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Original Article

Role of age and comorbidities in mortality of patients with infective endocarditis

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A R T I C L E I N F O

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A B S T R A C T

Purpose: The aim of this study was to analyse the characteristics of patients with IE in three groups of age and to assess the ability of age and the Charlson Comorbidity Index (CCI) to predict mortality.
Methods: Prospective cohort study of all patients with IE included in the GAMES Spanish database between 2008 and 2015.Patients were stratified into three age groups: < 65 years,65 to 80 years,and ≥ 80 years.The area under the receiver-operating characteristic (AUROC) curve was calculated to quantify the diagnostic accuracy of the CCI to predict mortality risk.
Results: A total of 3120 patients with IE (1327 < 65 years;1291 65-80 years;502 ≥ 80 years) were enrolled.Fever and heart failure were the most common presentations of IE, with no differences among age groups.Patients ≥80 years who underwent surgery were significantly lower compared with other age groups (14.3%,65 years; 20.5%,65-79 years; 31.3%, ≥80 years). In-hospital mortality was lower in the < 65-year group (20.3%, < 65 years;30.1%,65-79 years;34.7%, ≥80 years;$p < 0.001$) as well as 1-year mortality (3.2%, < 65 years; 5.5%, 65-80 years;7.6%, ≥80 years; $p = 0.003$).Independent predictors of mortality were age ≥ 80 years (hazard ratio [HR]:2.78;95% confidence interval [CI]:2.32–3.34), CCI ≥ 3 (HR:1.62; 95% CI:1.39–1.88),and non-performed surgery (HR:1.64;95% CI:11.16–1.58).When the three age groups were compared,the AUROC curve for CCI was significantly larger for patients aged < 65 years($p < 0.001$) for both in-hospital and 1-year mortality.
Conclusion: There were no differences in the clinical presentation of IE between the groups. Age ≥ 80 years, high comorbidity (measured by CCI),and non-performance of surgery were independent predictors of mortality in patients with IE.CCI could help to identify those patients with IE and surgical indication who present a lower risk of in-hospital and 1-year mortality after surgery, especially in the < 65-year group.

1. Introduction

Infective endocarditis (IE) is a life-threatening disease with high morbidity and mortality [1–4]. Its incidence in older patients has increased for different reasons, such as the aging of the general population and the increasing percentage of comorbidities [5–14]. Clinical presentation seems to be similar between the younger and older population [15–19]; however, there is no agreement on the role of age in general mortality or in the mortality related to surgery as a treatment for IE [2,8,10].

On the other hand, international guidelines have established the indication for surgery (repair or valve replacement) in certain situations, such as valve dysfunction resulting in heart failure, abscess, recurrent embolic events with residual vegetation, persistent bacteraemia, or especially aggressive microorganisms (i.e., *Staphylococcus aureus*) [20–22]; however, there are no recommendations in the guidelines addressing the elderly population. Moreover, in patients with IE, several scores have been proposed to predict early mortality after surgery with the goal of helping physicians make the most appropriate surgical decision. Although these scores could be applied to elderly patients, a specific risk score system for this population may be necessary [13,23,24].

Among scores of burdens of chronic diseases, the Charlson Comorbidity Index (CCI) [25,26] is a well-known scale designed to estimate the baseline situation and prognosis of patients based on a range of medical conditions. Easy to apply, objective, and reproducible, the classical "3-points-cutoff" of the CCI has been studied in different clinical situations [27–29], and it has been related to a high burden of comorbidity.

The objectives of our study were to analyse the epidemiological characteristics of IE in three different age groups of patients (< 65 years, 65–79 years, and ≥ 80 years) and to assess the weight of aging and comorbidity to predict the in-hospital and 1-year mortality risk in each group.

2. Methods

2.1. Study population

All consecutive patients with definite or possible IE, according to the modified Duke criteria [30,31], were prospectively included in the Spanish Collaboration on Endocarditis—Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España (GAMES) registry maintained by 39 Spanish hospitals from January 2008 to April 2015. Multidisciplinary teams, including infectious disease physicians, cardiologists, heart surgeons, echocardiographers, microbiologists, and imaging specialists, completed standardized case report forms with IE episode and follow-up data that included clinical, microbiological, and echocardiographic sections [32].

2.2. Ethics

The study was performed in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Ethics Committee at all participating hospitals, according to local standards. Informed consent was obtained from each patient.

2.3. Definitions and data collection

Active IE was defined as endocarditis with at least one of the

Table 1
Characteristics of 3120 patients diagnosed with IE according to three age groups.

	Patients < 65y N = 1327	Patients 65-79y N = 1291	Patients ≥ 80y N = 502	p-value[a]
Male gender, n (%)	987 (74.4)	835 (64.7)	286 (57.2)	< 0.001
Comorbidities, n (%)				
Chronic pulmonary disease	174 (15)	280 (24.3)	107 (23.7)	< 0.001
Coronary arterial disease	251 (19)	388 (30.1)	129 (25.7)	< 0.001
Congestive heart failure	336 (25.4)	468 (36.3)	203 (40.5)	< 0.001
Diabetes mellitus	272 (20.5)	433 (33.6)	154 (30.7)	< 0.001
Solid organ transplant recipients	35 (2.6)	20 (1.6)	0 (0)	0.001
Moderate/severe renal disease	170 (12.8)	213 (16.5)	107 (21.4)	< 0.001
Moderate/severe liver disease	83 (6.3)	44 (3.4)	5 (1)	< 0.001
Charlson Comorbidity Index ≥3	405 (30.6)	522 (40.6)	232 (46.2)	< 0.001
Baseline Cardiac Status, n(%)				
Congenital cardiac disease	158 (11.9)	18 (1.4)	4 (0.8)	< 0.001
Degenerative valvular disease	487 (36.7)	597 (46.2)	275 (54.8)	< 0.001
Previous IE	135 (10.2)	77 (6)	21 (4.2)	< 0.001
Previous cardiac surgery	382 (28.9)	530 (41.1)	158 (31.6)	< 0.001
Clinical features at presentation, n (%)				
Fever	1100 (82.9)	1057 (81.9)	409 (81.4)	0.274
Arterial emboli	429 (32.3)	346 (26.8)	121 (24.1)	0.001
New valvular regurgitation	498 (37.5)	426 (33.0)	159 (31.7)	0.050
Splenomegaly	229 (17.3)	124 (9.6)	27 (5.4)	< 0.001
Heart failure	521 (39.2)	521 (40.4)	205 (40.8)	0.893
Heart block	103 (7.8)	118 (9.1)	44 (8.8)	0.325
Acute renal insufficiency	391 (29.5)	551 (42.7)	189 (37.6)	< 0.001
Angor	9 (0.7)	16 (1.4)	14 (3)	0.003
Septic shock	187 (14.1)	134 (10.4)	43 (8.6)	0.003
Epidemiological characteristics of IE, n (%)				
Natural valve affected	896 (67.5)	713 (55.2)	311 (62)	< 0.001
Prosthetic valve affected	324 (24.4)	482 (37.3)	132 (26.3)	< 0.001
Endovascular device	143 (10.8)	150 (11.3)	82 (16.3)	0.004
Site of acquisition				
Community	837 (63.1)	666 (51.6)	284 (56.7)	< 0.001
Nosocomial	321 (24.4)	458 (35.5)	16.5 (30.7)	
Health care related	124 (9.4)	104 (8.1)	41 (8.2)	
Type of affected valve				
Aortic	605 (45.6)	685 (53.1)	227 (45.2)	< 0.001
Mitral	575 (43.3)	555 (43)	220 (43.8)	0.948
Pulmonary	37 (2.8)	8 (0.6)	0 (0)	< 0.001
Tricuspid	108 (8.1)	43 (3.3)	17 (3.4)	< 0.001
Etiology, n (%)				
S. aureus	318 (24.0)	276 (21.4)	100 (19.9)	0.099
CNS	202 (15.2)	273 (21.1)	72 (14.3)	< 0.001
S. bovis	66 (6.0)	89 (6.9)	43 (8.6)	0.013
S. viridans	165 (12.4)	104 (8.1)	49 (9.7)	0.001
Enterococcus spp.	130 (9.8)	205 (15.8)	96 (19.1)	< 0.001
Gramnegative bacilli	65 (4.9)	42 (3.3)	18 (3.6)	0.88
Candida spp.	20 (1.5)	26 (2.0)	8 (1.6)	0.590
Polimicrobial IE	28 (2.1)	25 (1.9)	8 (1.6)	0.856
No etiology	122 (9.2)	113 (8.8)	48 (9.6)	0.848

IE: infective endocarditis; CoNS: coagulase-negative staphylococci.
[a] Two-tailed Chi-squared test or Fisher's exact test as appropriate in each case.

following: positive blood cultures, fever, leucocytosis, raised inflammation markers, or current antibiotic treatment [30,31]. Microbiological diagnosis was made by blood, valve cultures, and/or molecular techniques. Transthoracic and transoesophageal echocardiography were performed on patients with clinical or microbiological suspicion of IE. To assess comorbidity, the CCI was calculated [23,24]. In-hospital mortality was defined as death, regardless of its cause, that occurred during the hospital admission. One-year mortality was defined as death, regardless of its cause, that occurred within 1 year after hospital discharge. Indication of surgical treatment was considered based on the criteria of American Heart Association[21] and European Society of Cardiology [22].

Data from patients with IE were analysed, including epidemiological and medical conditions, heart valve involvement, clinical manifestations at IE presentation, microorganisms identified, the appropriateness of antibiotic treatment used (defined as appropriate when the selected antibiotic was sensitive to an isolated microorganism, and the dose, dosing interval and duration of treatment were adequate according to the guidelines of IE), and morbidity and mortality during hospitalization. We also evaluated indications for surgery treatment, whether there was a consultation with the cardiac surgery team and its recommendation, and what were the reasons for not performing the surgery. All patients were followed for at least 1-year post-discharge.

2.4. Statistical analyses

Quantitative variables were expressed as mean and standard deviation (SD); qualitative variables were expressed as frequency and percentage. Statistical analysis was performed using a two-tailed χ^2 test and a Fisher's exact test, or an analysis of variance test, as appropriate in each case. In-hospital mortality and 1-year mortality were defined as all-cause mortality. A multivariate Cox regression model was adjusted to estimate survival rate over time as a function of several covariates. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. The area under the receiver-operating characteristic (AUROC) curve with a 95% CI was calculated to quantify the diagnostic accuracy of the CCI to predict mortality risk. Sensitivity, specificity, and positive and negative predictive values and their 95% CIs were calculated.

A two-tailed $p < 0.05$ was considered statistically significant. Data were analysed using SPSS package v19.0 (SPSS Inc., Chicago, IL) and Stata statistical software (Release 11.0, Stata Corporation, College Station, TX).

3. Results

3.1. Patients characteristics

During the study period, 3120 patients (67.5% men) with definite or possible IE were enrolled: 1327 (42.6%) patients <65 years, 1291 (41.4%) between 65 and 79 years, and 502 (16%) ≥80 years. Overall, the mean follow-up of IE patients was 386.0 days (range, 14–698 days).

The patients' comorbidities conditions, baseline cardiac status, and clinical and epidemiological characteristics of IE among all three groups are shown in Table 1. The group aged ≥80 years had a significantly higher percentage of cases with CCI ≥ 3 (46.2%), degenerative valvular disease (54.8%), renal disease (21.4%), affected natural valve (62%), and endovascular device IE (16.3%) than patients in other age groups. There were no differences among age groups in the proportion with

Table 2
Treatment and outcome of 3120 patients with endocarditis in the three age groups.

	Patients < 65y N = 1327	Patients 65-79y N = 1291	Patients ≥ 80y N = 502	*p-value*[a]
Treatment, n(%)				
Appropriate antimicrobial treatment	1268 (95.5)	1233 (95.5)	476 (94.8)	0.828
Surgical indication	898 (67.7)	858 (66.5)	261 (52.0)	< 0.001
Surgical performance	709 (53.4)	594 (46.0)	104 (20.7)	< 0.001
Indications for surgery, n(%)				
Severe regurgitation	346 (26.1)	230 (17.8)	49 (9.8)	< 0.001
Myocardial affectation	127 (9.6)	122 (9.5)	23 (4.6)	0.002
Persistence of sepsis	62 (4.7)	60 (4.6)	20 (4.0)	0.815
Aggressive microorganism	169 (12.7)	152 (11.8)	28 (5.6)	< 0.001
Recidive of IE	15 (1.1)	11 (0.9)	1 (0.2)	0.166
Prosthetic IE				
Early	59 (4.4)	93 (7.2)	8 (1.6)	< 0.001
Late	85 (6.4)	79 (6.1)	19 (3.8)	0.099
Heart failure	319 (24.0)	278 (21.5)	66 (13.1)	< 0.001
Systemic emboli	72 (5.4)	43 (3.3)	13 (2.6)	0.006
Reasons for NO surgery, n(%)				
Ictus	33 (2.5)	47 (3.6)	18 (3.6)	0.231
Intracranial hemorrhage	29 (2.2)	16 (1.2)	6 (1.2)	0.094
Hemodynamic instability	43 (3.2)	67 (5.2)	24 (4.8)	0.050
Complexity of surgery	24 (1.8)	38 (2.9)	26 (5.2)	0.001
Negative of patient	21 (1.6)	43 (3.3)	50 (10.0)	< 0.001
Negative of surgeon	58 (4.4)	81 (6.3)	48 (9.6)	< 0.001
Death	24 (1.8)	28 (2.2)	17 (3.4)	0.154
Complications after surgery, n(%)				
Ictus	6 (0.5)	14 (1.1)	3 (0.6)	0.150
Intracranial hemorrhage	13 (1.0)	10 (0.8)	1 (0.2)	0.258
Hemodynamic instability	102 (7.7)	117 (9.1)	18 (3.6)	0.001
Surgical site infection	6 (0.5)	5 (0.4)	5 (1.0)	0.218
Nosocomial pneumonia	37 (2.8)	44 (3.4)	10 (2.0)	0.273
Sepsis related to catheter	12 (0.9)	20 (1.5)	1 (0.2)	0.034
Renal failure	74 (5.6)	95 (7.4)	15 (3.0)	0.002
Cardiac blockage	35 (2.6)	35 (2.7)	9 (1.8)	0.562
Outcome, n(%)				
In-hospital mortality	270 (20.3)	388 (30.1)	174 (34.7)	< 0.001
1-year mortality	60 (11.2)	95 (11.7)	59 (20.4)	< 0.001

IE: infective endocarditis. MOD: multiple organ dysfunction. CNS: coagulase-negative *Staphylococci.*

[a] Two-tailed Chi-squared test or Fisher's exact test (as appropriate in each case).

Table 3
Predictors of mortality in 3120 patients with IE.

	HR (95% CI)	Adjusted HR[a] (95% IC)
Age, years		
< 66	1	1
66–80	1.59 (1.38–1.84)	1.56 (1.32–1.84)
> 80	2.17 (1.83–2.58)	2.05 (1.67–2.50)
Age, years (per year)	1.023 (1.018–1.028)	1.021 (1.016–1.027)
Female sex (ref.: male)	1.34 (1.18–1.52)	1.14 (0.98–1.32)
Charlson Comorbidity Index ≥3	1.93 (1.69–2.20)	1.62 (1.39–1.88)
Prosthetic valve IE	1.23 (1.08–1.40)	1.16 (1.00–1.35)
Nosocomial IE	1.56 (1.37–1.78)	1.21 (1.04–1.40)
Sepsis with MOD	2.60 (2.26–2.99)	1.72 (1.46–2.04)
Septic shock	3.80 (3.28–4.39)	2.78 (2.32–3.34)
Abscess	1.65 (1.41–1.93)	1.60 (1.34–1.91)
S. aureus IE	1.70 (1.48–1.94)	1.34 (1.14–1.58)
No surgery	1.64 (1.44–1.87)	1.36 (1.16–1.58)

IE: infective endocarditis. HR: hazard ratio; CI: confidence interval. MOD: multiple organ dysfunction.

[a] Multivariate Cox regression: adjusted by age, sex, Charlson Index ≥ 3, nosocomial valve IE, prosthetic valve IE, presence of abscess, sepsis with MOD, septic shock, *S. aureus* IE and performance of surgery.

fever as a clinical presentation of IE. However, patients aged < 65 years presented a significantly higher frequency of septic shock (14.1%), new valvular regurgitation (37.5%), and splenomegaly (17.5%). Other clinical data presented at the time of the diagnosis are shown in Table 1.

3.2. Etiology

Overall, *S. aureus* was the most common microorganism isolated (22.2%), followed by coagulase-negative staphylococci (CoNS) (17.5%), *Enterococcus* spp. (13.8%), and *Streptococcus viridans* (10.2%). *S. viridans* was significantly more common in patients aged < 65 years (12.4%), while CoNS was prevalent in the 65- to 80-year group (21.1%) and both *Streptococcus bovis* and enterococci were noted in the ≥80-year group (8.6% and 19.1%, respectively). Gram-negative bacilli and *Candida* spp. were similar among groups, as was the proportion of IE without microbiologic isolation (Table 1).

3.3. Treatment

The appropriateness of antibiotic treatment in the three groups of patients was > 90%, without statistically significant differences between them (Table 2). There was a significant difference between the proportion of patients who had surgical indication and those who underwent surgery; this difference increased significantly with age: 14.3%, 20.5%, and 31.3% in patients < 65 years, 65 to 79 years, and ≥ 80 years, respectively. Patients ≥ 80 years who underwent surgery had significantly less hemodynamic instability (3.6%), renal failure (3%), and cardiac blockage (1.8%) as complications of surgery than the other groups of patients (Table 2).

3.4. Outcome

In the ≥80-year group, there was a significantly higher in-hospital mortality (34.7%) and one-year mortality (20.4%) (Table 2). To analyse the role of age, comorbidity, and performance of surgery on mortality, multivariate Cox regression models were performed (Table 3). The main independent predictors of mortality were septic shock (adjusted HR: 2.78 [95% CI: 2.32–3.34] and age ≥ 80 years (adjusted HR: 2.05 [95% CI: 1.67–2.50]). CCI ≥ 3 presented an adjusted HR of 1.62 (95% CI: 1.39–1.88), and non-performance of surgery had an adjusted HR of 1.36 (95% CI: 1.16–1.58).

Patients with surgical indication (n = 2011) were analysed separately, comparing their outcome regarding whether or not surgery was performed. There were many significant differences in the characteristics

Table 4
Characteristics of 2011 patients with IE and surgical indication, according to performance of surgery.

	Surgery (n = 1368)	No surgery (n = 643)	*p-value*[a]
Male, n(%)	1015 (74.3)	409 (63.5)	< 0.001
Age (years), mean value ± SD	62.2 (15.5)	69.5 (14.7)	< 0.001
Age < 65y, n (%)	694 (50.7)	204 (31.4)	< 0.001
Age 65–79, n (%)	577 (42.11)	281 (43.43)	0.577
Age ≥ 80y, n (%)	99 (7.2)	162 (25)	< 0.001
CCI, mean value ± SD	1.9 (1.8)	2.9 (2.3)	< 0.001
CCI ≥3, n (%)	405 (29.6)	311 (48.4)	< 0.001
Type of IE, n (%)			
Native	775 (56.6)	408 (63.1)	0.006
Prosthesis	976 (71.2)	419 (64.8)	0.003
Fever, n(%)	1087 (79.9)	552 (85.7)	0.002
New valvular regurgitation, n (%)	802 (58.7)	400 (62.1)	0.147
Heart failure, n(%)	676 (49.4)	347 (53.8)	0.064
Sepsis with MOD, n(%)	212 (15.5)	156 (24.2)	< 0.001
Septic shock, n(%)	148 (10.8)	128 (19.8)	< 0.001
Main microorganisms, n(%)			
S. aureus	241 (17.6)	197 (30.4)	< 0.001
CNS	311 (22.7)	110 (17)	0.003
S. bovis	62 (5.2)	34 (5.9)	0.525
S. viridans	152 (12.8)	47 (8.2)	0.005
In-hospital mortality, n (%)	304 (22.2)	352 (54.4)	< 0.001
One-year mortality, n (%)	64 (6.6)	57 (21.3)	< 0.001

IE: infective Endocarditis. SD: standard deviation. CCI: Charlson Comorbidity Index. MOD: multiple organ dysfunction. CNS: coagulase-negative *Staphylococci*.

[a] Two-tailed Chi-squared test or Fisher's exact test (as corresponding) for categorical variables and ANOVA test for continuous variables.

between the 2 groups, with higher values among non-operated patients, highlighting the following variables: proportion of patients aged ≥80 years (25% vs. 7.2%), CCI ≥ 3 (48.4% vs. 29.6%), sepsis with multiple organ dysfunction (24.2% vs. 15.5%), *S. aureus* IE (30.4% vs. 17.6%), in-hospital mortality (54.4% vs. 22.2%), and 1-year mortality (21.3% vs. 6.6%). Other significant differences are shown in Table 4.

Among patients who finally underwent surgery (n = 1370), those with CCI ≥ 3 had significant differences in the distribution of the following variables: male gender, age, septic shock, in-hospital mortality, and 1-year mortality (Table 5).

Table 5
Characteristics of 1370 patients with IE operated, grouped by Charlson Comorbidity Index (CCI) score < 3 and ≥ 3.

	CCI ≥ 3 (n = 406)	CCI < 3 (n = 964)	p-value[a]
Male, n(%)	317 (78.0)	698 (72.6)	0.042
Age (years), mean value ± SD	65.8 (12.3)	60.6 (16.4)	< 0.001
Age < 65y, n (%)	186 (45.81)	523 (54.2)	0.004
Age 65–79, n (%)	183 (45.07)	380 (39,5)	0.066
Age ≥ 80y, n (%)	37 (9.1)	61 (6.3)	0.084
Prosthetic IE, n (%)	288 (71.7)	687 (71.3)	0.932
Fever, n(%)	324 (80.8)	762 (79.5)	0.598
Heart failure, n(%)	206 (50.9)	468 (48.6)	0.454
Sepsis with MOD, n(%)	73 (18.0)	139 (14.4)	0.094
Septic shock, n(%)	57 (14.1)	90 (9.3)	0.010
S. aureus IE, n(%)	79 (19.5)	162 (16.2)	0.234
In-hospital mortality, n(%)	125 (30.9)	178 (18.5)	< 0.001
One-year mortality, n(%)	28 (10.9)	36 (5.1)	0.001

IE: infective Endocarditis. CCI: Charlson Comorbidity Index. SD: standard deviation. MOD: multiple organ dysfunction.

[a] Two-tailed Chi-squared test or Fisher's exact test (as corresponding) for categorical variables and ANOVA test for continuous variables.

Table 6
Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for CCI ≥ 3 to predict in-hospital and 1-year mortality in 2011 patients with surgical indication for IE.

	Dead (TP/total)	Alive (TN/total)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
CCI ≥ 3 for In-hospital mortality						
All patients	315/654	956/1357	48.2 (44.3–52.0)	70.5 (68.0–72.9)	44.0 (40.4–47.6)	73.8 (71.4–76.2)
Surgical indication and surgery	125/303	785/1065	41.3 (35.7–46.8)	73.7 (71.1–76.4)	30.9 (26.4–35.4)	81.5 (79.1–84.0)
Surgical indication and no surgery	190/351	171/292	54.1 (48.9–59.3)	58.5 (52.9–64.2)	61.1 (55.7–66.5)	51.5 (46.1–56.9)
CCI ≥ 3 for one-year mortality						
All patients	57/121	803/1113	47.1 (38.2–56.0)	72.1 (69.5–74.8)	15.5 (11.8–19.2)	92.6 (90.9–94.4)
Surgical indication and surgery	28/64	675/905	43.8 (31.6–55.9)	74.6 (71.7–77.4)	10.9 (7.6–14.6)	94.9 (93.6–96.5)
Surgical indication and no surgery	29/57	128/208	50.9 (37.9–63.9)	61.5 (54.9–68.2)	26.6 (18.3–34.9)	82.1 (76.0–88.1)

CCI: Charlson Comorbidity Index; IE: infective Endocarditis; TN: true negative; TP: true positive; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

From these results, we analysed whether CCI ≥ 3 could predict in-hospital and 1-year mortality among patients with surgical indication, helping to select the best candidates for surgery (Table 4). Overall, for in-hospital mortality, CCI ≥ 3 showed a sensitivity and specificity of 48.2% and 70.5%, respectively; the PPV was 44.0% and NPV 73.8%. For 1-year mortality, CCI ≥ 3 showed a sensitivity and specificity of 47.1% and 72.2%, respectively, with a PPV of 15.5% and NPV of 92.6% (Table 6).

The AUROC for CCI was 0.64 (CI: 0.62–0.67) for the prediction of in-hospital mortality (Fig. 1 A) and 0.65 (CI: 0.60–0.70) for 1-year mortality (Fig. 1 C). When the three age groups compared, the AUROC curve for CCI was significantly larger for patients aged <65 years than for those aged 65 to 79 years or ≥ 80 years for in-hospital mortality (0.67 [95% CI: 0.63–0.71] vs. 0.62 [95% CI: 0.58–0.66] vs. 0.54 [95% CI: 0.48–0.61], respectively; $p < 0.001$; Fig. 1B). These results were similar for 1-year mortality: age < 65 years: 0.70 (95% CI: 0.61–0.79), age 65 to 79 years: 0.63 (95% CI: 0.55–0.71), and ≥ 80 years: 0.46 (95% CI: 0.34–0.58; $p < 0.001$; Fig. 1D).

4. Discussion

This multicentric prospective study evaluates the main epidemiological characteristics of patients with IE in different age groups. It is worth noting the high proportion of older patients with IE in our study, since this special population currently presents an increasing incidence of IE [5,7,9,10]. As it has been observed in other studies, IE was more frequent in male patients, probably due to the higher proportion of valvular disease in this population. [14,19]. The increasing in the proportion of female patients with age could be related to the higher life expectancy of women [8]. It is accepted that older patients presented more comorbidities [8,14,15]. We found two exceptions: the presence of liver disease and the percentage of solid organ transplant recipients, both of them more frequent in younger patients. First condition could be related to the higher mortality of patients with advanced liver disease. Solid organ transplants are also performed more frequently in younger patients, although due to the small proportion of patients is difficult to draw conclusions about this finding.

Fever and heart failure were the most common presentations of IE, with no differences among age groups. These results are consistent with the current evidence since, although it has been usually accepted that clinical features are less marked in older people than in younger patients [2,10], recent studies do not find clear differences in clinical presentation between both groups [14,15]. The higher frequency of a new heart murmur in the <65-year group could be related to the misattribution of cardiac murmurs in older patients to degenerative valvular disease, which is more frequent in this population. Therefore, the diagnosis of IE could be challenging, but main signs and symptoms of presentation do not seem very different between younger and older patients.

Cases of IE with *S. viridans* isolation were more common in patients aged <65 years, while cases of IE with *S. bovis* and *Enterococcus* spp. isolation were more prevalent in patients older than 80 years, probably related to the more frequent odontogenic origin of IE in the younger population and to the gastrointestinal and genitourinary origin in octogenarian patients [8,14,15,33]. The isolation of the CoNS was more frequent in the group of 65 to 79 years, which could be explained by the higher proportion of prosthetic valve IE and nosocomial IE among these patients [5,8]. Similarly, to other studies, we did not find differences among all three groups in the proportion of gram-negative bacilli and *Candida* spp. IE, as well as in the proportion of IE without microbiologic isolation [14,19].

Mortality among our patients was high, especially in elder patients, as has been remarked in other studies [2,7,15,17,33,34]. There is no doubt that the greater degree of comorbidity that these patients presented has contributed to this. On the other hand, the value of surgery in the outcome of IE is well known [35]. Our data showed that increasing age, in particular the oldest old patients (≥80 years), CCI ≥ 3, and non-performance of surgery were independently associated with mortality.

In all three groups, the proportion in whom surgery was performed was less than the surgical indication. However, we found that the percentage of patients ≥80 years who underwent surgery was significantly lower compared with other age groups. Only 21% of the octogenarian group underwent surgery, although surgical intervention was indicated in 52%. This fact means that 31% of patients aged ≥80 years with surgical indications did not undergo surgery, compared with 14% or 20% in the groups of <65 years and 65 to 79 years, respectively. Thus, in our cohort, the non-performance of surgery in patients in whom it was indicated could also contribute to the higher mortality rate observed in older patients. The results agree with the findings by Oliver et al. [19], who showed that very old patients with IE could benefit from surgery, since mortality in surgical candidates reached 72.7% in the case of medical treatment alone compared with 6.3% for patients who received both medical and surgical treatment. In addition, in our study, patients ≥80 years who underwent surgery did not present more complications than the other groups of patients and had significantly fewer hemodynamic complications or renal failure. Nonetheless, these results must be interpreted with caution since the operated patients had a stricter selection and significantly less hemodynamic instability or complexity of surgery than in the other age groups. However, a negative of patient and a negative of surgeon were the main reasons for non-performance of surgery in the older patients. As suggested by Chirillo [13], age per se should not be a contraindication to surgery.

Given these findings, we studied whether the degree of comorbidity calculated by the ICC could be useful to select patients with lower

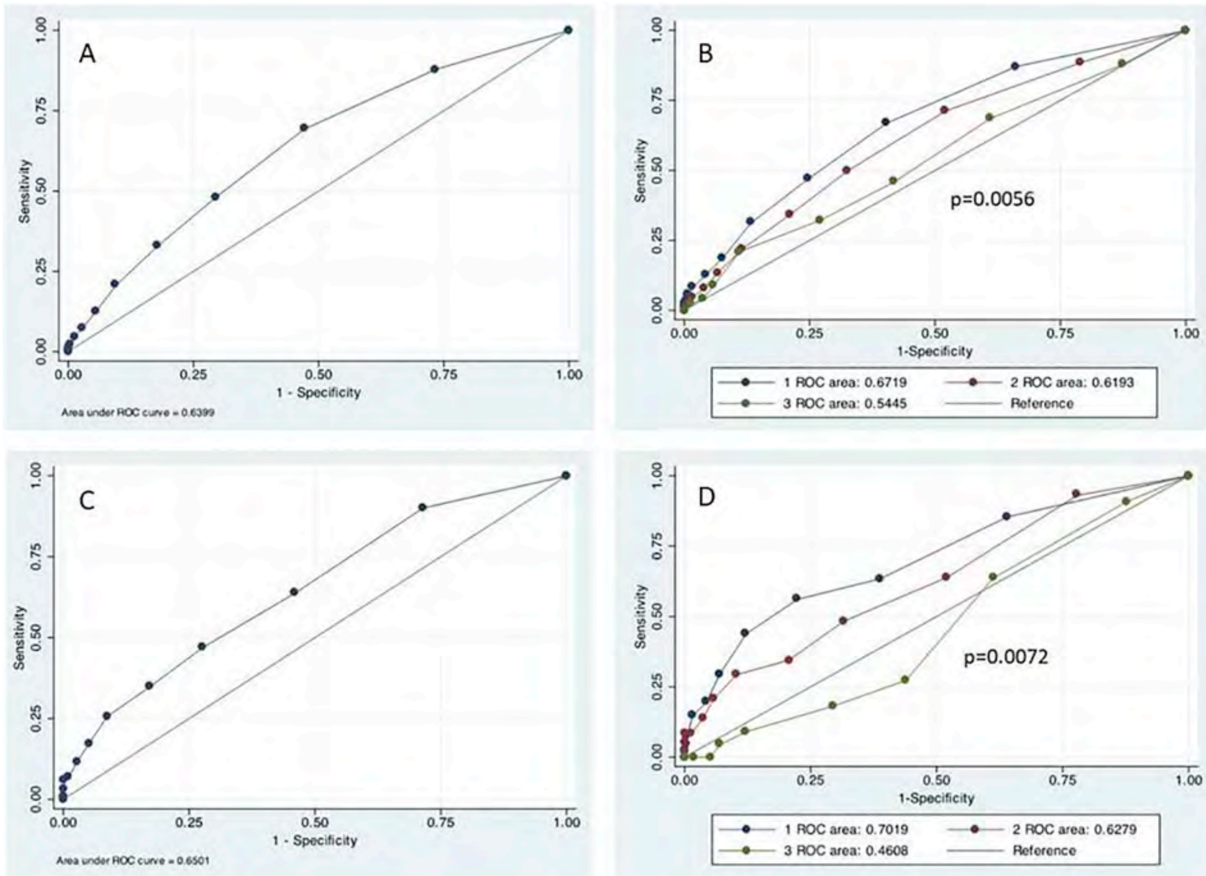

Fig. 1. ROC curves to assess the accuracy of the CCI in predicting in-hospital and 1 year-mortality according to CCI in 2011 patients with surgical indication (global and distributed by age group: group 1: patients < 65 years; group 2: patients 65 to 79 years; group 3: patients ≥80 years) A: Global in-hospital mortality; B: In-hospital mortality comparing age groups; C: Global 1-year mortality; D: 1-year mortality comparing age groups.

surgical risk. The CCI was applied to all patients with surgical indication. The score showed a high negative predictive value for in-hospital and 1-year mortality, especially in the group of patients aged < 65 years who underwent surgery. The modest value of the AUROC curve in patients aged 65 to 80 years and in those ≥80 years make us take these results with caution in those populations.

This study presents some limitations. It is part of a multicentre collection of data, and some recordings of clinical or diagnostic characteristics might be influenced by interobserver variability. Second, not all participating hospitals have a Cardiovascular Surgery Service, although all of them have a referral hospital, with cardiovascular surgeons as part of their IE teams. Finally, our data form did not include scales of basal situation and frailty, which, if associated with comorbidity, could better estimate the daily condition of older patients with IE. Nevertheless, this study shows one of the largest multicentric published cohorts, with a clearly established protocol, which allows us to analyse the effect of age and comorbidity on the outcome of IE.

In view of our results, we can conclude that mortality, both in-hospital and at 1 year, remains high in IE, being age, comorbidity and non-performance of surgery independent predictors of mortality. Therefore, it is necessary to individualize the most appropriate treatment in older patients, in order to identify best candidates of surgery in that population. Preoperative multidisciplinary evaluation (cardiologist, cardiac surgeons, specialists in geriatrics, in infectious diseases) in each patient is essential to evaluate the benefit and the risk of the operation, and professionals with experience in the assessment of elderly patients could enrich the IE teams.

Conflicts of interest

Dr. Miro reports grants and personal fees from AbbVie, Angelini, Bristol-Myers Squibb, Contrafect, Jansen, Genentech, Medtronic, Merck, Novartis, Gilead Sciences, and ViiV Healthcare, outside the submitted work.

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