female gender is associated with several modifiable parameters that should be taken into account. Yet, more ongoing multicenter studies are needed to evaluate intervention options.

Authors' Contribution

J.J.M. and C.F. shared the responsibility for conceptualization, methodology, validation, investigation, and project administration. J.J.M. was more responsible for data curation, whereas C.F. was mainly in charge of the formal analysis. They both wrote the original draft and did the review and editing.

Conflict of Interest

None declared.

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