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ORIGINAL ARTICLE

Gender Based Analysis of a Population Series of Patients Hospitalized with Infective Endocarditis in Portugal – How do Women and Men Compare?

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Abstract

Background: The impact of gender on the outcome of patients hospitalized with infective endocarditis (IE) is not fully understood.

Objective: To verify the association between gender and the clinical profile of patients hospitalized with IE, treatment strategies, and clinical outcomes.

Methods: This is a retrospective nationwide study of patients hospitalized with IE, based on hospital admissions between 2010 and 2018 in Portugal. Descriptive statistics were used to present variables. An inferential analysis was performed using multiple logistic regression. A 95% confidence interval and a 5% significance level were considered.

Results: In total, 3266 (43.1%) women and 4308 (56.9%) men were hospitalized with IE. The women were older (76 vs 69 years old, p<0.001), more frequently presented arterial hypertension (39.8% vs 35.4%, p<0.001) and atrial fibrillation (29.5% vs 21.2%, p<0.001), and had less cardiovascular comorbidities. Acute heart failure was more common in women (32.9 vs 26.9%, p<0.001) and acute renal failure (13.6% vs 11.7%, p<0.001) and sepsis (12.1% vs 9.1%, p<0.001), in men. Women were less likely to undergo cardiac surgery (OR 0.48 – 95%CI 0.40–0.57, p<0.001) and had a higher postoperative mortality (OR 1.84, 95% CI 1.19–2.84, p=0.006). In-hospital mortality rates were comparable between genders (20.3% vs 19.6%, p=0.45).

Conclusions: Women were less likely to undergo cardiac surgery when hospitalized with IE, and the female gender was a predictor factor for postoperative mortality. Overall, in-hospital mortality was not influenced by gender. Further research is necessary to fully clarify the impact of gender on IE management and outcomes.

Keywords: Endocarditis; Gender and Health; Cardiac Surgery; Mortality.

Introduction

Cardiovascular diseases, including coronary heart disease, heart failure, and cerebrovascular disease, constitute leading causes of cardiovascular morbidity and mortality worldwide.[1] Great advances in cardiovascular prevention and management[2–4] have dramatically altered the outcome of these patients. Still, this trend has not been homogeneous between men and women. In the last decades, a growing awareness of the similarities and differences between men and women regarding cardiovascular function, disease burden, and epidemiology has been noted. Several initiatives issued by scientific societies have increasingly

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recognized the need for reducing the gender gap in clinical care and research.[5] Various publications have highlighted the impact of gender on several fields of cardiology such as coronary artery disease[6–8] or heart failure,[9,10] as well as in general medicine involving sepsis[11] or pneumonia.[9]

Infective endocarditis (IE) constitutes a rare condition with significant morbidity and mortality. Demographic changes, with an aging population associated with an upward trend in the implantation of prosthetic cardiac valves and cardiac devices, have justified a similar trend in the incidence of this pathology.[12–14]

The impact of gender in the clinical profile and outcome of patients with IE has been seldom approached. A higher incidence among men has been noted[15,16] in international registries. Moreover, a recent systematic review of observational series from Portugal[17] concluded that a higher prevalence of men was noted in all studies and this predominance was also noted in all surgical series (men constituted more than two-thirds of all operated patients). Still, scarce and conflicting evidence persists regarding the influence of gender on the access to cardiac surgery and fatal outcome,[18–24] being mostly based on single-center cohorts. Populational studies addressing this issue are rare,[23] yet crucial to avoid selection bias in observational studies performed in tertiary centers.

Therefore, using population-based data, the authors sought to explore the association of gender and the clinical profile of patients hospitalized with IE, access to surgical interventions, and clinical outcomes.

Methods

Study design

This is a nationwide cross-sectional study using inpatient discharge data from all public hospitals of the Portuguese National Health System (NHS) considering patients admitted with IE. A comparative analysis based on gender (women and men) was performed.

Our data source and study population were described elsewhere.[25] In brief, our data comprised hospital discharge reports including clinical information (gender, age, geographical region, hospital, date of admission and discharge, length of hospital stay, destination — home, unknown, another acute hospital, a palliative care institution or outpatient clinic, discharge against medical advice, deceased), a clinical diagnosis list (one primary diagnosis and up to nineteen secondary diagnoses), and procedures (up to twenty). The hospital discharge report used the International Classification of Diseases (ICD)-9 until 2016, and ICD-10 from then onwards. All hospitalizations of patients with an IE diagnosis at discharge (ICD-9-CM codes 421.0, 421.1, 421.9, and 424.9; ICD-10-CM I33.0, I33.9, I38, and I39) between January 1, 2010 and December 31, 2018 were considered. Each patient and hospitalization episode were linked to the first institution of hospitalization.

Variables

For each index IE hospitalization associated with valvular surgery, we identified the year of hospitalization, date of surgery (when available), presence of a cardiothoracic unit at the first hospital of admission, clinical information (gender, age, year of discharge, length of hospital stay), cardiovascular history and comorbidities (diabetes mellitus, non-rheumatic valve disease, rheumatic valve disease, affected cardiac valve, arterial hypertension, chronic kidney disease, chronic coronary artery disease, cancer, human immunodeficiency virus [HIV] infection, cardiac devices and heart valve prostheses, atrial fibrillation, chronic liver disease, chronic obstructive pulmonary disease, use of opioid drugs, congenital heart disease), microorganisms (*Staphylococcus, Staphylococcus aureus, Streptococcus, Enterococcus*, Gram-negative bacteria, anaerobes, fungi, *Brucella*), complications compatible with IE (heart failure, embolic stroke, ischemic stroke, transient ischemic attack, septic shock, splenic abscess, acute renal failure, acute coronary syndrome, central nervous system abscess, or meningitis), cardiac surgery, and in-hospital death using the ICD-9 and ICD-10 codes — Supplement Table S1.

Definition of postoperative and in-hospital mortality

Postoperative mortality was defined as all-cause deaths that occurred during the index hospitalization in patients who underwent cardiac surgery.

In-hospital mortality was defined as all-cause deaths that occurred during the index hospitalization in all patients hospitalized with IE.

Statistical analysis

Continuous variables were presented as means ± standard deviations if following a normal distribution; otherwise, medians and interquartile ranges were displayed. Categorical variables were expressed as frequencies and percentages. For the bivariate analysis, the comparison between continuous variables was performed through

Table 1 – Baseline characteristics of women and men hospitalized with IE in Portugal between 2010 and 2018

	Overall	Men	%	Women	%	*p*
N	7574	4308	56.9	3266	43.1	-
Age, years – median (interquartile range)	72(21)	69(22)	-	76(18)	-	**<0.001**
Cardiothoracic unit on site , number of beds (%)	3302 (43.6)	1876	43.5	1426	56.4	0.92
Length of hospital stay, days - median (interquartile range)	18(34)	22(36)	-	14(29)	-	**<0.001**
Medical history, n (%)						
Diabetes mellitus	2016 (26.6)	1116	25.9	900	27.6	0.11
Arterial hypertension	2828 (37.3)	1527	35.4	1301	39.8	**<0.001**
Atrial fibrillation	1876 (24.8)	912	21.2	964	29.5	**<0.001**
HIV	133 (1.8)	107	2.5	26	0.8	**<0.001**
CRF	887 (11.7)	515	12.0	372	11.4	0.47
CRF on hemodialysis	324 (4.3)	192	4.5	132	4.0	0.39
Non-rheumatic cardiac valve disease	1590 (21)	1044	24.2	546	16.7	**<0.001**
Rheumatic valve disease	709 (9.4)	396	9.2	313	9.6	0.58
Mitral valve disease	913 (12.1)	564	13.1	349	10.7	0.001
Aortic valve disease	903 (11.)	611	13.1	292	8.9	**<0.001**
Aortic and mitral valve disease	405 (5.3)	237	5.5	168	5.1	0.26
Right heart valve disease	447 (5.9)	243	5.6	204	6.2	0.15
Cardiac valve prosthesis	914 (12.1)	537	12.5	379	11.6	0.24
Cardiac implantable electronic devices	649 (8.6)	386	9.0	263	8.1	0.17
Coronary artery disease	970 (12.8)	606	14.1	364	11.1	**<0.001**
Previous PCI	108 (1.4)	79	1.8	29	0.9	**0.001**
Previous CABG	183 (2.4)	136	3.2	47	1.4	**<0.001**
Congenital heart disease	42 (1)	24	0.6	18	0.6	0.88
Cancer	1018 (13.4)	627	14.6	391	12.0	**0.001**
COPD	702 (9.3)	397	9.2	305	9.3	0.87
Opioid consumption	103 (1.4)	90	2.1	13	0.4	**<0.001**
Chronic liver disease	366 (4.8)	279	6.5	87	2.7	**<0.001**
Infectious agents, n (%)						
Staphylococcus	1242 (16.4)	812	18.8	430	13.2	<0.001
Staphylococcus aureus	470 (6.2)	308	7.1	162	5.0	**<0.001**
Streptococcus	1030 (13.6)	728	16.9	302	9.2	**<0.001**
Enterococcus	535 (7.1)	359	8.3	176	5.4	**<0.001**
Gram-negative bacteria	898 (11.9)	453	10.5	445	13.6	**<0.001**
Anaerobes	20 (0.3)	16	0.4	4	0.1	**0.004**
Fungi	10 (0.1)	6	0.1	4	0.1	0.99

Brucella	9 (0.1)	8	0.2	1	0.0	0.09
In-hospital complications/outcomes, n (%)						
Heart failure	2232 (29.5)	1159	26.9	1073	32.9	**<0.001**
Sepsis	968 (12.7)	586	13.6	382	11.7	**<0.01**
Ischemic stroke	706 (9.3)	403	9.4	303	9.3	0.94
Transient ischemic attack	37(0.5)	16	0.4	21	0.6	0.19
Hemorrhagic stroke	204 (2.7)	134	3.1	70	2.1	**0.01**
Systemic embolism	97 (1.3)	60	1.4	37	1.1	0.35
Splenic abscess	73 (1)	46	1.1	27	0.8	0.34
Central nervous system abscess/meningitis	91 (1.2)	60	1.4	31	0.9	0.09
Acute renal failure	819 (10.8)	523	12.1	296	9.1	**<0.001**
Acute myocardial infarction	220 (2.9)	124	2.9	96	2.9	0.89
Cardiac surgery, n (%)	937 (12.4)	705	16.4	232	7.1	**<0.001**
In-hospital death, n (%)	1513 (20)	874	20.3	639	19.6	0.45

IE: infective endocarditis; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; HIV: human immunodeficiency virus; PCI: percutaneous coronary intervention.

an unpaired Student's t-test for normally distributed data or a Mann-Whitney test, and the comparison between categorical variables used the chi-squared test or a Fisher's exact test. The mentioned analysis was stratified by gender. Normality was verified through the Kolmogorov-Smirnov test and analysis of kurtosis and skewness values.

To assess the factors associated with in-hospital surgical intervention and in-hospital mortality, inferential analysis was performed using multiple logistic regression (a generalized linear model using binomial distribution for the error and the logit link function). The stepwise (forward) method, based on Akaike information criteria minimization, was used for the selection of variables included in the model. The adjusted odds ratio, as well as the 95% confidence interval (95% CI), were estimated for each variable included in the regression model.

All tests were 2-tailed. The level of significance was set to α=0.05.

Data were analyzed using IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, NY, USA).

Results

Main clinical features of the overall cohort

During the study period, 3266 (43.1%) women and 4308 (56.9%) men were hospitalized with IE — see Table 1. The length of hospital stay was superior in men. Women were on average older than men and presented higher prevalence of arterial hypertension (39.8% vs 35.5%) and atrial fibrillation (29.5% vs 21.2%). In contrast, men presented higher rates of non-rheumatic valve disease, coronary artery disease, HIV, and chronic liver disease. *Staphylococcus* and specifically *Staphylococcus aureus* were the most prevalent. *Streptococcus* and *Enterococcus* were more commonly identified in men; Gram-negative agents were more frequent in women. Regarding valve disease, left heart valve involvement was more frequent in men.

In-hospital complications were similar between the two groups except for heart failure, which was more common in women, and hemorrhagic stroke, acute renal failure, and sepsis, which were more prevalent in men.

Men underwent surgery more often. Finally, the in-hospital fatal outcome was analogous between men and women. A bivariate analysis of exclusively medically managed patients revealed that women proportionally had a lower in-hospital mortality (19.4% vs 21.6%, p=0.026).

Table 2 shows a stepwise logistic regression approach to assess the in-hospital surgical management of patients hospitalized with IE. Women were less likely to undergo cardiac surgery during hospitalization (OR 0.48 – 95% CI 0.40–0.57, p<0.001).

In-hospital surgical cohort

In total, 232 (24.7%) women and 705 (75.3%) men underwent cardiac surgery during the index hospitalization for IE — Supplement Table S2.

Both groups were quite similar regarding comorbid conditions. A higher rate of atrial fibrillation was noted in women and a higher rate of malignancy , in men. Aortic valve and right heart valve disease were more prevalent in men. Regarding in-hospital complications, a higher rate of ischemic stroke was noted in men. Overall, postoperative mortality was significantly higher in women.

Postoperative mortality

Independent predictors of postoperative mortality are shown on Table 3. Female gender was an independent predictor of fatal outcome (OR 1.8, 95% CI 1.20–2.84, p=0.002). Other independent prognostic factors of in-hospital mortality in patients with IE subjected to surgery were previous coronary intervention, chronic kidney or liver disease, *Staphylococcus* or *Streptococcus* infection, acute renal failure, and sepsis. Younger patients were less likely to have a fatal outcome.

Discussion

In a contemporary populational cohort of patients hospitalized with IE in Portugal and after controlling for several risk factors, important differences were noted between women and men. Men were more prevalent, being younger and with a higher rate of comorbidities. On the other hand, women were less likely to undergo cardiac surgery during the incident hospitalization for IE, with a higher post-operative mortality rate. Even so, overall in-hospital mortality was comparable among men and women.

Our data showed a 1.3 man/woman ratio, which is in accordance with a higher prevalence of IE in men in populational studies.[12–14] The reasons for this remain speculative, but factors such as a higher valve disease prevalence in men and different hormone profiles have been previously mentioned.[19] Women were older but men presented a higher burden of comorbid conditions such as coronary artery disease, cardiac valve disease, liver failure, or malignancy. Infectious agents such as *Staphylococcus*, *Streptococcus,* or *Enterococcus* were more common in men whereas women presented a higher rate of Gram-negative agents. In-hospital complications were analogous, with women presenting a higher rate of acute heart failure while men had a higher rate of acute renal failure and sepsis. All these aspects were noted in previous gender-based studies.[18,21,23]

The male/female ratio increased to 3.0 in the surgical subgroup. Indeed, women were less likely to undergo cardiac surgery, which is a common finding with other studies.[18,19,21,23,26] Nonetheless, general indications for performing cardiac surgery in the context of IE[27] include acute heart failure, uncontrolled infection, and embolism. In this cohort, the profile of in-hospital-related complications was comparable between men and women, the latter group presenting a higher incidence of heart failure; this fails to explain the gender disparity in the access to surgical treatment among patients with IE. Additionally, men presented a higher incidence of hemorrhagic stroke, which normally delays and sometimes excludes cardiac interventions. Physician awareness[28] and other comorbidities not taken into account in this study such as frailty score,[29] dementia,[30] or neurologic sequelae could also have contributed individually to the decision to perform cardiac surgery and should be considered. Age, female gender, and endocarditis are variables included in cardiac surgery risk stratification scores such as EUROSCORE[31] or the STS[32] and the fact that women were older could have precluded cardiac surgery.

Additionally, women who underwent surgery in our study had a higher rate of fatal outcome when compared to men and constituted an independent risk factor for postoperative mortality. Demographics, comorbidities, infectious agents, and in-hospital-related complications in this surgical cohort were similar between men and women. This real-world data validates the increased surgical risk in women with IE, which is already considered in the above-mentioned risk scores. The higher surgical susceptibility of women was also found by Curlier et al.[23] and in a recent meta-analysis by Varela et al.[33] Weber et al.[22] concluded that a higher postoperative mortality rate in women was due to the presence of more comorbidities and perioperative risk factors, which was apparently not the case in the current study. This higher mortality after surgery in the female sex was also noted in other fields of cardiac surgery, such as after coronary artery bypass graft surgery.[34] Older age, a lower body surface area,[35] a higher incidence of heart failure, and referral bias[21] could also partially justify this higher surgical susceptibility.

Table 2 – Logistic regression analysis of in the characteristics of patients who underwent cardiac surgery due to IE

	Adjusted OR	95% CI		p
Gender (female)	0.481	0.403	0.573	**<0.001**
Age	0.969	0.965	0.974	**<0.001**
Non-rheumatic cardiac valve disease	3.040	2.242	4.121	**<0.001**
Arterial hypertension	1.596	1.351	1.885	**<0.001**
HIV	0.298	0.144	0.616	0.001
Cancer	0.679	0.522	0.884	0.004
Cardiac valve prostheses	1.524	1.220	1.905	**<0.001**
Cardiac devices	0.576	0.412	0.806	0.001
Chronic liver disease	0.389	0.254	0.595	**<0.001**
Mitral valve disease	2.032	1.547	2.670	**<0.001**
Aortic and mitral disease	5.425	4.161	7.071	**<0.001**
Aortic valve disease	2.181	1.637	2.905	**<0.001**
Staphylococcus	1.345	1.102	1.642	0.004
Streptococcus	1.825	1.466	2.273	**<0.001**
Enterococcus	1.544	1.164	2.047	0.003
Heart failure	1.684	1.423	1.994	**<0.001**
Hemorrhagic stroke	0.438	0.257	0.747	0.002
Systemic embolism	2.830	1.700	4.713	**<0.001**
Splenic abscess	2.039	1.145	3.632	0.016
Acute renal failure	1.508	1.210	1.879	**<0.001**

IE: infective endocarditis; CI: confidence interval; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; OR: odds ratio. Dependent variable: surgical management. Reference categories: male (gender); no (for remaining factors). Age was included as a numeric variable (covariate).

Finally, regarding in-hospital mortality, no significant differences were noted between men and women. This is similar to findings from Curlier et al.[23] It would be critical to analyze the causes of death in these patients. Actually, a recent study based on national death certificate data in Portugal[36] concluded that, in a cohort whose basic cause of death was IE, women presented a 19% higher death rate than men. Conversely, Thuny et al.[37] concluded that a high burden of comorbidities and aortic valve involvement may explain an increased death rate among women.

In our study, women differed from men in significant aspects of clinical presentation and treatment options. They were older and less likely to undergo cardiac surgery when hospitalized with IE, despite presenting less comorbid conditions and a comparable complication rate. Higher postoperative mortality, but not overall in-hospital mortality, was observed. Further research is needed to understand reasons that can explain individualized management strategies and the impact of surgery on survival in women hospitalized with IE.

Our study has several limitations. First, ICD-9 and ICD-10 codes were used to identify individual cases of IE and clinical variables on an administrative database. The authors were unable to consult the patient's electronic database to confirm the diagnosis and to identify other important variables. Therefore, diagnosis or coding errors could have occurred. Second, the authors were unable to trace patients beyond the index hospitalization and cardiac surgery could have been performed after discharge. This could lead to an underestimation of the number of cardiac surgeries performed in this cohort. Therefore, only in-hospital surgical management during

Table 3 – Logistic regression analysis of in-hospital mortality in patients who underwent cardiac surgery

	Adjusted OR	95% CI		p
Gender (female)	1.839	1.188	2.845	0.006
Age	1.062	1.043	1.082	**<0.001**
Chronic renal failure	2.694	1.475	4.920	0.001
Previous ICP	4.026	1.293	12.533	0.016
Previous CABG	8.661	2.493	30.094	0.001
Chronic liver disease	3.976	1.533	10.314	0.005
Staphylococcus	1.637	1.032	2.599	0.036
Streptococcus	0.307	0.174	0.543	**<0.001**
Hemorrhagic stroke	3.780	0.954	14.972	0.058
Acute renal failure	1.979	1.240	3.156	0.004
Sepsis	4.568	2.795	7.467	**<0.001**

CI: Confidence interval; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; OR: odds ratio. Dependent variable: in-hospital death. For medical history conditions, infectious agents, in-hospital complications, and cardiac surgery, the reference categories were "absence/no." Age was included as a numeric variable (covariate).

the index hospitalization was assessed. Third, this is a populational study; management strategies by individual physicians and the patients' personal treatment options could thus eventually lead to a referral bias towards cardiac surgery. Fourth, variables such as microbiological subgroups, source of bacteremia (community vs healthcare-related), presence of dementia, frailty score, or a socioeconomic situation that could have further explained our findings were not available for analysis.

Conclusions

In Portugal between 2010 and 2018, hospitalization with IE occurred less frequently in women, who were older and presented fewer comorbidities. A comparable rate of in-hospital complications was observed, with a higher prevalence of acute heart failure. Regarding surgical treatment, women were less likely to undergo cardiac surgery and female gender was an independent predictor of postoperative mortality. Further research is warranted to understand the reasons behind the influence of gender on treatments and outcomes of this disease. The individualized management of IE is frequently challenging, and the influence of gender should be carefully considered together with comorbidities and complications to improve the outcome of these patients.

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Data availability statement

Data supporting the findings of this study are available from ACSS but restrictions apply to the availability of these data, which were used under license for the current study, thus not being publicly available. Data are however available from the authors upon reasonable request and only after permission by ACSS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CAML - *Universidade Lisboa* under the protocol number 349/19. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Anonimized data was used.

Author contributions

Conception and design of the research: Sousa C, Nogueira P, Pinto F. Acquisition of data: Sousa C, Nogueira P. Analysis and interpretation of the data: Sousa C, Nogueira P. Writing of the manuscript: Sousa C. Critical revision of the manuscript for intellectual content: Sousa C, Nogueira P, Pinto F.

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*Supplemental Materials

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