



openheart Surgical treatment for infective endocarditis in the ageing society: a nationwide retrospective study in Japan

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ABSTRACT

Objective The current status of surgical treatment for infective endocarditis (IE) among very elderly people is unclear.

Methods We extracted data on patients in Japan with community-acquired IE who were admitted and discharged between April 2010 and February 2018 using a nationwide inpatient, the Diagnosis Procedure Combination database. We divided patients into three groups: non-elderly (<65 years), elderly (65–79 years) and very elderly (≥80 years). A 1:1 propensity score matching was performed to compare proportions of surgical treatment and in-hospital mortality among the groups.

Results We identified 20 667 eligible patients (median age 70 years, 61.0% men). The proportion of very elderly patients significantly increased (19.1% in 2010 to 29.7% in 2018). The proportion of surgical treatment was significantly lower, and in-hospital mortality was significantly higher in very elderly patients. This tendency was more pronounced among patients with in-hospital complications such as heart failure, stroke or embolism. Surgical treatment was significantly associated with lower in-hospital mortality even in very elderly patients, both in an unmatched (OR 0.61; 95% CI 0.47 to 0.78) and a propensity score matched cohort (OR 0.61; 95% CI 0.43 to 0.85).

Conclusions The proportion of very elderly patients with IE was increasing, and very elderly patients had higher in-hospital mortality. The proportion of surgical treatment for IE among very elderly patients was low, but it was associated with lower in-hospital mortality. Further studies are needed to establish the optimal strategy for IE among very elderly patients.

INTRODUCTION

Infective endocarditis (IE) is a rare infectious disease that nevertheless has a high burden of mortality and morbidity. The annual incidence of IE is 3–10 cases per 100 000 inhabitants in developed countries^{1–5}; however, short-term IE mortality is up to 25% and has not changed in the last decade despite recent improvements in diagnosis and management.^{2 6 7}

Key questions

What is already known about this subject?

► The incidence of infective endocarditis (IE) among elderly patients over 80 years old has doubled in the last few decades, which can be an unignorable issue. However, previous studies have defined elderly individuals as those older than 65 or 70 years because the scarcity of IE makes sampling difficult. Therefore, previous results do not reflect the current status of IE in the ageing population.

What does this study add?

► Our study elucidates the current status of surgical treatment and in-hospital mortality for IE in very elderly patients aged 80 years or older using a nationwide inpatient database in Japan.

How might this impact on clinical practice?

► IE among very elderly patients was rapidly increasing, and very elderly patients had higher in-hospital mortality than non-elderly patients. Although surgical treatment was less frequently conducted in very elderly patients, it was associated with lower in-hospital mortality even after propensity score matching. Our findings highlight the clinical importance of selecting optimal candidates for surgical treatment even in very elderly patients with IE.

One possible reason for the sustained high mortality of IE is the current ageing population. Although ageing is a well-known strong prognostic factor for IE,^{6 8} some epidemiological studies showed that the incidence of IE among very elderly patients aged 80 years or older doubled in the last few decades while the overall incidence has remained static.^{5 9}

Ageing is a heterogeneous process which results in a wide spectrum of patients' profile, and optimal IE management of very elderly patients should be differentiated from that of non-elderly patients. Particularly, the current status of surgical treatment, which is a cornerstone of IE treatment, is still unclear among very elderly patients. Previous studies

suggest that surgical treatment has a beneficial effect on IE among elderly patients.^{10–17} In those studies, elderly patients were defined as those over 65 or 70 years, owing to the rarity of IE and the difficulty of collecting sufficient target samples.^{10–17}

In the real-world clinical setting, the number of healthier elderly people is increasing. Such individuals may be suited to similar treatment strategies as non-elderly people; in contrast, clinicians struggle to manage very elderly patients with IE. However, observational studies of very elderly people are scarce, and rarely mentioned in the guidelines of the American Heart Association and the European Society of Cardiology.^{18 19}

Japan is the most rapidly ageing society in the world and is confronting various unique geriatric issues. The current status of very elderly patients with IE in Japan may be an indicator of the future worldwide status of IE. In the present study, we used a nationwide Japanese inpatient database to elucidate the current status of surgical treatment and clinical outcomes among very elderly patients hospitalised with IE.

METHODS

Study design and data source

This was a retrospective cohort study using the Diagnosis Procedure Combination database, a nationwide Japanese inpatient database.^{20 21} This database contains hospital administrative claims data and clinical data for approximately 8 million hospitalised patients per year from participating hospitals, including more than 1000 acute care hospitals and all 82 academic hospitals. The database includes the following data: individual hospital identifier; patient admission and discharge date; patient background (eg, age and sex); consciousness level at admission according to Japan Coma Scale (JCS) score²²; diagnosis at admission including main diagnosis, admission-precipitating diagnosis, and most and second most resource-consuming diagnosis; comorbidities at admission and complications after admission as described by the *International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* codes; daily records of drugs, devices and procedures, including surgical treatment, coded with original code during hospitalisation; and discharge status.

Patient and public involvement

Patients or the public were not involved in this research project.

Patient selection

We identified patients with IE aged ≥ 20 years who were admitted and discharged between 1 April 2010 and 28 February 2018. Records of patients with IE were extracted using the relevant ICD-10 code with the main diagnosis, admission-precipitating diagnosis, or most and second most resource-consuming diagnosis (see online supplemental table 1). Only the first episode of IE recorded for an individual during

study enrolment, for which any antibiotics were started within 2 days after admission, was counted as community-acquired IE and used for the analysis. Eligible patients were divided into three groups: non-elderly (< 65 years), elderly (65–79 years) and very elderly (≥ 80 years).

Variables and outcomes

For baseline variables, we obtained data on patient characteristics: patient age and sex; body mass index (BMI) categorised as < 18.5 , 18.5–24.9, 25.0–29.9, ≥ 30 kg/m²; smoking and activities of daily living (Barthel Index score categorised as < 20 (total dependence), 20–35 (severe dependence), 40–55 (moderate dependence), 60–95 (mild dependence) and 100 (independence))²³; consciousness level at admission according to JCS score²²; type of admission (planned or emergency); and supply of pre-hospital home medical care. We extracted data on hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, malignancy, chronic pulmonary disease, chronic liver disease, chronic renal disease and previous valve replacement as comorbid conditions at admission (see online supplemental table 1). The data on hospital volume were classified into three groups (low, middle, high) and type of hospital was recorded (eg, clinical training hospital). For in-hospital complications, we extracted data on heart failure (with New York Heart Association classification if listed); stroke, including ischaemia and haemorrhage; any embolism of the coronary system, spleen, kidney, lung, abdominal artery or extremities; shock; and disseminated intravascular coagulation as common complications of IE (see online supplemental table 1). We defined penicillin system, cephem system, carbapenem, aminoglycoside, glycopeptide, daptomycin, linezolid and antifungal antibiotics used for more than 2 weeks during hospitalisation as antibiotics targeted to IE. Transthoracic echocardiography and transoesophageal echocardiography (TEE) during hospitalisation were investigated. Data on intensive treatment within 2 days after admission, including admission to high care unit/intensive care unit, inotropic therapy and mechanical support (ventilation support, renal replacement therapy and direct hemoperfusion with polymyxin B immobilised fibre), were extracted for severity assessment. Surgical treatment for IE was defined according to the following ICD-10 codes: K542, K554, K555, K557-3 and K560.

Statistical analysis

Categorical variables are shown as numbers (percentages) and consecutive data are presented as medians (IQRs). χ^2 tests were used to compare categorical variables and the Kruskal-Wallis test was used to compare consecutive variables. A 1:1 propensity score matching was conducted using nearest neighbour matching with a calliper width set at 20% SD

of the logit of the estimated propensity scores to adjust differences in baseline characteristics between patients with and without surgical treatment among the three subgroups (non-elderly, elderly and very elderly). The propensity score was estimated using a non-parsimonious logistic regression model with surgical treatment as the dependent variable. Covariates included in this model were baseline characteristics, admission year, hospital type, admission type, comorbid conditions, complications, antibiotics and procedures within 2 days (see online supplemental table 2a–c). Differences between the two groups before and after propensity score matching were assessed using standardised mean differences. Absolute standardised mean differences of less than 10% suggest a negligible difference in baseline characteristics between two groups.²⁴ The multivariate logistic regression analysis was performed to find factors associated with in-hospital mortality among very elderly patients with IE. In this model, in-hospital mortality was adopted as a dependent variable, and independent variables included baseline characteristics, hospital type, comorbid conditions and complications. We performed statistical analyses using IBM SPSS (V.25.0; IBM SPSS) and Stata (V.16; Stata Corp). P values of <0.05 were considered statistically significant.

RESULTS

Study population

We studied 20 667 eligible patients with community-acquired IE. The distribution of non-elderly, elderly and very elderly patients was 7803 (37.8%), 7874 (38.1%) and 4990 (24.1%), respectively.

Figure 1 shows the transition of IE prevalence according to age category. The proportion of

non-elderly patients decreased from 42.5% in 2010 to 32.1% in 2018, and that of elderly patients remained unchanged from 38.5% in 2010 to 38.2% in 2018. The proportion of very elderly patients significantly increased from 19.1% in 2010 to 29.7% in 2018.

Baseline patient characteristics

Table 1 summarises the baseline characteristics for all patients. The median age was 70 years (57–79 years), and 12 603 patients (61.0%) were men. The median BMI was 21.3 (19.0–23.9). Very elderly patients were more likely to be women and have lower BMI and lower Barthel Index scores than non-elderly patients. Furthermore, very elderly patients had more emergency hospitalisations and lower consciousness at admission than non-elderly patients. Most comorbid conditions, including hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation and malignancy, significantly increased with age. Regarding IE complications, heart failure occurred more frequently in very elderly patients, whereas stroke and all types of embolism were more common in non-elderly patients.

Antibiotic therapy, echocardiography and procedures

Table 2 shows antibiotic use, echocardiography use and intensive treatment during hospitalisation. Penicillin system, cephem system and aminoglycoside were administered more frequently to non-elderly patients. Glycopeptide, daptomycin and antifungal antibiotics were administered more frequently to elderly patients. Regarding echocardiography, more than 90% of patients in each age category received transthoracic echocardiography, whereas the proportion of TEE was significantly lower in very elderly patients. Regarding intensive treatment within 2 days after admission, non-elderly patients more frequently received intensive treatment such as admission to

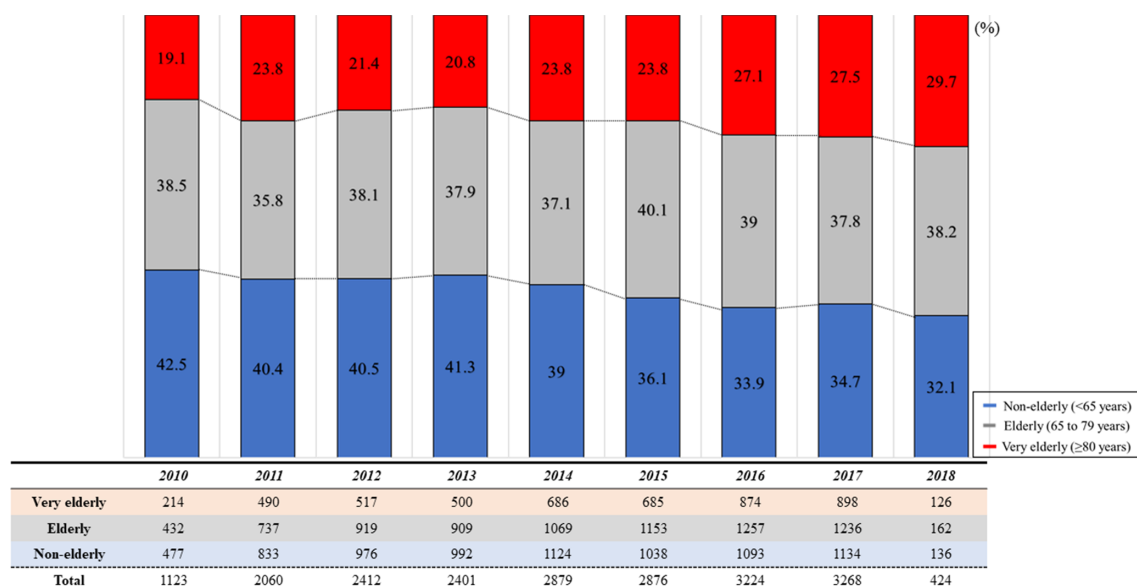


Figure 1 Transition of IE prevalence according to age category. The proportion of the non-elderly patients decreased, and that of the very elderly patients significantly increased, from April 2010 to February 2018. IE, infective endocarditis.

Table 1 Baseline patient characteristics

Variables	Non-elderly (n=7803)	Elderly (n=7874)	Very elderly (n=4990)	P value
Age, years	51 (40–59)	72 (68–76)	84 (82–88)	<0.001*
Male gender	5508 (70.6%)	4899 (62.2%)	2196 (44.0%)	<0.001*
BMI, kg/m ²	21.5 (19.1–24.3)	21.6 (19.3–24.0)	20.6 (18.3–23.1)	<0.001*
<18.5	1419 (18.2%)	1354 (17.2%)	1171 (23.5%)	
18.5–24.9	4393 (56.3%)	4678 (59.4%)	2657 (53.2%)	
25.0–29.9	1197 (15.3%)	1059 (13.4%)	463 (9.3%)	
≥30	331 (4.2%)	213 (2.7%)	76 (1.5%)	
Smoking	3841 (49.2%)	3289 (41.8%)	1495 (30.0%)	<0.001*
Barthel Index	100 (50–100)	75 (5–100)	25 (0–85)	<0.001*
<20 (total dependence)	1249 (16.0%)	1900 (24.1%)	1967 (39.4%)	<0.001*
20–35 (severe dependence)	261 (3.3%)	373 (4.7%)	310 (6.2%)	
40–55 (moderate dependence)	376 (4.8%)	589 (7.5%)	473 (9.5%)	
60–95 (mild dependence)	890 (11.4%)	856 (10.9%)	522 (10.5%)	
100 (independence)	4028 (51.6%)	2768 (35.2%)	848 (17.0%)	
JCS				<0.001*
0 (alert)	6738 (86.4%)	6341 (80.5%)	3358 (67.3%)	
1–3 (drowsy)	710 (9.1%)	1058 (13.4%)	1156 (23.2%)	
10–30 (somnolence)	196 (2.5%)	284 (3.6%)	318 (6.4%)	
100–300 (coma)	159 (2.0%)	191 (2.4%)	158 (3.2%)	
Hospital volume				<0.001*
Low (<4)	183 (2.3%)	256 (3.3%)	282 (5.7%)	
Middle (4≤ and <14)	1033 (13.2%)	1213 (15.4%)	1139 (22.8%)	
High (≥14)	6587 (84.4%)	6405 (81.3%)	3569 (71.5%)	
Clinical training hospital	6820 (87.4%)	6641 (84.3%)	4043 (81.0%)	<0.001*
Emergent admission	5874 (75.3%)	6163 (78.3%)	4266 (85.5%)	<0.001*
Pre-hospital home medical care	60 (0.8%)	142 (1.8%)	288 (5.8%)	<0.001*
Comorbid conditions				
Hypertension	1697 (21.7%)	2341 (29.7%)	1588 (31.8%)	<0.001*
Diabetes mellitus	1068 (13.7%)	1666 (21.2%)	791 (15.9%)	<0.001*
Dyslipidaemia	537 (6.9%)	768 (9.8%)	437 (8.8%)	<0.001*
Atrial fibrillation	423 (5.4%)	1031 (13.1%)	698 (14.0%)	<0.001*
Malignancy	224 (2.9%)	616 (7.8%)	397 (8.0%)	<0.001*
Chronic pulmonary disease	191 (2.4%)	258 (3.3%)	210 (4.2%)	<0.001*
Chronic liver disease	361 (4.6%)	327 (4.2%)	152 (3.0%)	<0.001*
Chronic renal disease	529 (6.8%)	954 (12.1%)	471 (9.4%)	<0.001*
Previous valve replacement	78 (1.0%)	172 (2.2%)	35 (0.7%)	<0.001*
In-hospital complications				
Heart failure	2314 (29.7%)	2718 (34.5%)	1984 (39.8%)	<0.001*
NYHA II	385 (4.9%)	420 (5.3%)	206 (4.1%)	0.001*
NYHA III	274 (3.5%)	319 (4.1%)	176 (3.5%)	
NYHA IV	242 (3.1%)	269 (3.4%)	202 (4.0%)	
Stroke	1071 (13.7%)	1011 (12.8%)	542 (10.9%)	<0.001*
Ischaemic	903 (11.6%)	855 (10.9%)	484 (9.7%)	0.004*
Haemorrhagic	216 (2.8%)	195 (2.5%)	66 (1.3%)	<0.001*
Embolism	391 (5.0%)	217 (2.8%)	96 (1.9%)	<0.001*
Coronary	37 (0.5%)	36 (0.5%)	23 (0.5%)	0.987

Continued

Table 1 Continued

Variables	Non-elderly (n=7803)	Elderly (n=7874)	Very elderly (n=4990)	P value
Spleen	126 (1.6%)	70 (0.9%)	17 (0.3%)	<0.001*
Kidney	133 (1.7%)	26 (0.3%)	4 (0.1%)	<0.001*
Lung	68 (0.9%)	25 (0.3%)	16 (0.3%)	<0.001*
Abdominal artery	3 (0.0%)	9 (0.1%)	4 (0.1%)	0.232
Extremities	85 (1.1%)	62 (0.8%)	35 (0.7%)	0.039*
Shock	149 (1.9%)	141 (1.8%)	73 (1.5%)	0.165
DIC	266 (3.4%)	277 (3.5%)	176 (3.5%)	0.912

Data are expressed as the median (IQR) or number (percentage).

*P values are significant.

BMI, body mass index; DIC, disseminated intravascular coagulation; JCS, Japan Coma Scale; NYHA, New York Heart Association.

intensive care units, inotropic therapy and ventilation support. Continuous renal replacement therapy and intermittent renal replacement therapy were more frequently provided to elderly patients. Very elderly patients received all intensive treatments less frequently. The proportions of surgical treatment

were 37.1%, 28.5% and 9.3% in non-elderly, elderly and very elderly patients, respectively ($p<0.001$).

Clinical outcomes

Table 3 shows clinical outcomes. In-hospital mortality was 6.6%, 14.2% and 22.8% in non-elderly, elderly

Table 2 Antibiotics, echocardiography and procedures

Variables	Non-elderly (n=7803)	Elderly (n=7874)	Very elderly (n=4990)	P value
Antibiotics for more than 2 weeks				
Penicillin system	3364 (43.1%)	3177 (40.3%)	1730 (34.7%)	<0.001*
Cephem system	2489 (31.9%)	2202 (28.0%)	1356 (27.2%)	<0.001*
Carbapenem	600 (7.7%)	687 (8.7%)	458 (9.2%)	0.007*
Aminoglycoside	2961 (37.9%)	2468 (31.3%)	1153 (23.1%)	<0.001*
Glycopeptide	1237 (15.9%)	1452 (18.4%)	783 (15.7%)	<0.001*
Daptomycin	275 (3.5%)	298 (3.8%)	130 (2.6%)	0.001*
Linezolid	142 (1.8%)	119 (1.5%)	45 (0.9%)	<0.001*
Antifungal antibiotics	131 (1.7%)	237 (3.0%)	102 (2.0%)	<0.001*
Others	1785 (22.9%)	2119 (26.9%)	1585 (31.8%)	<0.001*
Echocardiography				
TTE	7263 (93.1%)	7251 (92.1%)	4556 (91.3%)	0.001*
TEE	4007 (51.4%)	3700 (47.0%)	1494 (29.9%)	<0.001*
Intensive treatment within 2 days after admission				
Admission to HCU	266 (3.4%)	305 (3.9%)	178 (3.6%)	0.289
Admission to ICU	1255 (16.1%)	1055 (13.4%)	347 (7.0%)	<0.001*
Inotropic therapy	1236 (15.8%)	1205 (15.3%)	500 (10.0%)	<0.001*
Ventilation Support	754 (9.7%)	674 (8.6%)	237 (4.7%)	<0.001*
CRRT	135 (1.7%)	175 (2.2%)	49 (1.0%)	<0.001*
IRRT	348 (4.5%)	498 (6.3%)	145 (2.9%)	<0.001*
PMX-DHP	36 (0.5%)	29 (0.4%)	7 (0.1%)	0.01*
Surgical treatment	2894 (37.1%)	2246 (28.5%)	465 (9.3%)	<0.001*

Data are expressed as number (percentage).

*P values are significant.

CRRT, continuous renal replacement therapy; HCU, high care unit; ICU, intensive care unit; IRRT, intermittent renal replacement therapy; PMX-DHP, Polymyxin B-immobilised fibre column-direct hemoperfusion; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Table 3 Clinical outcomes

Variables	Non-elderly (n=7803)	Elderly (n=7874)	Very elderly (n=4990)	P value
In-hospital mortality	514 (6.6%)	1118 (14.2%)	1138 (22.8%)	<0.001*
Length of hospital stay, days	37 (21–54)	38 (19–59)	36 (19–57.3)	0.014*
Transfer to nursing home or other hospital	2276 (29.2%)	3390 (43.1%)	2724 (54.6%)	<0.001*
Post-hospital home medical care	71 (0.9%)	157 (2.0%)	252 (5.1%)	<0.001*

Data are expressed as the median (IQR) or number (percentage).

*P values are significant.

and very elderly patients, respectively ($p < 0.001$). Very elderly patients were transferred to nursing homes or other hospitals and received post-hospital home medical care more frequently ($p < 0.001$).

Surgical treatment among patients with in-hospital complications

The proportions of surgical treatment among patients with specific in-hospital complications were compared between each age category (figure 2). The proportions of surgical treatment were 47.6%, 36.6% and 10.3% among patients with concomitant heart failure; 47.9%, 32.1% and 11.3% among those with stroke; and 46.8%, 30.0% and 7.3% among those with embolism for non-elderly, elderly and very elderly patients, respectively (all $p < 0.001$).

Association between surgical treatment and in-hospital mortality in an unmatched and a propensity score matched cohort

We evaluated the association between surgical treatment and in-hospital mortality in each age category using an unmatched and a propensity score matched cohort.

Patient characteristics after propensity score matching in non-elderly, elderly and very elderly patients are shown in online supplemental table 2a–c. All the variables in each age category were well balanced between

patients with and without surgical treatment. Propensity score matching created 1785 pairs in non-elderly, 1625 in elderly, and 414 in very elderly patients.

Table 4 shows the association between surgical treatment and in-hospital mortality in an unmatched and a propensity score matched cohort. Surgical treatment was associated with lower in-hospital mortality in all groups, not only in the unmatched cohort (non-elderly, OR 0.60 (95% CI 0.49 to 0.73); elderly, OR 0.67 (95% CI 0.57 to 0.78); very elderly, 0.61 (95% CI 0.47 to 0.78)) but also in the propensity score matched cohort (non-elderly, OR 0.52 (95% CI 0.39 to 0.69); elderly, OR 0.68 (95% CI 0.55 to 0.84); very elderly, 0.61 (95% CI 0.43 to 0.85)).

Risk factors of in-hospital mortality among IE patients aged 80 years or older

In multivariable logistic regression analysis, older age, lower Barthel Index, higher JCS, hypertension, dyslipidemia, chronic renal disease, heart failure, stroke, DIC, and surgical treatment were associated with higher in-hospital mortality among IE patients aged 80 years or older (online supplemental table 3).

DISCUSSION

This nationwide inpatient cohort study produced several important findings. First, the proportion of very

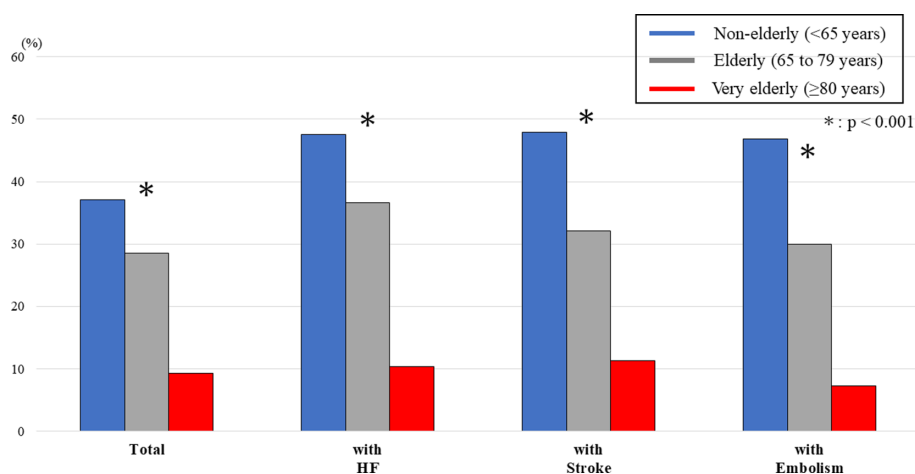


Figure 2 Proportions of surgical treatment for IE according to age category among patients with in-hospital complications. The figure shows that surgical treatment was performed less frequently with advancing age. The tendency was even more pronounced in the presence of complications such as heart failure, stroke and embolism. IE, infective endocarditis.

Table 4 Association between surgical treatment and in-hospital mortality in an unmatched and a propensity score matched cohort

Subgroup	Unmatched cohort				Propensity score matched cohort			
	In-hospital mortality				In-hospital mortality			
	Surgical treatment (–)	Surgical treatment (+)	OR (95% CI)	P value	Surgical treatment (–)	Surgical treatment (+)	OR (95% CI)	P value
Non-elderly	377/4909 (7.7%)	137/2894 (4.7%)	0.60 (0.49 to 0.73)	<0.001*	151/1785 (8.5%)	82/1785 (4.6%)	0.52 (0.39 to 0.69)	<0.001*
Elderly	873/5628 (15.5%)	245/2246 (10.9%)	0.67 (0.57 to 0.78)	<0.001*	242/1625 (14.9%)	173/1625 (10.6%)	0.68 (0.55 to 0.84)	<0.001*
Very elderly	1065/4525 (23.5%)	73/465 (15.7%)	0.61 (0.47 to 0.78)	<0.001*	104/414 (25.1%)	70/414 (16.9%)	0.61 (0.43 to 0.85)	0.004*

*P values are significant.

elderly patients among the whole IE population is obviously increasing whereas that of non-elderly patients is decreasing. Second, surgical treatment was performed on more than one-third of non-elderly patients, but on less than 10% of very elderly patients. Third, surgical treatment was beneficially associated with in-hospital mortality not only in non-elderly and elderly patients, but also in very elderly patients in both an unmatched and a propensity score matched cohort.

IE has become increasingly frequent in aged patients, especially in very elderly patients, over the past few decades. Shah *et al* reported that IE incidence in very elderly patients had doubled while remaining static or decreasing in the younger population over the past two decades,⁹ which indicates that IE in very elderly people is becoming an important issue in ageing societies. This escalation of IE among very elderly individuals is multifactorial, and includes changes in the incidence of degenerative valvular heart disease, an increase in invasive therapeutic cardiac interventions and improvements in survival rate for multiple comorbidities.¹² Several studies have reported the similarities and the differences of IE among elderly compared with non-elderly patients, some of which showed the conflicting result regarding clinical characteristics such as causative microorganisms and echocardiographic findings.^{10–17} This contradiction may be explained by the diversity in health conditions across elderly people. Ageing is a highly variable process characterised by a wide spectrum of conditions: some aged individuals are healthy whereas others are bedridden. Contrasting study findings may also reflect inconsistent definitions of ‘elderly’, which can range from over 65 years to over 70 years.^{10–17}

To the best of our knowledge, the present study is one of the largest to focus on IE among very elderly patients. The large sample enabled us to comprehensively investigate the characteristics of IE among very elderly patients in a clinical setting. Our overall cohort seemed relatively older than participants in other epidemiological studies.^{2 5 7–9} This possibly reflects the fact that Japan is a representative ageing society, and is consistent with

our previous study findings.²⁵ Although men dominated this cohort, the proportion of women increased with age, similar to previous studies.^{12 26} Regarding in-hospital complications, heart failure was more common in very elderly patients, whereas vascular manifestations of IE, such as stroke and other embolic events, were less common in very elderly patients. Patients with advanced age are prone to concomitant heart failure symptoms owing to underlying heart disease and degenerative changes; in addition, age-related decline in immune system and haemostatic function contributes to fewer embolic events with gradual progression of vegetation formation.^{10 12 27} Very elderly patients received TEE and antibiotic treatment less frequently than patients in the other two age categories. Up to 6 weeks of antibiotic therapy to eradicate the growing bacteria present in the IE vegetation is an established medical treatment recommended in the American Heart Association and the European Society of Cardiology guidelines.^{18 19} Moreover, TEE may be a more practical tool than transthoracic echocardiography for elderly patients with IE because valvular calcification, which is commonly seen in elderly patients, makes it difficult to evaluate the presence of the vegetation and the vegetation itself is smaller than that in non-elderly patients.¹⁷ The less usage of TEE in very elderly patients in this study can be attributed to several factors. The first reason is the less complexity of the valve lesion in very elderly patients with surgical treatment. The other reasons could be that the number of surgical treatments itself is less in very elderly patient, and that the very elderly have a higher hurdle for the invasive TEE procedures than non-elderly or elderly patients. Low frequency of TEE and antibiotic treatment may be associated with worse in-hospital mortality in very elderly patients, and further study is warranted to explore this association.

Surgical treatment is a cornerstone of IE treatment, especially in cases with decompensated heart failure and repeated emboli. However, in the real-world clinical setting, elderly patients tend to receive more conservative treatment, and a low proportion undergoes surgical treatment owing to concerns about surgical complications.^{12 28}

The validity of surgical treatment among elderly patients has been investigated by several retrospective analyses focusing on patients over 65 or 70 years.^{10–17} Lin *et al* investigated the mid-term outcome of left-sided native valve IE in 179 patients and concluded that mid-term outcomes are promising once elderly patients over 65 years are stabilised by surgical treatment.¹⁴ However, there are scarce clinical data on the efficacy of surgical treatment for IE among the very elderly population. One randomised controlled trial of surgical treatment for IE excluded very elderly patients over 80 years old.²⁹ Our nationwide study investigated the current status of surgical treatment in very elderly patients, and indicated that the proportion of surgical treatment for very elderly patients with IE was significantly lower than in younger patients (<10%). This tendency was more pronounced among those with specific complications such as heart failure, stroke and embolic events, which could be an indication of surgical treatment. However, our analyses also showed an inverse association between surgical treatment and in-hospital mortality among very elderly patients in a propensity score matched cohort that included a wide variety of confounding factors. This result indicates that surgical treatment may be an appropriate therapeutic option for selected patients with IE, even in very elderly patients. Our findings are consistent with the description in the European Society of Cardiology guideline: ‘Age per se is not a contraindication to surgery’.¹⁹ However, as the OR for very elderly patients was higher than that for non-elderly patients, the selection of optimal candidates for surgical treatment requires care.

The present study has several clinical implications. This comprehensive analysis of Japanese patients showed a rapidly increasing proportion of IE among very elderly patients, which is consistent with other epidemiological studies.^{5,9} Therefore, optimal management of IE in very elderly patients is becoming an important issue. Of note, implementation of surgical treatment for IE among very elderly patients was obviously low (less than 10%) in our study. The propensity score analysis indicated an inverse association between surgical treatment and in-hospital mortality even in very elderly patients; therefore, appropriate patient selection for surgical treatment is required irrespective of age. The mechanism of IE in very elderly people is more complicated than in non-elderly people, so optimal decision making that includes early diagnosis and therapeutic strategies should be facilitated using a multidisciplinary approach. Further studies are needed to elucidate appropriate management for IE among very elderly patients.

We acknowledge several study limitations. First, although the reported validity of the diagnoses and procedures in our database was high,³⁰ recorded diagnoses are generally considered less well validated because of the nature of administrative data and retrospective studies. Second, this database lacks some clinical data on causative micro-organisms, infected valves, the location and size of vegetation, and cardiac function. In

particular, detailed past surgical histories and details of the surgeries performed on IE are lacking, however, the surgical results may be influenced by the complexity of valve lesions and surgical procedures. Third, we defined the antibiotic drugs used more than 2 weeks as drugs used for IE, but this might be insufficient to determine whether those antibiotic drugs were used for IE. Fourth, the database does not include any information after discharge, so long-term mortality could not be assessed. Finally, this was a retrospective observational study with non-random treatment assignment; therefore, the results may be biased by unmeasured confounders. However, several confounders (patient background, activities of daily living, comorbidities, in-hospital complications, in-hospital acute care) were adjusted using propensity score matching. Despite these limitations, and given the difficulty of implementing a randomised controlled trial of surgical treatment for IE in very elderly patients owing to ethical aspects, we believe this large-scale database study is useful in indicating the beneficial potential of surgical treatment for very elderly patients.

CONCLUSION

The analysis of a nationwide inpatient database showed that IE among very elderly patients is increasing and is associated with worse in-hospital mortality than in non-elderly patients. Although surgical treatment for IE was less frequently performed in very elderly patients, it was associated with lower in-hospital mortality in not only non-elderly and elderly patients but also in very elderly patients, suggesting the clinical importance of selecting optimal candidates for surgical treatment even in very elderly patients with IE.

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Patient consent for publication Not required.

Ethics approval The present study was approved by the clinical research review board of the University of Tokyo (3501-(3)) on 25 December 2017. The requirement for informed consent was waived because of the anonymous nature of the database. We conducted this study in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Our data are from the Diagnosis Procedure Combination database, a nationwide Japanese inpatient database.

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Supplemental Table 1. ICD-10 Codes Used to Define Etiology

Etiology	ICD-10 codes
Infective endocarditis	I38, I01.0, I01.1, I07.8, I33.0, I33.9, I39.8
Hypertension	I10, I11, I12, I13, I15
Diabetes mellitus	E10, E11, E12, E13, E14
Dyslipidemia	E78
Atrial fibrillation	I48
Malignancy	C, D00, D01, D02, D03, D04, D05, D06, D07, D08, D09
Chronic pulmonary disease	I27, J40, J41, J42, J43, J44, J45, J47, J60, J61, J62, J63, J64, J65, J66, J67, J70
Chronic liver disease	B18, K70, K71, K72, K73, K74, K76
Chronic renal disease	N18
Heart failure	I50.0, I50.1, I50.9
Stroke	
- Ischemic	I63
- Hemorrhagic	I60, I61, I62
Embolism	
- Coronary	I21, I22
- Spleen	D73.5
- Kidney	N28.0
- Lung	I26
- Abdominal artery	K55.0
- Extremities	I26
Shock	R57
DIC	D65
ICD-10, International Classification of Diseases, 10th Revision; DIC, Disseminated intravascular coagulation.	

Supplemental Table 2a. Unmatched and Propensity-matched Patient Characteristics (<65 years)

Variables	Unmatched Cohort			Propensity-matched Cohort		
	Surgical treatment	Surgical treatment	SMD	Surgical treatment	Surgical treatment	SMD
	(-) (n = 4,909)	(+) (n = 2,894)		(-) (n = 1,785)	(+) (n = 1,785)	
Age, years	51 [39-59]	51[41-59]	0.04	52 [40-59]	51 [41-59]	0.009
Male gender	3,384 (68.9%)	2,124 (73.4%)	0.099	1,284 (71.9%)	1,287 (72.1%)	0.004
BMI, kg/m ²						
<18.5 kg/m ²	845 (17.2%)	574 (19.8%)	0.068	336 (18.8%)	347 (19.4%)	0.016
18.5-24.9 kg/m ²	2,707 (55.1%)	1,686 (58.3%)	0.063	1,032 (57.8%)	1,032 (57.8%)	0.000
25.0-29.9 kg/m ²	769 (15.7%)	428 (14.8%)	-0.024	267 (15.0%)	259 (14.5%)	-0.013
≥30 kg/m ²	239 (4.9%)	92 (3.2%)	-0.086	61 (3.4%)	62 (3.5%)	0.003
Missing	349 (7.1%)	114 (3.9%)	-0.139	89 (5.0%)	85 (4.8%)	-0.010
Smoking	2,305 (47.0%)	1,536 (53.1%)	0.123	911 (51.0%)	908 (50.9%)	-0.003
Barthel Index						
Total dependence	668 (13.6%)	581 (20.1%)	0.173	281 (15.7%)	268 (15.0%)	-0.020
Severe dependence	143 (2.9%)	118 (4.1%)	0.063	64 (3.6%)	60 (3.4%)	-0.012
Moderate dependence	236 (4.8%)	140 (4.8%)	0.001	90 (5.0%)	87 (4.9%)	-0.008
Mild dependence	573 (11.7%)	317 (11.0%)	-0.023	196 (11.0%)	208 (11.7%)	0.021
Independence	2726 (55.5%)	1302 (45.0%)	-0.212	925 (51.8%)	935 (5.2%)	0.011
Missing	563 (11.5%)	436 (15.1%)	0.106	229 (12.8%)	227 (12.7%)	-0.003
JCS						
0 (alert)	4,254 (86.7%)	2,484 (85.8%)	-0.024	1,543 (86.4%)	1,540 (86.3%)	-0.005
1-3 (drowsy)	441 (9.0%)	269 (9.3%)	0.011	157 (8.8%)	156 (8.7%)	-0.002
10-30 (somnolence)	117 (2.4%)	79 (2.7%)	0.022	48 (2.7%)	50 (2.8%)	0.007

100-300 (coma)	97 (2.0%)	62 (2.1%)	0.012	37 (2.1%)	39 (2.2%)	0.008
Admission year						
2010	299 (6.1%)	178 (6.2%)	0.002	106 (5.9%)	109 (6.1%)	0.007
2011	562 (11.4%)	271 (9.4%)	-0.068	186 (10.4%)	174 (9.7%)	-0.022
2012	598 (12.2%)	378 (13.1%)	0.026	220 (12.3%)	222 (12.4%)	0.003
2013	613 (12.5%)	379 (13.1%)	0.018	253 (14.2%)	239 (13.4%)	-0.023
2014	696 (14.2%)	428 (14.8%)	0.017	268 (15.0%)	268 (15.0%)	0.000
2015	652 (13.3%)	386 (13.3%)	0.002	228 (12.8%)	233 (13.1%)	0.008
2016	695 (14.2%)	398 (13.8%)	-0.012	240 (13.4%)	244 (13.7%)	0.007
2017	700 (14.3%)	434 (15.0%)	0.021	260 (14.6%)	269 (15.1%)	0.014
2018	94 (1.9%)	42 (1.5%)	-0.036	24 (1.3%)	27 (1.5%)	0.014
Hospital Volume						
Low (<4)	176 (3.6%)	7 (0.2%)	-0.246	6 (0.3%)	7 (0.4%)	0.009
Middle (4≤ & <14)	916 (18.7%)	117 (4.0%)	-0.474	86 (4.8%)	104 (5.8%)	0.045
High (≥14)	3,817 (77.8%)	2,770 (95.7%)	0.549	1,693 (94.8%)	1,674 (93.8%)	-0.046
Clinical training hospital	4,157 (84.7%)	2,663 (92.0%)	0.230	1,632 (91.4%)	1,620 (90.8%)	-0.024
Emergent admission	3,603 (73.4%)	2,271 (78.5%)	0.119	1,341 (75.1%)	1,337 (74.9%)	-0.005
<i>Comorbid conditions</i>						
Hypertension	992 (20.2%)	705 (24.4%)	0.100	426 (23.9%)	420 (23.5%)	-0.008
Diabetes Mellitus	676 (13.8%)	392 (13.5%)	-0.007	227 (12.7%)	248 (13.9%)	0.035
Dyslipidemia	343 (7.0%)	194 (6.7%)	-0.011	143 (8.0%)	131 (7.3%)	-0.025
Atrial Fibrillation	248 (5.1%)	175 (6.0%)	0.043	106 (5.9%)	105 (5.9%)	-0.002
Malignancy	173(3.5%)	51 (1.8%)	-0.110	49 (2.7%)	42 (2.4%)	-0.025
Chronic Pulmonary Disease	135 (2.8%)	56 (1.9%)	-0.054	42 (2.4%)	43 (2.4%)	0.004
Chronic Liver Disease	266 (5.4%)	95 (3.3%)	-0.105	69 (3.9%)	65 (3.6%)	-0.012
Chronic Renal Disease	359(7.3%)	170 (5.9%)	-0.058	126 (7.1%)	122 (6.8%)	-0.009
<i>In-hospital Complications</i>						

Heart failure	1,212 (24.7%)	1,102 (38.1%)	0.292	577 (32.3%)	581 (32.5%)	0.005
- NYHA II	200 (4.1%)	185 (6.4%)	0.104	108 (6.1%)	109 (6.1%)	0.002
- NYHA III	114 (2.3%)	160 (5.5%)	0.166	73 (4.1%)	75 (4.2%)	0.006
- NYHA IV	81 (1.7%)	161 (5.6%)	0.211	56 (3.1%)	58 (3.2%)	0.006
Stroke	558 (11.4%)	513 (17.7%)	0.181	272 (15.2%)	265 (14.8%)	-0.011
Embolism	208 (4.2%)	183 (6.3%)	0.093	98 (5.5%)	93 (5.2%)	-0.012
Shock	45 (0.9%)	104 (3.6%)	0.181	35 (2.0%)	40 (2.2%)	0.020
DIC	151 (3.1%)	115 (4.0%)	0.049	55 (3.1%)	61 (3.4%)	0.019
<i>Antibiotics for more than 2 weeks</i>						
Penicillin system	1,781 (36.3%)	1,583 (54.7%)	0.376	934 (52.3%)	922 (51.7%)	-0.013
Cephem system	1,282 (26.1%)	1,207 (41.7%)	0.334	659 (36.9%)	654 (36.6%)	-0.006
Carbapenem	260 (5.3%)	340 (11.7%)	0.233	163 (9.1%)	152 (8.5%)	-0.022
Aminoglycoside	1,512 (30.8%)	1,449 (50.1%)	0.400	855 (47.9%)	849 (47.6%)	-0.007
Glycopeptide	541 (11.0%)	696 (24.0%)	0.348	335 (18.8%)	326 (18.3%)	-0.013
Daptomycin	130 (2.6%)	145 (5.0%)	0.123	73 (4.1%)	70 (3.9%)	-0.009
Linezolid	49 (1.0%)	93 (3.2%)	0.155	39 (2.2%)	40 (2.2%)	0.004
Antifungal antibiotics	46 (0.9%)	85 (2.9%)	0.145	33 (1.8%)	30 (1.7%)	-0.013
<i>Intensive Treatment within 2 days after admission</i>						
Admission to HCU	148 (3.0%)	118 (4.1%)	0.057	67 (3.8%)	64 (3.6%)	-0.009
Admission to ICU	317 (6.5%)	938 (32.4%)	0.694	251 (14.1%)	227 (12.7%)	-0.039
Inotropic therapy	336 (6.8%)	900(31.1%)	0.650	234 (13.1%)	207 (11.6%)	-0.046
Ventilation Support	203 (4.1%)	551 (19.0%)	0.479	139 (7.8%)	129 (7.2%)	-0.021
CRRT	49 (1.0%)	86 (3.0%)	0.142	35 (2.0%)	34 (1.9%)	-0.004
IRRT	247 (5.0%)	101 (3.5%)	-0.076	82 (4.6%)	74 (4.1%)	-0.022
PMX-DHP	17 (0.3%)	19 (0.7%)	0.044	9 (0.5%)	8 (0.4%)	-0.008

Data are expressed as the median [interquartile range] or number (percentage). SMD, standardized mean difference; BMI, Body mass index; JCS, Japan Coma Scale; NYHA, New York Heart Association; DIC, Disseminated intravascular coagulation; HCU, high care unit; ICU, intensive care unit; CRRT, continuous renal replacement therapy; IRRT, intermittent renal replacement therapy; PMX-DHP, Polymyxin B-immobilized fiber column-direct hemoperfusion.

Supplemental Table 2b. Unmatched and Propensity-matched Patient Characteristics (65 to 79 years)

Variables	Unmatched Cohort			Propensity-matched Cohort		
	Surgical treatment	Surgical treatment	SMD	Surgical treatment	Surgical treatment	SMD
	(-) (n = 5,628)	(+) (n = 2,246)		(-) (n = 1,625)	(+) (n = 1,625)	
Age, years	73 [69-76]	71 [68-75]	-0.209	72 [68-75]	72 [68-75]	-0.005
Male gender	3,440(61.1%)	1,459(65.0%)	0.080	1038 (63.9%)	1,043 (64.2%)	0.006
BMI, kg/m ²						
<18.5 kg/m ²	957 (17.0%)	397 (17.7%)	0.018	280 (17.2%)	274 (16.9%)	-0.010
18.5-24.9 kg/m ²	3,296 (58.6%)	1,382 (61.5%)	0.061	999 (61.5%)	985 (60.6%)	-0.018
25.0-29.9 kg/m ²	761 (13.5%)	298 (13.3%)	-0.007	226 (13.9%)	228 (14%)	0.004
≥30 kg/m ²	147 (2.6%)	66 (2.9%)	0.020	43 (2.6%)	52 (3.2%)	0.033
Missing	467 (8.3%)	103 (4.6%)	-0.152	77 (4.7%)	86 (5.3%)	0.025
Smoking	2,312(41.1%)	977 (43.5%)	0.049	696 (42.8%)	706 (43.4%)	0.012
Barthel Index						
Total dependence	1,335 (23.7%)	565 (25.2%)	0.033	362 (22.3%)	366 (22.5%)	0.006
Severe dependence	266 (4.7%)	107 (4.8%)	0.002	78 (4.8%)	75 (4.6%)	-0.009
Moderate dependence	430 (7.6%)	159 (7.1%)	-0.021	131(8.1%)	124 (7.6%)	-0.016
Mild dependence	656 (11.7%)	200 (8.9%)	-0.091	156 (9.6%)	156 (9.6%)	0.000
Independence	1996 (35.5%)	772 (34.4%)	-0.023	593 (36.5%)	608 (37.4%)	0.019
Missing	945 (16.8%)	443 (19.7%)	0.076	305 (18.8%)	296 (18.2%)	-0.014
JCS						
0 (alert)	4,473 (79.5%)	1,868 (83.2%)	0.095	1,378 (84.8%)	1,357 (83.5%)	-0.035
1-3 (drowsy)	783 (13.9%)	275 (12.2%)	-0.050	179 (11%)	189 (11.6%)	0.019
10-30 (somnolence)	228 (4.1%)	56 (2.5%)	-0.088	40 (2.5%)	45 (2.8%)	0.019
100-300 (coma)	144 (2.6%)	47 (2.1%)	-0.031	28 (1.7%)	34 (2.1%)	0.027

Admission year

2010	317 (5.6%)	115 (5.1%)	-0.023	90 (5.5%)	80 (4.9%)	-0.028
2011	585 (10.4%)	152 (6.8%)	-0.130	123 (7.6%)	123 (7.6%)	0.000
2012	646 (11.5%)	273 (12.2%)	0.021	193 (11.9%)	194 (11.9%)	0.002
2013	631 (11.2%)	278 (12.4%)	0.036	199 (12.2%)	199 (12.2%)	0.000
2014	738 (13.1%)	331 (14.7%)	0.047	226 (13.9%)	239 (14.7%)	0.023
2015	826 (14.7%)	327 (14.6%)	-0.003	216 (13.3%)	223 (13.7%)	0.013
2016	894 (15.9%)	363 (16.2%)	0.008	274 (16.9%)	262 (16.1%)	-0.020
2017	863 (15.3%)	373 (16.6%)	0.035	274 (16.9%)	277 (17%)	0.005
2018	128 (2.3%)	34 (1.5%)	-0.056	30 (1.8%)	28 (1.7%)	-0.009

Hospital Volume

Low (<4)	254 (4.5%)	2 (0.1%)	-0.298	2 (0.1%)	2 (0.1%)	0.000
Middle (4≤ & <14)	1,097 (19.5%)	116 (5.2%)	-0.447	93 (5.7%)	111 (6.8%)	0.046
High (≥14)	4,277 (76.0%)	2,128 (94.7%)	0.550	1,530 (94.2%)	1,512 (93%)	-0.045
Clinical training hospital	4,613 (82.0%)	2,028 (90.3%)	0.243	1,435 (88.3%)	1,441 (88.7%)	0.012
Emergent admission	4,382 (77.9%)	1,781 (79.3%)	0.035	1,251 (77%)	1,259 (77.5%)	0.012

Comorbid conditions

Hypertension	1,671 (29.7%)	670 (29.8%)	0.003	500 (30.8%)	500 (30.8%)	0.000
Diabetes Mellitus	1,250 (22.2%)	416 (18.5%)	-0.092	309 (19%)	323 (19.9%)	0.022
Dyslipidemia	571 (10.1%)	197 (8.8%)	-0.047	166 (10.2%)	164 (10.1%)	-0.004
Atrial Fibrillation	731 (13.0%)	300 (13.4%)	0.011	211 (13.0%)	219(13.5%)	0.015
Malignancy	503 (8.9%)	113 (5.0%)	-0.154	96 (5.9%)	95 (5.8%)	-0.003
Chronic Pulmonary Disease	211 (3.7%)	47 (2.1%)	-0.098	47 (2.9%)	40 (2.5%)	-0.027
Chronic Liver Disease	263 (4.7%)	64 (2.8%)	-0.096	50 (3.1%)	50 (3.1%)	0.000
Chronic Renal Disease	727 (12.9%)	227 (10.1%)	-0.088	173 (10.6%)	171 (10.5%)	-0.004

In-hospital Complications

Heart failure	1,722 (30.6%)	996 (44.3%)	0.287	666 (41%)	669 (41.2%)	0.004
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- NYHA II	283 (5.0%)	137 (6.1%)	0.047	100 (6.2%)	94 (5.8%)	-0.016
- NYHA III	179 (3.2%)	140 (6.2%)	0.145	86 (5.3%)	85 (5.2%)	-0.003
- NYHA IV	144 (2.6%)	125 (5.6%)	0.153	75 (4.6%)	67 (4.1%)	-0.024
Stroke	686 (12.2%)	325 (14.5%)	0.067	220 (13.5%)	219 (13.5%)	-0.002
Embolism	152 (2.7%)	65 (2.9%)	0.012	52 (3.2%)	46 (2.8%)	-0.022
Shock	57 (1.0%)	84 (3.7%)	0.180	33 (2%)	37 (2.3%)	0.017
DIC	176 (3.1%)	101 (4.5%)	0.072	56 (3.4%)	59 (3.6%)	0.010
<i>Antibiotics for more than 2 weeks</i>						
Penicillin system	1,953 (34.7%)	1,224 (54.5%)	0.406	874 (53.8%)	853 (52.5%)	-0.026
Cephem system	1,383 (24.6%)	819 (36.5%)	0.260	564 (34.7%)	545 (33.5%)	-0.025
Carbapenem	349 (6.2%)	338 (15.0%)	0.290	167 (10.3%)	179 (11%)	0.024
Aminoglycoside	1,496 (26.6%)	972 (43.3%)	0.356	696 (42.8%)	666 (41%)	-0.037
Glycopeptide	776 (13.8%)	676 (30.1%)	0.402	405 (24.9%)	393 (24.2%)	-0.017
Daptomycin	152 (2.7%)	146 (6.5%)	0.182	88 (5.4%)	81 (5.0%)	-0.019
Linezolid	39 (0.7%)	80 (3.6%)	0.200	28 (1.7%)	27 (1.7%)	-0.005
Antifungal antibiotics	93 (1.7%)	144 (6.4%)	0.244	55 (3.4%)	59 (3.6%)	0.013
<i>Intensive Treatment within 2 days after admission</i>						
Admission to HCU	209 (3.7%)	96 (4.3%)	0.029	68 (4.2%)	67 (4.1%)	-0.003
Admission to ICU	410 (7.3%)	645 (28.7%)	0.581	248 (15.3%)	248 (15.3%)	0.000
Inotropic therapy	499 (8.9%)	706 (31.4%)	0.586	293 (18%)	289 (17.8%)	-0.006
Ventilation Support	267 (4.7%)	407 (18.1%)	0.430	141 (8.7%)	151 (9.3%)	0.022
CRRT	91 (1.6%)	84 (3.7%)	0.132	37 (2.3%)	42 (2.6%)	0.020
IRRT	386 (6.9%)	112 (5.0%)	-0.079	96 (5.9%)	91 (5.6%)	-0.013
PMX-DHP	16 (0.3%)	13 (0.6%)	0.045	5 (0.3%)	4 (0.2%)	-0.012

Data are expressed as the median [interquartile range] or number (percentage). SMD, standardized mean difference; BMI, Body mass index; JCS, Japan Coma Scale; NYHA, New York Heart Association; DIC, Disseminated intravascular coagulation; HCU, high care unit; ICU,

intensive care unit; CRRT, continuous renal replacement therapy; IRRT, intermittent renal replacement therapy; PMX-DHP, Polymyxin B-immobilized fiber column-direct hemoperfusion.

Supplemental Table 2c. Unmatched and Propensity-matched Patient Characteristics (≥80 years)

Variables	Unmatched Cohort			Propensity-matched Cohort		
	Surgical treatment	Surgical treatment	SMD	Surgical treatment	Surgical treatment	SMD
	(-) (n = 4,525)	(+) (n = 465)		(-) (n = 414)	(+) (n = 414)	
Age, years	85 [82-88]	82 [81-84]	-0.825	82 [81-84]	82 [81-84]	0.046
Male Gender	2,568 (56.8%)	226 (48.6%)	-0.164	211 (51.0%)	209 (50.5%)	-0.010
BMI, kg/m ²						
<18.5 kg/m ²	1,081 (23.9%)	90 (19.4%)	-0.110	78 (18.8%)	83 (20.0%)	0.031
18.5-24.9 kg/m ²	2,354 (52.0%)	303 (65.2%)	0.269	275 (66.4%)	265 (64.0%)	-0.051
25.0-29.9 kg/m ²	414 (9.1%)	49 (10.5%)	0.047	39 (9.4%)	45 (10.9%)	0.048
≥30 kg/m ²	67 (1.5%)	9 (1.9%)	0.035	6 (1.4%)	7 (1.7%)	0.019
Missing	609 (13.5%)	14 (3.0%)	-0.387	16 (3.9%)	14 (3.4%)	-0.026
Smoking	1,316 (29.1%)	179 (38.5%)	0.200	158 (38.2%)	155 (37.4%)	-0.015
Barthel Index						
Total dependence	1,832(40.5%)	135(29.0%)	-0.242	111 (26.8%)	118 (28.5%)	0.038
Severe dependence	285(6.3%)	25(5.4%)	-0.039	16 (3.9%)	23 (5.6%)	0.080
Moderate dependence	432(9.5%)	41(8.8%)	-0.025	30 (7.2%)	37 (8.9%)	0.062
Mild dependence	470 (10.4%)	52 (11.2%)	0.026	52 (12.6%)	47 (11.4%)	-0.037
Independence	722 (16.0%)	126 (27.1%)	0.274	121 (29.2%)	111 (26.8%)	-0.054
Missing	784 (17.3%)	86 (18.5%)	0.030	84 (20.3%)	78 (18.8%)	-0.037
JCS						
0 (alert)	2,990 (66.1%)	368 (79.1%)	0.296	337 (81.4%)	325 (78.5%)	-0.072
1-3 (drowsy)	1,086 (24.0%)	70 (15.1%)	-0.227	59 (14.3%)	67 (16.2%)	0.054
10-30 (somnolence)	301 (6.7%)	17 (3.7%)	-0.136	11 (2.7%)	14 (3.4%)	0.042
100-300 (coma)	148 (3.3%)	10 (2.2%)	-0.069	7 (1.7%)	8 (1.9%)	0.018

Admission year

2010	191 (4.2%)	23 (4.9%)	0.035	19 (4.6%)	20 (4.8%)	0.011
2011	467 (10.3%)	23 (4.9%)	-0.203	20 (4.8%)	22 (5.3%)	0.022
2012	470 (10.4%)	47 (10.1%)	-0.009	44 (10.6%)	45 (10.9%)	0.008
2013	445 (9.8%)	55 (11.8%)	0.064	51 (12.3%)	52 (12.6%)	0.007
2014	621 (13.7%)	65 (14.0%)	0.007	49 (11.8%)	56 (13.5%)	0.051
2015	604 (13.3%)	81 (17.4%)	0.113	73 (17.6%)	70 (16.9%)	-0.019
2016	794 (17.5%)	80 (17.2%)	-0.009	68 (16.4%)	67 (16.2%)	-0.007
2017	817 (18.1%)	81 (17.4%)	-0.017	82 (19.8%)	74 (17.9%)	-0.049
2018	116 (2.6%)	10 (2.2%)	-0.027	8 (1.9%)	8 (1.9%)	0.000

Hospital Volume

Low (<4)	282 (6.2%)	0 (0.0%)	-0.365	0 (0.0%)	0 (0.0%)	0.000
Middle (4≤ & <14)	1,116 (24.7%)	23 (4.9%)	-0.578	19 (4.6%)	22 (5.3%)	0.033
High (≥14)	3,127 (69.1%)	442 (95.1%)	0.719	395 (95.4%)	392 (94.7%)	-0.033
Clinical training hospital	3,644 (80.5%)	399 (85.8%)	0.141	354 (85.5%)	358 (86.5%)	0.028
Emergent admission	3,894 (86.1%)	372 (80.0%)	-0.162	321 (77.5%)	330 (79.7%)	0.053

Comorbid conditions

Hypertension	1,439 (31.8%)	149 (32.0%)	0.005	129 (31.2%)	133 (32.1%)	0.021
Diabetes Mellitus	711 (15.7%)	80 (17.2%)	0.040	55 (13.3%)	64 (15.5%)	0.062
Dyslipidemia	386 (8.5%)	51 (11.0%)	0.082	42 (10.1%)	42 (10.1%)	0.000
Atrial Fibrillation	637 (14.1%)	61 (13.1%)	-0.028	52 (12.6%)	52 (12.6%)	0.000
Malignancy	365 (8.1%)	32 (6.9%)	-0.045	35 (8.5%)	29 (7%)	-0.054
Chronic Pulmonary Disease	197 (4.4%)	13 (2.8%)	-0.084	16 (3.9%)	13 (3.1%)	-0.039
Chronic Liver Disease	130 (2.9%)	22 (4.7%)	0.097	18 (4.3%)	19 (4.6%)	0.012
Chronic Renal Disease	428 (9.5%)	43 (9.2%)	-0.007	51 (12.3%)	40 (9.7%)	-0.085

In-hospital Complications

Heart failure	1,779 (39.3%)	205 (44.1%)	0.097	187 (45.2%)	184 (44.4%)	-0.015
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- NYHA II	182 (4.0%)	24 (5.2%)	0.054	20 (4.8%)	23 (5.6%)	0.033
- NYHA III	153 (3.4%)	23 (4.9%)	0.078	21 (5.1%)	21 (5.1%)	0.000
- NYHA IV	166 (3.7%)	36 (7.7%)	0.176	29 (7%)	31 (7.5%)	0.019
Stroke	481 (10.6%)	61 (13.1%)	0.077	44 (10.6%)	52 (12.6%)	0.060
Embolism	89 (2.0%)	7 (1.5%)	-0.035	6 (1.4%)	7 (1.7%)	0.019
Shock	53 (1.2%)	20 (4.3%)	0.193	14 (3.4%)	18 (4.3%)	0.050
DIC	154 (3.4%)	22 (4.7%)	0.067	20 (4.8%)	20 (4.8%)	0.000
<i>Antibiotics for more than 2 weeks</i>						
Penicillin system	1,517 (33.5%)	213 (45.8%)	0.253	186 (44.9%)	187 (45.2%)	0.005
Cephem system	1,178 (26.0%)	178 (38.3%)	0.264	164 (39.6%)	155 (37.4%)	-0.045
Carbapenem	378 (8.4%)	80 (17.2%)	0.267	59 (14.3%)	66 (15.9%)	0.047
Aminoglycoside	979 (21.6%)	174 (37.4%)	0.351	142 (34.3%)	147 (35.5%)	0.025
Glycopeptide	622 (13.7%)	161 (34.6%)	0.502	129 (31.2%)	134 (32.4%)	0.026
Daptomycin	101 (2.2%)	29 (6.2%)	0.200	26 (6.3%)	25 (6.0%)	-0.010
Linezolid	31 (0.7%)	14 (3.0%)	0.173	7 (1.7%)	8 (1.9%)	0.018
Antifungal antibiotics	70 (1.5%)	32 (6.9%)	0.268	23 (5.6%)	21 (5.1%)	-0.022
<i>Intensive Treatment within 2 days after admission</i>						
Admission to HCU	162 (3.6%)	16 (3.4%)	-0.008	18 (4.3%)	15 (3.6%)	-0.037
Admission to ICU	219 (4.8%)	128 (27.5%)	0.647	81 (19.6%)	83 (20%)	0.012
Inotropic therapy	369 (8.2%)	131 (28.2%)	0.537	87 (21%)	90 (21.7%)	0.018
Ventilation Support	153 (3.4%)	84 (18.1%)	0.488	48 (11.6%)	48 (11.6%)	0.000
CRRT	30 (0.7%)	19 (4.1%)	0.226	17 (4.1%)	15 (3.6%)	-0.025
IRRT	128 (2.8%)	17 (3.7%)	0.047	19 (4.6%)	15 (3.6%)	-0.049
PMX-DHP	6 (0.1%)	1 (0.2%)	0.020	2 (0.5%)	1 (0.2%)	-0.040

Data are expressed as the median [interquartile range] or number (percentage). SMD, standardized mean difference; BMI, Body mass index; JCS, Japan Coma Scale; NYHA, New York Heart Association; DIC, Disseminated intravascular coagulation; HCU, high care unit; ICU,

intensive care unit; CRRT, continuous renal replacement therapy; IRRT, intermittent renal replacement therapy; PMX-DHP, Polymyxin B-immobilized fiber column-direct hemoperfusion.

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Supplemental table 3. Risk Factors of In-hospital Mortality among IE patients aged 80 years or older				
Variable	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
Age, year	1.06 (1.05-1.08)	<0.001 [†]	1.04 (1.02 – 1.06)	< 0.001 [†]
Male Gender	1.02 (0.89-1.16)	0.80	1.17 (0.98 – 1.40)	0.08
BMI, kg/m ²	0.97 (0.95-0.99)	0.002 [†]	0.99 (0.97-1.01)	0.30
Smoking	1.09 (0.95-1.26)	0.24	1.09 (0.91-1.31)	0.37
Barthel Index				
Total dependence	Reference		Reference	
Severe dependence	0.50(0.37-0.67)	<0.001 [†]	0.66 (0.48-0.92)	0.02 [†]
Moderate dependence	0.24 (0.17-0.32)	<0.001 [†]	0.33 (0.24-0.47)	<0.001 [†]
Mild dependence	0.23 (0.18-0.31)	<0.001 [†]	0.34 (0.24-0.47)	<0.001 [†]
Independence	0.24 (0.19-0.30)	<0.001 [†]	0.37 (0.28-0.49)	<0.001 [†]
JCS				
0 (alert)	Reference		Reference	
1-3 (drowsy)	1.92 (1.64-2.24)	<0.001 [†]	1.36 (1.13-1.64)	0.001 [†]
10-30 (somnolence)	3.36 (2.65-4.28)	<0.001 [†]	2.02 (1.51-2.69)	<0.001 [†]
100-300 (coma)	5.96 (4.30-8.26)	<0.001 [†]	3.33 (2.24-4.95)	< 0.001 [†]
Hospital Volume				
Low (<4)	Reference		Reference	
Middle (4≤ & <14)	1.17 (0.86-1.61)	0.32	1.26 (0.86 – 1.83)	0.23
High (≥14)	1.11 (0.82-1.49)	0.50	1.22 (0.86 – 1.75)	0.26
Hypertension	2.07 (1.77-2.42)	<0.001 [†]	1.47 (1.23 - 1.77)	<0.001 [†]
Diabetes Mellitus	0.89 (0.74-1.07)	0.22	1.04 (0.84-1.29)	0.73
Dyslipidemia	2.68 (1.96-3.67)	<0.001 [†]	1.65 (1.17 - 2.33)	0.005 [†]

Atrial Fibrillation	1.09 (0.90-1.31)	0.39	1.23 (0.99-1.54)	0.07
Malignancy	0.83 (0.64-1.07)	0.15	0.96 (0.72-1.29)	0.79
Chronic Pulmonary Disease	1.56 (1.07-2.26)	0.02 [†]	1.23 (0.82-1.84)	0.32
Chronic Liver Disease	1.13 (0.78-1.65)	0.51	1.18 (0.75-1.84)	0.48
Chronic Renal Disease	1.90 (1.55-2.33)	<0.001 [†]	2.10 (1.66-2.66)	<0.001 [†]
Heart failure				
- NYHA II	Reference		Reference	
- NYHA III	1.00 (0.59-1.72)	0.99	0.80 (0.44-1.46)	0.47
- NYHA IV	3.48 (2.20-5.50)	<0.001 [†]	2.61 (1.55-4.39)	<0.001 [†]
Stroke	1.68 (1.38-2.04)	<0.001 [†]	1.38 (1.09-1.74)	0.007 [†]
Embolism	1.26 (0.80-1.99)	0.31	1.14 (0.66-1.96)	0.64
Shock	2.13 (1.33-3.44)	0.002 [†]	1.33 (0.75-2.37)	0.33
DIC	4.79 (3.52-6.50)	<0.001 [†]	3.81 (2.68-5.42)	<0.001 [†]
Surgical treatment	0.61 (0.47-0.78)	<0.001 [†]	0.69 (0.52-0.94)	0.02 [†]

CI, confidence interval. † p Values are significant.

IE, infective endocarditis; BMI, body mass index; JCS, Japan Coma Scale; NYHA, New York Heart Association; DIC, Disseminated intravascular coagulation.