Supplementary data

A. **Supplementary data for the Methods section**

A.1. Additional definitions and protocol details

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A. Methods

For this study, adult patients of both sexes, aged ≥ 18 years at the time of diagnosis, with a definite diagnosis of left-sided active IE, diagnosed or referred after diagnosis at either participating hospital during the inclusion period, were included.

Regarding the definition of a definite episode, until 2002, diagnoses were established according to the Duke criteria; thereafter, the modified Duke criteria were used until 2015. Since 2015, the European Society of Cardiology (ESC) modified diagnostic criteria have been used, which were updated in 2023.

A.1. Additional definitions and protocol details

Past and current clinical history, physical examination findings, data regarding blood tests and cultures, echocardiography, other imaging tests when carried out, clinical course during hospitalization, surgical indications, and surgery details when surgery was performed, were prospectively collected.

The definitions of the main variables analyzed are presented as follows.

Infection acquisition was defined as community-acquired if diagnosed ≤ 48 hours after admission without meeting criteria for a health care-associated infection, and as nosocomial if it manifested > 72 hours after admission, or within 8 weeks following hospital discharge.

As for comorbidities, prior chronic kidney disease (CKD) was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines; diabetes mellitus (DM) was diagnosed based on the criteria of the American Diabetes Association, and chronic obstructive pulmonary disease (COPD) as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 report.

In terms of clinical presentation, acute-onset IE was defined as cases with less than 15 days between symptom onset and diagnosis. Fever was defined as a temperature greater than 37.8ºC, with or without chills and/or deterioration of overall clinical status. Cardiac presentation was defined by the presence of symptoms and/or signs of heart failure, conduction disorders, acute ischemia, or new-onset murmurs; neurological presentation was based on the diagnosis of ischemic or hemorrhagic stroke, meningitis and/or brain abscess, or delirium without evidence of the former. The presence of asthenia, anorexia, and unintentional weight loss (at least 5% over a maximum period of 6 months) were the criteria that defined constitutional syndrome. Septic shock at any time of the IE episode was defined based on the Third International Consensus Definitions as persistent hypotension (systolic blood pressure < 90 mmHg and mean arterial pressure <65 mmHg) and peripheral tissue hypoperfusion (lactate > 2 mmol/L), despite adequate fluid resuscitation, in the context of sepsis. Septic shock is characterized by a decrease in systemic vascular resistance, with a generally preserved cardiac index. Acute kidney injury was defined as any of the following: increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours; or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 mL/kg/h for 6 hours. The diagnosis of systemic embolism was based on clinical signs and/or findings from imaging studies performed at the discretion of the treating physicians. Although no systematic screening was conducted, incidental findings from imaging performed for clinical reasons were included. Vegetations were measured in various planes and the greatest diameter was recorded for subsequent analysis. If there were multiple vegetations, the largest was measured.

Blood cultures were systematically obtained on admission in all patients included in the study. Empirical antibiotic therapy was initiated in accordance with guideline recommendations and was

subsequently adjusted based on antimicrobial susceptibility testing. Follow-up blood cultures were performed 48 to 72 hours after antibiotic initiation.

The indication and timing for cardiac surgery were decided by a multidisciplinary Endocarditis Team, always following the recommendations of the European guidelines (ie, heart failure, uncontrolled infection, and embolism prevention). Cardiac surgery was urgent if performed during antibiotic therapy, generally within the first week after indication; emergent if done within 24 hours of diagnosis or before the next working day, and elective if conducted after completion of antibiotic therapy. When a patient meeting surgical criteria did not undergo surgery, the reason was either patient refusal, unacceptably high surgical risk/frailty, or death before the date of surgery.

A.2. Statistical analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are expressed as mean ± standard deviation or median [interquartile range]. Normality was assessed using the Kolmogorov-Smirnov test. Qualitative variables were compared using the chi-square test or Fisher exact test. Quantitative variables were compared using the Student *t*-test, or the Mann-Whitney U test for nonnormally distributed variables.

The Cochran-Armitage test and the linear-by-linear trend test were used to evaluate trends across different periods.

Logistic regression analyses were performed to identify variables associated with in-hospital mortality, both in the whole cohort and in patients with PPBC. Variables that were statistically significant in the univariable analysis or considered clinically relevant were included in the multivariable regression analysis. Ten outcomes per one tested variable were considered to prevent overfitting. The model was developed using the Akaike information criterion.

For the final model, we calculated odds ratios (OR) adjusted for each of the variables included, along with their 95% confidence intervals (95%CI).

The models' performance was evaluated by assessing discrimination using the receiver operating characteristic curve and goodness-of-fit with the Hosmer-Lemeshow test. No significant

multicollinearity was found, as determined by variance inflation factors. The proportion of missing data was below 10% for all variables analyzed.

To assess the impact of surgical timing while minimizing immortal time bias and confounding by indication, we performed 3 complementary analyses. First, cardiac surgery was modelled as a time-dependent covariate in a Cox proportional-hazards model, with follow-up measured from the date of diagnosis and the baseline hazard stratified by hospital; patients contributed person-time to the nonoperated state until the day of surgery. Second, we estimated the average treatment effect of early surgery (≤ 7 days) using inverse-probability-of-treatment weighting (IPTW). The propensity score was derived from a logistic model including variables relevant for clinical decision-making. Stabilized weights were truncated at the 99th percentile, and covariate balance was assessed using standardized mean differences (balance defined as < 0.10). Third, time from diagnosis to surgery was modelled as a continuous variable using restricted cubic splines with 5 knots placed at standard percentiles. Finally, to evaluate surgical timing while minimizing immortal time bias, we conducted a landmark analysis at day 7, including only patients alive and not considered unsuitable for surgery at that time point, and comparing those who underwent surgery within vs beyond the first 7 days using an IPTW-weighted, hospital-stratified Cox model. In a sensitivity analysis, the day-7 landmark was restricted to patients still considered surgical candidates at that time point, excluding those in whom surgery had not been indicated or had been deemed prohibitive beforehand. Robust standard errors were used throughout. To evaluate the potential influence of the surgical era on outcomes, a surgery-by-era interaction term to day-7 was included in the landmark model.

A 2-tailed *P* value of < .05 was considered statistically significant. All analyses were performed using Stata 17 (StataCorp, College Station, TX).

B. Supplementary tables

Table S1. Comparison of epidemiological, clinical, microbiological, echocardiographic characteristics, and outcomes between patients with persistently positive blood cultures and those with blood culture clearance at 48 to 72 hours

	PPBC (n = 283)	Blood culture clearance (n = 548)	*P*
Epidemiological profile			
Age, y	70 [61-77]	69 [59-77]	.344
Male sex	182 (64.3)	365 (66.6)	.509
Nosocomial IE	87 (30.7)	115 (21)	**.002**
Referred from another hospital	126 (44.5)	252 (46)	.83
Intravenous drug user	5 (1.8)	11 (2)	.811
Comorbidities			
Diabetes mellitus	90 (31.8)	136 (24.8)	**.032**
Cancer	34 (12)	56 (10.2)	.43
Chronic anemia	59 (20.9)	111 (20.3)	.861
COPD	37 (13.1)	43 (7.9)	**.015**
CKD	43 (15.2)	82 (15)	.946
Predisposing valve disease			
Rheumatic valve disease	26 (9.2)	59 (10.8)	.477
Degenerative valve disease	68 (24)	147 (26.8)	.383
Prosthetic valve carrier	133 (47)	197 (36)	**.002**
Clinical manifestations at admission			
Acute onset	175 (62.1)	308 (56.6)	.125
Time from hospital admission to diagnosis, d	3 [1-8]	3 [0-7]	.073
Fever	239 (84.8)	460 (84.7)	.989
Constitutional syndrome	66 (23.5)	175 (32.2)	**.009**
Cardiac symptoms	93 (33)	168 (30.1)	.55
Neurological symptoms	53 (18.9)	114 (21)	.47
Microbiological profile			
Viridans group streptococci	22 (7.8)	123 (22.5)	**< .001**
Streptococcus gallolyticus	9 (3.2)	40 (7.3)	**.017**
Enterococci	54 (19.1)	66 (12)	**.006**
Staphylococcus aureus	94 (33.2)	102 (18.6)	**< .001**
Coagulase-negative staphylococci	54 (19.1)	93 (17)	.45
Gram-negative bacilli	11 (3.9)	18 (3.3)	.654
Fungi	11 (3.9)	3 (0.55)	**< .001**
HACEK group	3 (1.1)	3 (0.6)	.408
Anaerobes	1 (0.4)	4 (0.7)	.506
Polymicrobial	14 (5)	22 (4)	.532
Other	3 (1.1)	12 (2.2)	.246
Positive valve culture	40 (14.1)	58 (10.6)	.133
Echocardiographic data			
Aortic valve infection	116 (41.0)	235 (42.9)	.567
Mitral valve infection	120 (42.4)	237 (43.3)	.567
Mitral-aortic infection	47 (16.6)	76 (13.9)	.567
Prosthetic valve IE	132 (46.6)	193 (35.2)	**.001**
Severe valve regurgitation	83 (29.3)	240 (43.8)	**< .001**
Vegetation detection	248 (87.6)	462 (84.3)	.198
Vegetation maximum diameter, mm	13 [9-20]	13 [8-18]	.129
Periannular complications	85 (30)	158 (28.8)	.718
In-hospital complications occurring before surgery			
Acute heart failure	154 (54.4)	264 (48.2)	.088
Acute kidney injury	108 (38.2)	163 (29.7)	**.014**
Septic shock	66 (23.3)	133 (16)	**< .001**
Stroke	68 (24)	135 (24.6)	.847
Systemic embolisms	90 (31.8)	156 (28.5)	.318
Surgery			
Cardiac surgery	169 (59.7)	319 (58.2)	.676
Time from diagnosis to cardiac surgery, d	7 [3-15]	9 [3-18]	.388
Time from diagnosis to cardiac surgery <7 d	88 (52.1)	133 (46.4)	.237
Surgical indication: heart failure	91 (57.6)	206 (71.5)	**.003**
Surgical indication: uncontrolled infection	113 (71.5)	146 (50.7)	**< .001**
Surgical indication: embolic prevention	68 (43.0)	94 (32.6)	**.029**
Surgical procedure: mechanical prosthesis	77 (45.6)	176 (55.2)	**.012**
Surgical procedure: biological prosthesis	70 (41.4)	97 (30.4)	**.027**
Surgical procedure: stentless bioproshtesis	3 (1.8)	0 (0)	**.019**
Surgical procedure: aortic tube graft	4 (2.4)	13 (4.1)	.296
Surgical procedure: homograft	4 (2.4)	3 (0.9)	.226
Surgical procedure: mitral valve repair	3 (1.8)	14 (4.4)	.118
Outcomes			
In-hospital mortality	102 (36)	122 (22.3)	**< .001**

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IE, infective endocarditis; PPBC, persistently positive blood cultures.

The data are presented as No. (%) or median [interquartile range]. Bold values are significant. Acute onset was defined as a time from symptom onset to hospital admission of less than 15 days. Percentages for surgery-related variables were calculated based on the total number of patients who underwent surgery in each group.

Table S2. Epidemiological, clinical, microbiological, echocardiographic characteristics, and outcomes of episodes of left-sided infective endocarditis treated from 2020 to 2024, comparing patients with persistently positive blood cultures and those with blood culture clearance at 48 to 72 hours

	PPBC (n = 75)	Blood cultures clearance (n = 144)	*P*
Epidemiological profile			
Age, y	71 [63-78]	72 [62-79]	.985
Male sex	46 (61.3)	103 (71.5)	.125
Nosocomial IE	29 (38.7)	23 (15.6)	**< .001**
Referred from another hospital	41 (54.7)	59 (41.0)	.054
Intravenous drug user	1 (1.3)	3 (2.1)	.694
Comorbidities			
Diabetes mellitus	22 (29.3)	33 (22.9)	.299
Cancer	9 (12)	19 (13.2)	.802
Chronic anemia	16 (21.3)	25 (17.4)	.475
COPD	10 (13.5)	18 (12.5)	.832
CKD	14 (18.7)	28 (19.4)	.89
Predisposing valve disease			
Rheumatic valve disease	6 (8)	15 (10.4)	.564
Degenerative valve disease	27 (36)	54 (37.5)	.827
Prosthetic valve carrier	33 (44)	55 (38.2)	.406
Clinical manifestations at admission			
Fever	62 (82.7)	120 (83.3)	.901
Constitutional syndrome	18 (24)	47 (32.6)	.184
Cardiac symptoms	24 (32)	57 (39.6)	.27
Neurological symptoms	12 (16)	33 (22.9)	.229
Microbiological profile			
Viridans group streptococci	3 (4)	27 (18.8)	**.003**
Streptococcus gallolyticus	1 (1.3)	11 (7.6)	.052
Enterococci	18 (24)	21 (14.6)	.084
Staphylococcus aureus	30 (40)	24 (16.7)	**< .001**
Coagulase-negative staphylococci	11 (14.7)	31 (21.5)	.221
Gram-negative bacilli	4 (5.3)	5 (3.5)	.51
Fungi	5 (6.7)	2 (1.4)	**.035**
Echocardiographic data			
Prosthetic valve IE	32 (42.7)	57 (39.6)	.659
Severe valve regurgitation	23 (30.1)	56 (38.9)	.229
Vegetation detection	60 (80)	114 (79.2)	.885
Vegetation maximum diameter, mm	12 [9-19]	12 [8-18]	.814
Periannular complications	23 (30.1)	42 (29.2)	.818
In-hospital complications			
Acute heart failure	40 (53.3)	70 (48.6)	.507
Acute kidney injury	14 (18.7)	28 (19.4)	.89
Septic shock	11 (14.7)	21 (14.6)	.987
Stroke	21 (28)	41 (28.5)	.941
Systemic embolisms	24 (32)	43 (29.9)	.744
Outcomes			
Cardiac surgery	42 (56)	87 (60.4)	.528
No surgery despite indication	15 (20)	31 (21,8)	.754
Time from diagnosis to cardiac surgery, d	6 [3-11]	4 [1-14]	.575
Surgical indication: heart failure	26 (65.0)	50 (72.5)	.414
Surgical indication: uncontrolled infection	31 (77.5)	38 (55.1)	**.019**
Surgical indication: embolic prevention	25 (62.5)	33 (47.8)	.139
In-hospital mortality	17 (22.7)	38 (26.4)	.547

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IE, infective endocarditis; PPBC, persistently positive blood cultures.

The data are presented as No. (%) or median [interquartile range]. Bold values are significant. Percentages for surgery-related variables (time to surgery and surgical indication) were calculated based on the total number of patients who underwent surgery in each group.

Table S3. Univariable analysis of factors associated with in-hospital mortality in patients with left-sided infective endocarditis, positive blood cultures at admission, and control blood cultures at 48 to 72 hours

	Odds ratio	95% confidence interval		P
Age	1.02	1.01	1.03	**<.001**
Male sex	0.99	0.72	1.36	.941
Nosocomial IE	1.36	1.08	1.71	**.008**
Intravenous drug user	1.05	0.76	1.45	.771
Diabetes mellitus	1.66	1.19	2.31	**.003**
Cancer	0.98	0.6	1.61	.948
CKD	2.22	1.5	3.3	**<.001**
COPD	1.84	1.14	2.98	**.012**
Viridans group streptococci infection	0.31	0.18	0.52	**<.001**
Streptococcus gallolyticus infection	0.51	0.24	1.11	.089
Enterococci infection	0.88	0.57	1.39	.602
Staphylococcus aureus infection	3.08	2.19	4.33	**<.001**
Coagulase-negative staphylococci infection	1.1	0.74	1.64	.627
Gram-negative bacilli infection	1.69	0.79	3.64	.18
Fungi infection	0.45	0.1	2.01	.294
HACEK group infection	0.54	0.06	4.65	.575
Aortic valve infection	0.71	0.52	0.97	**.03**
Mitral valve infection	2	1.4	2.8	**<.001**
Mitral-aortic infection	1.01	0.81	1.26	.918
Prosthetic valve IE	1.12	0.82	1.53	.482
Severe valve regurgitation	0.69	0.5	0.95	**.024**
Vegetation detection	1.41	0.89	2.25	.144
Vegetation size	1.03	1.01	1.05	**.004**
Periannular complications	1.28	0.92	1.78	.145
Acute heart failure	2.5	1.81	3.44	**<.001**
Acute kidney failure	4.7	3.39	6.51	**<.001**
Septic shock	7.74	5.17	11.59	**<.001**
Systemic embolisms	1.08	0.77	1.51	.645
Stroke	1.26	0.89	1.79	.186
EuroSCORE I	1.05	1.03	1.07	**<.001**
RiskE score	1.04	1.03	1.06	**<.001**
Performance of cardiac surgery	0.6	0.44	0.82	**.001**
No surgery despite indication	5.76	3.83	8.64	**<.001**
Time from diagnosis to cardiac surgery	1.34	1.1	1.63	**.003**
Time from diagnosis to cardiac surgery > 7 d	0.9	0.58	1.41	.646
Persistently positive blood cultures at 48-72 h	1.97	1.44	2.7	**<.001**

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IE, infective endocarditis.

Bold values are significant.

Table S4. Trends in epidemiological, clinical, microbiological, echocardiographic, and prognostic variables in patients with left-sided infective endocarditis and persistently positive blood cultures at 48 to 72 hours

	Total (n = 283)	1998-2004 (n = 49)	2005-2009 (n = 35)	2010-2014 (n = 63)	2015-2019 (n = 61)	2020-2024 (n = 75)	*P*
Epidemiological profile							
Age, y	70 [61-77]	65 [48-70]	69 [59-75]	71 [64-78]	74 [67-80]	71 [63-78]	**< .001**
Male sex	182 (64.3)	33 (67.4)	21 (60)	39 (61.9)	43 (70.5)	46 (61.3)	.85
Nosocomial IE	87 (30.7)	9 (18.4)	14 (40)	13 (20.6)	22 (36.1)	29 (38.7)	**.002**
Referred from another hospital	126 (44.5)	16 (32.7)	10 (28.6)	31 (49.2)	28 (45.9)	41 (54.7)	**.002**
Intravenous drug user	5 (1.8)	4 (8.2)	0 (0)	0 (0)	0 (0)	1 (1.3)	**.019**
Comorbidities							
Diabetes mellitus	90 (31.8)	14 (28.6)	13 (37.1)	23 (36.5)	18 (29.5)	22 (29.3)	.733
Cancer	34 (12)	3 (6.1)	3 (8.6)	8 (12.7)	11 (18)	9 (12)	.172
Chronic anemia	59 (20.9)	4 (8.1)	9 (25.7)	15 (23.8)	15 (24.6)	16 (21.3)	.158
COPD	37 (13.1)	5 (10.2)	2 (5.7)	11 (17.4)	9 (14.8)	10 (13.5)	.383
CKD	43 (15.2)	5 (10.2)	5 (14.3)	11 (17.5)	8 (13.1)	14 (18.7)	.287
Predisposing valve disease							
Rheumatic valve disease	26 (9.2)	0 (0)	6 (17.1)	10 (15.9)	4 (6.6)	6 (8)	.682
Degenerative valve disease	68 (24)	3 (6.1)	7 (20)	11 (17.5)	20 (32.8)	27 (36)	**< .001**
Prosthetic valve carrier	133 (47)	28 (57.1)	9 (25.7)	31 (49.2)	32 (52.5)	33 (44)	.759
Clinical manifestations at admission							
Fever	239 (84.8)	44 (89.8)	31 (88.6)	50 (80.7)	52 (85.3)	62 (82.7)	.29
Constitutional syndrome	66 (23.5)	16 (32.7)	6 (17.1)	17 (27.9)	9 (14.8)	18 (24)	.264
Cardiac symptoms	93 (33)	15 (31)	11 (31.4)	21 (33.9)	22 (36.1)	24 (32)	.64
Neurological symptoms	53 (18.9)	7 (14.3)	8 (22.9)	14 (23)	12 (19.7)	12 (16)	.939
Microbiological profile							
Viridans group streptococci	22 (7.8)	7 (14.3)	1 (2.9)	8 (12.7)	3 (4.9)	3 (4)	.06
Streptococcus gallolyticus	9 (3.2)	3 (6.1)	2 (5.7)	1 (1.6)	2 (3.3)	1 (1.3)	.123
Enterococci	54 (19.1)	6 (12.2)	4 (11.4)	13 (20.6)	13 (21.3)	18 (24)	.054
Staphylococcus aureus	94 (33.2)	16 (32.7)	12 (34.3)	19 (30.2)	17 (27.9)	30 (40)	.529
Coagulase-negative staphylococci	54 (19.1)	11 (22.5)	7 (20)	11 (17.5)	14 (23)	11 (14.7)	.402
Gram-negative bacilli	11 (3.9)	3 (6.1)	1 (2.9)	1 (1.6)	2 (3.3)	4 (5.3)	.995
Fungi	11 (3.9)	0 (0)	1 (2.9)	1 (1.6)	4 (6.6)	5 (6.7)	**.031**
HACEK group	3 (1.1)	0 (0)	1 (2.9)	1 (1.6)	1 (1.6)	0 (0)	.736
Anaerobes	1 (0.4)	0 (0)	0 (0)	1 (1.6)	0 (0)	0 (0)	.846
Polymicrobial	14 (5)	2 (4.1)	2 (5.7)	4 (6.4)	4 (6.7)	2 (2.7)	.72
Other	3 (1.1)	0 (0)	2 (5.7)	0 (0)	1 (1.6)	0 (0)	.456
Echocardiographic data							
Prosthetic valve IE	132 (46.6)	28 (57.1)	9 (25.7)	31 (49.2)	32 (52.5)	32 (42.7)	.652
Severe valve regurgitation	83 (29.3)	14 (28.6)	10 (28.6)	21 (33.3)	15 (24.6)	23 (30.7)	.991
Vegetation detection	248 (87.6)	42 (85.7)	31 (88.6)	58 (92.1)	57 (93.4)	60 (80)	.42
Vegetation maximum diameter, mm	13 [9-20]	17 [11-20]	14 [8-19]	13 [9-17]	13 [10-20]	12 [9-19]	.332
Periannular complications	85 (30)	18 (36.7)	8 (22.9)	20 (31.8)	16 (26.2)	23 (30.7)	.621
In-hospital complications occurring before surgery							
Acute heart failure	154 (54.4)	26 (53.1)	17 (48.6)	37 (58.7)	34 (55.7)	40 (53.3)	.83
Acute kidney failure	108 (38.2)	27 (55.1)	13 (37.1)	30 (47.6)	24 (39.3)	14 (18.7)	**< .001**
Septic shock	66 (23.3)	18 (36.7)	8 (22.9)	17 (27)	12 (19.7)	11 (14.7)	**.005**
Stroke	68 (24)	12 (24.5)	6 (17.1)	14 (22.2)	15 (24.6)	21 (28)	.419
Systemic embolisms	90 (31.8)	14 (28.6)	8 (22.9)	25 (39.7)	19 (31.2)	24 (32)	.556
Outcome							
Cardiac surgery	169 (59.7)	28 (57.1)	21 (60)	39 (61.9)	39 (63.9)	42 (56)	.961
Time from diagnosis to cardiac surgery, d	7 [3-15]	14 [3-30]	12 [8-22]	7 [2-15]	7 [3-14]	6 [3-11]	**.003**
In-hospital mortality	102 (36)	28 (57.1)	10 (28.6)	24 (38.1)	23 (37.7)	17 (22.7)	**.001**

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IE, infective endocarditis.

The data are presented as No. (%) or median [interquartile range]. Bold values are significant.

Table S5. Comparison of patients with persistently positive blood cultures at 48 to 72 hours who underwent cardiac surgery within the first 7 days after diagnosis and those who underwent surgery more than 7 days after diagnosis

	Time from diagnosis to surgery < 7 d (n = 88)	Time from diagnosis to surgery ≥ 7 d (n = 81)	*P*
Age, y	68 [56-75]	69 [61-75]	.282
Diabetes mellitus	26 (29.6)	26 (32.1)	.719
Cancer	4 (4.6)	10 (12.4)	.066
Chronic anemia	13 (14.8)	14 (17.3)	.656
COPD	5 (5.8)	10 (12.4)	.134
CKD	10 (11.4)	9 (11.1)	.959
Rheumatic valve disease	6 (6.8)	9 (11.1)	.327
Degenerative valve disease	23 (26.1)	13 (16.1)	.11
Prosthetic valve carrier	36 (40.9)	36 (44.4)	.642
Fever	71 (80.7)	69 (86.3)	.333
Constitutional syndrome	17 (19.3)	24 (30)	.107
Cardiac symptoms	29 (33)	23 (28.8)	.556
Neurological symptoms	18 (20.5)	19 (23.8)	.607
Viridans group streptococci	3 (3.4)	11 (13.6)	**.017**
Streptococcus gallolyticus	3 (3.4)	6 (7.4)	.248
Enterococci	8 (9.1)	12 (14.8)	.25
Staphylococcus aureus	38 (43.1)	20 (24.7)	**.011**
Coagulase-negative staphylococci	18 (20.5)	16 (19.8)	.91
Gram-negative bacilli	2 (2.3)	2 (2.5)	.933
Fungi	7 (8)	4 (5)	.427
HACEK group	1 (1.1)	1 (1.2)	.953
Anaerobes	1 (1.1)	0 (0)	.336
Polymicrobial	4 (4.6)	6 (7.4)	.431
Prosthetic valve IE	37 (42.1)	35 (43.2)	.878
Severe valve regurgitation	38 (43.2)	28 (34.6)	.252
Vegetation detection	80 (90.9)	71 (87.7)	.493
Vegetation maximum diameter, mm	16 [11-20]	12 [8-19]	.097
Periannular complications	29 (33)	34 (42)	.226
Acute heart failure	46 (52.3)	42 (51.9)	.956
Acute kidney injury	32 (36.4)	27 (33.3)	.68
Septic shock	21 (23.9)	9 (11.1)	**.03**
Stroke	19 (21.6)	26 (32.1)	.123
Systemic embolisms	29 (33)	33 (40.7)	.294
In-hospital mortality	19 (21.5)	29 (35.8)	**.049**

CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; IE: infective endocarditis.

The data are presented as No. (%) or median [interquartile range]. Bold values are significant.

Table S6. Propensity-score covariate balance (IPTW): standardized mean differences

Covariate	Unweighted SMD	ITPW-weighted SMD
Age, y	−0.141	+0.032
Male sex	+0.267	+0.028
Frailty (Frail scale)	−0.021	+0.002
S. aureus infection	+0.372	+0.030
Septic shock	+0.356	+0.008
Acute kidney failure	−0.003	+0.013
Acute heart failure	+0.070	+0.022
CNS embolism	−0.244	−0.047
Cerebral hemorrhage	−0.132	−0.021

IPTW, inverse probability of treatment weighting; SMD, standardized mean difference between early (≤ 7 d) and late (> 7 d) surgery. |SMD|< 0.10 indicates good balance. After IPTW all covariates were well balanced (|SMD|<0.05), including frailty and cerebral hemorrhage.