

ORIGINAL RESEARCH

# Surgery Is Underused in Elderly Patients With Left-Sided Infective Endocarditis: A Nationwide Registry Study

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**BACKGROUND:** Infective endocarditis is associated with higher mortality in elderly patients, but the role of surgery in this group has not been fully evaluated. The aim of this study was to assess outcomes of left-sided infective endocarditis in elderly patients and to determine the influence of surgery on mortality in the elderly.

**METHODS AND RESULTS:** A nationwide retrospective study was performed of 2186 patients with left-sided infective endocarditis recorded in the SRIE (Swedish Registry of Infective Endocarditis), divided into patients aged <65 years (n=864), 65 to 79 years (n=806), and ≥80 years (n=516). Survival analysis was performed using the Swedish National Population Registry, and propensity score matching was applied to assess the effect of surgery on survival among patients of all ages. The rate of surgery decreased with increasing age, from 46% in the <65 group to 6% in the ≥80 group. In-hospital mortality was 3 times higher in the ≥80 group compared with the <65 group (23% versus 7%) and almost twice that of the 65 to 79 group (12%). In propensity-matched 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]).

**CONCLUSIONS:** The proportion of elderly patients with infective endocarditis who underwent surgery was low compared with that of younger patients. Surgery was associated with lower mortality irrespective of age. In matched elderly patients, long-term mortality was higher in patients who did not undergo surgery, suggesting that surgery is underused in elderly patients.

**Key Words:** elderly ■ infective endocarditis ■ outcome ■ valve surgery

Despite improvements in diagnostic and therapeutic strategies for infective endocarditis (IE), neither short- nor long-term mortality (IE) rates have significantly decreased since the 1970s.<sup>1</sup>

## See Editorial by Ghanta and Pettersson

The incidence of IE in the general population is on the rise.<sup>2,3</sup> Epidemiological studies show that this increase is mostly in the elderly population,<sup>4</sup> that it is mainly associated with healthcare procedures,<sup>5</sup> and

that age-related degenerative valve disease is the most common underlying heart condition contributing to the increased incidence of IE in the elderly.<sup>5,6</sup> In addition, intracardiac electronic devices such as pacemakers, implantable cardioverter-defibrillators, and valve prostheses implanted surgically or by transcatheter aortic valve replacement are frequently used in this population.

IE in the elderly has a different microbiology than IE in younger patients, a greater propensity for women, and higher mortality.<sup>7–9</sup> Cardiac surgery carries significant risks, and increasing age is one of the most

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## CLINICAL PERSPECTIVE

### What Is New?

- The surgery rate in elderly patients with left-sided infective endocarditis was much lower than in younger patients and surgery was associated with lower mortality among all ages in matched groups of patients who did and did not undergo surgery.

### What Are the Clinical Implications?

- Surgery seems to be underused in elderly patients with left-sided infective endocarditis.

## Nonstandard Abbreviations and Acronyms

<b>EuroSCORE</b>	European System for Cardiac Operative Risk Evaluation
<b>HACEK</b>	Haemophilus species, Aggregatibacter aphrophilus, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae
<b>IE</b>	infective endocarditis
<b>SRIE</b>	Swedish Registry of Infective Endocarditis
<b>TEE</b>	transesophageal echocardiography

important determinants of poor survival after cardiac surgery.<sup>8</sup> Data on the influence of surgery on survival in elderly populations is scarce, and the few observational studies that have been published have presented data from tertiary centers only, often with a limited number of elderly patients.<sup>10,11</sup>

The aims of the present study were to: (1) describe clinical and microbiological profiles of elderly patients with left-sided IE compared with younger patients; (2) assess the short- and long-term outcomes of IE in different age groups; and (3) determine the effect of surgery on mortality in elderly patients with IE using nationwide data from the SRIE (Swedish Registry of Infective Endocarditis).

## METHODS

### Study Design and Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. We conducted a retrospective cohort study using data in the SRIE on episodes from December 6, 2006, until February 23, 2017. The data were submitted using an internet-based report. The

registry contains information on 4151 episodes of IE in patients aged  $\geq 18$  years with suspected or confirmed IE. There are 275 variables in the registry, including demographics, baseline characteristics, mode of acquisition, microbiology, complications, and outcomes. A more detailed description of the SRIE is provided in Data S1. The primary study end points were short-term and long-term mortality. The patients were divided into 3 groups according to their age:  $< 65$  years (group 1), between 65 and 79 years (group 2), and  $\geq 80$  years (group 3). A propensity score–matched analysis was performed comparing patients undergoing surgery with those who had conservative treatment. Our study protocol was approved by the regional ethical review board in Lund (reference number 2017-1051). Informed consent was waived.

### Patient Selection

Patients with left-sided IE were selected by consecutively employing the following exclusion criteria: (1) “possible IE,” “rejected,” or missing information on the modified Duke criteria ( $n=1123$ ); (2) right-sided IE ( $n=291$ ); (3) IE affecting both sides of the heart ( $n=212$ ); (4) cardiac implantable electronic device IE ( $n=183$ ); (5) any nonprimary episode ( $n=74$ ); and (6) duplicate of episode entry, not a resident in Sweden, or restricted patient identification ( $n=82$ ). Finally, a total of 2186 patients with left-sided IE were included in the analysis.

### Variables in the SRIE

Between 2006 and 2012, the variables diabetes mellitus, cancer, pacemaker, implantable cardioverter-defibrillator, chronic intravenous catheter, and end-stage renal disease (ESRD) were not negated, but only filled if the outcome was positive. We therefore assumed missing entries to be negative. The variable maximal vegetation size was optional and 44% of patients with a vegetation had a reported vegetation size.

### Follow-Up

Follow-up was defined as the period between start of antimicrobial treatment for IE to the most recent status. In 40 patients, the start date of treatment was missing and was therefore assumed to be the same as the day of admission. Follow-up was finished in November 2017 using the Swedish National Population Registry, and was 100% complete, comprising 7282 patient-years with a median follow-up of 2.8 years (interquartile range, 0.9–5.3 years).

### Statistical Analysis

Normally distributed continuous variables are presented as mean $\pm$ SD. Non-normally distributed continuous variables are expressed as median (interquartile range). Results for categorical data are given

as percentages. The cumulative probability of survival was calculated using the Kaplan-Meier estimator. The log-rank test was used to compare between-group differences in survival. The following variables were assessed by univariate Cox regression analysis to determine whether they were associated with long-term survival: age, sex, diabetes mellitus, ESRD, previous IE, injection drug use, community-acquired IE, healthcare-related IE, heart failure, mitral valve location, prosthetic valve IE, vegetations, abscess formation, central nervous system embolism, and pathogen. All variables with a  $P < 0.2$  were included in the propensity score–matched analysis and propensity scores were computed by a multivariate logistic regression model. Propensity score matching was conducted using nearest neighbor matching with calipers of 0.2 SD. After propensity score matching, the resulting data set was analyzed using Cox regression. The model allowed for different effects of age for the surgery and nonsurgery groups. This was done in order to estimate whether the effect of age differed between the surgery and the nonsurgery groups. To improve the fit, penalized splines with 4 degrees of freedom were used to model the age variables and the relative mortality rate was plotted. To evaluate the effect of surgery in elderly patients and younger patients separately, the cohort was divided into patients aged  $< 75$  years and patients aged  $\geq 75$  years. Propensity score matching was performed following the same approach as used to balance the treatment groups in the overall population. Propensity score matching could not be performed for groups 1, 2, and 3 because of the small number of patients who underwent surgery in group 3 ( $n=30$ ). Survival in the matched groups was estimated with the Kaplan-Meier method. The long-term outcome was subsequently determined on the matched data and plotted. Statistical analyses were performed with SPSS statistical software (version 25.0, IBM) and R (The R Foundation, <https://www.r-project.org>).

## RESULTS

### Patient Characteristics

Patients' characteristics are displayed in Table 1. The proportion of women was age dependent, with 48% in group 3 compared with 24% in group 1. Diabetes mellitus was most common in group 2, whereas ESRD and injection drug use decreased with increasing age. The proportion of patients with pacemakers increased with increasing age. The time interval from symptoms to diagnosis was shorter with increasing age, and heart failure was more common in the elderly. However, the incidence of new or major valve insufficiency decreased with increasing age. Abscess formation was 3 times more likely to occur in the  $< 65$  group compared

with the  $\geq 80$  group. In general, any type of embolism was less likely to occur with increasing age. This included central nervous system embolism, which occurred in 19%, 18%, and 13% in groups 1, 2, and 3, respectively ( $P=0.01$ ).

### Microbial Pathogenesis of IE

Positive blood culture was recorded in 77% of patients, with no significant difference between age groups, and a causative pathogen was identified in 99% of cases. Table 2 summarizes the microbiological findings. The distribution of pathogens was similar in all groups. *Staphylococcus aureus* tended to be more common in elderly patients, while the HACEK (*Haemophilus* species, *Aggregatibacter aphrophilus*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) group was more common in younger patients.

### Short- and Long-Term Outcomes

Short-term outcomes and 1- and 5-year survival are presented in Table 3. Surgery was performed in 46% of cases in group 1, 29% in group 2, and 5.8% in group 3. Short-term mortality increased with age. The in-hospital mortality in group 3 was 3 times that of group 1 and twice that of group 2. Long-term survival was worse in group 2 compared with group 1, and it was the worst in group 3, and there was a significant association between age and long-term survival (log-rank,  $P < 0.001$ ).<sup>12</sup> The overall long-term survival is shown in Figure S1.

### Influence of Surgery

The following variables were used to calculate propensity scores: age, sex, diabetes mellitus, ESRD, previous IE, injection drug use, healthcare-related IE, heart failure, mitral valve location, prosthetic valve endocarditis, vegetations, and pathogen (Table S1). Propensity score matching resulted in 560 matches (Figure 1). The standardized mean differences are shown in Table 4. The results from Cox regression with splines are shown in Figure 2. The graph shows the relative mortality compared with a 60-year-old patient who did not have surgery. Between the ages of 53 years and 82 years, the death rate was significantly lower in the surgery group.

The propensity score matching in patients aged  $< 75$  years and those  $\geq 75$  years resulted in 442 and 88 matches, respectively (Figures S2 and S3). Standardized mean differences are shown in Table 4. Figure 3 shows the long-term survival in both matched groups. In the  $< 75$  group, 1-year survival after surgery was 72% compared with 63% without surgery, and in the  $\geq 75$  group, 1-year survival with surgery was 53% compared with 17% without surgery. Cox regression showed that the hazard ratio (HR) for surgery was 0.53

**Table 1. Patient Characteristics**

Variable	Group 1	Group 2	Group 3	P Value* All Groups	P Value† Groups 2 and 3
	<65 y (n=864)	65–79 y (n=806)	≥80 y (n=516)		
Age, y	50.6±11.8	72.1±4.3	85.0±3.9	<0.001	<0.001
Women	208 (24)	249 (31)	245 (48)	<0.001	<0.001
Comorbidities					
Diabetes mellitus (type 1 or type 2)	106 (13)	175 (23)	89 (18)	<0.001	0.04
Cancer	42 (5.0)	128 (17)	83 (17)	<0.001	0.90
ESRD <sup>‡,§</sup>	41 (4.9)	27 (3.5)	6 (1.2)	0.002	0.01
Risk factors					
Known heart disease	181 (21)	152 (19)	121 (23)	0.13	0.04
Bicuspid aortic valve	97 (11)	10 (1.2)	2 (0.4)	<0.001	0.14
Mitral valve prolapse	53 (6.1)	49 (6.1)	22 (4.3)	0.29	0.15
Congenital heart disease	24 (2.8)	9 (1.1)	1 (0.2)	<0.001	0.10
Valve prosthesis	161 (19)	215 (27)	132 (26)	<0.001	0.66
Pacemaker	24 (2.9)	46 (5.9)	61 (12)	<0.001	<0.001
ICD	13 (1.6)	15 (2.0)	2 (0.4)	0.08	0.02
Chronic intravenous catheter	15 (1.8)	24 (3.1)	4 (0.8)	0.02	0.007
Rheumatic heart disease	4 (0.4)	7 (0.9)	3 (0.6)	0.57	0.75
Previous IE	85 (10)	31 (3.8)	22 (4.3)	<0.001	0.71
Mode of acquisition					
IDU	129 (15)	5 (0.6)	0 (0.0)	<0.001	0.16
Community acquired	743 (86)	675 (84)	430 (83)	0.31	0.84
Healthcare associated	93 (11)	119 (15)	74 (14)	0.03	0.83
Time from symptoms to diagnosis (days)	12 (4–30)	8 (4–25)	7 (3–19)	<0.001	0.049
Clinical features					
Fever	683 (79)	625 (78)	385 (75)	0.16	0.22
Vascular phenomena	274 (32)	216 (27)	94 (18)	<0.001	<0.001
Immunological phenomena	41 (4.7)	29 (3.6)	18 (3.5)	0.38	0.92
Heart failure <sup>†</sup>	212 (25)	227 (28)	181 (35)	<0.001	0.008
Positive blood culture	647 (75)	633 (79)	400 (78)	0.19	0.67
Location					
Aortic valve	448 (52)	445 (55)	248 (48)	0.04	0.01
Mitral valve	400 (46)	366 (45)	259 (50)	0.21	0.09
Prosthetic valve endocarditis	93 (12)	124 (16)	71 (14)	0.02	0.42
Echocardiographic data					
Transthoracic echocardiogram	472 (55)	440 (55)	314 (61)	0.04	0.03
Transesophageal echocardiogram	749 (87)	701 (87)	379 (73)	<0.001	<0.001
Severe aortic insufficiency	232 (27)	130 (16)	46 (8.9)	<0.001	<0.001
Severe major mitral insufficiency	194 (23)	149 (19)	90 (17)	0.04	0.63
Vegetations <sup>§</sup>	693 (80)	662 (82)	436 (85)	0.13	0.26
Abscess	116 (13)	84 (10)	22 (4.3)	<0.001	<0.001
Embolism					
CNS embolism	164 (19)	145 (18)	66 (13)	0.01	0.01
Meningitis (embolism)	13 (1.5)	9 (1.1)	2 (0.4)	0.16	0.22
Spondylitis (embolism)	54 (6.3)	72 (8.9)	36 (7.0)	0.10	0.21

(Continued)

**Table 1. Continued**

Variable	Group 1	Group 2	Group 3	P Value* All Groups	P Value† Groups 2 and 3
	<65 y (n=864)	65–79 y (n=806)	≥80 y (n=516)		
Other skeletal or joint embolism	61 (7.1)	54 (6.7)	23 (4.5)	0.13	0.09
Skin (embolism)	90 (10)	44 (5.5)	17 (3.3)	<0.001	0.07
Coronary embolism	6 (0.7)	5 (0.6)	7 (1.4)	0.30	0.16
Spleen embolism	40 (4.6)	27 (3.3)	5 (1.0)	0.001	0.006
Liver embolism	11 (1.3)	8 (1.0)	2 (0.4)	0.26	0.33
Lung embolism	25 (2.9)	11 (1.4)	8 (1.6)	0.06	0.78
Other embolisms	60 (6.9)	48 (6.0)	18 (3.4)	0.03	0.045

Dichotomous variables are expressed as number of patients (percentage within age group). Continuous normally distributed variables are expressed as mean±SD. Non-normally distributed continuous variables are expressed as median (interquartile range). CNS indicates central nervous system; ESRD, end-stage renal disease; ICD, implantable cardioverter-defibrillator; and IDU, injection drug use.

\*P value, statistical testing among all 3 groups.

†P value, statistical testing between groups 2 and 3.

‡Before or during treatment of infective endocarditis (IE).

§Any size visualized by means of echocardiography.

(95% CI, 0.41–0.67;  $P<0.001$ ) in the <75 group and 0.36 (95% CI, 0.24–0.54;  $P<0.001$ ) in the ≥75 group.

## DISCUSSION

The present study presents nationwide data on left-sided IE in different age groups, including >500 patients aged ≥80 years. The results are likely generalizable, as the study included data from patients at secondary and tertiary care centers in an entire nation. We found that the rate of surgical treatment decreased dramatically with increasing age, despite an increase in heart failure and a higher proportion of patients with *S aureus* IE. In matched-groups analysis, patients who underwent surgery had a significantly lower death rate

among a wide age range. In addition, after matching elderly patients ≥75 years who underwent surgery with those who did not, those who had surgery showed significantly better survival.

Left-sided IE in the elderly is associated with poor prognosis. Our results show that mortality increases significantly with older age. In-hospital mortality in the ≥80 group was 3 times that of the <65 group. These findings are similar to previous results showing increased in-hospital mortality with increasing age,<sup>2,5,7-9,11,13-15</sup> although the cutoffs differ among studies.

Although in-hospital mortality increases with advanced age, López-Wolf et al,<sup>9</sup> Oliver et al,<sup>7</sup> and Gatti et al<sup>16</sup> have all found that older age is not an independent predictor of in-hospital mortality. However, several

**Table 2. Microbial Pathogenesis of IE**

Pathogen	<65 y (n=864)	65–79 y (n=806)	≥80 y (n=516)	P Value*	P Value†
<i>Staphylococcus aureus</i> ‡	268 (31)	263 (33)	195 (38)	0.03	0.05
Coagulase negative staphylococci	35 (4.1)	43 (5.3)	30 (5.9)	0.28	0.71
α-Hemolytic streptococci	273 (31)	225 (27)	148 (29)	0.23	0.76
β-Hemolytic streptococci	50 (5.8)	42 (5.2)	35 (6.8)	0.49	0.23
<i>Streptococcus pneumoniae</i>	15 (1.7)	11 (1.4)	2 (0.4)	0.10	0.08
<i>Streptococcus bovis</i>	13 (1.5)	13 (1.6)	17 (3.3)	0.045	0.045
Enterococci	81 (9.4)	108 (13)	61 (12)	0.03	0.40
HACEK	25 (2.9)	13 (1.6)	1 (0.2)	0.001	0.01
Other gram-positive	47 (5.4)	51 (6.3)	15 (2.9)	0.02	0.005
Other gram-negative	20 (2.3)	14 (1.7)	4 (0.8)	0.11	0.14
Fungi	5 (0.6)	5 (0.6)	2 (0.4)	0.85	0.71
Unknown pathogen	32 (3.7)	18 (2.2)	6 (1.2)	0.01	0.16

Variables are expressed as number (percentage) of patients. HACEK indicates *Haemophilus* species, *Aggregatibacter aphrophilus*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*; and IE, infective endocarditis.

\*Chi-square test among all 3 groups.

†Chi-square test between groups 2 and 3.

‡Methicillin-sensitive *S aureus* (n=734), methicillin-resistant *S aureus* (age <65 years, n=3; age 65–79 years, n=5; age ≥80 years, n=3).

**Table 3. Unadjusted Short-Term and Long-Term Outcomes**

Variable	<65 y (n=864)	65–79 y (n=806)	≥80 y (n=516)	P Value*	P Value†
Surgery for IE	400 (46)	231 (29)	30 (5.8)	<0.001	<0.001
Length of hospitalization‡	32 (23–43)	33 (25–45)	33 (25–42)	0.18	0.16
30-d Mortality	40 (4.7)	71 (8.9)	99 (19)	<0.001	<0.001
90-d Mortality	56 (6.6)	111 (14)	158 (31)	<0.001	<0.001
Overall in-hospital mortality	56 (6.5)	99 (12)	118 (23)	<0.001	<0.001
In-hospital mortality for the surgical group	16 (4.0)	28 (12)	6 (20)	<0.001	<0.001
In-hospital mortality for the nonsurgical group	40 (8.6)	71 (12)	112 (23)	<0.001	<0.001
Long-term survival, Kaplan-Meier estimates					
1-y Survival	89 (87–91)	77 (74–80)	55 (51–59)		
Patients at risk, 1 y	746	595	274		
5-y Survival	75 (71–78)	57 (53–61)	22 (18–26)		
Patients at risk, 5 y	323	219	52		

Dichotomous variables are expressed as number (percentage) of patients. Non-normally distributed continuous are expressed as median (interquartile range). Estimated 1- and 5-year survival rates are reported as percentage (95% CI). Patients at risk are shown. IE indicates infective endocarditis.

\*P value, statistical testing among all 3 groups.

†P value, statistical testing between groups 2 and 3.

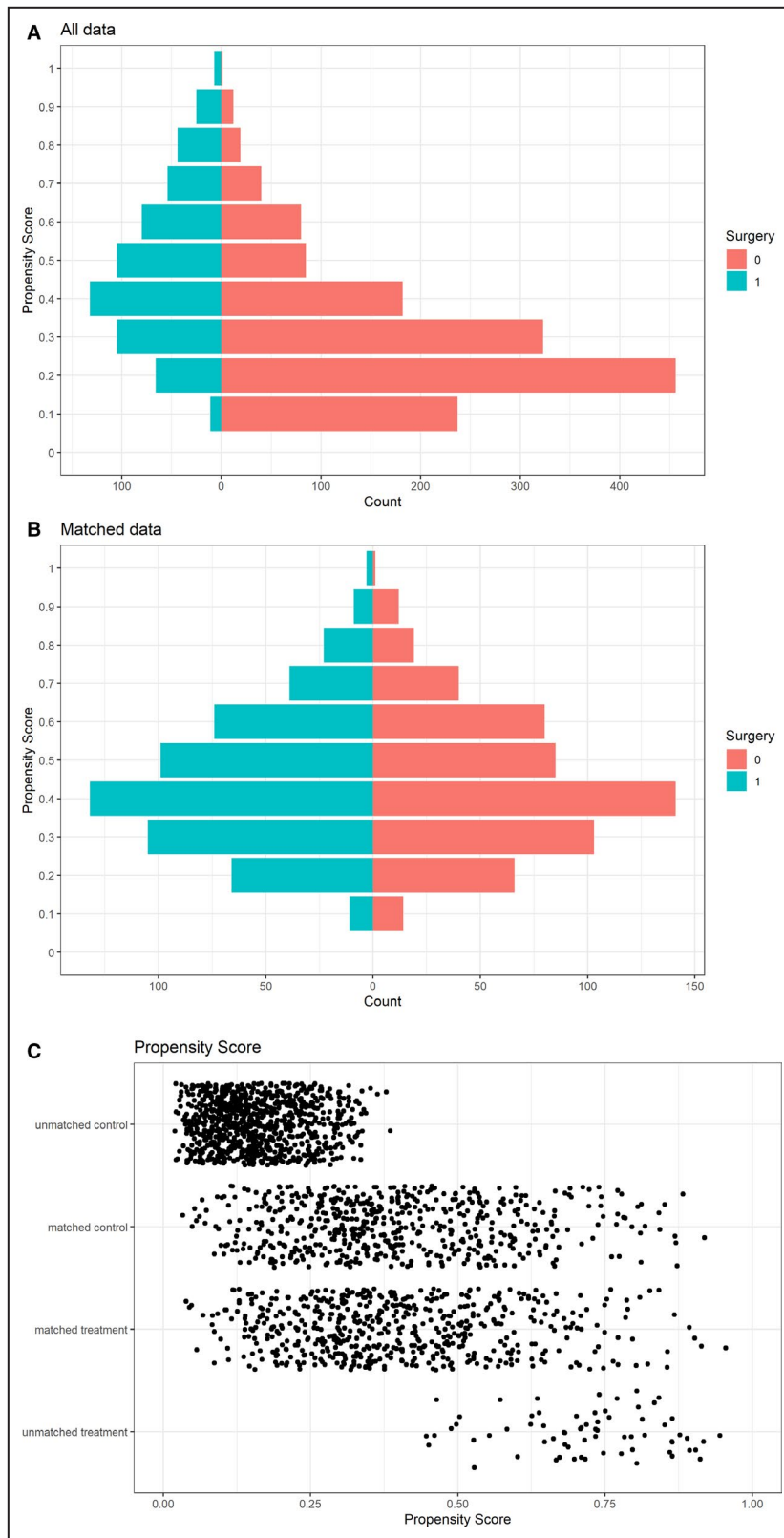
‡Groups 1 and 2, P=0.17; groups 1 and 3, P=0.88; groups 2 and 3, P=0.16.

other studies have shown that advanced age is independently associated with in-hospital mortality.<sup>5,11,17</sup> In-hospital mortality may be explained to a greater extent by the severity of IE and by comorbidities than by age. Long-term survival is also worse with older age, and in the present study only 22% of patients aged ≥80 years survived beyond 5 years. This is confirmed by studies that have shown that age is an independent predictor of long-term mortality.<sup>7,15</sup>

In the current study, <6% of cases of IE in the ≥80 group were treated with surgery, while surgery was performed in almost half of the cases in the <65 group. Other authors have also found that elderly patients undergo surgery less frequently than younger patients,<sup>5,7–9,15</sup> but most have reported higher numbers of patients who undergo surgery than the current study. Durante-Mangoni et al<sup>5</sup> reported that 37% of patients >70 years underwent surgery for IE, and Arminanzas et al<sup>15</sup> and Di Salvo et al<sup>13</sup> reported that 21% and 41% of patients aged ≥80 years underwent surgery. The reason for this discrepancy is unclear, but it could be that secondary care centers that report patients to the SRIE are not referring the oldest patients for tertiary care. There is some justification for deferring surgery in the elderly, whether because there is a lower incidence of valve impairment in this group, or because the relatively high comorbidity among these patients makes the surgical risk unacceptable.<sup>8,9</sup> Nevertheless, Oliver et al<sup>7</sup> posited that the European Society of Cardiology guidelines have been poorly implemented among older patients, in that a significant proportion of patients who had an indication for surgery were did not undergo surgery. They concluded that surgery was underused in

patients aged ≥80 years because patients who underwent surgery in the oldest group had a much better 1-year survival than those who did not undergo surgery. Furthermore, Arminanzas et al<sup>15</sup> have shown that the absolute difference between the proportion of patients with surgical indication and the proportion of patients actually undergoing surgery increases with age. Whereas 52% of octogenarian patients in that study had an indication for surgery, only 21% ultimately had surgery. In contrast, 68% of patients who were <65 years had a surgical indication, and 53% had surgery.<sup>15</sup>

Advanced age is strongly associated with short-term mortality following any type of cardiac surgery and is included in all risk models for mortality after cardiac surgery.<sup>18</sup> This is also true of surgery for IE, where short-term mortality is higher among elderly patients who undergo either urgent or elective surgery.<sup>8</sup> In our study, the in-hospital mortality among patients aged ≥80 years who underwent surgery was high and was similar to the in-hospital mortality of patients who did not undergo surgery. After propensity score matching of surgical and nonsurgical cases, we were able to show that long-term mortality expressed as the relative mortality rate was significantly lower among a wide age range, from 54 to 82 years, in patients who underwent surgery compared with comparable patients who did not undergo surgery. We could further show that a 60-year-old patient who did not undergo surgery had the same mortality risk as a 77-year-old patient who did undergo surgery. Although the margin of error was too wide to demonstrate a statistically significant difference, the death rate was lower in patients who underwent surgery up to 90 years of age compared



**Figure 1.** Propensity score matching for (A) all data and (B) unmatched data, with (C) the scatter plot of matched and unmatched patients.

**Table 4. Standardized Mean Difference for Matched Data**

Risk factor	All Data	Age <75 y	Age ≥75 y
	560 Pairs	442 Pairs	88 Pairs
Age	0.0162	...	
Female sex	0.0405	-0.0262	0.0467
Diabetes mellitus	0.0055	-0.0207	0.0000
End-stage renal disease	0.0298	0.0000	-0.1516
Embolism to the CNS	0.0042	-0.0218	0.0495
Intravenous drug use	-0.0707	-0.0456	...
Healthcare-related	0.0607	-0.0321	0.1274
Heart failure	0.0364	0.0232	-0.0679
Mitral valve location	-0.0108	-0.0183	-0.1135
Prosthetic valve IE	0.0255	-0.0196	0.0000
Vegetation	0.0261	-0.0455	0.1119
Pathogen	0.0167	-0.0172	0.0100

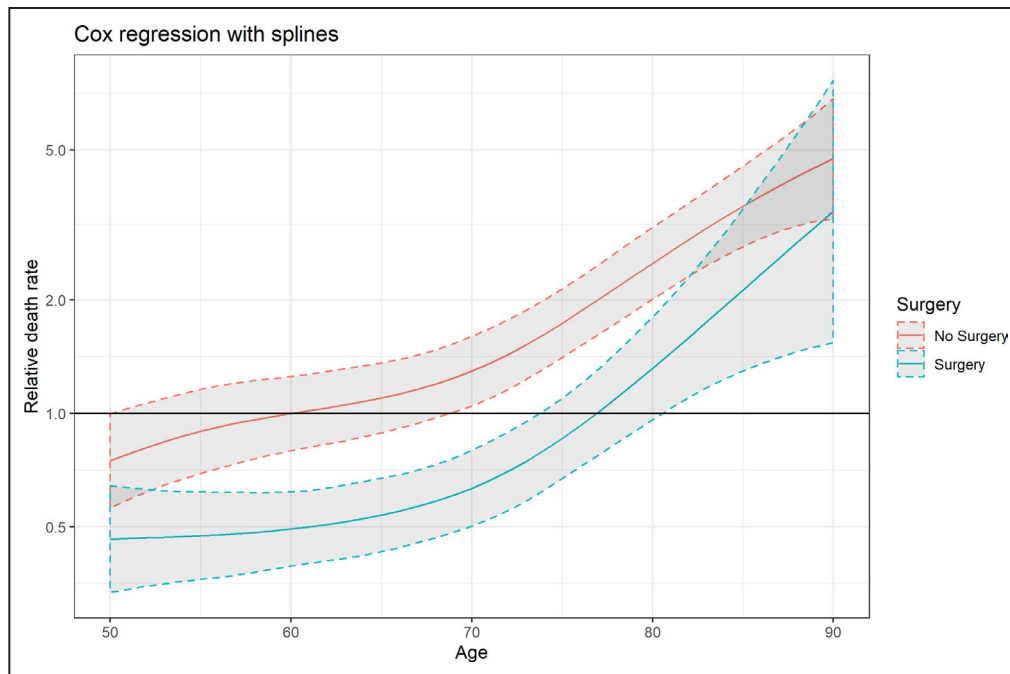
CNS indicates central nervous system; and IE, infective endocarditis

with those who did not undergo surgery. The propensity score matching was good, and no variables had a standardized mean difference of >0.1. When we applied propensity score matching analysis after splitting the patients into <75 and ≥75 age groups, we found that the benefit of surgery was significant in both sets of matched groups, and the HR of surgery was lower

in the ≥75 group than in the younger group, indicating a greater effect of surgery in this group.

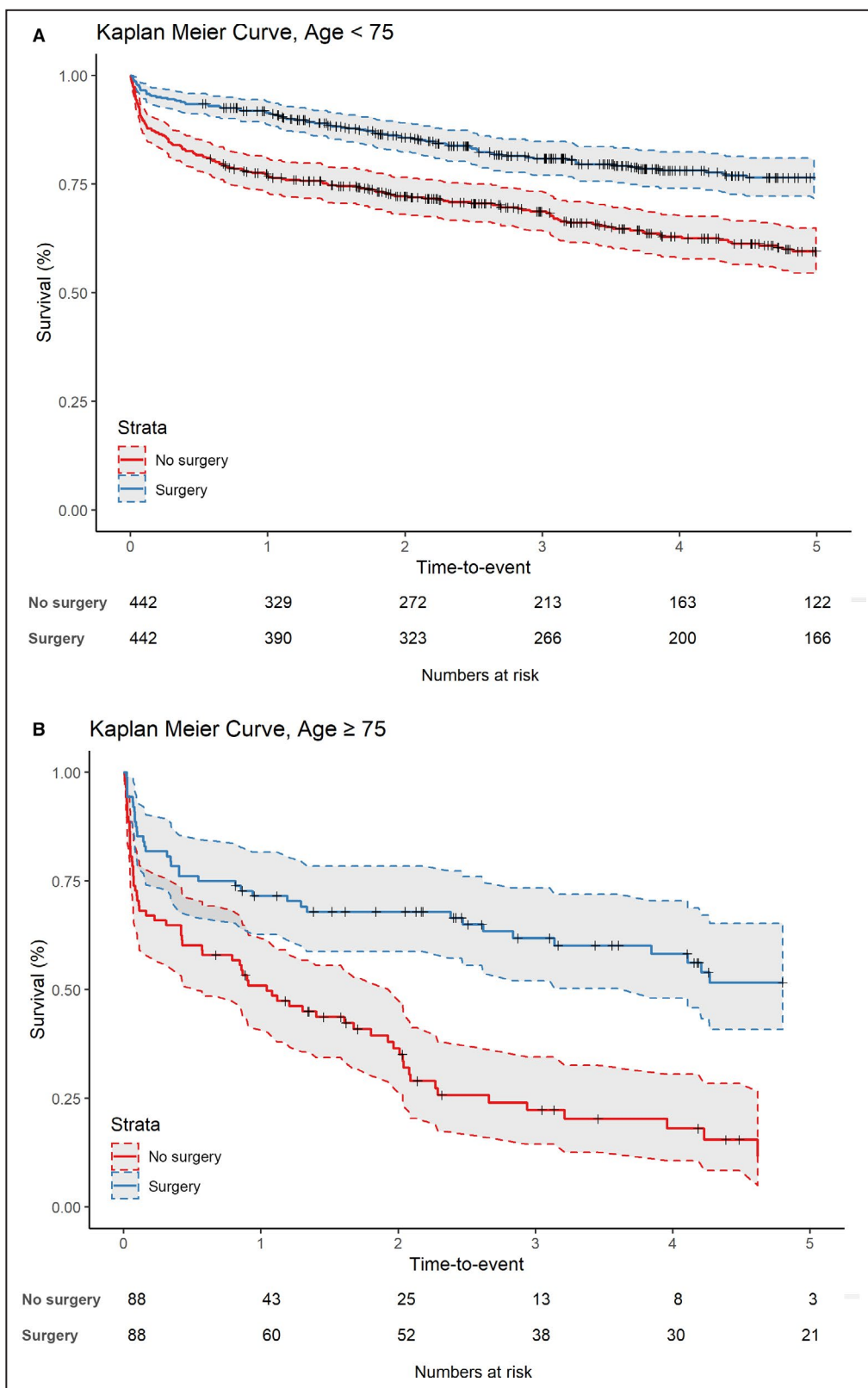
The rate of *S aureus* IE increased with age. *S aureus* IE accounted for 37% of cases in the ≥80 group, and was significantly more common in this group than in the patients who were aged 65 to 79 years. This was the case even though conditions that are often associated with *S aureus* bacteremia, such as diabetes mellitus, ESRD, and cancer, were all less common in the older group. Both López-Wolf et al<sup>9</sup> and Oliver et al,<sup>7</sup> to the contrary, have reported lower rates of *S aureus* in older patients, but a higher incidence of enterococci and *Streptococcus bovis*. Our analysis showed no significant difference in the frequency of enterococci among age groups. This also contrasts with the reports from López et al and Arminanzas et al, which showed an increased incidence of enterococci among elderly patients.<sup>9,15</sup> *S bovis* was most common in elderly patients in both studies. This is to be expected, as this pathogen is associated with gastrointestinal lesions that are more common in the elderly.<sup>19</sup>

Elderly patients were more likely to have transthoracic echocardiography, and the use of transeophageal echocardiography (TEE) decreased with increasing age, despite the fact that the sensitivity of TEE in detecting vegetative lesions is superior to that of transthoracic echocardiography, also in the elderly.<sup>9,20</sup> This suggests that elderly patients are treated differently than younger patients, which is concerning, because the proportion of IE cases where TEE is the only



**Figure 2. Spline curve showing the effect of age on the relative mortality rates of patients with left-sided infective endocarditis treated with and without surgery.**





**Figure 3.** Propensity score matching for long-term survival of in (A) patients aged <75 years and (B) patients ≥75 years.

evidence of IE was found to increase with age.<sup>5</sup> Wider application of TEE could therefore lead to an important diagnostic gain in older patients. However, cooperation of elderly patients for TEE may be difficult because of cognitive disorder or agitation caused by IE.

## Strengths and Limitations

The major strength of this study is that it includes data from a nationwide registry on IE, with patients treated at secondary and tertiary centers. The large number of elderly patients allowed us to compare the effects of surgery from young to advanced age. The limitation of this study is that it is retrospective in nature, albeit on a prospective database, with potential biases. It is not mandatory to report all IE episodes to the SRIE, which may lead to underreporting, especially of elderly patients and patients who are not treated by infectious disease specialists. The SRIE only recently introduced a category for patients with an indication for surgery who do not undergo surgery. Our analyses were therefore performed on all eligible patients with left-sided IE, including those who did not have an indication for surgery. Matching patients who underwent surgery to patients who did not with propensity scores may have limitations in that there may be factors that influence whether patients undergo surgery or not that are not apparent to the authors. We were not able to include estimated surgical risk in our propensity score models. The SRIE does not include European System for Cardiac Operative Risk Evaluation (EuroSCORE) or any other surgical risk estimation. Although many of the variables that are used to calculate EuroSCORE (such as age, female sex, and diabetes mellitus) were used in calculating the propensity scores, several important EuroSCORE variables are not included in the SRIE, which prevented us from calculating the EuroSCORE.

## CONCLUSIONS

The current study adds valuable information on the influence of surgery in elderly patients. We have shown that surgery is associated with a lower death rate among all ages in matched groups of patients who did and did not undergo surgery, with a significantly lower death rate between the ages of 54 and 82 years. When patients aged  $\geq 75$  years who underwent surgery were matched with patients who did not undergo surgery, there was significantly better survival associated with surgery. When the low proportion of elderly patients who undergo surgery is taken into consideration, we conclude that surgery is underused in the elderly.

## ARTICLE INFORMATION

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## Disclosures

None.

## Supplementary Material

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Table S1  
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## **SUPPLEMENTAL MATERIAL**

## Data S1.

### Supplemental Methods

#### Treatment of infective endocarditis in Sweden

In Sweden, there are 30 departments of infectious diseases (ID) that have regional responsibility for the care of patients with severe infections, including infective endocarditis (IE). There are eight hospitals that perform cardiothoracic surgery in Sweden, including all seven university hospitals. There are no private clinics that treat infective endocarditis in Sweden. Patients requiring acute surgery for IE are, in most cases, treated in ID departments during the pre- and/or postoperative period. Thus, a vast majority of patients with IE will be treated at an ID during the disease course.

#### The Swedish Registry on Infective Endocarditis

##### Background

The Swedish Registry on Infective Endocarditis (SRIE) is maintained by the Swedish Society for Infectious Diseases since 1995. Over 7000 episodes of IE have been reported to the registry and all 30 ID departments in Sweden have participated in the registry since its inception. Since 2008 all cases are reported in an internet-based reporting system at time of discharge and after follow-up (mean: 3 months after treatment). The current study only includes patients that were entered through the internet-based reporting system. The last major update on variables in the registry was done in 2019 and none of the patients entered into the registry after that time are included in the current study.

##### Coverage and completeness

Reporting to the registry is not mandatory. However, it is estimated that 60-70% of all IE episodes in Sweden are reported to the registry. Most variables (non-string variables) in the registry are more than 95% complete. In the current study, each episode had information on background characteristics, admission and discharge date, information on etiology, echocardiography, and antibiotic treatment.

##### Data entry and variables

Data is entered online (<https://www.infektionsregistret.se/Login.aspx>) by an ID specialist after logging in with a username and password. Data regarding sex, age, comorbidity, risk factors, heart failure, affected valve, the presence of any prosthetic valve, the type of prosthetic valve, the time since surgery, and the presence of other implantable cardiac devices such as a pacemaker or implantable cardioverter defibrillator (ICD) are collected. Clinical characteristics at presentation such as fever, new murmurs, and the presence of vascular and immunological phenomena are recorded. The origin of the etiologic agent is verified using, for example, blood cultures, cultures from valves during surgery, and polymerase chain reaction (PCR) from tissue samples of valves. Information about findings on echocardiography, delay from onset of symptoms to start of treatment, antibiotic treatment, need for surgery, and treatment outcome is also included. In the SRIE, vegetation

size is not a mandatory variable to fill in and in the current study, the vegetation size was reported in 896 of the total number of 1791 patients with a vegetation (66% missing).

#### Quality of the registry

The data in the SRIE are entered by ID specialists. A formal validation of the registry has not been carried out. The authors hope that this will be carried out in the near future. Data from the SRIE has been used in numerous studies in recent years<sup>21-28</sup>.

#### Follow-up

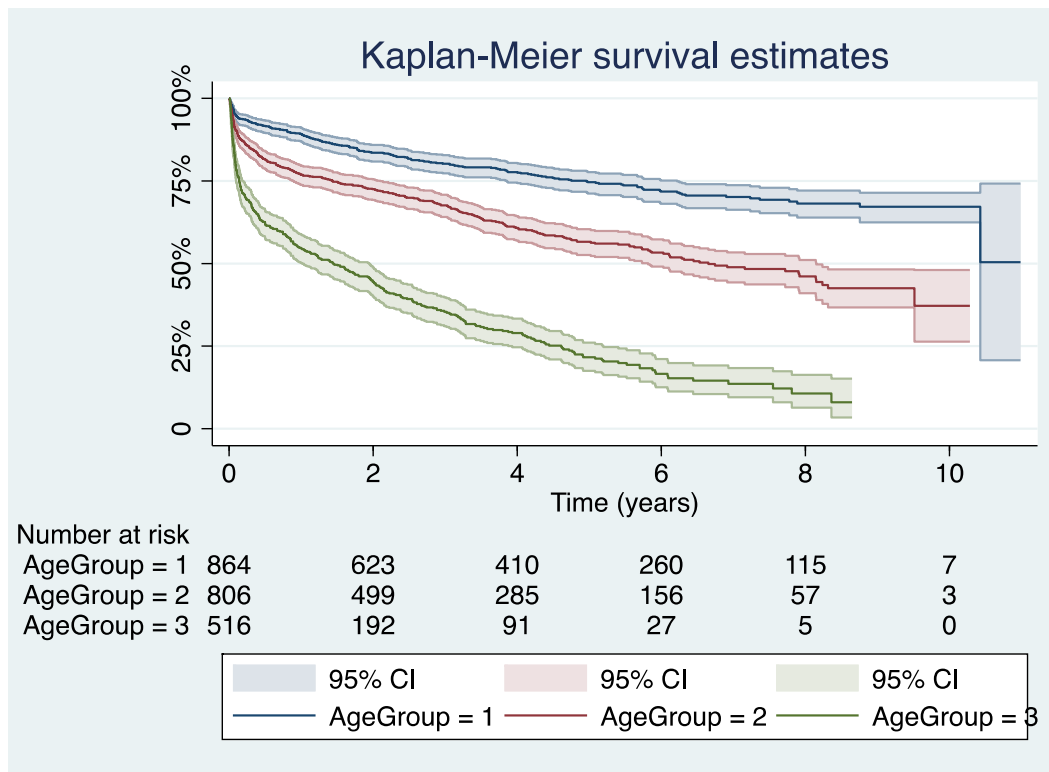
All patients in Sweden have a national personal identification number. This number is registered in the SRIE. By cross-referencing to the Swedish National Population Registry, we could determine whether patients were alive or not at follow-up and if they were deceased, the date of death could be determined.

**Table S1. Results from univariate Cox regression analysis.**

<b>Risk Factor</b>	<b>p-value</b>
Age	<0.001
Sex	<0.001
Diabetes mellitus	<0.001
ESRD	<0.001
Previous Endocarditis	0.329
Injection drug use	0.057
Community acquired	<0.001
Health care related acquisition	<0.001
Heart Failure	<0.001
Mitral valve location	0.095
Prosthetic valve endocarditis	0.034
Vegetation	0.007
Abscess	0.372
Central nervous system embolism	0.197
Pathogen	<0.001

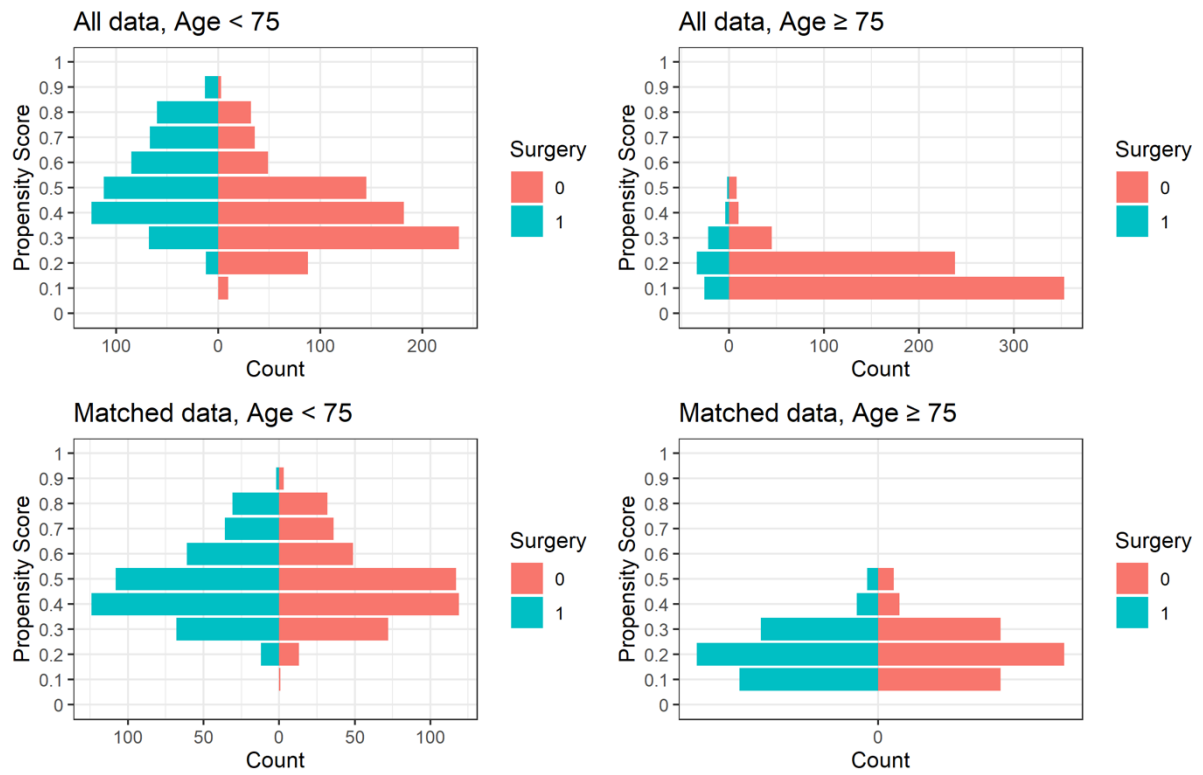
ESRD: End stage renal disease

**Figure S1. Kaplan-Meier estimates of overall survival for the three age groups (Group 1, <65 years; Group 2, 65-79 years; Group 3, 80 years and older).**





**Figure S2. Propensity score matching in patients younger than 75 years and patients 75 years and older.**



**Figure S3. Scatterplot of matched and unmatched patients. Left: patients younger than 75 years. Right: patients 75 years and older.**

