

Sex Differences in Native-Valve Infective Endocarditis in a Single Tertiary-Care Hospital

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The aim of this study was to assess whether the clinical characteristics, management, and outcomes of infective endocarditis differ in women and men through a prospective observational cohort study at a single tertiary care teaching hospital. From January 2000 to December 2008, 271 new cases of infective endocarditis were diagnosed (183 in men, 88 in women) according to modified Duke criteria, and patients were followed for 1 year. Women were older than men (mean age 63 ± 16 vs 58 ± 18 years, $p = 0.006$); more women were taking immunosuppressants (14% vs 3%, $p = 0.006$) and had mitral valve involvement (52% vs 36%, $p = 0.02$). However, more men had human immunodeficiency virus infection than women. There were no gender differences in Charlson index, regurgitation severity, culprit pathogens, or major complications. When surgery was indicated, women were less likely to undergo the procedure (26% vs 47%, relative risk [RR] 0.4, 95% confidence interval [CI] 0.2 to 0.7), $p = 0.001$). Mortality tended to be higher in women in the hospital (32% vs 23%, RR 1.58, 95% CI 1 to 2.5, $p = 0.05$) and at 1 year (38% vs 26%, RR 1.7, 95% CI 1.0 to 2.9, $p = 0.04$). Surgical treatment was a protective factor against death in the hospital (RR 0.18, 95% CI 0.04 to 0.77, $p = 0.02$) and at 1 year (RR 0.12, 95% CI 0.03 to 0.48, $p = 0.03$) after adjustment for age, gender, Charlson index, infection by *Staphylococcus aureus*, severity at presentation, heart failure, acute renal failure, stroke, and the ejection fraction. In conclusion, women with infective endocarditis were slightly older than men but showed similar co-morbidities. Women underwent surgery less frequently and consequently had worse prognosis than men. © 2010 Elsevier Inc. All rights reserved. (Am J Cardiol 2010;106:92–98)

Differences in clinical characteristics, treatment choices, and outcomes between men and women continue to be a subject of debate in the published research. Previous studies have shown that infective endocarditis (IE) is more frequent in men than in women,^{1,2} and the possibility that estrogens may protect women against endothelial damage has been suggested.³ Women, however, have usually been found to have a higher incidence of co-morbid conditions, such as diabetes mellitus and renal failure, and this can contribute to worse outcomes.^{4,5} Some investigators have suggested that a gender-based treatment bias may explain why women have significantly different management and outcomes than men in other cardiovascular diseases.^{6,7} Several studies have documented less aggressive management of such diseases in women, a difference that is especially true in

coronary disease. However, few studies have looked at the impact of gender in IE. Recently, Aksoy et al⁵ reported that preexisting and coexisting conditions were the most important determinants of the different gender-related outcomes in IE, but it is possible that bias in management could also influence worse prognosis in women. The aim of our study was to determine gender-related differences in clinical presentation, management, and early and 1-year mortality in patients admitted to the hospital with IE.

Methods

This was a prospective observational cohort study at a single tertiary care hospital. The center is a 1,250-bed teaching hospital that includes all major medical and surgical departments and is a referral center for cardiac surgery. All consecutive patients aged ≥ 18 years diagnosed with confirmed or possible IE according to the modified Duke classification⁸ who were treated from January 2000 to December 2008 were enrolled. Patients were identified by the cardiology or infectious diseases department on the basis of positive follow-up culture, echocardiographic disturbances suggesting IE, or referral from other facilities.

All demographic, clinical, diagnostic, management, and outcome variables were recorded prospectively during the admission period. Follow-up was clinical and echocardiographic at 1 year after discharge. Charts were reviewed to record all causes of death.

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Table 1
Differences in clinical and echocardiographic characteristics of infective endocarditis between men and women

Variable	Overall (n = 271)	Women (n = 88)	Men (n = 183)	p Value*
Baseline characteristics				
Age (years)	57 ± 18	63 ± 16	58 ± 18	0.006
Co-morbidities				
Type 2 diabetes mellitus	50 (18%)	18 (20%)	32 (18%)	0.67
Hemodialysis	15 (6%)	9 (10%)	6 (3%)	0.05
HIV infection	20 (7%)	1 (1%)	19 (11%)	0.01
Cancer	38 (14%)	12 (14%)	26 (14%)	0.9
Immunosuppression therapy	18 (7%)	12 (14%)	6 (3%)	0.006
General condition				
Charlson index	2.02 ± 2.6	1.80 ± 1.85	2.2 ± 2.46	0.19
Affected valve				
Aortic	112 (41%)	27 (31%)	85 (46%)	0.02
Mitral	111 (41%)	46 (52%)	65 (36%)	0.02
Tricuspid, pulmonary	48 (18%)	15 (17%)	33 (18%)	0.8
Culprit pathogens				
<i>Staphylococcus aureus</i>	74 (27%)	23 (26%)	51 (28%)	0.93
CoNS	19 (7%)	7 (8%)	12 (7%)	
Enterococci	28 (10%)	11 (13%)	17 (9%)	
<i>Streptococcus viridians</i>	62 (23%)	19 (22%)	43 (24%)	
Negative culture	11 (4%)	3 (3%)	8 (4%)	
Other	77 (28%)	25 (28%)	52 (28%)	
Health care associated	72 (22%)	26 (24.1)	46 (21%)	0.5
Major complications				
Heart failure	227 (84%)	74 (84%)	153 (84%)	1
Acute renal failure	128 (47%)	41 (47%)	87 (48%)	0.98
Stroke	76 (28%)	23 (26%)	53 (29%)	0.7
Peripheral or visceral embolism	50 (19%)	10 (11%)	40 (21%)	0.05
Disturbance of conduction [†]	98 (36%)	34 (39%)	64 (35%)	0.6
Provisional pacemaker (in patients with conduction disturbances)	38 (14%)	15 (17%)	23 (12%)	0.4
Definitive pacemaker (in patients with conduction disturbances)	6 (16%)	4 (27%)	2 (9%)	0.1
8 (21%)	1 (7%)	7 (30%)	0.1	
Echocardiographic findings				
Underlying valve disease	61 (19%)	26 (24%)	35 (16%)	0.09
Moderate to severe aortic regurgitation (when aortic valve was affected [‡])	83 (74%)	20 (74%)	63 (74%)	1.0
Moderate to severe mitral regurgitation (when mitral valve was affected)	75 (68%)	30 (65%)	45 (69%)	0.81
Ejection fraction (%)	60.5 ± 10.3	62.9 ± 8.1	59.5 ± 10.9	0.52
Vegetation	237 (88%)	77 (87%)	160 (87%)	1.0
Vegetation diameter (mm)	12 ± 9	12.3 ± 12	11.6 ± 8	0.53
Paravalvular complications				
Valve perforation	105 (39%)	23 (26%)	82 (45%)	0.003
Abscess	46 (17%)	7 (8%)	39 (21%)	0.006
Valve rupture	28 (10%)	8 (9%)	20 (11%)	0.41
Fistulae	33 (12%)	7 (8%)	26 (14%)	0.17
	7 (3%)	2 (2%)	5 (2.7%)	1.0

Data are expressed as mean ± SD or as number (percentage).

* Results were compared using the chi-square test, with the exception of HIV infection, pacemaker use (provisional and definitive), and presentation of fistulae, which were compared using Fisher's exact test.

[†] Percentages are of a subgroup of 38 patients.

[‡] Percentages are of a subgroup of 112 patients.

CoNS = coagulase-negative staphylococci; HIV = human immunodeficiency virus.

IE was defined according to the modified Duke classification.⁸ The Charlson index⁹ was used at hospital admission to stratify patients according to overall morbidity. This co-morbidity index predicts 1-year mortality for a patient who may have a range of conditions, such as heart disease, acquired immune deficiency syndrome, or cancer. IE was defined as associated with health care according to a published definition.¹⁰

Surgical indications were established according to the guidelines of the European Society of Cardiology¹¹ and the American Heart Association and American College of Cardiology.¹² All surgical interventions were performed by the same team during the study period. When surgery was indicated but not performed, the main reason for the decision was recorded. Only inpatient cardiac surgery was considered.

Table 2
Gender differences in treatment of infective endocarditis and overall outcomes

Variable	Overall (n = 271)	Women (n = 88)	Men (n = 183)	p Value*
Treatment				
Medical treatment				
First choice	141 (52%)	57 (64%)	84 (46%)	0.003
Because surgery was ruled out	19 (7%)	7 (8%)	12 (7%)	0.8
Surgery				
Indicated	130 (48%)	32 (36%)	98 (54%)	0.008
Performed	111 (41%)	24 (26%)	87 (47%)	0.001
Surgical delay (days)	10.9 ± 9	11.9 ± 8.6	10.74 ± 11	0.6
Reasons for not performing surgery				
Elevated surgical risk	13 (68%)	6 (86%)	7 (58%)	0.33
Heart failure	2 (11%)	1 (14%)	1 (8%)	0.68
Hemodynamic instability	3 (16%)	2 (29%)	1 (8%)	0.52
Death	2 (11%)	1 (14%)	1 (8%)	0.68
Mortality				
Overall				
In hospital	70 (26%)	28 (32%)	42 (23%)	0.05
1 year	80 (29%)	34 (38%)	47 (26%)	0.04
Medical treatment				
Overall[†]				
In hospital	47 (29%)	21 (34%)	25 (27%)	0.29
1 year	57 (36%)	27 (40%)	30 (31%)	0.1
First choice[‡]				
In hospital	37 (26%)	17 (30%)	19 (18%)	0.06
1 year	47 (33%)	23 (39%)	24 (29%)	0.09
Because surgery was ruled out[§]				
In hospital	10 (53%)	4 (57%)	6 (50%)	0.7
1 year	10 (53%)	4 (57%)	6 (50%)	0.7
Surgery performed				
In hospital	24 (22%)	7 (30%)	17 (19%)	0.2
1 year	24 (22%)	7 (30%)	17 (19%)	0.2

Data are expressed as mean ± SD or as number (percentage).

* Results were compared using the chi-square test, with the exception of heart failure, hemodynamic instability, and death (under reasons for not performing surgery) and decision to provide medical treatment because surgery was ruled out, which were compared using Fisher's exact test.

[†] Percentages were calculated for a subgroup of 160 patients.

[‡] Percentages were calculated for a subgroup of 141 patients.

[§] Cases in which surgery was ruled out for medical reasons or life-threatening disease. Percentages were calculated for a subgroup of 19 patients.

^{||} Percentages were calculated for a subgroup of 111 patients.

IE complications were defined as (1) persistent fever (present 7 days after the start of treatment), (2) heart failure, (3) intracardiac abscess (diagnosed by echocardiography or during surgery), (4) new conduction abnormality, (5) stroke, (6) systemic embolism other than stroke, and (7) acute renal failure (defined as a 50% increase from the baseline creatinine concentration).

In-hospital mortality was defined as death from any cause during hospitalization. One-year cumulative mortality was defined as death from any cause within the year after the diagnosis of IE.

Patients were assessed in the outpatient clinic on days 30, 90, and 365 after hospital discharge. Blood samples were obtained for culture 2 days after completion of antimicrobial treatment and 30 and 90 days after hospital discharge. Echocardiographic examinations were performed during admission, at the end of treatment, and at least once again during the first year of follow-up.

Continuous variables are expressed as mean ± SD. Categorical variables are described using absolute numbers and

relative frequencies (percentages) of patients in each category. The distribution of categorical variables was compared using the chi-square test or Fisher's exact test as appropriate; Student's *t* test was used to compare continuous variables. A 2-tailed *p* value <0.05 was considered significant. Kaplan-Meier actuarial analysis was used to determine the probability of mortality during follow-up, and the resulting survival curves were compared using the Mantel-Cox log-rank test. For the multivariate analysis, the effects on in-hospital and 1-year mortality of variables that were determined to be clinically important and/or statistically significant in the univariate analysis (*p* <0.10) were analyzed by logistic regression. Vegetation size ≤10 mm was not included in the multivariate analyses, because this variable was missing for 170 patients. When models were constructed for the subset of patients who did have this variable recorded, no changes were seen in the levels of significance of variables accounting for the gender-specific differences in either in-hospital or 1-year mortality. Statistical analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, Illinois).

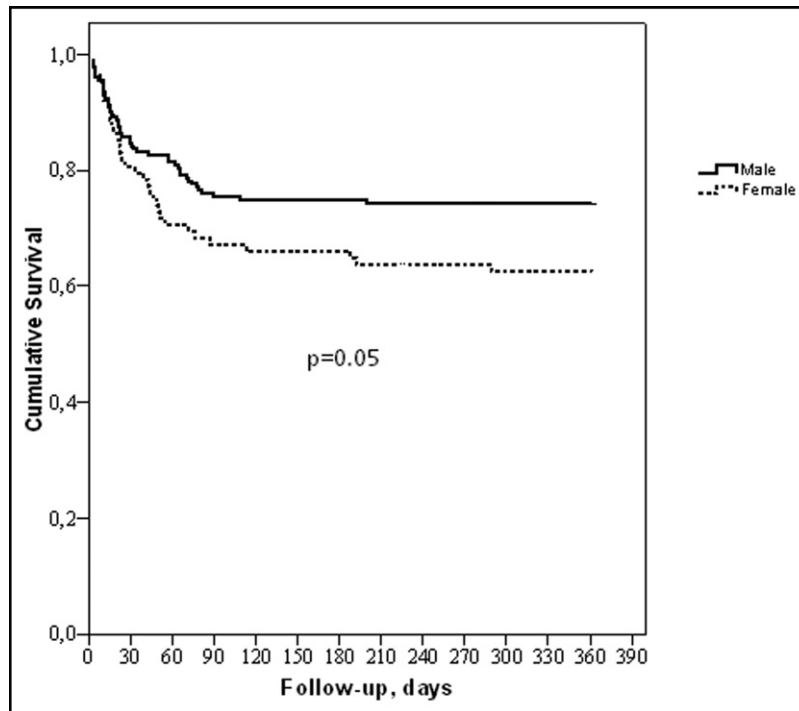


Figure 1. Differences in cumulative survival in men and women.

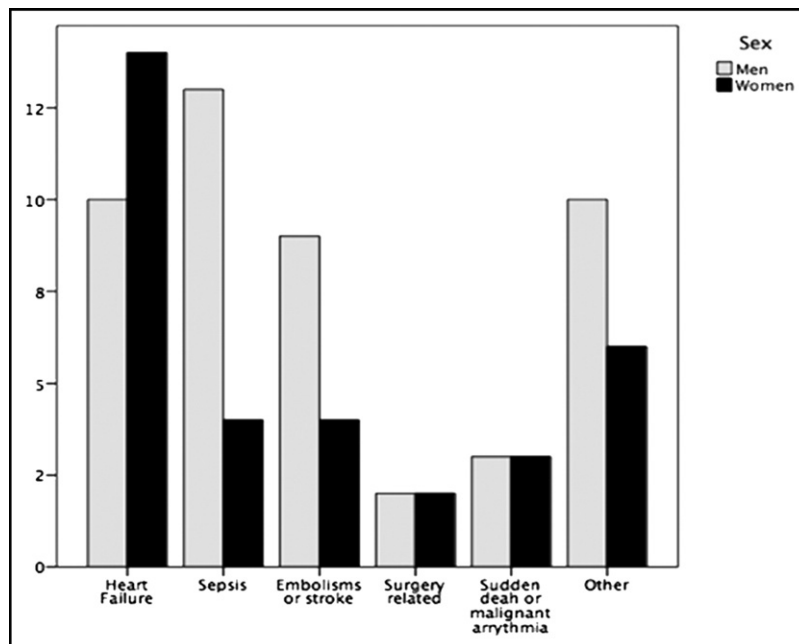


Figure 2. Comparison of causes of death between men and women.

Results

A total of 271 episodes of IE in 264 patients were studied; 183 (67.5%) occurred in men and 88 (32.5%) in women. The mean age of patients was 57 ± 18 years. Differences in baseline clinical characteristics, echocardiographic findings, and clinical course are listed in Table 1.

Women were older than men, and more women than men were taking immunosuppressants, although more men had human immunodeficiency virus infections than women. Charl-

son index on admission, rate of nosocomial IE, culprit pathogens, and rate of negative culture were similar in men and women. There were no differences in underlying cardiac disease. Infection more frequently involved the mitral valve in women than in men. The frequency of use of transesophageal echocardiography was similar in men and women ($p = 0.46$). Men were more likely to have paravalvular complications due to valve perforation.

Major complications were common: 227 patients (83.8%) experienced ≥ 1 complication during hospitalization. The in-

Table 3
Univariate and multivariate analysis of predictors of in-hospital mortality for the entire cohort of patients with infective endocarditis

Variable	Univariate Analysis			Multivariate Analysis		
	RR	95% CI	p Value*	RR	95% CI	p Value
Female gender	1.58	1.00–2.52	0.05	0.85	0.22–3.20	0.8
Age \geq 70 years	1.44	0.82–2.50	0.20	1.08	0.30–3.90	0.7
Type 2 diabetes mellitus	1.29	0.65–2.5	0.47			
Hemodialysis	2.0	0.68–5.80	0.50			
Intravenous drug use	0.88	0.29–2.30	0.90			
HIV infection	0.95	0.30–2.70	0.90			
Cancer	1.6	0.77–3.3	0.23			
Charlson index \geq 3	2.53	1.43–4.49	0.02	2.83	0.65–12.23	0.16
<i>Staphylococcus aureus</i> or CoNS	2.46	1.40–4.30	0.002	0.50	0.12–2.01	0.33
Persistent fever	1.8	0.90–3.60	0.06	4.70	0.84–19.78	0.08
Underlying valve disease	1.85	1.00–3.30	0.04	0.72	0.17–2.90	0.65
Moderate to severe mitral regurgitation	1.4	0.77–2.53	0.20	1.34	0.41–4.40	0.6
Moderate to severe aortic regurgitation	0.72	0.39–1.33	0.30			
Ejection fraction $<$ 50%	2.33	0.40–13.2	0.30	0.32	0.04–2.37	0.4
Vegetation size \geq 10 mm	2.2	1.20–4.90	0.03			
Heart failure	3.6	2.01–6.46	$<$ 0.001	19.5	3.51–108.2	0.001
Acute renal failure	5.57	3.08–10.07	$<$ 0.001	3.69	1.08–12.6	0.03
Stroke	5.42	2.82–10.40	$<$ 0.001	5.50	1.20–25.05	0.02
Embolism	0.82	0.40–1.40	0.50			
Paravalvular complications	0.98	0.52–1.60	0.77			
Surgery performed	0.65	0.37–1.15	0.15	0.18	0.04–0.77	0.02

* Univariate comparisons were made using the chi-square test.

Abbreviations as in Table 1.

Table 4
Univariate and multivariate analysis of predictors of 1-year mortality for the entire cohort of patients with infective endocarditis

Variable	Univariate Analysis			Multivariate Analysis		
	RR	95% CI	p Value*	RR	95% CI	p Value
Female gender	1.73	1.00–2.92	0.04	1.64	0.50–5.37	0.4
Age \geq 70 years	3.00	0.73–2.15	0.4	1.23	0.37–4.05	0.5
Type 2 diabetes mellitus	1.15	0.59–2.23	0.7			
Hemodialysis	2.9	1.02–8.30	0.04			
Intravenous drug use	0.88	0.33–2.30	0.8			
HIV infection	1.65	0.65–4.20	0.3			
Cancer	1.68	0.82–3.43	0.1			
Charlson index \geq 3	2.6	1.49–4.53	0.001	2.80	0.72–10.8	0.13
<i>Staphylococcus aureus</i> or CoNS	2.61	1.51–4.47	0.001	0.45	0.12–1.61	0.5
Persistent fever	1.85	1.01–3.10	0.04	7.11	1.71–29.5	0.007
Underlying valve disease	1.23	0.64–2.32	0.1	0.72	0.19–2.69	0.62
Moderate to severe mitral regurgitation	1.52	0.86–2.67	0.1	2.36	0.78–7.14	0.13
Moderate to severe aortic regurgitation	0.74	0.41–1.32	0.3			
Ejection fraction $<$ 50%	1.8	0.33–10.5	0.4	0.50	0.08–2.79	0.4
Vegetation size \geq 10 mm	1.91	0.99–3.69	0.06	2.34	0.60–9.16	0.22
Heart failure	2.61	1.52–4.46	$<$ 0.001	15.36	3.51–67.23	$<$ 0.0001
Acute renal failure	4.68	2.64–8.29	$<$ 0.001	5.07	1.54–16.7	0.008
Stroke	4.6	2.42–8.75	$<$ 0.001	3.59	0.85–15.15	0.08
Embolism	0.79	0.45–1.38	0.1	0.79	0.38–2.54	0.45
Paravalvular complications	0.74	0.43–1.27	0.7			
Surgery performed	0.49	0.28–0.86	0.01	0.12	0.03–0.48	0.03

* Univariate comparisons were made using the chi-square test.

Abbreviations as in Table 1.

cidences of heart failure, peripheral embolism, acute renal failure, stroke, persistent fever, and conduction disturbance were similar between women and men (Table 1).

Conservative nonsurgical treatment was considered the first-choice management option for 141 patients (52%). In

the remaining patients, surgery was indicated because of the presence of complications. Cardiac valve surgery was less often indicated and less often performed in women than in men (26% vs 47%, relative risk [RR] 0.4, 95% confidence interval [CI] 0.2 to 0.7, $p = 0.001$), even after adjustment

for age (RR 0.98, 95% CI 0.9 to 1.0, $p = 0.10$), severe mitral regurgitation (RR 1.2, 95% CI 0.54 to 2.58, $p = 0.70$), persistent fever (RR 1.5, 95% CI 0.5 to 4.4, $p = 0.40$), ejection fraction $\leq 50\%$ (RR 1.4, 95% CI 0.1 to 18.2, $p = 0.04$), Charlson index (RR 0.2, 95% CI 0.08 to 0.5, $p = 0.001$), periannular complications (RR 3.1, 95% CI 1.2 to 7.7, $p = 0.01$), severe aortic regurgitation (RR 3.52, 95% CI 1.60 to 7.57, $p < 0.001$), and heart failure (RR 9.74, 95% CI 4.48 to 21.18, $p < 0.0001$). There were no significant gender differences in reasons for declining surgery, and operative mortality was similar in men and women (Table 2).

Seventy patients (26%) died before hospital discharge, and this mortality rate tended to be higher in women than in men (32% vs 23%, $p = 0.05$). At 1 year, 80 patients (29%) had died; this mortality rate was significantly higher in women (38% vs 26%, $p = 0.05$). The mean survival rates were $81 \pm 4\%$ in women and $85 \pm 3\%$ in men at 30 days and $62 \pm 5\%$ in women and $74 \pm 3\%$ in men at 1 year (log-rank $p = 0.05$; Figure 1). Causes of death are shown in Figure 2. More women than men died from congestive heart failure, which was the main cause of death in women.

In the univariate analysis for the entire cohort, female gender approached significance as a predictor of in-hospital mortality and was clearly an independent predictor of 1-year mortality. However, the multivariate logistic regression model did not indicate that gender was a predictor of in-hospital mortality after adjustment for age, co-morbid conditions, infection by *Staphylococcus aureus* or coagulase-negative staphylococci, persistent fever, underlying valve disease, presentation severity, the ejection fraction, and major complications. The presence of heart failure, renal failure, or stroke was associated with in-hospital mortality (Table 3).

Likewise, gender also did not emerge as a predictor of 1-year mortality on multivariate analysis. Factors that were significantly associated with 1-year mortality were persistent fever, heart failure, and acute renal failure. Interestingly, surgical treatment emerged as a protective variable against in-hospital mortality and 1-year mortality (Tables 3 and 4).

Discussion

This is the first study to systematically evaluate gender difference in native valve IE. Our study revealed gender differences in patient and clinical characteristics, management, and prognosis of IE. Our data collection process was consistent because the study was conducted at a single tertiary care teaching hospital, and the medical and surgical team remained stable throughout the study period, ensuring homogeneity concerning clinical decisions.

Women with IE were older than men in our study and were more frequently taking immunosuppressants than men. In addition, IE involved the mitral valve more often in women, consistent with reports from other patient series.^{5,13} Although the rate of major complications during the active phase was similar in both genders, women in our cohort underwent surgery less often, and mortality tended to be higher in women during the active phase and was significantly higher in the long term.

On the basis of these data, we raise the question of whether systematic bias affecting the management of

women may be occurring, given that women are usually older than men and have greater co-morbidities, factors that ultimately influence the decision to rule out surgery. In our cohort, a multivariate analysis showed that the following factors were related to a decision to schedule surgery: male gender, the presence of an ejection fraction $< 50\%$, Charlson index < 3 , the presence of severe aortic regurgitation, periannular complications, and heart failure. It might be supposed that the decision to operate on men might have been influenced partly by the fact that IE was more often found to affect the aortic valve in men; such a finding is associated with more paravalvular complications, thus necessitating surgery during the active phase. However, arguing against that assumption, male gender was an independent factor associated with surgical treatment in our study, consistent with other studies reporting bias in the management of women with IE with regard to surgical criteria.^{5,13,14} This is an important observation because performing surgery affects outcome.

Differences in treatment on the basis of gender have been a cause for concern in recent years.^{15–18} In our study, the treatment difference was somewhat reflected in different mortality rates. Our data clearly illustrate that surgery was associated with improved in-hospital and 1-year mortality in the entire cohort but that it was less likely to be undertaken in women, who demonstrated increased in-hospital and 1-year mortality, despite having a similar operative mortality rate as men and despite correction for confounding variables.

The most frequent cause of death in women in our cohort was congestive heart failure. This complication of IE is more likely to occur if surgery is delayed or withheld, and surgery has been consistently linked to reduced mortality and the restoration of life expectancy in patients with IE.^{11,12} Systematic bias (underreferral of women with IE for valve surgery) will thus have an adverse impact on overall outcome. In agreement with other investigators, we believe that more women with IE should be offered more aggressive treatment and particularly that they should undergo surgery more frequently.^{5,14}

A certain selection bias probably affected our study, which was performed at a tertiary care hospital; the high mortality rate we found is probably partially attributable to this. Nonetheless, we provide evidence of gender differences in the management of IE, and these were found to affect outcomes, leading to a worse survival rate for women, possibly because they received less aggressive therapy. We believe that it is extremely difficult to explain the management differences between the genders in terms of the variables we have measured, but clearly, personalized decisions are being taken to tailor treatment, and this must be taken into account when considering any general tendencies.

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2. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, Karchmer AW, Olaison L, Pappas PA, Moreillon P, Chambers ST, Chu VH, Falcó V, Holland DJ, Jones P, Klein JL, Raymond NJ, Read KM, Tripodi MF, Utili R, Wang A, Woods CW, Cabell CH; International Collaboration on Endocarditis-Pro prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis—Prospective Cohort Study 2009. *Arch Intern Med* 2009;169:463–473.
3. Cabell CH, Abrutyn E. Progress toward a global understanding of infective endocarditis. Early lessons from the International Collaboration on Endocarditis investigation. *Infect Dis Clin N Am* 2002;16:255–272.
4. Moreno R, Zamorano J, Almeria C, Villate A, Rodrigo JL, Herrera D, Alvarez L, Morán J, Aubele A, Mataix L, De Marco E, Sánchez-Harguindey L. Influence of diabetes mellitus on the short and long term outcome in patients with active infective endocarditis. *J Heart V Dis* 2002;11:651–659.
5. Aksoy O, Meyer LT, Cabell CH, Kourany WM, Pappas PA, Sexton DJ. Gender differences in infective endocarditis: pre- and co-morbid conditions lead to different management and outcomes in female patients. *Scand J Infect Dis* 2007;39:101–107.
6. Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, Manhapra A, Mallik S, Krumholz HM; National Registry of Myocardial Infarction Investigators. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J Med* 2005;353:671–682.
7. Akhter N, Milford-Beland S, Roe M, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J* 2009;157:141–148.
8. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–638.
9. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
10. Fernández-Hidalgo N, Almirante B, Tornos P, Pigrau C, Sambola A, Igual A, Pahissa A. Contemporary epidemiology and prognosis of health care associated infective endocarditis. *Clin Infect Dis* 2008;47:1287–1297.
11. Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology; European Society of Clinical Microbiology and Infectious Diseases; International Society of Chemotherapy for Infection and Cancer; Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Müller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL; ESC Committee for Practice Guidelines; Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, McGregor K, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J* 1996;30:2369–2413.
12. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani LY, Gewitz MH, Tong DC, Steckelberg JM, Baltimore RS, Shulman ST, Burns JC, Falace DA, Newburger JW, Pallasch TJ, Takahashi M, Taubert KA; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; Council on Cardiovascular Disease in the Young; Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia; American Heart Association; Infectious Diseases Society of America. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation* 2005;111:e394–e434.
13. Castillo JC, Anguita MP, Delgado M, Ruiz M, Mesa D, Romo E, Crespín M, García D, Arizón JM, Suárez de Lezo J. Clinical characteristics and prognosis of infective endocarditis in women. *Rev Esp Cardiol* 2008;61:36–40.
14. Netzer RO, Altwegg SC, Zollinger E, Tauber M, Carrel T, Seiler C. Infective endocarditis: determinants of long term outcome. *Heart* 2002;88:61–66.
15. Stone PH, Thompson B, Anderson HV, Kronenberg MW, Gibson RS, Rogers WJ, Diver DJ, Théroux P, Warnica JW, Nasmith JB, Kells C, Kleiman N, McCabe CH, Schactman M, Knatterud GL, Braunwald E. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: the TIMI III registry. *JAMA* 1996;275:1104–1112.
16. Ghali WA, Faris PD, Galbraith PD, Norris CM, Curtis MJ, Saunders LD, Dzavik V, Mitchell LB, Knudtson ML; Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. Sex differences in access to coronary revascularization after cardiac catheterization: importance of detailed clinical data. *Ann Intern Med* 2002;136:723–732.
17. King KM, Ghali WA, Faris PD, Curtis MJ, Galbraith PD, Graham MM, Knudtson ML. Sex differences in outcomes after cardiac catheterization. *JAMA* 2004;291:1220–1225.
18. Scirica BM, Moliterno DJ, Every NR, Anderson HV, Aguirre FV, Granger CB, Lambrew CT, Rabbani LE, Sapp SK, Arnold A, Booth JE, Ferguson JJ, Cannon CP; The GUARANTEE Investigators. Differences between men and women in the management of unstable angina pectoris (the GUARANTEE registry). *Am J Cardiol* 1999;84:1145–1150.