Association Between Valvular Surgery and Mortality Among Patients With Infective Endocarditis Complicated by Heart Failure

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Context  Heart failure (HF) is the most common complication of infective endocarditis. However, clinical characteristics of HF in patients with infective endocarditis, use of surgical therapy, and their associations with patient outcome are not well described.

Objectives  To determine the clinical, echocardiographic, and microbiological variables associated with HF in patients with definite infective endocarditis and to examine variables independently associated with in-hospital and 1-year mortality for patients with infective endocarditis and HF, including the use and association of surgery with outcome.

Design, Setting, and Patients  The International Collaboration on Endocarditis–Prospective Cohort Study, a prospective, multicenter study enrolling 4166 patients with definite native- or prosthetic-valve infective endocarditis from 61 centers in 28 countries between June 2000 and December 2006.

Main Outcome Measures  In-hospital and 1-year mortality.

Results  Of 4075 patients with infective endocarditis and known HF status enrolled, 1359 (33.4% [95% CI, 31.9%-34.8%]) had HF, and 906 (66.7% [95% CI, 64.2%-69.2%]) were classified as having New York Heart Association class III or IV symptom status. Within the subset with HF, 839 (61.7% [95% CI, 59.2%-64.3%]) underwent valvular surgery during the index hospitalization. In-hospital mortality was 29.7% (95% CI, 27.2%-32.1%) for the entire HF cohort, with lower mortality observed in patients undergoing valvular surgery compared with medical therapy alone (20.6% [95% CI, 17.9%-23.4%] vs 44.8% [95% CI, 40.4%-49.0%], respectively; P < .001). One-year mortality was 29.1% (95% CI, 26.0%-32.2%) in patients undergoing valvular surgery vs 58.4% (95% CI, 54.1%-62.6%) in those not undergoing surgery (P < .001). Cox proportional hazards modeling with propensity score adjustment for surgery showed that advanced age, diabetes mellitus, heart care–associated infection, causative microorganism (Staphylococcus aureus or fungi), severe HF (New York Heart Association class III or IV), stroke, and paravalvular complications were independently associated with 1-year mortality, whereas valvular surgery during the initial hospitalization was associated with lower mortality.

Conclusion  In this cohort of patients with infective endocarditis complicated by HF, severity of HF was strongly associated with surgical therapy and subsequent mortality, whereas valvular surgery was associated with lower in-hospital and 1-year mortality.

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have shown a mortality benefit for valvular surgery in infective endocarditis complicated by HF, and this indication for surgery is strongly recommended in current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines.

The patient characteristics associated with HF in those with infective endocarditis are not clearly defined. Furthermore, the use and timing of valvular surgery in patients with infective endocarditis and HF have been evaluated, with conflicting results. Several studies have reported no reduction of in-hospital mortality with valvular surgery compared with medical therapy alone, whereas other investigators have observed an early and sustained mortality benefit.

The objectives of the present study were to determine the clinical, echocardiographic, and microbiological variables associated with the development of HF in patients with definite infective endocarditis and to examine variables independently associated with in-hospital and 1-year mortality for patients with infective endocarditis and HF, including the use and effects of surgery on outcome.

METHODS

Data from the International Collaboration on Endocarditis—Prospective Cohort Study (ICE-PCS) were used for this study. The background and inclusion criteria of this prospective, multicenter, international registry of infective endocarditis have been reported. Between June 2000 and December 2006, 4166 patients with definite native- or prosthetic-valve endocarditis by the modified Duke criteria from 61 centers in 28 countries were enrolled. The ICE-PCS database is maintained at the coordinating center for International Collaboration on Endocarditis according to standard definitions. Data were collected during the index hospitalization and entered at the coordinating center or by site investigators using an Internet-based data entry system.

To describe longer-term outcome of infective endocarditis, sites enrolling patients in ICE-PCS were queried in 2008 regarding 1-year outcome of these patients. An additional case report form was used to collect data retrospectively from the date of index hospital admission to 1 year. One-year outcome was determined by site investigators using medical records and national death records, as available.

Definitions

The definitions used in the ICE-PCS data set have been described. The presence of HF was determined by physicians at each enrolling site based on clinical symptoms, signs, and laboratory and radiographic findings. Severity of heart failure was categorized according to New York Heart Association (NYHA) functional classification. Paravalvular complication was defined as transthoracic or transesophageal echocardiographic evidence of intracardiac abscess or fistula. Health care–associated infective endocarditis was specified as nosocomial or nonnosocomial acquisition of health care–associated infective endocarditis. Stroke was defined as acute development of a neurologic deficit of vascular origin lasting more than 24 hours. Prosthetic valve was defined as any nonnative valve (eg, mechanical, bioprosthetic, homograft, or autograft) or annuoplasty ring.

Statistical Analysis

Patient demographic and clinical variables were evaluated with counts and percentages in contingency tables or with medians and interquartile ranges (IQRs). The statistical significance of the associations between congestive heart failure and these variables were assessed using the Kruskal-Wallis test for continuous measures and the Fisher exact test for cross-classifications of categorical data. Risk estimates for in-hospital mortality are presented as odds ratios (ORs) and 95% confidence intervals. Associations with \( P < .05 \) were considered statistically significant; all significance tests were 2-sided.

Multivariable logistic regression modeling to evaluate surgical treatment for endocarditis was performed to determine the factors independently associated with surgery among patients with HF. This model included all demographic and clinical variables considered a priori by an experienced cardiologist (A.W.) to contribute to surgical treatment of endocarditis and included age in 4 categories (≤45 years, 46-60 years, 61-70 years, >70 years), sex, geographic region (North America, South America, Europe, other), time since first manifestation of infective endocarditis, transfer from another facility, diabetes mellitus, hemodialysis, injection drug use, valve status (native, prosthetic), location of infective endocarditis (left- or right-sided), health care–associated infective endocarditis, new valvular regurgitation, intravascular vegetation, paravalvular complications, stroke, embolization, persistent bacteremia, NYHA class III or IV (vs NYHA class I or II), positive blood culture result, and causative microorganism. The patients’ probabilities for surgical treatment derived from this model were used to calculate
The study population is shown in Figure 1. Within the ICE-PCS cohort of patients with definite infective endocarditis and known HF status (n = 4075), HF was present in 1359 (33.4% [95% CI, 31.9%-34.8%]) and absent in 2716 (66.6% [95% CI, 65.2%-68.1%]). Heart failure status was not specified in an additional 91 patients (2.2% [95% CI, 1.7%-2.6%]). Among the patients with HF, the distribution of HF severity included NYHA class I symptom status in 37 patients (2.7% [95% CI, 1.9%-3.6%]), NYHA class II in 205 (15.1% [95% CI, 13.2%-17.0%]), NYHA class III in 390 (28.7% [95% CI, 26.3%-31.1%]), NYHA class IV in 516 (38.0% [95% CI, 35.4%-40.5%]), and unspecified HF severity in 211 (15.5% [95% CI, 13.6%-17.5%]). During the years of patient enrollment, the percentage of patients with infective endocarditis and HF ranged from 30% to 35%, without variation in incidence. For 2457 patients with available chest radiography data (before the removal of this variable from the case report forms in August 2005), radiographic evidence of pulmonary edema was present in 6 of 23 (26.1% [95% CI, 8.1%-44.0%]) patients with NYHA class I symptoms, 35 of 124 (28.2% [95% CI, 20.3%-36.1%]) with NYHA class II symptoms, 99 of 251 (39.4% [95% CI, 33.4%-45.5%]) with NYHA class III symptoms, and 194 of 312 (62.2% [95% CI, 56.8%-67.6%]) with NYHA class IV symptoms.

The presence of HF with infective endocarditis was associated with significantly higher in-hospital mortality when compared with infective endocarditis without HF (29.7% [95% CI, 27.2%-32.1%] vs 13.1% [95% CI, 11.8%-14.4%], respectively; OR, 2.80 [95% CI, 2.38-3.29]; P < .001) (Figure 1). The frequency of valvular surgery by year did not change consistently during the study period (range, 44%-53%). In addition, the median duration from hospital admission to surgery did not differ between the groups with and without HF (7 [IQR, 2-18] days vs 8 [IQR, 3-20] days, P=.10). Surgical valvular procedures included aortic valve surgery (n=612, including mechanical valve replacement in 274, xenograft biologic replacement in 192, homograft in 60, repair in 21, and autograft in 6); mitral valve surgery (n=429, including mechanical valve replacement in 204, xenograft biologic replacement in 108, and repair in 106); and tricuspid valve surgery (n=93, including repair in 59, xenograft biologic replacement in 19, and mechanical valve replacement in 7). For patients with heart failure in infective endocarditis, clinical characteristics as a function of surgical therapy are shown in Table 2. One hundred twenty-six of 240 (52.5% [95% CI, 46.2%-58.8%]) patients with NYHA class I or II symptoms and 572 of 904 (63.3% [95% CI, 60.1%-66.4%]) with NYHA class III or IV symptoms underwent surgery.

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### Table 1. Comparison of Patients With or Without Heart Failure Complicating Infective Endocarditis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heart Failure (n = 1359)</th>
<th>No Heart Failure (n = 2716)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>59.4 (47.4-73.2)</td>
<td>56.9 (43.5-71.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Men</td>
<td>914 (67.3)</td>
<td>1858 (68.5)</td>
<td>.41</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>247 (18.2)</td>
<td>456 (16.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>South America</td>
<td>164 (12.1)</td>
<td>205 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>707 (52.0)</td>
<td>1391 (51.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>241 (17.7)</td>
<td>664 (24.4)</td>
<td></td>
</tr>
<tr>
<td>Transferred from another facility</td>
<td>672 (49.9)</td>
<td>1113 (41.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>257 (19.4)</td>
<td>434 (16.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>93 (6.8)</td>
<td>198 (7.3)</td>
<td>.65</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>115 (8.7)</td>
<td>257 (9.8)</td>
<td>.30</td>
</tr>
<tr>
<td>Predisposing native-valve disease</td>
<td>443 (33.5)</td>
<td>829 (31.0)</td>
<td>.11</td>
</tr>
<tr>
<td>Health care–associated infection</td>
<td>339 (26.2)</td>
<td>586 (22.7)</td>
<td>.02</td>
</tr>
<tr>
<td>New or worsening murmur</td>
<td>822 (60.5)</td>
<td>1213 (44.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Causative microorganism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>381 (28.0)</td>
<td>833 (30.7)</td>
<td>.09</td>
</tr>
<tr>
<td>Viridians group streptococcus</td>
<td>206 (15.2)</td>
<td>510 (18.8)</td>
<td>.005</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided, native valve</td>
<td>871 (64.1)</td>
<td>1533 (56.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left-sided, prosthetic valve</td>
<td>244 (18.0)</td>
<td>459 (16.9)</td>
<td>.40</td>
</tr>
<tr>
<td>Right-sided vegetation only</td>
<td>116 (9.1)</td>
<td>413 (16.1)</td>
<td></td>
</tr>
<tr>
<td>New aortic regurgitation</td>
<td>597 (44.9)</td>
<td>719 (27.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>New mitral regurgitation</td>
<td>577 (43.1)</td>
<td>857 (32.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paravalvular complication</td>
<td>426 (31.8)</td>
<td>561 (20.9)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

Heart failure is a common complication of infective endocarditis and a major influence on the high morbidity and mortality associated with this serious condition. The main findings of the current study, to our knowledge the largest prospective, multinational evaluation of HF in patients with infective endocarditis to date, are that (1) HF was strongly related to new or worsening left-sided valvular regurgitation, rather than to predisposing heart conditions (eg, previous native-valve disease, presence of a prosthetic valve, or congenital heart disease) or causative microorganism; (2) despite a high incidence of severe HF and its poor prognosis, less than two-thirds of patients with infective endocarditis and HF underwent surgery, which was more frequently performed in younger patients with severe HF and paravalvular complications; and (3) surgery was associated with a significant reduction in inhospital and 1-year mortality after adjustment for selection and survival bias.

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ases and across the spectrum of HF severity and surgical propensity.

Previous studies have reported a prevalence of HF with left-sided infective endocarditis ranging from 19% to 44%.9,21-23 In the present work, HF occurred in 33% of definite cases of infective endocarditis, with a high percentage of severe (NYHA class III or IV) symptoms occurring shortly after diagnosis of endocarditis. Clinical characteristics previously associated with the development of HF in patients with infective endocarditis include new heart murmur, aortic valve infective endocarditis, high comorbidity index, and severe valvular regurgitation.22 Our findings confirm these earlier results and suggest that a greater degree of new valvular regurgitation was related to the development of HF. Of note, preexisting heart conditions, such as native-valve disease, presence of a prosthetic valve, congenital heart disease, and a causative microorganism such as Staphylococcus aureus, were not associated with HF in patients with infective endocarditis.

Heart failure in the setting of valvular dysfunction and left-sided infective endocarditis is a widely accepted indication for valvular surgery and is a class I guideline recommendation from the American College of Cardiology/American Heart Association and the European Society of Cardiology.4,5 Surgical treatment of infective endocarditis and HF was performed in 62% of patients with active infection in this multicenter study, a rate higher than rates reported in other series,2,18 and early in the course of active infective endocarditis. In addition to the presence of heart failure alone as an indication for surgery, our study has identified a number of other factors that increased the likelihood of surgery for HF in patients with infective endocarditis, including severity of HF, younger age, paravalvular complication, and transfer from another hospital.

These factors suggest that surgery was performed in patients with the most serious complications of infective endocarditis (eg, severe HF, paravalvular complications) who had acceptable operative risk. Patients with less severe HF (NYHA

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Our finding that nearly one-third of patients with HF and high surgical propensity did not have surgery emphasizes the need for such multidisciplinary, guideline-based management of infective endocarditis.

The in-hospital mortality rates reported in smaller studies of left-sided infective endocarditis and HF have ranged from 24% to 43% \(^{7,21,22}\) and have been associated with uncontrolled infection, major neurologic event, and S. aureus infective endocarditis. \(^{21}\) Later onset of HF in the course of infective endocarditis has also been associated with higher mortality. \(^{28}\) In the present study, severity of HF was the strongest predictor of both in-hospital and 1-year mortality, although surgical treatment significantly reduced mortality at early as well as later points after propensity adjustment for this intervention. In a recent, single-center study without adjustment for selection or survival bias, valvular surgery was performed in 46% of patients with left-sided infective endocarditis and HF, which was also associated with lower in-hospital and 1-year mortality but not related to the severity of HF. \(^{22}\) An earlier study used propensity matching to adjust for characteristics of patients treated with surgery and found that the survival benefit of surgery on 6-month outcome in infective endocarditis was limited to those patients with severe (NYHA class III or IV) HF, with no survival benefit in patients with no or mild HF. \(^{2}\)

In the current study, the association between surgery and survival for HF in patients with infective endocarditis was apparent across the spectrum of HF severity. Although the relationship with absolute mortality risk reduction was greater for patients with advanced, NYHA class III or IV symptoms, an association with lower mortality was also present for patients with NYHA class I or II symptoms. However, the association between surgical treatment and 1-year survival was greatest in patients with higher propensity for surgery. The in-hospital mortality rate for surgically treated patients was 20%, higher than that reported in other studies (8%-15%) \(^{2,18,23}\) and potentially related to the severity of HF and other adverse prognostic factors. In a recent study of the Society of Thoracic Surgery Adult Cardiac Surgery Database of 19 543 operations performed for infective endocarditis from 2002-2008, operative mortality was 8.2%, but active endocarditis was present in only 52% of cases and was independently associated with a 2-fold higher mortality rate. \(^{20}\)

Our study has several limitations. The diagnosis and severity of HF were determined by physicians at the individual centers using symptoms, signs, and/or radiographic findings at the time of study enrollment and are subject to variability and potential bias. Measurement of left ventricular ejection fraction was not collected in this registry, although the majority of patients in this study had left-sided infective endocarditis with acute valvular regurgitation, and the prevalence of HF in our population was consistent with previous studies of infective endocarditis. \(^{2,18}\) Furthermore, physician assessment of heart failure severity by NYHA classification correlated with radiographic evidence of pulmonary edema, a more specific but less sensitive diagnostic criterion. Time of heart failure symptom onset was not collected. Selection bias resulting from the nonrandomized use of surgery has the potential to influence the results of observational data analysis, and clinical
reasons for lack of surgical treatment of HF in patients with infective endocarditis, including all variables needed to calculate operative risk by validated cardiac surgery models (eg, Society of Thoracic Surgery or euroSCORE), were not available. Although surgery was performed early in the treatment of infective endocarditis in our cohort, the association between surgical timing and outcome was not evaluated, although a recent study found higher operative mortality in urgent cases or active infective endocarditis.29

Despite the use of propensity score adjustment to reduce selection bias and proportional hazards modeling to reduce survival bias, other variables not evaluated may confound the results of this analysis. A nonmatching propensity score method was used to avoid a si-
significant reduction in study sample size in light of the observed differences in baseline characteristics and predicted probability for surgery between the surgical vs nonsurgical groups. Although a randomized trial of surgical vs medical therapy in infective endocarditis would reduce selection bias as a factor in assessing outcome, it is highly unlikely that patients with HF, particularly acute, severe HF, could be ethically enrolled.

In conclusion, based on this large, prospective, international, multicenter analysis of definite infective endocarditis, HF complicates one-third of cases and typically is of advanced degree. In-hospital and 1-year mortality rates were high and were associated with HF severity, older age, paravalvular complications, diabetes mellitus, and stroke. Valvular surgery is strongly associated with lower in-hospital and 1-year mortality in patients with HF but is performed in only 62% of cases. Additional studies are needed to better risk-stratify patients with infective endocarditis and HF and optimize the use of surgery for this serious condition.

Author Contributions: Dr Park had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tribouilloy, Miró, Murdoch, Moreillon, Uttili, Wang.

Acquisition of data: Tribouilloy, Cortes, Casillo, Delahaye, Durante-Mangoni, Edathamu, Falces, Logar, Miró, Naber, Tripodi, Murdoch.


Drafting of the manuscript: Kiefer, Park, Durante-Mangoni, Falces, Miró.

Critical revision of the manuscript for important intellectual content: Kiefer, Park, Durante-Mangoni, Falces, Miró, Murdoch, Wang.

Obtained funding: Chu.

Administrative, technical, or material support: Tribouilloy, Chu, Murdoch.

Study supervision: Tribouilloy, Falces, Miró, Tripodi, Uttili.

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INFECTIVE ENDOCARDITIS AND HEART FAILURE

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