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RESEARCH ARTICLE

Characteristics, management, and outcomes of patients with left-sided infective endocarditis complicated by heart failure: a substudy of the ESC-EORP EURO-ENDO (European infective endocarditis) registry

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Aims To evaluate the current management and survival of patients with left-sided infective endocarditis (IE) complicated by congestive heart failure (CHF) in the ESC-EORP European Endocarditis (EURO-ENDO) registry.

Methods and results Among the 3116 patients enrolled in this prospective registry, 2449 (mean age: 60 years, 69% male) with left-sided (native or prosthetic) IE were included in this study. Patients with CHF (n = 698, 28.5%) were older, with more comorbidity and more severe valvular damage (mitro-aortic involvement, vegetations >10 mm and severe regurgitation/new prosthesis dehiscence) than those without CHF (all $p \leq 0.019$). Patients with CHF experienced higher 30-day and 1-year mortality than those without (20.5% vs. 9.0% and 36.1% vs. 19.3%, respectively) and CHF remained strongly associated with 30-day (odds ratio[OR] 2.37, 95% confidence interval [CI] [1.73–3.24; $p < 0.001$) and 1-year mortality (hazard ratio [HR] 1.69, 95% CI 1.39–2.05; $p < 0.001$) after adjustment for established outcome predictors, including early surgery, or after propensity matching for age,

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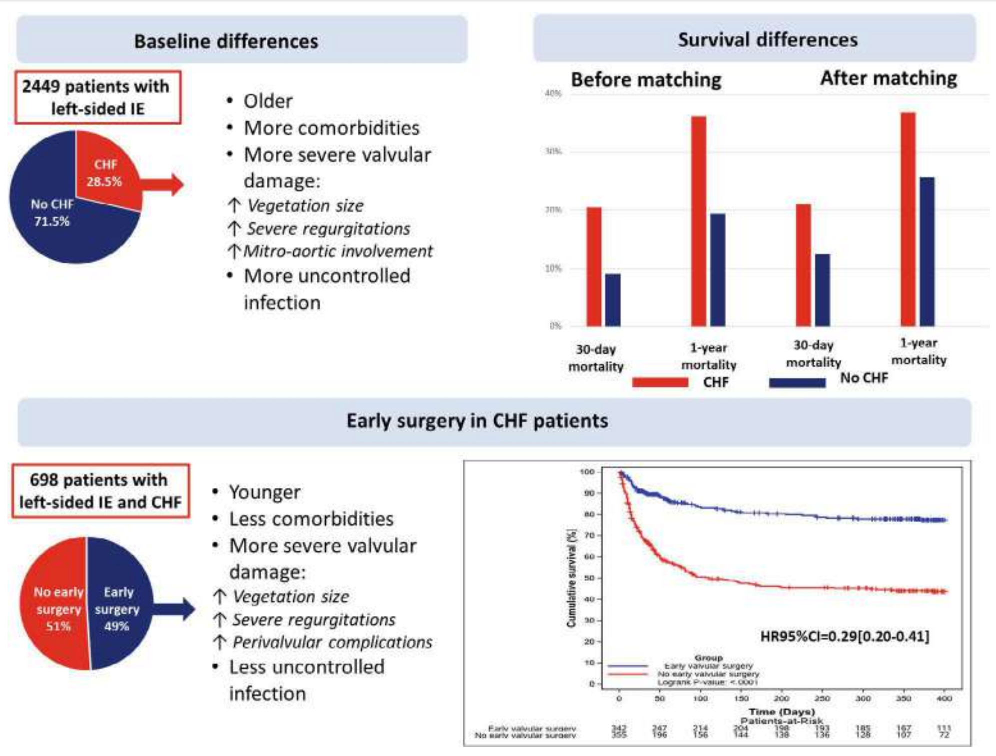
sex, and comorbidity (n = 618 [88.5%] for each group, both $p < 0.001$). Early surgery, performed on 49% of these patients with IE complicated by CHF, remained associated with a substantial reduction in 30-day mortality following multivariable analysis, after adjustment for age, sex, Charlson comorbidity index, cerebrovascular accident, *Staphylococcus aureus* IE, streptococcal IE, uncontrolled infection, vegetation size >10 mm, severe valvular regurgitation and/or new prosthetic dehiscence, perivalvular complication, and prosthetic IE (OR 0.22, 95% CI 0.12–0.38; $p < 0.001$) and in 1-year mortality (HR 0.29, 95% CI 0.20–0.41; $p < 0.001$).

Conclusion Congestive heart failure is common in left-sided IE and is associated with older age, greater comorbidity, more advanced lesions, and markedly higher 30-day and 1-year mortality. Early surgery is strongly associated with lower mortality but is performed on only approximately half of patients with CHF, mainly because of a surgical risk considered prohibitive.

Graphical Abstract



Characteristics, survival and impact of early surgery in left-sided infective endocarditis (IE) complicated by congestive heart failure (CHF). CI, confidence interval; HR, hazard ratio.

Keywords Infective endocarditis • Congestive heart failure • Survival • Outcome • Early surgery • EURO-ENDO

Introduction

Despite major advances in diagnosis, antimicrobial and surgical management, infective endocarditis (IE) remains a deadly disease,[1,2] associated with serious complications and substantial mortality.[1–6]

Congestive heart failure (CHF) is a strong prognostic factor in native valve[7,8] and prosthetic IE[8,9] and is one of the main indications for early surgery.[5,6] Approximately a decade ago, two studies reported that CHF is common in IE and an independent predictor of in-hospital and 1-year mortality and that, although early surgery is independently associated with reduced mortality of these patients, it is only performed in approximately 50% to 60% of cases.[7,8] No recent data have been published on the clinical characteristics, management, or outcomes of patients with left-sided IE complicated by CHF. However, the epidemiology of IE has significantly changed over the years and new strategies have been developed to improve its diagnosis and prognosis.[5,6] In this context, we aimed to use data from the European Society of Cardiology EURObservational Research Programme (ESC-EORP) European Endocarditis (EURO-ENDO) registry,[6] which was prospectively designed to assess the current clinical, epidemiological, microbiological, therapeutic, and prognostic characteristics of IE in Europe.[9] The aims of this study on this large contemporary cohort were four-fold: (i) to describe the characteristics of patients with left-sided IE complicated by CHF, to evaluate the (ii) management and (iii) survival of these patients relative to those with left-sided IE but without CHF – before and after propensity matching – and, finally, (iv) to investigate outcome predictors and the impact of early surgery on CHF patients.

Methods

Study population and data collection

The ESC-EORP EURO-ENDO registry is a prospective multicentre observational study that was conducted between 1 January 2016 and 31 March 2018 in 156 centres in 40 countries (76.9% from ESC-affiliated countries). A more detailed description of the inclusion and data collection has already been published.[6,9] Briefly, 3116 patients with a diagnosis of definite IE (or possible IE considered and treated as IE), based on the 2015 ESC IE diagnostic criteria,[5] were included in the registry. Patients with isolated right-sided – native or prosthetic – IE or isolated pacemaker/intracardiac defibrillator IE were excluded and, finally, 2449 patients (78.6%) were included in the study. Demographic, clinical, biological, microbiological, and imaging data were collected at inclusion and during hospitalization. An index summing the patients' individual comorbidities (Charlson comorbidity index) was calculated.[10] Perivalvular complications were defined as abscesses or pseudoaneurysms[5] and uncontrolled infection as positive blood cultures after 48 h of antimicrobial treatment and/or increasing vegetation size under treatment and/or septic shock. The presence of CHF was determined by clinicians at each recruitment site on the basis of clinical symptoms, signs, laboratory results, and chest X-rays according to the Framingham criteria.[11] The registry was supervised by an executive committee and managed by the EORP department of the ESC, which was in charge of study management, data quality control, and statistical analysis. National coordinators, in conjunction with local centres, (or) participating centres (depending on whether they are country/centre based) managed the approvals of national or regional ethics committees or Institutional Review Boards, according to local regulations. Written informed consent was given by all participants.[6,9]

Follow-up and endpoints

The primary endpoints were 30-day and 1-year mortality. Data on complications (embolic events, infectious, and haemodynamic complications) and surgery (theoretical indications and timing) were collected during hospitalization. Theoretical indications for surgery were defined set by the attending physician, based on guidelines and divided into three categories: haemodynamic (acute regurgitation, obstruction or fistula causing refractory pulmonary oedema or cardiogenic shock or symptoms of CHF), embolic (large vegetations after embolic complications of very large vegetations) and infectious (perivalvular complications or uncontrolled infection).[5] The 1-year follow up was performed by contacting participants by telephone and/or scheduled appointments at outpatient clinics.[6,9] Early surgery was defined as surgery performed within 30 days of IE diagnosis.

Statistical analysis

For descriptive analyses, continuous variables were reported as means ± standard deviations or medians and interquartile ranges (IQRs) and categorical variables as counts and percentages. Patients were divided into two groups according to the presence or absence of CHF at baseline. Comparisons between groups were performed using a χ^2 test for categorical variables and a Kruskal–Wallis test for continuous variables. Before performing multivariable analysis, multicollinearity was investigated on candidate variables (correlation matrix, variance inflation, tolerance, Eigen value and condition index). Multivariable logistic regression was performed to identify independent predictors of 30-day mortality in both the overall and CHF populations with variables associated with a $p \leq 0.15$ in univariate analysis, which were considered to be of clinical relevance (age, sex, Charlson index, cerebrovascular accident, *Staphylococcus aureus* infection, Streptococcal infection, uncontrolled infection, vegetation>10 mm, severe valvular regurgitation and/or new prosthetic dehiscence, perivalvular complication, and prosthetic IE) and early surgery included in the model.[7,8,12–17] No interaction was tested and Hosmer and Lemeshow goodness of fit test, percent concordant and C-statistic were calculated. Kaplan–Meier curves for time to death due to all causes were generated. Multivariable Cox analyses were performed to identify independent predictors of 1-year mortality. Cox multivariable models incorporated the above-mentioned classical prognostic factors and early surgery. A propensity analysis was also performed to account for the imbalance of covariates between CHF and non-CHF patients. The propensity score was fitted using gender, age, and Charlson index. The logit of the propensity score was used in computing differences between pairs of observations and the caliper was 0.30. In this matched population, McNemar's test was used for binary variables, Bowker's test for qualitative variables with more than two possibilities and rank-signed tests for quantitative variables. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC, USA) and R version 3.5.1.

Results

Patient characteristics and management

Overall population

Among the 2449 patients included in this study (mean age 60 years, 69% male), 698 (28.5%) presented with CHF (39.3% in New York Heart Association [NYHA] class I–II and 60.7% in NYHA class III–IV). Patients with CHF were older, with higher creatinine serum levels and more comorbidity, as reflected by the Charlson index (all $p < 0.001$) (*Table 1*). Patients without CHF more often had fever, cerebrovascular accidents, embolic events, and positive

Table 1 Baseline characteristics between infective endocarditis patients with and without congestive heart failure on admission in the overall study population

Characteristics	Total (*n* = 2449)	Patients with CHF (*n* = 698)	Patients without CHF (*n* = 1751)	*p*-value
Region of origin, n (%)				**0.008**
Europe	1676 (68.4)	493 (70.6)	1183 (67.6)	
Oceania	65 (2.7)	20 (2.9)	45 (2.6)	
Africa	122 (5.0)	45 (6.4)	77 (4.4)	
America	212 (8.7)	59 (8.5)	153 (8.7)	
Asia	374 (15.3)	81(11.6)	293 (16.7)	
Patient characteristics				
Age (years), mean ± SD	60.41 ± 17.28	62.80 ± 17.62	59.46 ± 17.05	**<0.001**
Male sex, *n* (%)	1683 (68.7)	485 (69.5)	1198 (68.4)	0.607
Diabetes mellitus, *n* (%)	547/2445 (22.4)	203/698 (29.1)	344/1747 (19.7)	**<0.001**
Charlson index, mean ± SD	3.52 ± 2.87	4.41 ± 3.11	3.15 ± 2.68	**<0.001**
Previous IE, *n* (%)	200 (8.2)	43 (6.2)	157 (9.0)	**0.022**
Intracardiac devices (PM/ICD/CRT), *n* (%)	211 (8.6)	80 (11.5)	131 (7.5)	**0.002**
Fever, *n* (%)	1857/2418 (76.8)	505/692 (73.0)	1352/1726 (78.3)	**0.005**
Cerebrovascular accident, *n* (%)	191/2418 (7.9)	35/692 (5.1)	156/1726 (9.0)	**0.001**
Embolic events, *n* (%)	613 (25.0)	151 (21.6)	462 (26.4)	**0.014**
Biochemistry, median (IQR)				
Serum creatinine (μmol/L)	92.0 (71.6–131.0)	106.1 (79.6–153.0)	88.4 (70.7–120.0)	**<0.001**
CRP (mg/L)	63.0 (18.3–130.5)	64.3 (20.0–137.0)	62.1 (18.0–130.0)	0.779
Haemoglobin (g/dl)	10.7 (9.3–12.2)	10.4 (9.0–11.7)	11.0 (9.5–12.3)	**<0.001**
Microbiology on admission, *n* (%)				
Positive blood culture	1938 (79.1)	523 (74.9)	1415 (80.8)	**0.001**
Any type of *Staphylococcus aureus*	499/1938 (25.7)	144/523 (27.5)	355/1415 (25.1)	0.274
Methi-S *Staphylococcus aureus*	390/1938 (20.1)	107/523 (20.5)	283/1415 (20.0)	0.823
Methi-R *Staphylococcus aureus*	114/1938 (5.9)	38/523 (7.3)	76/1415 (5.4)	0.116
Any type of coagulase-negative *Staphylococcus*	237/1938 (12.2)	61/523 (11.7)	176/1415 (12.4)	0.644
Methi-S coagulase-negative *Staphylococcus*	116/1938 (6.0)	23/523 (4.4)	93/1415 (6.6)	0.073
Methi-R coagulase-negative *Staphylococcus*	125/1938 (6.4)	38/523 (7.3)	87/1415 (6.1)	0.374
Streptococcus viridans	274/1938 (14.1)	65/523 (12.4)	209/1415 (14.8)	0.189
Enterococcus	334/1938 (17.2)	103/523 (19.7)	231/1415 (16.3)	0.081
Streptococcus bovis	146/1938 (7.5)	44/523 (8.4)	102/1415 (7.2)	0.372
Gram-negative bacillus	61/1938 (3.1)	20/523 (3.8)	41/1415 (2.9)	0.300
Other	472/1938 (24.4)	106/523 (20.3)	366/1415 (25.9)	**0.011**
Location of IE, *n* (%)				
Aortic	1514 (61.8)	448 (64.2)	1066 (60.9)	0.129
Mitral	1284 (52.4)	370 (53.0)	914 (52.2)	0.717
Aortic and mitral	349 (14.3)	120 (17.2)	229 (13.1)	**0.009**
Tricuspid	104 (4.2)	39 (5.6)	65 (3.7)	**0.038**
Prosthetic IE	817 (33.4)	229 (32.8)	588 (33.6)	0.714
Antimicrobial therapy, *n* (%)				
B-lactamine (penicillin G + amoxicillin + ceftriaxone + oxacillin)	1573/2431(64.7)	429/694(61.8)	1144/1737 (65.9)	0.059
Vancomycin	1017/2431 (41.8)	311/694 (44.8)	706/1737 (40.6)	0.060
Daptomycin	266/2431 (10.9)	84/694 (12.1)	182/1737 (10.5)	0.246
Rifampicin	435/2431 (17.9)	114/694 (16.4)	321/1737 (18.5)	0.233
Gentamicin	1401/2431 (57.6)	375/694 (54.0)	1026/1737 (59.1)	**0.023**
Echocardiographic findings				
Vegetations >10 mm, *n* (%)	836/2153 (38.8)	264/618 (42.7)	572/1535 (37.3)	**0.019**
Abscess or pseudoaneurysm, *n* (%)	379 (15.5)	118 (16.9)	261 (14.9)	0.217
Severe regurgitation or new prosthetic dehiscence, *n* (%)	1095 (44.7)	414 (59.3)	681 (38.9)	**<0.001**
Left ventricular ejection fraction (%), median (IQR)	59.0 (50.0–65.0)	55.0 (46.0–62.0)	60.0 (55.0–65.0)	**<0.001**
Right ventricular systolic pressure (mmHg), median (IQR)	38.0 (30.0–50.0)	46.0 (35.0–58.0)	35.0 (28.0–45.0)	**<0.001**
Uncontrolled infection, *n* (%)	560/2428 (23.1)	192/696 (27.6)	368/1732 (21.2)	**<0.001**
Positive blood cultures after 48 h	315/2425 (13.0)	95/694 (13.7)	220/1731 (12.7)	0.517
Increasing vegetation size	157 (6.4)	51 (7.3)	106 (6.1)	0.253
Septic shock	229 (9.4)	104 (14.9)	125 (7.1)	**<0.001**

CHF, congestive heart failure; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; IE, infective endocarditis; IQR, interquartile range; Methi-R, methicillin-resistant; Methi-S, methicillin-sensitive; PM, pacemaker; SD, standard deviation.

Table 2 Results of the multivariable logistic regression for 30-day mortality and the multivariable Cox analysis for 1-year mortality in the overall study population

Predictors of 30-day mortality	Odds ratio	95% CI	*p*-value
CHF	2.37	1.73–3.24	**<0.001**
Age (per 10-year increase)	0.99	0.89–1.11	0.923
Male sex	0.98	0.71–1.34	0.874
Charlson index (per unit)	1.13	1.06–1.19	**<0.001**
Cerebrovascular accident	2.00	1.24–3.23	**0.005**
Staphylococcus aureus IE	1.48	1.05–2.09	**0.026**
Streptococcal IE	0.44	0.25–0.79	**0.005**
Uncontrolled infection[a]	2.67	1.96–3.64	**<0.001**
Vegetation >10 mm	2.00	1.46–2.73	**<0.001**
Severe regurgitation/new prosthetic dehiscence	1.46	1.04–2.05	**0.028**
Perivalvular complication[b]	1.24	0.81–1.89	0.316
Prosthetic IE	1.41	1.01–1.97	**0.046**
Early surgery	0.37	0.26–0.53	**<0.001**
Predictors of 1-year mortality	**Hazard ratio**	**95% CI**	***p*-value**
CHF	1.69	1.39–2.05	**<0.001**
Age (per 10-year increase)	1.02	0.95–1.10	0.551
Male sex	1.03	0.85–1.26	0.737
Charlson index (per unit)	1.12	1.08–1.15	**<0.001**
Cerebrovascular accident	1.38	1.02–1.88	**0.037**
Staphylococcus aureus IE	1.40	1.14–1.73	**0.001**
Streptococcal IE	0.60	0.44–0.83	**0.002**
Uncontrolled infection[a]	2.26	1.87–2.73	**<0.001**
Vegetation >10 mm	1.32	1.09–1.60	**0.005**
Severe regurgitation/new prosthetic dehiscence	1.30	1.06–1.60	**0.012**
Perivalvular complication[b]	1.30	1.01–1.66	**0.040**
Prosthetic IE	1.10	0.90–1.35	0.346
Early surgery	0.46	0.37–0.57	**<0.001**

CHF, congestive heart failure; CI, confidence interval; IE, infective endocarditis.
[a]Positive blood cultures after 48 h of antimicrobial treatment and/or increasing vegetation size and/or septic shock.
[b]Abscess or pseudoaneurysm.

blood cultures than those with CHF (all $p \leq 0.014$). CHF patients had lower ejection fraction and greater pulmonary pressures. In terms of IE lesions, patients with CHF more frequently had both aortic and mitral valve involvement, vegetations larger than 10 mm and severe regurgitation or new prosthesis dehiscence than those without (all $p \leq 0.019$). Uncontrolled infection was more common among patients with CHF than those without signs of CHF, especially septic shock (14.9% vs. 7.1%, $p < 0.001$) (*Table 1*). CHF patients more frequently had a theoretical indication for early surgery (i.e. haemodynamic, infectious or embolic) than those without (81.5% vs. 68.4%, $p < 0.001$), which was mainly haemodynamic (71.4%) (online supplementary *Table S1*). Early surgery (<30 days) was performed on 1084 patients (44.3%) and was more frequent for CHF patients (49.1% vs. 42.4%, $p = 0.003$), with a shorter time from inclusion to surgery ($p = 0.007$) (online supplementary *Table S1*).

Propensity-matched cohort

A total of 618 patients with CHF (88.5%) were successfully matched (standardized differences for age, sex, and Charlson index were 0.03, 0.02, and 0.01, respectively, after matching) with 618 patients without CHF. Cerebrovascular accidents, embolic events, and positive blood cultures were still more frequent among patients without CHF, whereas vegetations >10 mm and severe regurgitation or new prosthesis dehiscence were more prevalent in CHF patients (all $p \leq 0.009$), on whom early surgery was more often performed (46.3% vs. 36.9%, $p < 0.001$) (online supplementary *Tables S2* and *S3*).

Outcomes

Overall population

Patients with CHF experienced higher 30-day mortality than those without (20.5% vs. 9.0%, $p < 0.001$) (online supplementary *Table S1*). CHF remained strongly associated with 30-day mortality following multivariable logistic regression, after adjustment for age, sex, Charlson index, cerebrovascular accident, *Staphylococcus aureus* IE, streptococcal IE, uncontrolled infection, vegetation size >10 mm, severe valvular regurgitation and/or new prosthetic dehiscence, perivalvular complication, prosthetic IE, and early surgery (odds ratio [OR] 2.37, 95% confidence interval [CI] 1.73–3.24, $p < 0.001$) (*Table 2*).

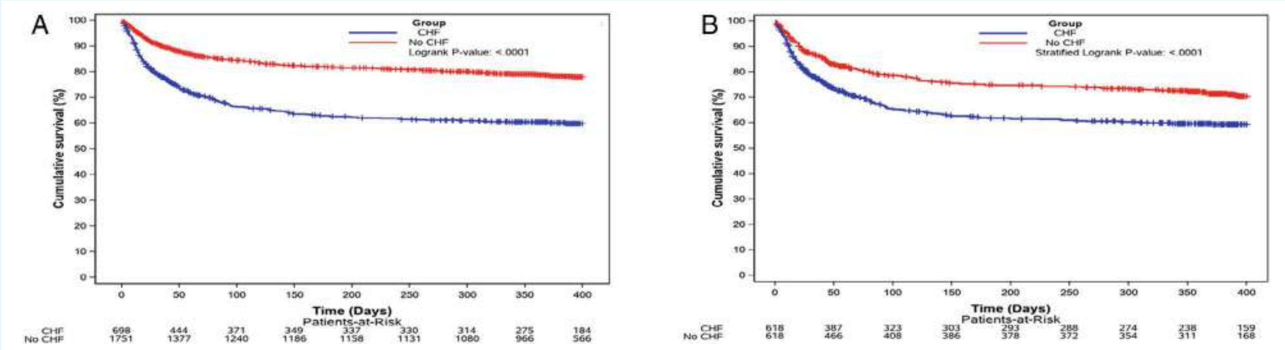


Figure 1 Kaplan–Meier 1-year survival curves (*A*) in the overall study population and (*B*) in the propensity-matched cohort (for age, sex, and Charlson index). CHF, congestive heart failure.

One year mortality was 36.1% for patients with CHF and 19.3% for those without (log-rank $p < 0.001$) (*Figure 1A*, online supplementary *Table S1*). CHF remained independently associated with 1-year mortality following multivariable Cox analysis (hazard ratio [HR] 1.69, 95% CI 1.39–2.05, $p < 0.001$) (*Table 2*).

Propensity-matched cohort

After propensity matching, patients with CHF still had higher 30-day mortality than those without (21.0% vs. 12.5%, $p < 0.001$) (online supplementary *Table S3*). One-year mortality was 36.7% for patients with CHF and 25.7% for those without (stratified log-rank $p < 0.001$) (*Figure 1B*, online supplementary *Table S3*).

Outcomes and management of congestive heart failure patients

Mortality

Baseline characteristics of CHF patients according to 30-day mortality are presented in *Table 3*. CHF patients who died within 30 days of inclusion were more often women, with a higher Charlson index and NYHA stage, lower left ventricular ejection fraction, higher creatinine and C-reactive protein values, more *Staphylococcus aureus* infections, and fewer streptococcal infections than those who survived (all $p \leq 0.033$). Uncontrolled infection was more common for deceased patients, particularly septic shock (39.2% vs. 8.6%, $p < 0.001$) (*Table 3*). By multivariable logistic regression, the Charlson index, vegetation size >10 mm, and uncontrolled infection were associated with 30-day mortality, whereas streptococcal IE and early surgery were associated with better 30-day survival (*Table 3*).

By multivariable Cox analysis, the Charlson index and uncontrolled infection remained associated with 1-year mortality, whereas early surgery was associated with improved survival (*Table 3*).

Performance and impact of early surgery

Four hundred patients (57.4% [data missing for one patient], 70.3% of those with theoretical indication for early surgery) with CHF underwent valvular surgery, including 342 (49.1%) within 30 days of IE diagnosis (median: 7 [3–14] days). The main reason advocated by the attending physician for not performing surgery when it was indicated was the operative risk (online supplementary *Table S1*). CHF patients who underwent early surgery were younger, more often men with a lower Charlson index, and had more *Streptococcus viridans* infections but fewer *Staphylococcus aureus* IE than patients under medical management (all $p \leq 0.010$) (*Table 4*). In terms of IE lesions and complications, CHF patients who underwent early surgery were more likely to have aortic valve lesions, vegetations larger than 10 mm, perivalvular complications, and severe regurgitation or new prosthesis dehiscence than other CHF patients but less likely to have a prosthetic IE or uncontrolled infection (all $p \leq 0.007$), with much less septic shock (7.9% vs. 21.7%, $p < 0.001$) (*Table 4*). Among CHF patients, early surgery was performed more frequently in case of streptococcal (55.3% of cases of streptococcus-related IE) or enterococcal (55% of cases) infection than in cases of staphylococcal infection (39.7% of cases, both $p < 0.01$).

Patients with CHF who underwent early surgery had lower 30-day (9.4% vs. 31.3%, $p < 0.001$) and 1-year mortality (19.0% vs. 52.7%, log-rank $p < 0.001$) than CHF patients under medical management (*Table 4*, *Figure 2*). Early surgery remained associated with a substantial reduction in 30-day (OR 0.22, 95% CI 0.12–0.38, $p < 0.001$) and 1-year mortality (hazard ratio [HR] 0.29, 95% CI 0.20–0.41, $p < 0.001$) following multivariable analysis, after adjustment for age, sex, Charlson index, cerebrovascular accident, *Staphylococcus aureus* IE, streptococcal IE, uncontrolled infection, vegetation size >10 mm, severe valvular regurgitation and/or new prosthetic dehiscence, perivalvular complication, and prosthetic IE (*Table 3*). Patients with CHF who underwent emergent surgery (<48 h) were younger with less comorbidity than those operated between 48 h and 30 days and experienced higher rates of 30-day mortality (14.8% vs. 7.5%; $p = 0.043$) (online supplementary *Table S5*). After adjustment, 30-day mortality (OR 0.97, 95% CI 0.31–3.09) and 1-year mortality (HR 1.10, 95% CI 0.59–2.05) were comparable in these two subgroups.

Table 3 Results of the multivariable logistic regression for 30-day mortality and the multivariable Cox analysis for 1-year mortality in congestive heart failure patients

Predictors of 30-day mortality	Odds ratio	95% CI	*p*-value
Age (per 10-year increase)	0.93	0.79–1.10	0.381
Male sex	0.71	0.45–1.14	0.160
Charlson index (per unit)	1.10	1.01–1.20	**0.026**
Cerebrovascular accident	1.49	0.56–3.92	0.424
Staphylococcus aureus IE	0.95	0.56–1.61	0.845
Streptococcal IE	0.30	0.12–0.76	**0.011**
Uncontrolled infection[a]	2.74	1.73–4.35	**<0.001**
Vegetation >10 mm	1.71	1.06–2.76	**0.027**
Severe regurgitation/new prosthetic dehiscence	1.38	0.85–2.25	0.191
Perivalvular complication[b]	1.02	0.53–1.94	0.959
Prosthetic IE	1.37	0.84–2.23	0.206
Early surgery	0.22	0.12–0.38	**<0.001**
Predictors of 1-year mortality	**Hazard ratio**	**95% CI**	***p*-value**
Age (per 10 years increase)	0.97	0.88–1.07	0.566
Male sex	0.95	0.70–1.28	0.731
Charlson index (per unit)	1.09	1.04–1.14	**<0.001**
Cerebrovascular accident	0.92	0.48–1.76	0.797
Staphylococcus aureus IE	1.18	0.85–1.62	0.322
Streptococcal IE	0.73	0.46–1.15	0.174
Uncontrolled infection[a]	2.17	1.63–2.88	**<0.001**
Vegetation >10 mm	1.17	0.87–1.57	0.305
Severe regurgitation/new prosthetic dehiscence	1.32	0.98–1.79	0.067
Perivalvular complication[b]	1.05	0.70–1.57	0.831
Prosthetic IE	0.96	0.71–1.30	0.782
Early surgery	0.29	0.20–0.41	**<0.001**

CHF, congestive heart failure; CI, confidence interval; IE, infective endocarditis.
[a]Positive blood cultures after 48 h of antimicrobial treatment and/or increasing vegetation size and/or septic shock.
[b]Abscess or pseudoaneurysm.

Discussion

This prospective study, based on a contemporary registry specifically designed to evaluate the current characteristics of IE in a wide range of centres, is the first large European report to assess the characteristics, outcomes, and management of patients with left-sided IE complicated by CHF. Our results can be summarized as follows: (i) CHF is frequent, encountered in 28.5% of patients with left-sided valve IE, and associated with an increased comorbidity index, bivalvular (aortic and mitral) involvement, severe regurgitation, larger vegetations, and uncontrolled infection; (ii) patients with IE complicated by CHF exhibit higher 30-day and 1-year mortality than those without, even after adjustment for established prognostic factors; and (iii) despite the fact that early surgery is independently associated with improved 30-day and 1-year survival for patients complicated by CHF, it is only performed on approximately half of these patients, mainly due to an operative risk considered to be too high by the clinicians (*Graphical Abstract*).

The prevalence of CHF in IE is estimated to be about one third of patients[3,8] and up to 40%–45% in left-sided native valve IE.[5,7,18] In our study on left-sided (native or prosthetic) IE, CHF was less prevalent (28.5%), but this difference is probably explained by the fact that previous studies[3,18] considered CHF on admission or occurring during hospitalization, whereas we focused on clinical signs at the time of IE diagnosis. Indeed, it appears to be important to have data on CHF at the time of admission for IE to assess its true impact on the prognosis and current management. In left-sided valve IE, CHF is mainly related to new or worsening aortic and/or mitral regurgitation, intracardiac fistulae,[19] and, rarely, valvular obstruction.[5] Clinical characteristics previously reported for patients with IE complicated by CHF are aortic valve involvement, severe valvular regurgitation, advanced age, and the presence of comorbidities.[5,7,8] Accordingly, in our study, patients complicated by CHF were older, with more comorbidity, and had more advanced lesions, with larger vegetations, severe regurgitation, and more frequent mitro-aortic involvement, which is associated with poor survival.[20] Interestingly, but as previously noted, the presence of a prosthetic valve[8] or *Staphylococcus aureus* infection[7,8] were not associated with CHF.

Congestive heart failure is one of the leading causes of death in IE.[5,21,22] In a study by Nadji *et al.*,[7] CHF was an independent predictor of in-hospital and 1-year mortality, but the authors did not identify predictors of outcome in CHF patients, probably due to their relatively small subset of patients. In the present study, CHF was strongly and independently associated with 30-day and 1-year mortality after adjustment for established prognostic factors

Table 4 Baseline characteristics and mortality of congestive heart failure patients according to initial management

Characteristics	Early surgery (*n* = 342)	Medical treatment (*n* = 355)	*p*-value
Region of origin, *n* (%)			0.588
Europe	244 (71.3)	248 (69.9)	
Oceania	11 (3.2)	9 (2.5)	
Africa	18 (5.3)	27 (7.6)	
America	32 (9.4)	27 (7.6)	
Asia	37 (10.8)	44 (12.4)	
Patient characteristics			
Age (years), mean ± SD	59.22 ± 16.57	66.35 ± 17.84	**<0.001**
Male sex, *n* (%)	258 (75.4)	226 (63.7)	**<0.001**
Diabetes mellitus, *n* (%)	81(23.7)	122 (34.4)	**0.002**
Charlson index, mean ± SD	3.57 ± 2.70	5.12 ± 3.26	**<0.001**
Previous IE, *n* (%)	15 (4.4)	28 (7.9)	0.055
Intracardiac devices (PM/ICD/CRT), *n* (%)	25 (7.3)	55 (15.5)	**<0.001**
Fever, *n* (%)	240/338 (71.0)	265/353 (75.1)	0.228
Cerebrovascular accident, *n* (%)	19/338 (5.6)	16/353 (4.5)	0.514
Embolic events, *n* (%)	77 (22.5)	74 (20.8)	0.593
NYHA class I–II, *n* (%)	133/338 (39.3)	139/353 (39.4)	0.994
NYHA class III–IV, *n* (%)	205/338 (60.7)	214/353 (60.6)	
Biochemistry, median (IQR)			
Serum creatinine (μmol/L)	97.2 (77.8–136.0)	116.0 (82.0–170.7)	**<0.001**
CRP (mg/L)	59.0 (20.0–132.0)	69.0 (19.2–145.0)	0.341
Haemoglobin (g/dl)	10.4 (9.0–11.6)	10.4 (9.0–11.7)	0.603
Microbiology on admission, *n* (%)			
Positive blood culture	251 (73.4)	272 (76.6)	0.325
Any type of *Staphylococcus aureus*	56/251 (22.3)	88/272 (32.4)	**0.010**
Methi-S *Staphylococcus aureus*	43/251 (17.1)	64/272 (23.5)	0.070
Methi-R *Staphylococcus aureus*	13/251 (5.2)	25/272 (9.2)	0.077
Any type of coagulase-negative *Staphylococcus*	25/251 (10.0)	36/272 (13.2)	0.244
Methi-S coagulase-negative *Staphylococcus*	9/251 (3.6)	14/272 (5.1)	0.384
Methi-R coagulase-negative *Staphylococcus*	16/251 (6.4)	22/272 (8.1)	0.451
Streptococcus viridans	41/251 (16.3)	24/272 (8.8)	**0.009**
Enterococcus	56/251 (22.3)	47/272 (17.3)	0.148
Streptococcus bovis	19/251 (7.6)	25/272 (9.2)	0.505
Gram-negative *bacillus*	8/251 (3.2)	12/272 (4.4)	0.466
Other	52/251 (20.7)	54/272 (19.9)	0.806
Antimicrobial therapy, *n* (%)			
B-lactamine (penicillin G + amoxicillin + ceftriaxone + oxacillin)	229/341 (67.2)	199/352 (56.5)	**0.004**
Vancomycin	150/341 (44.0)	161/352 (45.7)	0.643
Daptomycin	33/341 (9.7)	51/352 (14.5)	0.052
Rifampicin	58/341 (17.0)	56/352 (15.9)	0.696
Gentamicin	214/341 (62.8)	160/352 (45.5)	**<0.001**
Location of IE, *n* (%)			
Aortic	237 (69.3)	211 (59.4)	**0.007**
Mitral	170 (49.7)	199 (56.1)	0.093
Aortic and mitral	65 (19.0)	55 (15.5)	**0.219**
Tricuspid	15 (4.4)	24 (6.8)	0.173
Prosthetic IE	91 (26.6)	138 (38.9)	**<0.001**
Echocardiographic findings, *n* (%)			
Vegetations >10 mm	148/293 (50.5)	116/324 (35.8)	**<0.001**
Abscess or pseudoaneurysm	78 (22.8)	39 (11.0)	**<0.001**
Severe regurgitation or new prosthetic dehiscence	245 (71.6)	168 (47.3)	**<0.001**
Uncontrolled infection, *n* (%)	71/341 (20.8)	121/354 (34.2)	**<0.001**
Positive blood cultures after 48 h	38/339 (11.2)	57/354 (16.1)	0.061
Increasing vegetation size	22 (6.4)	29/(8.2)	0.379
Septic shock	27 (7.9)	77 (21.7)	**<0.001**
Death, *n* (%)			
Death at 30 days	32 (9.4)	111 (31.3)	**<0.001**
Death at 1 year	65 (19.0)	187 (52.7)	**<0.001**

CHF, congestive heart failure; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; IE, infective endocarditis; IQR, interquartile range; Methi-R, methicillin-resistant; Methi-S, methicillin-sensitive; NYHA, New York Heart Association; PM, pacemaker; SD, standard deviation.

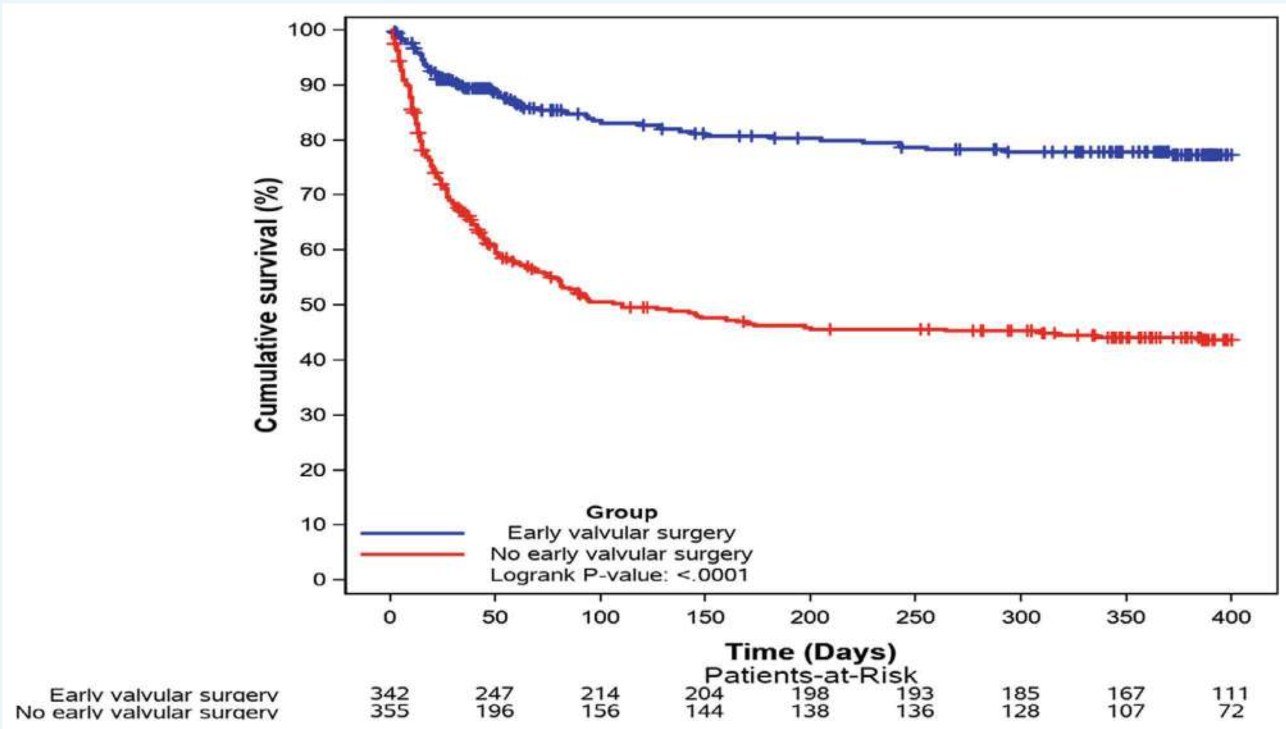


Figure 2 Kaplan–Meier 1-year survival curves for patients with congestive heart failure according to management (early surgery vs. medical treatment).

in IE, including age, comorbidity, staphylococcal or streptococcal infection, cerebrovascular accident, uncontrolled infection, severe valvular regurgitation, perivalvular complications, and early surgery. In CHF patients, the Charlson index, uncontrolled infection (mainly septic shock), and vegetation size >10 mm were associated with increased 30-day mortality, whereas streptococcal infection and early surgery were associated with better 30-day survival.

Although there are no randomized studies in this field, early surgery has consistently been associated with a substantial survival benefit in IE complicated by CHF.[7,8,23,24] Nadji *et al.*[7] reported that early surgery (<30 days), performed on 46% of CHF patients, was associated with more than a two-fold decrease in the relative risk of death in these patients, despite a perioperative mortality of 10%. In a report by Kiefer *et al.*,[8] surgery during hospitalization, performed on 61.7% of patients complicated by CHF, was associated with lower in-hospital (20.6% vs. 44.8%) and 1-year mortality (29.1% vs. 58.4%). The latter study identified the severity of CHF (NYHA class III–IV), younger age, and paravalvular complication to be factors associated with early surgery in CHF patients.[8] Similarly, in our study, early surgery was more frequent for younger patients with lower comorbidity and more advanced lesions, such as larger vegetations, severe regurgitation and perivalvular complications but the severity of CHF was comparable to that of medically managed patients. Early surgery was associated with significantly lower in-hospital (9.4% vs. 31.3%) and 1-year mortality rates (19.0% vs. 52.7%) for CHF patients, and was the most powerful factor associated with 30-day and 1-year survival after adjustment.

The operative mortality of 9.4% was high but expected in the setting of left-sided valve IE complicated by CHF. Compared to previous studies,[7,8] our study is the first to compare patients using a propensity score and although this method is not perfect, it appears relevant in this disease where randomized trials are difficult and ethically questionable. Furthermore, this is the first large European registry that addresses this question and shows that things have not really changed over the last 10–15 years. We believe that it is important to raise the awareness of the cardiology and infectious diseases community on the fact that the guidelines which are well established in this disease are poorly followed in our continent. Furthermore, it also seems important to raise the fact that despite the improvements in antibiotic and surgical treatment of endocarditis and in the treatment of heart failure, the mortality of these patients remains very high.

According to ESC guidelines,[5] unless severe comorbidity exists, the presence of CHF indicates early surgery for most patients with IE. The timing of surgery depends on clinical tolerance: emergency for refractory pulmonary oedema or cardiogenic shock,[25] urgent in cases of CHF due to severe valvular regurgitation, and not well defined for other CHF patients without another surgical indication.[5] Despite this strong recommendation, we found that less than half of CHF patients underwent early surgery. Although the exact reason to contraindicate early surgery in patients with a theoretical surgical indication was not reported in our database, it is probably related to a combination of several parameters (age, comorbidity, frailty, left or right ventricular dysfunction, and multiple organ failure due to septic shock). However, it is likely that many of these patients had no formal contraindication to surgery, suggesting that this recommendation is not well followed in European clinical practice. Earlier identification of signs of CHF would allow surgery to be considered earlier, before deterioration in the haemodynamic status or other complications occur. Indeed, to prevent complications and reduce mortality associated with CHF in IE, these patients should be systematically transferred to tertiary centres with surgical expertise and surgery should be discussed at the first sign of CHF. Natriuretic peptides are associated with outcomes in IE[26,27] and would probably be useful in the detection of early signs of CHF.

Limitations

Our study has several limitations. Despite adjustment for several prognostic factors in IE, other unassessed variables may have biased the results and the presence of frailty or other life-threatening comorbidities not included in the Charlson index or EuroSCORE II may have influenced the decision of the clinician regarding early surgery. Only a randomized trial between early surgery and medical treatment could overcome selection bias but it would be difficult and ethically questionable to conduct such a trial in the field of IE complicated by CHF.[28] The diagnosis of CHF was established by the clinicians at each centre on the basis of a combination of arguments according to the Framingham criteria and is therefore subject to variability. The time of onset of heart failure symptoms was not recorded. In this registry, the theoretical indication for surgery was set by the attending physician and it is likely that all patients with CHF have a theoretical indication for early surgery even if it is not always practicable for all. The rates of neurological complications were not significantly different between patients who underwent early surgery and those who did not. However, specific neurological complications that contraindicated surgery were not available in this registry. We cannot be certain that all centres actually included all their patients consecutively, as the study was based on voluntary participation. Furthermore, we cannot rule out the possibility that our patients may represent a selected cohort, as most centres were tertiary referral centres with cardiac surgical programmes. However, these limitations are partially offset by the large number of patients enrolled, the quality of data collection, and the representation of a wide range of academic and non-academic hospitals.[6] We did not match patients for staphylococcal infection in the propensity matching analysis, but after matching for age, sex and comorbidity, the two groups were comparable for *Staphylococcus aureus* and *Staphylococcus coagulase* negative infection.

Conclusion

Congestive heart failure is frequent in left-sided valve IE and associated with older age, greater comorbidity, advanced lesions, with more bivalvular involvement, larger vegetations, severe regurgitation, and uncontrolled infection. Patients with CHF at the time of IE diagnosis show higher 30-day and 1-year mortality than those without, even after adjustment for established outcome predictors in IE. Early surgery in patients with CHF is strongly and independently associated with lower 30-day and 1-year mortality but is performed in only about 50% of cases, mainly because of a surgical risk deemed to be prohibitive by clinicians. Further studies are needed to better stratify the operative risk in this high-risk population and to define the best timing for surgery, which should probably be discussed at the first signs of CHF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix

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