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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, health 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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INFECTIVE ENDOCARDITIS IS ASSOCIATED with substantial morbidity and mortality. Several published studies have reported in-hospital mortality of 15% to 20% and 1-year mortality of 40%.[1] In the United States alone, approximately 15 000 new cases of infective endocarditis are diagnosed each year.[1] A variety of complications contribute to the high rates of morbidity and mortality in infective endocarditis, particularly heart failure (HF), which occurs in approximately 40% of patients.[2,3] Several observational studies

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have shown a mortality benefit for valvular surgery in infective endocarditis complicated by HF,[2] and this indication for surgery is strongly recommended in current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines.[4,5]

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,[6-8] whereas other investigators have observed an early and sustained mortality benefit.[2,9]

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.[10,11] 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.[12] The ICE-PCS database is maintained at the Duke Clinical Research Institute, which is the coordinating center for International Collaboration on Endocarditis studies. Informed consent (oral or written) was obtained from patients as needed according to institutional review board or ethics committee guidelines at each center.

Patient Selection and Data Collection

Patients were identified prospectively using site-specific procedures to ensure consecutive enrollment.[10,12,13] To provide a cross-sectional, prospective characterization of infective endocarditis and in-hospital outcome, patients were enrolled in ICE-PCS if they met criteria for possible or definite infective endocarditis based on modified Duke criteria.[13] Only patients with definite infective endocarditis were included in the current study. To preserve the assumption of independence of observations, only the first episode of infective endocarditis recorded for an individual patient during study enrollment was used in the analysis.

The method of data collection for ICE-PCS has been reported.[14] Briefly, a standard case report form was used at all sites to collect data. This case report form included 275 variables and was developed by the 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.[14] The presence of HF was determined by physicians at each enrolling site based on clinical symptoms, signs, and laboratory and radiographic findings.[15] Severity of heart failure was categorized according to New York Heart Association (NYHA) functional classification.[14] Paravalvular complication was defined as transthoracic or transesophageal echocardiographic evidence of intracardiac abscess or fistula.[16,17] Health care–associated infective endocarditis was specified as nosocomial or nonnosocomial acquisition of health care–associated infective endocarditis.[18,19] Stroke was defined as acute development of a neurologic deficit of vascular origin lasting more than 24 hours.[14] Prosthetic valve was defined as any nonnative valve (eg, mechanical, bioprosthetic, homograft, or autograft) or annuloplasty 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

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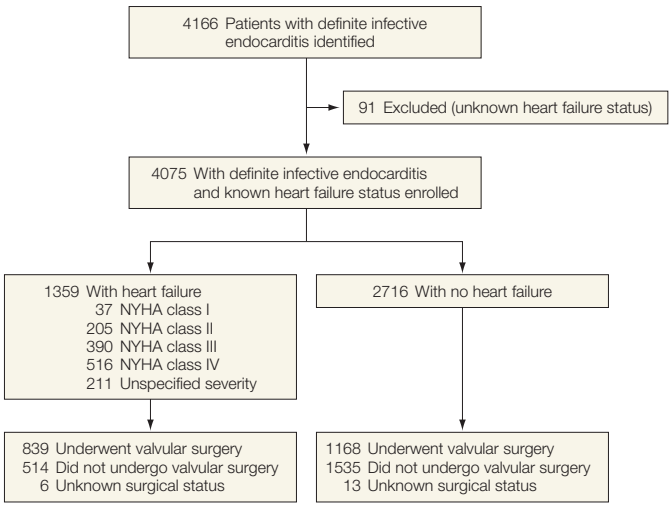
inverse probability of surgery weights as described previously,[20] and these were used as weights in proportional hazards models.

To evaluate the factors associated with mortality among patients with HF, proportional hazards models were fit for in-hospital mortality and for all mortality through 1 year after discharge. These models included as variables the patient demographic and clinical data. To account for individual differences in time between admission and surgery, surgery was modeled as a time-dependent factor. These models were further weighted by the inverse probability of treatment using the propensity score for surgery, which we derived from the logistic model previously described. All analyses were performed using SAS version 9.2.

Figure 1. Study Population of Patients With Infective Endocarditis



RESULTS

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 baseline characteristics of the overall study population are shown in TABLE 1. Older age, transfer from another hospital, health care–associated infection, new or worsening murmur, left-sided native-valvular infection with new aortic or mitral regurgitation, and paravalvular complications were significantly more common in patients with HF. For patients with infective endocarditis with or without HF, the prevalence of congenital heart disease (8.7% [95% CI, 7.3%-10.4%] vs 9.8% [95% CI, 8.7%-11.0%], respectively) and predisposing native-valve disease (33.5% [95% CI, 31.0%-36.1%] vs 31.0% [95% CI, 29.3%-32.8%], respectively) were not statistically different.

Of the 1359 patients with HF, 839 (61.7% [95% CI, 59.2%-64.3%]) underwent valvular surgery during the initial hospitalization, compared with 1168 (43.0% [95% CI, 41.1%-44.9%]) without HF (OR, 2.15 [95% CI, 1.88-2.45]; $P<.001$) (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.

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]; $P<.001$). The median duration of hospitalization for patients with HF (28 [IQR, 15-47] days) was similar to that for patients with-

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

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

Abbreviation: IQR, interquartile range.

out HF (29 [IQR, 16-44] days) ($P=.63$). Patients with HF who underwent surgical intervention had a significantly lower unadjusted in-hospital mortality rate compared with patients with HF not undergoing surgery (20.6% [95% CI, 17.9%-23.4%] vs 44.7% [95% CI, 40.4%-49.0%], respectively; $P<.001$). Among patients with NYHA class I or II HF, the mortality rate in surgically treated patients was 7.9% (95% CI, 3.2%-12.7%), vs 15.0% (95% CI, 8.5%-21.6%) in those not surgically treated ($P=.03$); for those with NYHA class III or IV HF, corresponding mortality rates were 23.4% (95% CI, 20.0%-26.9%) vs 54.5% (95% CI, 49.2%-59.9%), respectively ($P<.001$) (FIGURE 2).

Survival status at 1 year after index admission date was available for 1202 of 1358 patients (88.5%); 544 of 1358 patients with HF during the index hospitalization (40.1% [95% CI, 37.6%-42.8%]) had died. The 1-year mortality rate was 29.1% (244/839 [95% CI, 26.0%-32.2%]) for patients treated with surgery vs 58.4% (300/514 [95% CI, 54.1%-62.6%]) for patients treated with medical therapy alone during the index hospitalization (relative risk, 0.50 [95% CI, 0.43-0.57]; $P<.001$).

To reduce the potential selection bias for the use of surgery, propensity score adjustment (area under the curve, 0.797 for the multivariable model) by inverse probability weighting was performed (TABLE 3). In the Cox proportional hazards model with surgery included as a time-dependent covariate to account for survivor treatment bias, severity of HF (NYHA class III or IV), age older than 70 years, causative microorganism, duration of infective endocarditis symptoms before diagnosis, diabetes mellitus, stroke, and paravalvular complications were independently associated with in-hospital death (Table 3). Surgery during the initial hospitalization was statistically associated with a lower risk of in-hospital mortality (OR, 0.66 [95% CI, 0.56-0.77]).

The association between surgery and lower in-hospital mortality was evident across the quintiles of surgical propensity and most prominent in quintiles 3 and 4 (FIGURE 3). The distribution of propensity scores for surgically and nonsurgically treated patients demonstrated that 29% of patients with propensity scores in quintiles 3, 4, or 5 (propensity score >0.6) did not have surgery during the index hospitalization (eFigure, available at http://www.jama.com). In a manner similar to that for in-hospital outcome, 1-year mortality was independently associated with age older than 70 years, diabetes mellitus, and paravalvular complications of infective endocarditis, as well as health care–associated infection, causative microorganism, and severity of HF, with a higher survival rate for patients having surgery during the index hospitalization in a propensity-adjusted analysis (Table 3).

COMMENT

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 in-hospital and 1-year mortality after adjustment for selection and survival bi-

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Table 2. Characteristics of Patients With Infective Endocarditis and Heart Failure Associated With Surgery[a]

Characteristic	No. (%) [95% CI] Surgery (n = 839)	No. (%) [95% CI] No Surgery (n = 514)	*P* Value	OR (95% CI)
Age, y				
≤45	220 (26.2) [23.2-29.2]	65 (12.6) [9.8-15.5]	<.001	4.60 (2.75-7.69)
46-60	242 (28.8) [25.8-31.9]	117 (22.8) [19.1-26.4]		3.11 (2.02-4.80)
61-70	183 (21.8) [19-24.6]	88 (17.1) [13.9-20.4]		2.92 (1.93-4.42)
>70	194 (23.1) [20.3-26.0]	244 (47.5) [43.2-51.8]		1 [Reference]
Men	605 (72.1) [69.1-75.1]	305 (59.3) [55.1-63.6]	<.001	NA[b]
Region				
North America	144 (17.2) [14.6-19.7]	102 (19.8) [16.4-23.3]	.004	NA[b]
South America	113 (13.5) [11.2-15.8]	51 (9.9) [7.3-12.5]		
Europe	454 (54.1) [50.7-57.5]	250 (48.6) [44.3-53.0]		
Other	128 (15.3) [12.8-17.7]	111 (21.6) [18.0-25.2]		
≥1 mo since first infective endocarditis manifestation	234 (27.9) [24.9-30.9]	65 (12.6) [9.8-15.5]	<.001	1.69 (1.12-2.54)
Transferred from another facility	485 (57.8) [54.5-61.1]	186 (36.2) [32.0-40.3]	<.001	1.83 (1.33-2.51
Diabetes mellitus	125 (14.9) [12.5-17.3]	131 (25.5) [21.7-29.3]	<.001	
Hemodialysis	35 (4.2) [2.8-5.5]	57 (11.1) [8.4-13.8]	<.001	0.36 (0.18-0.75)
Left-sided, native-valve infective endocarditis	565 (67.3) [64.2-70.5]	302 (58.8) [54.5-63.0]	.002	1.61 (1.06-2.44)
Health care–associated infection	164 (19.5) [16.9-22.2]	172 (33.5) [29.4-37.5]	<.001	NA[b]
Causative microorganism				
Staphylococcus aureus	179 (21.3) [18.6-24.1]	200 (38.9) [34.7-43.1]	<.001	0.52 (0.31-0.86)
Viridans group streptococcus	139 (16.6) [14.1-19.1]	67 (13.0) [10.1-15.9]	.09	
NYHA class III or IV	572 (68.2) [65-71.3]	332 (64.6) [60.5-68.7]	.003	2.15 (1.49-3.11)
New valve regurgitation	698 (83.2) [80.7-85.7]	336 (66.4) [61.3-69.5]	<.001	1.79 (1.23-2.60)
Paravalvular complication	327 (39.0) [35.7-42.3]	99 (19.3) [15.9-22.7]	<.001	3.07 (2.15-4.39)
Stroke	153 (18.2) [15.6-20.8]	135 (26.3) [22.5-30.1]	<.001	NA[b]

Abbreviations: NYHA, New York Heart Association; OR, odds ratio; NA, not applicable.
[a] ORs and CIs calculated from the multivariable logistic model used to determine the propensity score for surgical treatment.
[b] Not statistically significant in multivariable model.

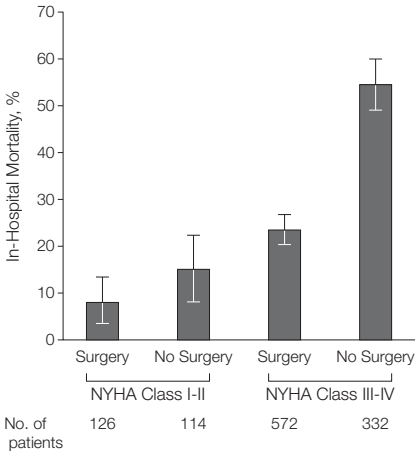
ases and across the spectrum of HF severity and surgical propensity.

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

Figure 2. In-Hospital Mortality Rates for Patients With Infective Endocarditis and Heart Failure as a Function of Surgical Treatment



Fisher exact $P < .05$ for surgery vs no surgery in the New York Heart Association (NYHA) class I-II cohort; $P < .001$ for surgery vs no surgery in the NYHA class III-IV cohort. Error bars indicate 95% confidence intervals.

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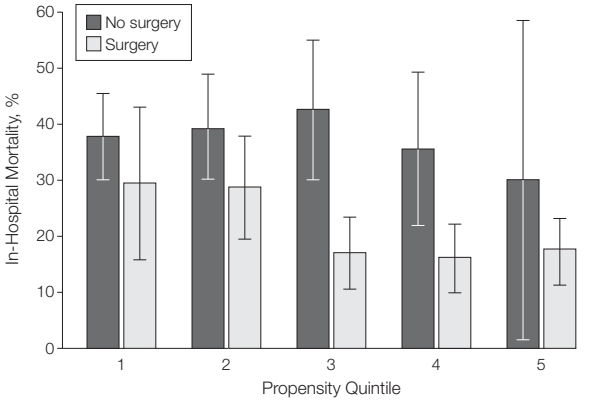
Figure 3. In-Hospital Mortality Rates for Surgically vs Nonsurgically Treated Patients Across Propensity Quintiles



Propensity, mean (range)	0.249 (0.021-0.376)	0.480 (0.376-0.577)	0.653 (0.577-0.728)	0.803 (0.728-0.864)	0.913 (0.864-0.976)
No. of patients					
No surgery	148	97	61	48	10
Surgery	44	94	130	143	181

Fisher exact $P < .001$ for surgery vs no surgery in propensity quintile 3; $P < .01$ for surgery vs no surgery in propensity quintile 4. Error bars indicate 95% confidence intervals.

class I or II) may have been treated medically with improvement or resolution of HF symptoms, thus attenuating the indication for surgery. Improved recognition of HF and institutional systems to promote appropriate treatment of infective endocarditis may enhance the rate of surgery for this indication. For instance, N-terminal pro-B-type natriuretic peptide level may be a more sensitive marker of HF presence and severity in patients with infective endocarditis, and recent small studies have found that patients with infective endocarditis and elevated levels of the peptide had poorer event-free survival.[24,25] Earlier recognition of heart failure in infective endocarditis may expedite surgical intervention, including transfer to a facility with surgical capability and expertise, before hemodynamic status deteriorates or other complications develop. In addition, management- or protocol-based approaches to treatment of infective endocarditis have been found to reduce 1-year mortality of infective endocarditis and improve compliance with antimicrobial therapy and surgical indications but without increasing the overall surgery rate.[26] 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%[7,21,22,27] and have been associated with uncontrolled infection, major neurologic event, and *S aureus* infective endocarditis.[22] 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.[29]

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

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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 sig-

Table 3. Cox Proportional Hazards Modeling of Variables Independently Associated With In-Hospital and 1-Year Mortality, With Propensity Adjustment for Cardiac Surgery

	In-Hospital Mortality		1-Year Mortality	
Variable	No./Total (%) [95% CI]	HR (95% CI)	No./Total (%) [95% CI]	HR (95% CI)
Age, y				
≤45	104/1036 (10.0) [8.2-11.9]	1 [Reference]	158/1040 (15.2) [13.0-17.4]	1 [Reference]
46-60	165/1071 (15.4) [13.2-17.6]	2.06 (1.49-2.90)	234/1071 (21.8) [19.4-24.3]	1.44 (1.13-1.84)
61-70	159/840 (18.9) [16.3-21.6]	2.37 (1.70-3.36)	208/840 (24.8) [21.8-27.7]	1.62 (1.26-2.09)
>70	359/1209 (29.7) [27.1-32.3]	3.76 (2.79-5.17)	455/1213 (37.5) [34.8-40.2]	2.40 (1.92-3.02)
≥1 mo from symptoms of infective endocarditis to diagnosis				
No	647/3075 (21.0) [19.6-22.5]	1 [Reference]	864/3081 (28.0) [26.5-29.6]	1 [Reference]
Yes	101/909 (11.1) [9.1-13.2]	0.81 (0.66-0.99)	138/911 (15.1) [12.8-17.5]	0.75 (0.62-0.91)
Geographic region				
Europe	446/2156 (20.7) [19.0-22.4]	1 [Reference]	553/2162 (25.6) [23.7-27.4]	1 [Reference]
North America	129/709 (18.2) [15.4-21.0]	1.19 (0.95-1.48)	228/710 (32.1) [28.7-35.5]	0.98 (0.82-1.17)
South America	73/372 (19.6) [15.6-23.7]	1.40 (1.08-1.80)	87/372 (23.4) [19.1-27.7]	1.03 (0.82-1.29)
Other	139/919 (15.1) [12.8-17.4]	0.49 (0.37-0.62)	187/920 (20.3) [17.7-22.9]	0.47 (0.38-0.59)
Diabetes mellitus				
No	560/3388 (16.5) [15.3-17.8]	1 [Reference]	762/3394 (22.5) [21.0-23.9]	1 [Reference]
Yes	208/700 (29.7) [26.3-33.1]	1.33 (1.10-1.58)	272/702 (38.7) [35.1-42.4]	1.34 (1.14-1.57)
Health care–associated infection				
No	436/3002 (14.5) [13.3-15.8]	1 [Reference]	584/3007 (19.4) [18.0-20.8]	1 [Reference]
Yes	306/949 (32.2) [29.3-35.2]	NA[a]	412/951 (43.3) [40.2-46.5]	2.02 (1.62-2.53)
Causative microorganism				
Viridans group streptococcus				
No	727/3431 (21.2) [19.8-22.6]	1 [Reference]	964/3437 (28.0) [26.5-29.5]	1 [Reference]
Yes	60/725 (8.3) [6.3-10.3]	0.65 (0.48-0.86)	91/727 (12.5) [10.1-14.9]	0.77 (0.59-0.98)
Streptococcus bovis				
No	760/3884 (19.6) [18.3-20.8]	1 [Reference]	1015/3892 (26.1) [24.7-27.5]	1 [Reference]
Yes	27/272 (9.9) [6.4-13.5]	0.45 (0.28-0.68)	40/272 (14.7) [10.5-18.9]	0.58 (0.40-0.82)
Staphylococcus aureus				
No	458/2916 (15.7) [14.4-17.0]	1 [Reference]	623/2921 (21.3) [19.8-22.8]	1 [Reference]
Yes	329/1240 (26.5) [24.1-29.0]	NA[a]	432/1243 (34.8) [32.1-37.4]	1.31 (1.12-1.53)
Fungi				
No	758/4086 (18.6) [17.4-19.7]	1 [Reference]	1016/4094 (24.8) [23.5-26.1]	1 [Reference]
Yes	29/70 (41.4) [29.9-53.0]	NA[a]	39/70 (55.7) [44.1-67.4]	1.77 (1.09-2.71)
NYHA class III or IV				
No	382/2957 (12.9) [11.7-14.1]	1 [Reference]	560/2959 (18.9) [17.5-20.3]	1 [Reference]
Yes	316/910 (34.7) [31.6-37.8]	3.38 (2.54-4.60)	385/910 (42.3) [39.1-45.5]	3.03 (2.45-3.80)
Paravalvular complication				
No	521/3093 (16.8) [15.5-18.2]	1 [Reference]	720/3099 (23.2) [21.7-24.7]	1 [Reference]
Yes	250/1009 (24.8) [22.1-27.4]	1.66 (1.42-1.95)	315/1011 (31.2) [28.3-34.0]	1.48 (1.28-1.70)
Stroke				
No	485/3284 (14.8) [13.6-16.0]	1 [Reference]	704/3285 (21.4) [20.0-22.8]	1 [Reference]
Yes	276/800 (34.5) [31.2-37.8]	1.61 (1.36-1.89)	323/801 (40.3) [36.9-43.7]	1.49 (1.28-1.72)
Surgery				
No	463/2092 (22.1) [20.4-23.9]	1 [Reference]	634/2094 (30.3) [28.3-32.2]	1 [Reference]
Yes	321/2044 (15.7) [14.1-17.3]	0.76 (0.58-0.99)	415/2047 (20.3) [18.5-22.0]	0.44 (0.34-0.56)

Abbreviations: HR, hazard ratio; NYHA, New York Heart Association; NA, no association.
[a]Variable not statistically associated with in-hospital mortality in the model (but associated with 1-year mortality in subsequent model).

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nificant 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.

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