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Surgery and outcome of infective endocarditis in octogenarians: prospective data from the ESC EORP EURO-ENDO registry

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Abstract

Purpose High mortality and a limited performance of valvular surgery are typical features of infective endocarditis (IE) in octogenarians, even though surgical treatment is a major determinant of a successful outcome in IE.

Methods Data from the prospective multicentre ESC EORP EURO-ENDO registry were used to assess the prognostic role of valvular surgery depending on age.

Results As compared to < 80 yo patients, ≥ 80 yo had lower rates of theoretical indication for valvular surgery (49.1% vs. 60.3%, $p < 0.001$), of surgery performed (37.0% vs. 75.5%, $p < 0.001$), and a higher in-hospital (25.9% vs. 15.8%, $p < 0.001$) and 1-year mortality (41.3% vs. 22.2%, $p < 0.001$). By multivariable analysis, age per se was not predictive of 1-year mortality, but lack of surgical procedures when indicated was strongly predictive (HR 2.98 [2.43–3.66]). By propensity analysis, 304 ≥ 80 yo were matched to 608 < 80 yo patients. Propensity analysis confirmed the lower rate of indication for valvular surgery (51.3% vs. 57.2%, $p = 0.031$) and of surgery performed (35.3% vs. 68.4%, $p < 0.0001$) in ≥ 80 yo. Overall mortality remained higher in ≥ 80 yo (in-hospital: HR 1.50[1.06–2.13], $p = 0.0210$; 1-yr: HR 1.58[1.21–2.05], $p = 0.0006$), but was not different from that of < 80 yo among those who had surgery (in-hospital: 19.7% vs. 20.0%, $p = 0.4236$; 1-year: 27.3% vs. 25.5%, $p = 0.7176$).

Conclusion Although mortality rates are consistently higher in ≥ 80 yo patients than in < 80 yo patients in the general population, mortality of surgery in ≥ 80 yo is similar to < 80 yo after matching patients. These results confirm the importance of a better recognition of surgical indication and of an increased performance of surgery in ≥ 80 yo patients.

Keywords Infective endocarditis · Elderly · Prognosis · Surgery · Propensity analysis

Introduction

Characteristics of patients with infective endocarditis (IE) have dramatically changed over recent decades, with a high prevalence and specific features of IE in elderly population [1–8]. Old age leads to surgical hesitancy by referring physicians, surgeons and patients themselves [9]. Furthermore, frequent associated comorbidities also influence the outcome of this fragile cohort [6]. As a result, increased mortality and less-frequent performance of valvular surgery are hallmarks of IE episodes in elderly as compared to younger patients. This is especially true in octogenarians who represent a growing part of IE population, who are often limited to medical therapy without being discussed for surgery just because of their age, even though surgical treatment is a well-known determinant of successful outcome in IE.

To date, the impact of age and associated comorbidities on prognosis have, however, been poorly investigated, as the rare studies published on the subject were limited by retrospective design, single-centre recruitment, and/or small numbers of patients. A recent study based on the Swedish

A complete list of the EURO-ENDO Investigators Group is provided in Supplementary Material Appendix 1.

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population between 2006 and 2017 emphasized the fact that surgery is underused in elderly. A propensity analysis to match patients according to the performance of surgery was used and showed significantly higher one-year mortality in patients who did not undergo surgery [10].

The ESC EORP Euro-Endo registry is a comprehensive prospective observational cohort that included 3113 patients with IE which is based on contemporary practices (2016–2018) in a wide range of countries and centres [11]. It aimed to assess how the 2015 ESC guidelines on the management of IE [12], which were endorsed by the European Association for Cardio-Thoracic Surgery (EACTS), and the European Association of Nuclear Medicine (EANM), were implemented in clinical practice. It therefore provides a unique opportunity to investigate the current influence of patients' age on the demographic, clinical, therapeutic, and prognostic profile of IE, taking into account the numerous confounding factors with an appropriate statistical power. The aim of our study was to describe the specific features of IE in octogenarians, with a special focus on the respective contribution of age, IE characteristics and comorbidities on surgical decision and outcome.

Methods

Study design and data collection

All patients from the prospective multicentre ESC EORP EURO-ENDO registry, apart from three patients, who retrospectively withdrew an informed consent, were included in our ancillary study. The detailed methodology of EURO-ENDO has *previously* been reported [11]. All consecutive patients aged ≥ 18 years with definite or possible IE *according to the ESC 2015 diagnostic criteria* [12] were included *during a one-year period in each centre* between January 2016 and March 2018. All participants signed informed consent. In total, 3113 index cases of IE from 156 centres across 40 countries were collected. Patients' management was supposed to be performed according to the 2015 ESC guidelines and main therapeutic decisions were supposed to be taken from a multidisciplinary approach including cardiologists, surgeons, ID specialists and microbiologists among Endocarditis Teams [12].

Baseline and follow-up data

Baseline data included clinical characteristics, biological and microbiological data, imaging data, treatment before admission and during hospitalization, complications under therapy, theoretical indication for valvular surgery, in-hospital valvular surgery performed, in-hospital mortality and 1-year follow-up.

Theoretical indication for valvular surgery was defined as the existence of any type of theoretical indication listed in the ESC guidelines (haemodynamic, embolic, infectious and/or other), as acknowledged by the practitioners taking care of the patients regardless of operative risk. This definition allowed us to classify patients in 3 subgroups regarding valvular surgery: patients without theoretical indication of surgery, patients with theoretical indication and surgery performed and patients with theoretical indication and surgery not performed.

Statistical analysis

Continuous and categorical variables were reported as mean ± SD or as median (interquartile range) as appropriate, and as absolute values and related percentages, respectively. Between-groups differences were tested with Kruskal–Wallis test and with chi-square test or Fisher's exact test for continuous and categorical variables, respectively.

Subjects were stratified into two groups: ≥ 80 years old (≥ 80 yo group) and < 80 years old (< 80 yo group) at inclusion.

Univariable and multivariable logistic regression were performed to analyse factors associated with actual performance of valvular surgery with age and gender forced in the model. Variables with $p < 0.10$ in univariable analysis were entered in the multivariable logistic model with a backward selection procedure and a significance level of $p = 0.05$.

Survival curves according to age and gender were calculated using Kaplan–Meier method and compared using the log-rank test.

Univariable analysis of mortality was performed with a Cox proportional hazards model. Variables with $p < 0.10$ and age and gender were entered in a multivariable adjusted Cox proportional hazards model with a backward selection procedure and a significance level of $p = 0.05$. The following variables were not included in the Cox multivariable model: Charlson comorbidity index due to collinearity with age, vegetation length due to missing data, cerebral complications, fistula and para-prosthetic regurgitation due to incidence < 10% in overall population. Goodness of fit, concordance and Schoenfeld residual tests were calculated to verify the adequacy of the models.

A propensity analysis was then performed to account for the imbalance in patient characteristics between ≥ 80 yo and < 80 yo patients. A propensity score was fitted using a non-parsimonious multivariable logistic model including variables usually recognised as linked to surgery and to prognosis (gender, history of heart failure, device therapy, previous stroke, chronic renal failure, diabetes mellitus, history of cancer, aortic/mitral location of IE, prosthetic valve IE, presence of an abscess, *Staphylococcus aureus* or viridans streptococci as responsible micro-organisms, cerebral embolic event and congestive heart failure as complications of IE; Supplementary Table 1). The options to perform the propensity dataset were the following: the calliper was 0.30, the gender should match exactly, the 2:1 matching was without replacement and no missing imputation was performed on baseline data. Because of missing data, 71 subjects were not included in the propensity analysis and 304 patients ≥ 80 yo were finally matched with 608 < 80 yo patients according to the closest propensity score (Fig. 1). Rates of theoretical surgical indications, of surgical performance were compared using McNemar's test for binary variables. In-hospital and 1-year mortality rates were compared using Cox proportional hazard model stratifying on matched pairs for time to event data. Same analyses were then performed among patients with only definite IE. A low number of patients with possible IE over 80 yo ($n = 56$) did not allow us to perform a propensity analysis with the same matching variables as for the whole population or the population of definite IE, and we matched the cases only on the following variables: gender but without exact matching, prosthetic valve IE, presence of an abscess, *Staphylococcus aureus* as responsible micro-organisms, congestive heart failure as complication of IE.

A two-sided p value < 0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.4.

One author (CL) had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Results

Comparison of IE characteristics according to age groups

Demographic and baseline characteristics

Among the 3113 patients included in the Euro-Endo registry, median age was 63.0 (46.0–73.0), 375 (12.0%) were ≥ 80 yo and 2378 were < 80 yo. Female patients were more frequent in the ≥ 80 yo group (44.0%).

Characteristics of the patients are displayed in Supplementary Table 2. Previous valvular surgery or cardiac implantable electronic devices (CIED) were more frequent in ≥ 80 yo than in < 80 yo.

Characteristics of IE

The proportion of definite and possible IE as well as that of community-acquired/health care-related IE was not significantly different among the two groups (Supplementary Table 3).

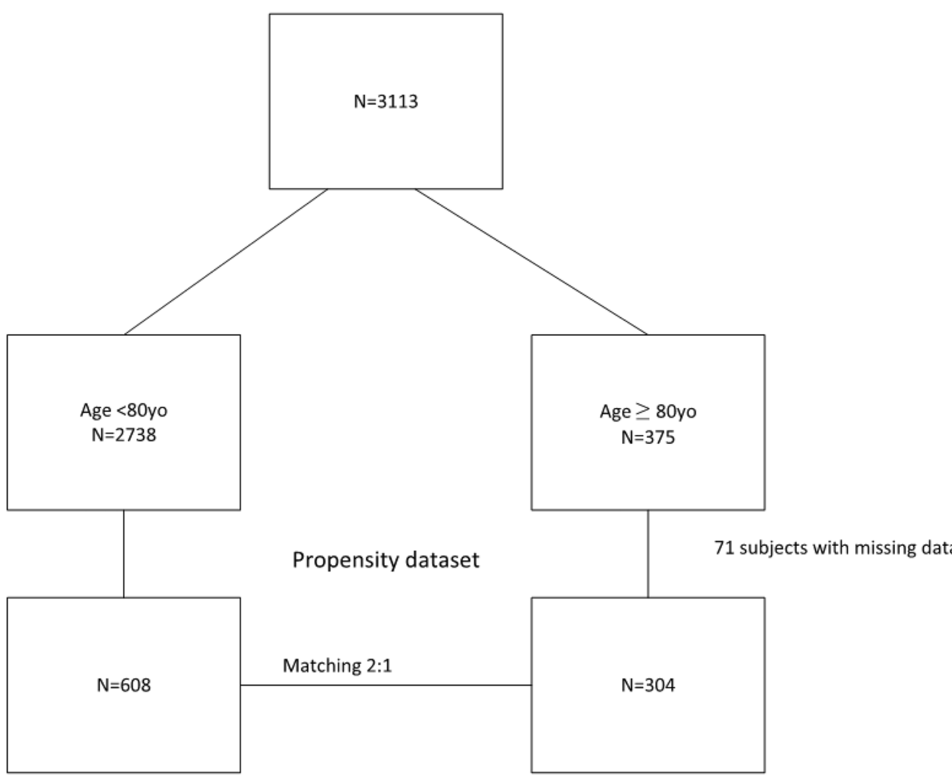

Fig. 1 Flow chart depicting how the propensity score dataset was formed

IE was more often located on prosthetic/repaired valves ($p < 0.0001$) or on CIED ($p < 0.0001$) in ≥ 80 yo patients. Embolic events both at admission (15.5% vs. 26.8%, $p < 0.0001$) and under therapy (12.8% vs. 21.7%, < 0.0001) were less frequent in the ≥ 80 yo. Blood cultures were more often positive (85.9% vs. 78.0%, $p = 0.0005$) with a higher proportion of micro-organisms of gastrointestinal tract in the ≥ 80 yo.

FDG PET/CT scan was more frequently used in the ≥ 80 yo (21.3% vs. 16.0%, $p = 0.0093$). Echocardiography was less frequently positive in ≥ 80 yo (66.9% vs. 80.2%, $p < 0.0001$), mostly because of less-frequent vegetations ($p < 0.0001$).

Therapy and outcome in the overall population

A theoretical indication for surgery was reported in 61% of the patients and surgery was finally performed in 44% of the overall population. Theoretical indication for valvular surgery was less frequently reported in ≥ 80 yo than in < 80 yo (49.1% vs. 60.3%, $p < 0.001$) (Table 1). Furthermore, among those with a theoretical indication, valvular surgery was less often performed in ≥ 80 yo (37.0% vs. 75.5%, $p < 0.0001$) (Supplementary Fig. 1A) and less often in female than in male patients in each group of age. Time delay between diagnosis and performance of surgery was similar in the two groups, as was the distribution between emergent, urgent, early and elective surgery as defined by the guidelines [11]. The proportion of patients with definite IE, who would have been classified as possible IE if they had not been operated on because of lack of the main pathological/microbiological criteria of IE) is quite low, 7% in the < 80 yo and 3.5% in the ≥ 80 yo group (Supplementary Table 4). 1-year mortality was 24% in the global population, 17% among those who were surgically treated and 32% among those who were medically treated, higher in those with theoretical indication who were not operated on (54%) than in those without surgical indication (20%). In-hospital and 1-year mortality were significantly higher in ≥ 80 yo (in-hospital: 25.9% vs. 15.8%; 1 year: 41.3% vs. 22.2%, $p < 0.0001$) (Supplementary Fig. 1B).

Therapy and outcome in the propensity score model

Propensity matching enabled baseline covariates to be equally balanced between ≥ 80 yo and < 80 yo (Supplementary Table 1). In the propensity score-matched analysis (Table 2), theoretical indication of valvular surgery remained significantly less frequent in ≥ 80 yo than in matched < 80 yo patients (51.3% vs. 57.2%, $p = 0.030$). The performance of valvular surgery when theoretically indicated was also significantly less frequent in ≥ 80 yo (35.3% vs. 68.4%, $p < 0.0001$).

In-hospital mortality and 1-year mortality were significantly higher in ≥ 80 yo (in-hospital: 26.0% vs. 20.4%, hazard ratio [HR] 1.50, 95% confidence interval [CI] 1.06–2.13, $p = 0.0210$; 1-year mortality: 41.8% vs. 29.1%, HR 1.58, 95% [CI] 1.21–2.05, $p = 0.0006$). However, when having a look on subgroups of patients related to indication and performance of valvular surgery, short- and long-term mortality in ≥ 80 yo were no longer significantly different from < 80 yo (Fig. 2). This was the case among patients with valvular surgery indicated but not performed where mortality rates were high in both groups and also in patients with no surgical indication. In those two subgroups, mortality rates tended nevertheless to be higher in ≥ 80 yo. Among those who were operated on, mortality rates were really similar in both groups (in-hospital: 19.7% vs. 20.0%, $p = 0.4236$; 1-year: 27.3% vs. 25.5%, $p = 0.7176$). Results were similar among patients with only definite IE (Supplementary Table 5). Results among the two propensity-matched groups of patients with possible IE are displayed in Supplementary Table 6. Of note, the higher mortality among operated patients in the ≥ 80 yo in this subgroup is related to the fact that only three patients with possible IE were operated on with one post-operative death (33% mortality).

Factors associated with valvular surgery according to age groups

The factors associated with the performance of valvular surgery during acute IE in multivariable analysis are displayed in Table 3. Older age and female gender were associated with a less-frequent use of valvular surgery. Definite IE and the presence of abscess were associated with more frequent surgery in the whole population and in both age groups.

Role of age in the multivariable prediction of death

The results of the univariable and multivariable analyses (Supplementary Table 7) (Fig. 3) in the whole population showed that neither age nor female gender were significant predictors of 1-year mortality. Regarding valvular surgery, the performance of surgery was associated with lower mortality (HR 0.77, 95% CI 0.62–0.97, $p = 0.0260$), whereas non-performance of surgery despite theoretical indication was highly associated with mortality (HR 2.98, 95% CI 2.43–3.66, $p < 0.0001$).

Discussion

The main age-related features of IE among the ESC EORP EURO-ENDO registry are the following: (1) specific features are confirmed regarding underlying heart disease, responsible micro-organisms and complications of IE

Table 1 Comparison of therapy and outcome of infective endocarditis according to the two groups of age

	< 80 years old (*n* = 2738)	≥ 80 years old (*n* = 375)	*p*-value
Risk score			
Euroscore II (*N*)	2334	298	
Median (IQR)	4.5 (1.8–11.3)	12.4 (5.5–25.2)	< 0.0001
Theoretical indication for valvular surgery			
Indication	1724/2737 (63.0%)	184/375 (49.1%)	< 0.001
Indication—surgery performed	1301/1724 (75.5%)	68/184 (37.0%)	< 0.001
Indication—no surgery performed	423/1724 (24.5%)	116/184 (63.0%)	< 0.001
Reasons for not performing surgery when indicated			
Patient refusal	76/423 (18.0%)	25/116 (21.6%)	0.381
Surgical risk	217/423 (51.3%)	93/116 (80.2%)	< 0.001
Death before surgery	102/423 (24.1%)	16/116 (13.8%)	0.017
Absence of surgery in the hospital	32/423 (7.6%)	3/116 (2.6%)	0.054
Neurological complication	53/423 (12.5%)	10/116 (8.6%)	0.246
Other	97/423 (22.9%)	16/116 (13.8%)	0.032
Indication			
Haemodynamic	892/1724 (51.7%)	83/184 (45.1%)	0.087
Embolic	606/1724 (35.2%)	52/184 (28.3%)	0.062
Infectious	1075/1724 (62.4%)	113/184 (61.4%)	0.802
Other	147/1724 (8.5%)	11/184 (6.0%)	0.233
Timing of surgery			
Median time between diagnosis and surgery (IQR) (days)	13.0 (6.0–26.0)	13.0 (8.0–23.0)	0.8016
Emergency surgery*	93/1416 (6.6%)	9/97 (9.3%)	0.1384
Urgent surgery†	359/1416 (25.4%)	15/97 (15.5%)	
Early surgery‡	448/1416 (31.6%)	36/97 (37.1%)	
Elective surgery§	516/1416 (36.4%)	37/97 (38.1%)	
In-hospital follow-up			
Death	432/2738 (15.8%)	97/375 (25.9%)	< 0.0001
Cause of death			
Cardiovascular	122/431 (28.3%)	29/97 (29.9%)	0.4400
Non-cardiovascular	122/431 (28.3%)	34/97 (35.1%)	
Cardiovascular + non-cardiovascular	161/431 (37.4%)	30/97 (30.9%)	
Unknown	26/431 (6.0%)	4/97 (4.1%)	
If surgery performed			
Death post valvular surgery	135/432 (31.3%)	15/97 (15.5%)	0.002
If patient alive, cardiac status			
Heart failure	299/2301 (13.0%)	71/278 (25.5%)	< 0.0001
Valve or prosthetic dysfunction	376/2304 (16.3%)	63/278 (22.7%)	0.0078
One-year follow-up			
Death	609/2738 (22.2%)	155/375 (41.3%)	< 0.0001
Among pts with valvular surgery	208/1301 (16.0%)	21/68 (30.9%)	0.001
Among medically treated patients	401/1437 (27.9%)	134/307 (43.6%)	< 0.001
With theoretical valvular surgical indication	215/423 (50.8%)	74/116 (63.8%)	0.013
Without theoretical valvular surgical indication	186/1013 (18.4%)	60/191 (31.4%)	< 0.001

IQR Interquartile range

*Emergency surgery: surgery performed within 24 h after diagnosis

†Urgent surgery within a few days

‡Early surgery within 1 week

§Elective surgery after at least 1–2 weeks of antibiotic therapy

Table 2 Comparison of therapy and outcome of infective endocarditis among the two propensity-matched subgroups (< 80 yo and ≥ 80 yo)

	Total ($n = 912$)	< 80 years old ($n = 608$)	≥ 80 years old ($n = 304$)	p value
Theoretical indication of valvular surgery	504/912 (55.3%)	348/608 (57.2%)	156/304 (51.3%)	0.0302
Indication				
Haemodynamic	250/504 (49.6%)	180/348 (51.7%)	70/156 (44.9%)	0.0151
Embolic	125/504 (24.8%)	86/348 (24.7%)	39/156 (25.0%)	0.6419
Infectious	310/504 (61.5%)	214/348 (61.5%)	96/156 (61.5%)	0.9183
Other	46/504 (9.1%)	36/348 (10.3%)	10/156 (6.4%)	0.2230
Valvular surgery performed when indicated	293/504 (58.1%)	238/348 (68.4%)	55/156 (35.3%)	< 0.0001
Overall population				
In-hospital mortality	203/912 (22.3%)	124/608 (20.4%)	79/304 (26.0%)	
HR [95%CI]*		Reference	1.50 [1.06–2.13]	0.0210
1-year mortality	304/912 (33.3%)	177/608 (29.1%)	127/304 (41.8%)	
HR [95%CI]		Reference	1.58 [1.21–2.05]	0.0006
Patients with valvular surgery indicated but not performed				
In-hospital mortality	85/211 (40.3%)	41/110 (37.3%)	44/101 (43.6%)	
HR [95%CI]		Reference	1.19 [0.48–2.95]	0.7008
1-year mortality	121/211 (57.3%)	56/110 (50.9%)	65/101 (64.4%)	
HR [95%CI]		Reference	0.90 [0.42–1.95]	0.7929
Patients with no indication for surgery				
In-hospital mortality	60/408 (14.7%)	36/260 (13.8%)	24/148 (16.2%)	
HR [95%CI]		Reference	2.17 [0.82–5.78]	0.1205
1-year mortality	104/408 (25.5%)	56/260 (21.5%)	48/148 (32.4%)	
HR [95%CI]		Reference	2.00 [1.00–4.00]	0.0499
Patients with valvular surgery performed				
In-hospital mortality	58/293 (19.8%)	47/238 (19.7%)	11/55 (20.0%)	
HR [95%CI]		Reference	2.00 [0.37–10.92]	0.4236
1-year mortality	79/293 (27.0%)	65/238 (27.3%)	14/55 (25.5%)	
HR [95%CI]		Reference	1.22 [0.42–3.51]	0.7176

*HR [95%CI]—hazard ratio [95% confidence interval]

in ≥ 80 yo patients; (2) theoretical indication of valvular surgery is less often recognised and, in particular, valvular surgery is less often performed in ≥ 80 yo than in < 80 yo patients; (3) in the overall population, both short- and long-term mortality are higher in ≥ 80 yo patients, as are mortality rates of operated patients and of non-operated patients with or without theoretical surgical indication; (4) multivariable and propensity score-matching analyses consistently show that significant differences in theoretical indication of surgery and in its actual performance are present among the two groups and strongly influence prognosis; (5) although mortality remains significantly higher in ≥ 80 yo patients after propensity matching, mortality rates of operated patients are no longer significantly different among age groups; (6) age per se is not a prognostic factor of mortality in multivariable analysis in the overall population.

Using an 80 yo limit for this study may be considered as arbitrary as age is a continuum and elderly population is very heterogeneous. However, this age was chosen with regard to surgery, as patients < 80 yo are quite easily referred to surgeon if necessary while this becomes less and less the case when age progressively increases over 80.

This large series of IE patients over 80 yo confirms that IE in the elderly have several peculiarities. As expected, elderly more often had comorbidities and previous non-cardiac procedures. Notably, and in contrast to what has been described in an Australian population-based study, there was no significant difference in the origin of IE (community or health care-associated) depending on age [13]. Nevertheless, IE on CIED and on valvular prosthesis/repair were more frequent in the elderly resulting from increasing use of more complex devices in old patients [14]. As previously reported, embolic events were less common in ≥ 80 yo patients, both before and after admission [4, 7].

Regarding responsible micro-organisms, *Staphylococcus aureus* was less frequent in elderly. Among

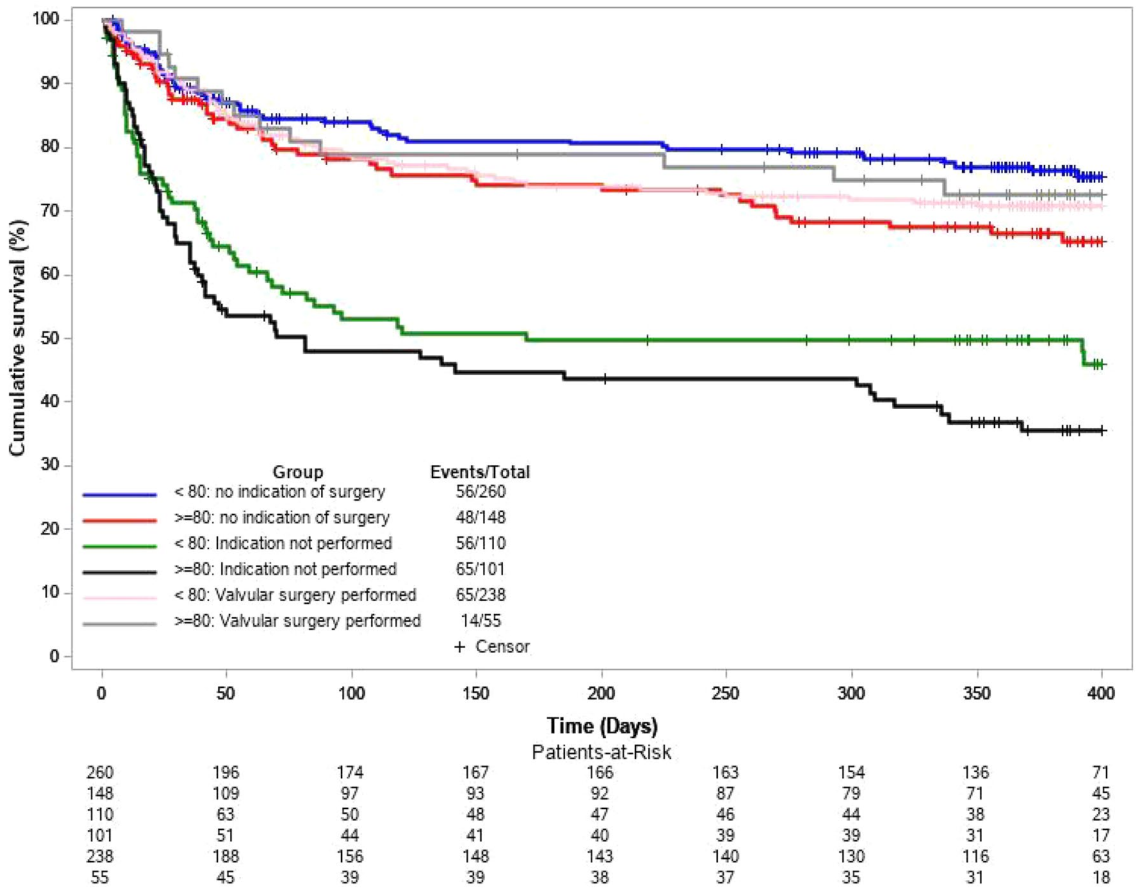

Fig. 2 Comparison of outcome of infective endocarditis among the 2 propensity-matched subgroups (< 80 yo and ≥ 80 yo) according to the indication and actual performance of surgery

Streptococcaceae, those colonizing the gastro-intestinal tract were more frequent in elderly, with a rate as high as 24% of enterococci. These results are consistent with most of previous series reporting an increased frequency of enterococcus from 10% in patients aged < 65 to > 20% in octogenarians [5, 15] and a 25% rate of *Enterococcus faecalis* in IE after aortic valve implantation [16]. However, a recent Swedish study reported a different repartition of responsible micro-organisms according to age, with a higher rate of *Staphylococcus aureus* in the ≥ 80 group and no significant difference in the frequency of enterococci among age groups [10].

Contemporary data indicate that surgery is now undertaken in approximately 50% of patients with acute IE [17, 18]. Theoretical indication according to the automated application of the guidelines has been reported to be present in more than 70% of patients in a French cohort [19]. In the Euro-Endo registry, the theoretical indication was the one recognised by the responsible practitioner, which is not exactly the same definition, and was reported in 61% of the whole population, less frequently in elderly (49% vs 63%). In the same manner, valvular surgery itself was less often performed when indicated in the elderly than in younger patients (37% vs 75%).

Of note, as per results shown in Supplementary Table 4, the proportion of patients classified as definite IE because of the main pathological/microbiological criteria defining the anatomically definite IE is a little bit lower among ≥ 80 yo than among < 80 yo suggesting that patients > 80 yo who are operated on have more other positive diagnostic criteria (imaging, clinical and microbiological criteria) than younger ones, i.e. that more objective criteria are mandatory in elderly to take a decision of surgery.

Propensity analysis gave us a unique opportunity to better analyse the actual performance of valvular surgery and the prognosis of octogenarians in this large cohort of patients. By matching on most of the classical factors of severity of IE, influencing both surgical indication and prognosis, we could better analyse the direct impact of age on surgery and outcome. We chose not to include baseline variables, such as frailty or surgical score, as they were strongly related to age and not to IE itself.

Propensity analysis was also used in a recent paper on data from the Swedish registry on Infective Endocarditis but

Table 3 Multivariable analysis of predictors of valvular surgery during hospital stay stratified on age groups

	Effect	Whole population			< 80 years old			≥ 80 years old		
		OR*	95% CI†	*p* Wald	OR	95% CI	*p* Wald	OR	95% CI	*p* Wald
Age and gender	Female < 80 yo	1								
	Female ≥ 80 yo	0.29	[0.18–0.47]	< 0.0001						
	Male < 80 yo	1.43	[1.17–1.75]	0.0005						
	Male ≥ 80 yo	0.36	[0.23–0.56]	< 0.0001						
Gender	Male				1.43	[1.17–1.75]	0.0004	1.48	[0.79–2.79]	0.2197
Type of IE	Native	1			1			1		
	PM/ICD‡	0.06	[0.03–0.11]	< 0.0001	0.06	[0.03–0.11]	< 0.0001	0.08	[0.01–0.62]	0.0157
	Prosthesis + Repair	0.70	[0.57–0.85]	0.0004	0.69	[0.56–0.85]	0.0005	0.70	[0.37–1.34]	0.2805
Classification	Definite IE§	1.92	[1.48–2.49]	< 0.0001	1.80	[1.38–2.36]	< 0.0001	3.65	[1.07–12.43]	0.0385
Source of infection	Community	1								
	Non-nosocomial	0.78	[0.58–1.05]	0.0985	0.83	[0.61–1.13]	0.2418			
	Nosocomial	0.66	[0.51–0.86]	0.0020	0.63	[0.48–0.83]	0.0009			
Staph. aureus	Yes	0.58	[0.46–0.73]	< 0.0001	0.58	[0.46–0.74]	< 0.0001			
Abscess	Yes	2.20	[1.63–2.96]	< 0.0001	2.11	[1.54–2.89]	< 0.0001	3.24	[1.39–7.55]	0.0063
Heart failure	Yes	0.69	[0.54–0.88]	0.0023	0.66	[0.51–0.85]	0.0011			
COPD‖/asthma	Yes	0.70	[0.52–0.94]	0.0189				0.16	[0.04–0.74]	0.0191
IVDU#	Yes	0.50	[0.36–0.70]	< 0.0001	0.53	[0.38–0.74]	0.0002			
Diabetes mellitus	Yes	0.79	[0.63–0.99]	0.0380						
Previous stroke/TIA**	Yes							2.24	[1.07–4.72]	0.0333

* *OR* odds ratio

† *CI* confidence interval

‡ *PM/ICD* pacemaker/implantable cardioverter defibrillator

§ *IE* infective endocarditis

‖ COPD—chronic obstructive pulmonary disease

\# *IVDU* intravenous drug abuse

** *TIA* transient ischemic attack

from a different point of view [10]. Although variables used for matching were globally similar to ours, matching was performed between surgical and non-surgical patients, and those two groups were subsequently separated according to age (with a limit of age of 75 years old), to estimate whether the effect of age differed between the surgery and the non-surgery groups. The mortality rate was significantly lower between the ages of 55 and 82 years in patients who underwent surgery compared with patients who did not undergo surgery. Surgery was also associated with better long-term survival in matched patients who were ≥ 75 years (hazard ratio, 0.36; 95% CI, 0.24–0.54, $p < 0.001$). However, this study did not take into account the indication bias and the factors that may have influenced whether the patient would undergo surgery or not. Furthermore, surgery was performed in only 6% of the elderly patients, which is a lower rate than in our series (18%).

In our study, despite similar features of IE and similar risk factors obtained by propensity matching, differences regarding surgical indication and performance remained significant with less often recognised indication for surgery (51% vs 57%), and far less often surgery performed when indicated (35% vs. 68%). Overall mortality rates also remained significantly higher in elderly group after propensity matching. When looking at the three subgroups of surgery, there remained a non-significant trend toward higher mortality for elderly among patients without indication for surgery and among patients with indication but without surgery. However, interestingly, mortality of surgically treated patients was remarkably similar in the two groups of age.

So, these two propensity analyses, one matching patients according to the performance or not of surgery, the other matching patients according to age groups, allow us to conclude that surgery is associated with better survival than non-performance of surgery in older patients, and that survival is similar to that of younger patients among operated patients after matching on most of the classical risk factors.

Frail condition, nutritional status and comorbidities obviously predispose elderly patients to higher morbidity and mortality. Nevertheless, neither age nor female gender was independent predictor of mortality in multivariable analysis, although comorbidities frequently associated with age were

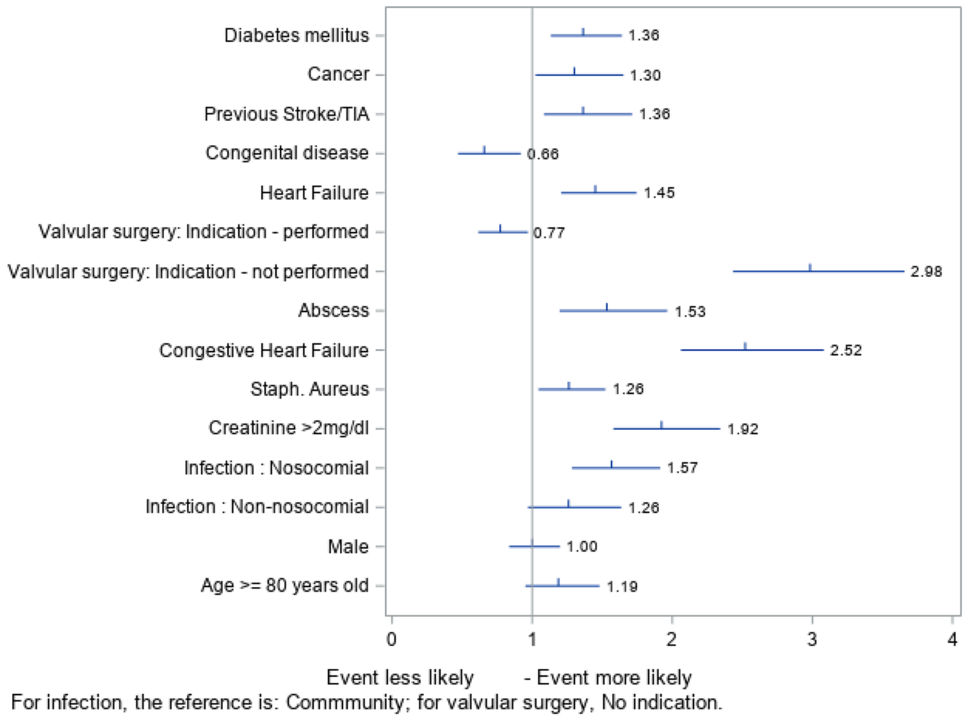

Fig. 3 Cox Regression Analysis for all causes of 1-year mortality with age and gender forced in the model

independent predictors of death. The strongest predictor of mortality by multivariate analysis was the non-performance of valvular surgery despite theoretical indication, whereas the actual performance of valvular surgery was associated with improved survival.

The consistent results of multivariable analysis and propensity score matching strongly suggest that less-frequent indications and interventions in elderly cannot be attributed only to more frequent comorbidities, *but also to a lack of recognition of indication in some cases*. The recognition of a theoretical indication by the responsible cardiologist is probably partly influenced by the subjective appreciation of the feasibility of surgery. Elderly population appears quite heterogeneous, from healthy people to bedridden ones, and general health status further rapidly deteriorates after hospitalisation [6]. Women gender, more frequent among elderly, also negatively influences surgical management, as shown in this study. The fact that theoretical indication for surgery remains significantly less frequent in the elderly even after propensity matching clearly indicates that age itself influences our clinical judgement and recognition of theoretical surgical indication. Similarly, age influences the performance of invasive diagnostic procedures, such as trans-esophageal echocardiography, which is not more frequently performed in elderly despite higher rates of intra-cardiac material.

At the very end, the decision not to perform surgery despite indication is also linked to several factors including not only age of the patient, but also survival-risk benefit, appreciation of future quality of life, refusal of the patient, local socioeconomic factors, etc. Lopez et al. already noted that the percentage of patients with surgical indications who were rejected for surgery increased significantly with age, due to several factors including frailty but also life's choice of the patient [7]. However, the French study also insisted on the fact that non-performance of surgery whatever the age was due to a non-recognition of the indication in half of the cases of non-operated patients despite theoretical indication *as defined by an automated application of the* guidelines [17].

These findings suggest that performance of surgery in well-selected elderly patients might increase their chance for survival. Our results are in concordance with previous smaller studies, which found that mortality in operated octogenarians was not higher compared to younger age groups [5, 20]. Lower rate of surgery in old patients is a well-described phenomenon [18–20]. So, the observed higher mortality in elderly suffering from IE could be, at least in part, a consequence of non-recognition of surgical indication and of a non-performance of surgery when indicated. This also partially explains the higher mortality of medically treated patients without surgical indication, as this group probably includes both patients without indication and patients with non-recognized indication.

Study limitations

These results were extracted from a large European and worldwide voluntary registry which has inherent limitations and is not a population-based sample; representativeness is therefore sub-optimal and selection bias cannot be excluded. However, since 3113 index cases from 156 hospitals were included, this represents a mean of 20 patients per centre per year which is a quite high number for such a rare disease. Furthermore, recruiting centres were mostly tertiary centres, inducing a referral bias, in particular, because older and/or inoperable patients are not transferred to tertiary centres.

No specific rules were given regarding the identification of responsible microorganisms. Microbiology analysis was performed according to the usual manners/rules of each institution; hence, we cannot exclude the theoretical possibility that other related bacterial species (such as *Aerococcus* spp.) could have been misidentified as viridans group streptococci, etc.

We chose to include not only definite but also possible cases of IE, as surgical therapy may be discussed in all patients. Furthermore, when surgery is not performed, macroscopic and histologic examinations that would have transformed a possible into a definite case are not available. Finally, part of our analysis is based on theoretical indication of valvular surgery as recognized by the responsible practitioner, which is in part subjective and not a "true" theoretical indication based on an automated analysis of specific IE features leading to indication according to guidelines.

Conclusion

This large study on IE in patients older than 80 years further confirms the strong influence of age on the demographic, clinical, therapeutic, and prognostic profile of IE. Non-recognition of surgical indication and non-performance of surgery when indicated are frequent in old patients and are strong predictors of mortality while age per se is not. After propensity matching on many prognostic factors of IE, mortality of surgically treated patients in octogenarians is not different from that of younger patients, suggesting that recognition of indication and performance of surgery in well-selected elderly patients might increase their chance for survival. Hence, the issue of surgery in elderly must be thoroughly discussed among Endocarditis Teams including geriatricians and considering not only the crude age of the patients to avoid underuse of surgery in that population.

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Declarations

Informed consent Informed consent was obtained from all individual participants included in the study. Our study complies with the Declaration of Helsinki, the research protocol has been approved by the locally appointed ethics committee; informed consent has been obtained from all the subjects (or their legally authorized representative).

Ethical approval Our study complies with all ethical standards.

Conflict of interest François Alla, Ilija Srdanović, Robert Riezebos, William KF Kong, Maria Carmo Pereira Nunes, Michal Pazderník, Luc Pierard, Bülent Mutlu, Hirotsugu Yamada, Andrea De Martino, Marcelo Haertel Miglioranza, Julien Magne, Cornelia Piper, Cécile Laroche, Patrizio Lancellotti, Gilbert Habib, Christine Selton-Suty have nothing to disclose. Bernard Iung reports personal fees from Edwards Lifesciences, other from Boehringer Ingelheim, outside the submitted work. Aldo P. Maggioni reports personal fees from Bayer, personal fees from Fresenius, personal fees from Novartis, outside the submitted work.

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