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Propensity score-matched analysis of patients with severe aortic stenosis undergoing surgical aortic valve replacement

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ABSTRACT

Objective Severe aortic stenosis (AS) is one of the most serious valve conditions. Patient demography and the aetiology of AS have substantially changed in the past several decades along with a drastic improvement of surgical aortic valve replacement (SAVR) and its associated procedures. Contemporary patients with severe AS have multiple comorbidities and live much longer. We aimed to elucidate the treatment effects of SAVR on long-term outcome in propensity score (PS)-matched and the entire patient populations.

Methods We retrospectively reviewed 570 patients with severe AS defined as an aortic valve area of 1.0 cm^2 or less. Systemic differences in 39 baseline characteristics between non-SAVR and SAVR groups were adjusted using PS matching method. The endpoints included all-cause mortality and cardiovascular events that included heart failure, non-fatal stroke, syncope and acute coronary syndrome.

Results Overall, 55% of the entire population (mean age 78 years; males 41%) were symptomatic. During 3.9 years of the median follow-up, 210 (36%) patients underwent SAVR and 231 (41%) died. Cumulative incidences of mortality and both mortality and cardiovascular events were significantly higher in the non-SAVR group than in the other group (p<0.001, each). Among 101 PS-matched pairs, SAVR correlated with a lower mortality risk (HR 0.35; 95% CI 0.21 to 0.59; p<0.001)) and mortality and cardiovascular events combined (HR 0.62; 95% CI 0.42 to 0.92; p=0.02). However, survival difference between both groups was markedly smaller among asymptomatic patients in the subgroup of matched patients.

Conclusion Patients with AS undergoing SAVR exhibit a lower incidence of all-cause mortality and major cardiovascular events than those not undergoing surgical interventions, even after the baseline characteristics are balanced by the PS matching. The correlation between SAVR and survival from cardiovascular events is less evident among asymptomatic patients.

Key questions

What is already known about this subject?
► Among patients with severe symptomatic aortic stenosis (AS), surgical aortic valve replacement (SAVR) has been demonstrated to improve survival compared with that in unoperated patients. However, a substantial imbalance in terms of baseline characteristics, for example, comorbidities, cardiovascular risks, valve severity, performance status (frailty) and socioeconomic background, can exist between operated and unoperated patients.

What does this study add?
► In this contemporary study, patients undergoing SAVR exhibited a lower incidence of death and major cardiovascular events than medically treated patients, even after baseline characteristics were balanced via propensity score matching. However, further studies are warranted to appropriately debate the appropriate indications, methods and timing of surgical intervention for asymptomatic patients or for those with renal dysfunction.

How might this impact on clinical practice?
► These findings can have substantial implications for informed decision-making during the management of patients with severe AS among heat team members and those seeking advice on prognosis of the critical disease. Our data are also more valuable in terms of the efficacy of surgical interventions on long-term clinical outcomes over medical management in the new era of transcatheter aortic valve replacement.

INTRODUCTION

The prevalence of aortic stenosis (AS) increases with ageing, and AS is one of the leading valve abnormalities. Recently, degenerative AS, the most prevalent aetiology, has rapidly increased, with a prevalence of 2%–7% in the population aged ≥65 years.[1 2] In the past several decades, patients' profiles have shifted remarkably, with the aetiology now dominated by senile calcific AS.[3] Moreover, patients are more likely to comprise marked comorbidities, such as multiple organ dysfunctions and concomitant cardiovascular diseases, all independently affecting

mortality, as we investigated previously.[4] Surgical aortic valve replacement (SAVR) is the most well-established therapy for severe AS. Besides demographic changes in patients with severe AS, remarkable advances in surgical techniques and innovative equipment have facilitated patients with operative risks to undergo surgical procedures safely.

The last two decades have witnessed the launching of minimally invasive transcatheter aortic valve replacement (TAVR) which was similar to SAVR with respect to mortality in patients with severe AS at intermediate operative risks.[5] This less invasive therapy might not be a complete alternative to SAVR, as simultaneous interventions on the mitral valve, coronary artery bypass grafting (CABG), are challenging in conjunction with TAVR, and data on long-term device durability remain scarce. In the modern era when aggressive interventions are recommended to patients with severe AS, ascertaining the efficacy and safety of surgical interventions for the contemporary population of patients with severe AS remains critical, as operative risks due to age and multiple comorbidities and long-term complications, such as structural valve deterioration, prosthetic valve endocarditis and anticoagulant-induced bleeding events, in surgically treated patients remain significant. Yet there exists, for ethical reasons, a limited number of randomised controlled trials. Thus, a well-organised, observational cohort study comparing SAVR and medical management should be designed with marked differences between surgically treated and medically treated groups being appropriately adjusted for their baseline risks.

Hence, this study aims to investigate the clinical impact of SAVR compared with nonsurgical treatment on mortality and incidences of adverse cardiovascular events in patients with severe AS with adjustments by propensity score (PS) matching. Furthermore, the study assesses the benefits of SAVR in various subgroups of our interest within the matched population.

METHODS
Study design and patient enrolment
This retrospective, observational cohort study was conducted at Kokura Memorial Hospital (Kitakyushu, Japan). We reviewed the echocardiographic database for patients with severe AS who visited the hospital from August 2009 to February 2012. We defined severe AS, based on international guidelines, as an aortic valve area (AVA) of ≤ 1.0 cm^2 by transthoracic echocardiography.[6] Initially, we identified 595 patients from the database. Of these, 18 patients who underwent TAVR during the follow-up period and 7 patients with lost follow-up data were excluded; the remaining 570 subjects were included in the final analysis (figure 1). The study was reviewed and approved by the Institutional Review Board of Kokura Memorial Hospital, Japan (Approval number: 201402210108).
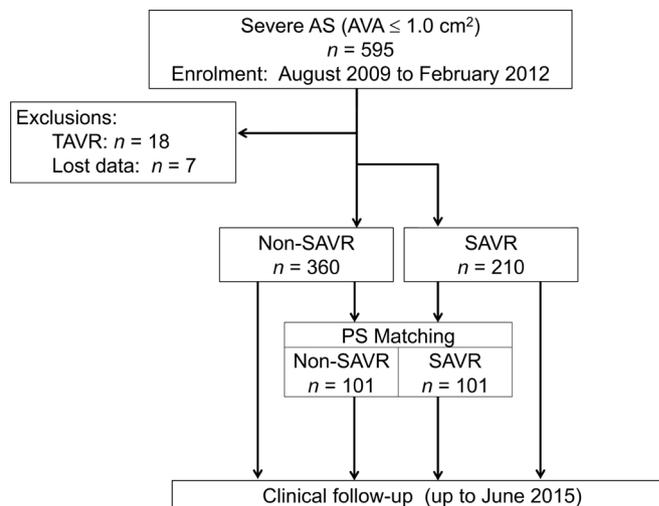

Figure 1 A flowchart of primary findings in the study population as severe aortic stenosis. AVA, aortic valve area; PS, propensity score; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Baseline characteristics and echocardiographic assessment
We collected comprehensive data, including patients' characteristics, medications and operational information from chart reviews based on the definitions provided. Activity level was defined as active if a patient lived an independent life and as limited if a patient required assisted care. Asymptomatic status was defined as no limitations of ordinary physical activity based on the New York Heart Association functional classification (NYHA class).

All patients underwent two-dimensional echocardiographic examinations, at least, once, during the study period, by professional sonographers using commercially available cardiac ultrasound machines (Vivid 7 Dimension and Vivid E9, GE Healthcare, Horten, Norway; iE33, Philips Medical Systems, Best, The Netherlands). Moreover, all patients who underwent SAVR received a preoperative echocardiographic examination within 1 month of their respective operation date. We considered these records as the baseline characteristics of those undergoing SAVR. Doppler echocardiographic measurements comprised the aortic mean pressure gradient using the simplified Bernoulli equation and an AVA using a standard continuity equation;[7] the severity of aortic regurgitation, mitral regurgitation and tricuspid regurgitation was assessed per international guidelines.[8]

Clinical follow-up and endpoints
The primary endpoint was all-cause mortality. Cardiovascular events, including hospital admission from worsened heart failure (HF), acute coronary syndrome, syncope and non-fatal stroke, were defined as other end points. We gathered information on clinical outcome from patients, families or physicians, either in person or by telephonic interviews. We followed all patients retrospectively until June 2015 to assess their survival status. Perhaps, a time delay before a patient receives surgical treatment can account for marked survival advantages in

the SAVR group. Hence, we defined the operation date as day 1 for the follow-up of the SAVR group, whereas the follow-up started on the day of index echocardiography (enrolment) for the non-SAVR group.

Statistical analysis

Although we compared the distributions of continuous variables using Student's t-test or Wilcoxon rank-sum test, χ^2 test was used for categorical variables. Continuous data are presented as mean±SD for normally distributed variables or median values with 25th and 75th percentiles for non-normally distributed variables, and categorical data are presented as absolute numbers and percentages. For survival analyses in both the entire population and the matched group, the Kaplan-Meier method was used to estimate the cumulative incidence of all-cause mortality and cardiovascular events in three ways: mortality, mortality and HF requiring admission and mortality and cardiovascular events. Using the log-rank test, we compared the survival and cumulative event-free survival between both groups.

We evaluated patients' PS, defined as the conditional probability that a patient is assigned to the SAVR group given the patient's demographics, and measured the disease status and comorbidities.[9] We selected 39 baseline covariates: age, sex, body mass index, body surface area, underweight, NYHA class III or IV, estimated glomerular filtration rate (eGFR), hypertension, diabetes mellitus, hyperlipidaemia, coronary artery disease, peripheral vascular disease, previous myocardial infarction, peripheral vascular disease, previous HF admission, prior heart surgery, chronic lung disease, malignancy, chronic liver disease, atrial fibrillation, haemodialysis treatment, peptic ulcer disease, limited activity, current smoker, aortic aneurysm or dissection, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker, antiplatelet therapy, anticoagulant, β-blocker, corticosteroid, AVA, mean aortic pressure gradient, peak aortic velocity ≥4.0 m/s, left ventricular ejection fraction, aortic regurgitation, mitral regurgitation, tricuspid regurgitation and EuroSCORE II. Then, we matched non-SAVR and SAVR patients using PS and a greedy matching technique with a calliper of 0.2 SD of the logit (PS).[10] Furthermore, we assessed the balance of the baseline characteristics' distribution between the two groups by evaluating the standardised mean difference (SMD) as SMD ≤0.1 suggests a balanced distribution of factors between the two groups.[11] By performing subgroup analyses, we assessed the correlation between treatment and mortality and cardiovascular events in the groups of patients with prespecified risk factors at baseline of interests—advanced age (≥80 years), asymptomatic status, renal insufficiency (eGFR ≤30 mL/min/1.73 cm^2)) and a history of HF.

All statistical analyses were performed using STATA V.14 (STATA, College Station, Texas, USA) and R Statistical Software (V.3.3.2; R Foundation for Statistical Computing, Vienna, Austria). Furthermore, we considered p<0.05 (two-sided) as statistically significant.

RESULTS

Clinical characteristics

During the observation period up to June 2015, 210 patients finally underwent SAVR and 360 were medically managed. The median interval between the enrolment and SAVR date was 121 days (IQR: 35–624 days). Table 1 summarises the patients' baseline characteristics. At enrolment, the average age was 79 years, 236 were males (41%), 314 (55%) were symptomatic and 97 (17%) presented severe daily symptoms (NYHA class III or IV). Regarding the AS severity assessments, SAVR patients exhibited a more severe valve status at the preoperative period concerning the AVA (non-SAVR vs SAVR, 0.76 vs 0.67 cm^2, p<0.001). For surgical intervention, bioprosthetic valves were more frequently used (n=161, 77%) than mechanical valves (n=44, 21%) and, notably, 49% of SAVR procedures were concomitant, including CABG (20%), mitral valve replacement or repair (24%), tricuspid valve replacement or repair (8%) and ascending aorta replacement (6%).

Clinical outcomes

During the follow-up (median 3.9 years; IQR, 1.8–5.2 years), 231 (41%) patients died. The median follow-up period was 3.5 years (IQR, 1.2–5.2 years) for the non-SAVR group and 4.1 years (IQR, 2.7–5.1 years) for the SAVR group. Based on the Kaplan–Meier survival analysis (figure 2), SAVR patients exhibited 1-year, 3-year and 5-year estimated survival rates (from each operation date) of 91%, 87% and 84%, respectively, compared with 81%, 57% and 43% in the non-SAVR group. Overall, survival and event-free survival rates were significantly higher in the SAVR group compared with the non-SAVR group during the follow-up period (p<0.001). Table 2 presents detailed clinical outcome data between the two groups. The rate of patients with HF admission was higher in the non-SAVR group within a 3-year period, whereas rates were similar during the complete follow-up period (non-SAVR, 38% and SAVR, 36%). We observed a gradual increment in the percentage of non-SAVR patients who developed syncope during the follow-up compared with <1% of SAVR patients having syncope following SAVR.

Clinical outcome and subgroup analysis in PS-matched patients

The distribution of created PS is presented in figure 3A, and PS matching yielded 101 matched pairs of patients from both groups with a c-statistic of 0.90. Furthermore, SMD was demonstrated in the unmatched and matched patients, highlighting that PS matching successfully decreased the SMD for 34 variables to an absolute value of ≤0.1 (figure 3B). In the non-SAVR group, 101 patients exhibited a markedly lower survival and cumulative event-free survival than 101 patients in the SAVR group (figure 4). In addition, these risks were significantly

Table 1 Baseline characteristics of the study patients according to the treatment

	Entire cohort	Non-SAVR	SAVR	
Variables	**N=570**	**N=360**	**N=210**	**P value***
Clinical demographics				
Age, years	78.6 (9.0)	80.9 (8.3)	74.6 (8.8)	<0.001
Age >80 years	297 (52)	224 (62)	63 (30)	<0.001
Male sex	236 (41)	142 (39)	94 (45)	0.22
BMI, kg/m^2	22.1 (3.4)	21.6 (3.4)	22.8 (3.2)	<0.001
Underweight (BMI <18.5 kg/m^2)	83 (15)	72 (20)	11 (5)	<0.001
BSA, m^2	1.47 (0.17)	1.44 (0.16)	1.51 (0.18)	<0.001
Symptom at enrolment				
NYHA class I	256 (45)	167 (46)	61 (29)	<0.001
NYHA class II	217 (38)	121 (34)	123 (59)	
NYHA class III	85 (15)	63 (18)	23 (11)	
NYHA class IV	12 (2)	9 (3)	3 (1)	
Hypertension	175 (31)	251 (70)	144 (69)	0.78
Diabetes	155 (27)	95 (26)	60 (29)	0.63
Dyslipidaemia	229 (40)	133 (37)	96 (46)	0.04
Hyperuricaemia	63 (11)	40 (11)	23 (11)	1.00
Prior heart failure	205 (36)	117 (33)	88 (42)	0.03
Coronary artery disease	230 (40)	155 (43)	75 (36)	0.09
Old myocardial infarction	78 (14)	60 (17)	18 (9)	0.01
Previous heart surgery	100 (18)	73 (20)	27 (13)	0.03
eGFR (mL/min/1.73 cm^2)	32 (20)	27 (19)	40 (20)	<0.001
Renal insufficiency	270 (47)	211 (59)	59 (28)	<0.001
Haemodialysis	69 (12)	49 (14)	20 (10)	0.18
Chronic lung disease	61 (11)	39 (11)	22 (11)	1.00
Previous stroke	77 (14)	54 (15)	24 (11)	0.26
Atrial fibrillation	105 (18)	68 (19)	37 (18)	0.74
Peripheral vascular disease	83 (15)	66 (18)	17 (8)	0.001
Aortic aneurysm or dissection	40 (7)	27 (8)	13 (6)	0.61
Malignancy	78 (14)	61 (17)	17 (8)	0.003
Chronic liver disease	25 (4)	16 (4)	9 (4)	1.00
Peptic ulcer disease	43 (8)	30 (8)	13 (6)	0.41
Limited activity	110 (19)	103 (29)	7 (3)	<0.001
Current smoker	36 (6)	22 (6)	14 (7)	0.86
EuroSCORE II (%)†	3.3 (2.0–5.4)	3.8 (2.6–6.2)	2.3 (1.5–3.9)	<0.001
STS score (PROM) (%)†	4.2 (2.8–6.6)	4.9 (3.4–7.5)	3.1 (1.9–4.1)	<0.001
Medication use				
Antiplatelet	290 (51)	192 (53)	98 (47)	0.14
β-blocker	144 (25)	88 (24)	56 (27)	0.55
ACE inhibitor or ARB	324 (57)	145 (40)	101 (48)	0.08
Statins	202 (35)	118 (33)	84 (40)	0.09
Calcium channel blockers	246 (43)	165 (46)	81 (39)	0.10
Anticoagulant	132 (23)	82 (23)	50 (24)	0.84
Corticosteroids	14 (3)	11 (3)	3 (1)	0.27
Echocardiographic assessment				

Table 1 Continued

Variables	Entire cohort N=570	Non-SAVR N=360	SAVR N=210	P value*
Left ventricular ejection fraction (%)	61 (12)	60 (13)	62 (11)	0.04
Aortic valve area (cm^2)	0.73 (0.18)	0.76 (0.18)	0.67 (0.15)	<0.001
Peak aortic velocity (m/s)	3.7 (0.9)	3.4 (0.9)	4.3 (0.8)	<0.001
Peak aortic velocity >4.0 m/s	233 (41)	90 (25)	143 (68)	<0.001
Mean aortic gradient (mm Hg)	34 (19)	29 (18)	45 (19)	<0.001
Aortic regurgitation (grade III–IV)	35 (6)	17 (5)	18 (9)	0.14
Mitral regurgitation (grade III–IV)	44 (8)	23 (6)	21 (10)	0.87
Tricuspid regurgitation (grade III–IV)	44 (8)	28 (9)	16 (9)	1.00
Surgical procedure				
Valve profile				
Bioprosthetic valve, *n* (%)			161 (77)	
Mechanical valve, *n* (%)			44 (21)	
Unknown			5 (2)	
Associated procedures, *n* (%)			102 (49)	
Coronary artery bypass grafting			43 (20)	
Mitral valve replacement or repair			50 (24)	
Tricuspid valve replacement or repair			17 (8)	
Ascending aorta replacement			13 (6)	

*P value refers to comparisons between the non-SAVR group at enrolment and the SAVR group at operation.
†Median and IQR. Data are mean (SD) or n (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BSA, body surface area; NYHA class, New York Heart Association functional classification; PROM, predicted risk of mortality; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgery; eGFR, estimated glomerular filtration rate.

higher in the non-SAVR group compared with the SAVR group (HR 0.35, 95% CI 0.21 to 0.59, p<0.001, for all-cause mortality; HR 0.53, 95% CI 0.34 to 0.82, p=0.004, for HF hospitalisation and mortality; HR 0.62, 95% CI 0.42 to 0.92, p=0.02, for cardiovascular events and mortality).

We performed a subgroup analysis for the PS-matched population (table 3). Patients aged ≥80 years (non-SAVR vs SAVR: HR 0.35; 95% CI 0.21 to 0.34; p<0.001), with cardiac symptoms (NYHA class II–IV; HR 0.19; 95% CI 0.10 to 0.37; p<0.001) or a history of admission due to HF (HR 0.38; 95% CI 0.19 to 0.78; p=0.009) exhibited a significant correlation with the survival benefit during

the follow-up period, although it was not significant in the population without cardiac symptoms (HR 0.83; 95% CI 0.38 to 1.84; p=0.66) or with renal insufficiency (HR 0.60; 95% CI 0.33 to 1.07; p=0.09).

DISCUSSION

This study established that SAVR markedly correlated with the survival improvement and prevention of major cardiovascular events compared with medical treatments during the follow-up period in both the entire severe AS and PS-matched populations. In a few recent studies, researchers attempted to more precisely investigate the treatment effect of SAVR on long-term outcome within a well-balanced sample. Pai *et al* reported that SAVR correlated with a survival benefit in three of the four strata produced by the PS stratification method.[12] Their findings are consistent with those of the present study, although approximately 55% of our population was symptomatic and there was a delay between the diagnosis and SAVR along with a possible baseline characteristic imbalance between the two groups. In addition, we observed that the overall survival rates of both groups were higher than a prior study in which the 1-year, 2-year and 5-year survival rates among 277 patients with severe AS were 87%, 78% and 68% in the SAVR group and 52%, 40%
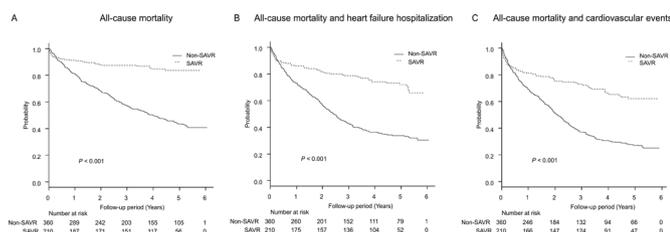

Figure 2 Cumulative event-free survival curves between the non-SAVR (n=360) and SAVR (n=210) groups in the entire population regarding (A) all-cause mortality, (B) all-cause mortality and heart failure hospitalisation and (C) all-cause mortality and cardiovascular events. SAVR, surgical aortic valve replacement.

Table 2 Yearly rates according to clinical events during the follow-up period between the non-SAVR (n=360) and SAVR (n=210) groups

Clinical events		Time (years)			Total in group (%)	Total	P value*
		1 (%)	2 (%)	3 (%)			
All-cause death	Non-SAVR	18.9	31.7	42.5	55.6	40.5%	<0.001
	SAVR	8.6	11.9	12.4	14.8		
HF admission	Non-SAVR	15.6	24.7	32.8	37.8	37.0%	<0.001
	SAVR	5.7	7.1	8.6	35.7		
Nonfatal stroke	Non-SAVR	2.5	6.1	7.5	9.7	8.6%	0.49
	SAVR	3.3	4.3	5.7	6.7		
Syncope	Non-SAVR	1.7	2.8	4.2	5.0	3.3%	0.002
	SAVR	0.0	0.0	0.0	0.5		
ACS	Non-SAVR	0.8	0.8	1.4	1.4	1.4%	0.42
	SAVR	0.5	0.5	0.5	1.4		

*P value refers to comparisons of event rates between the non-SAVR and SAVR groups at 3 years. Data are % values.
ACS, acute coronary syndrome; HF, heart failure; SAVR, surgical aortic valve replacement.

and 22% in the non-SAVR group, respectively; notably, their population comprised an older population (average age, 85 years) and more advanced stenosis (defined as AVA≤0.8 cm^2).[13] Bach and his colleagues reported that the mortality rate of symptomatic patients with severe AS and relatively low-operative risk based on the EuroSCORE II who did not undergo SAVR was 53% at 3 years.[14] The long-term outcome in this study seemed more reassuring at the 3-year mark, with a mortality of approximately 17% in the SAVR group. Regarding short-term mortality, SAVR-related operative risks have declined over the last two decades, although patients receiving SAVR are now much older and with a higher prevalence of comorbidities.[15] Studies have estimated a 30-day mortality of <3% for isolated SAVR and <4.5% for combined SAVR and CABG.[16] Our study obtained a remarkable achievement rate for 30-day mortality as only 5 (2%) of 210 patients died within 30 days of SAVR, in which 49% of SAVR patients underwent concomitant surgical procedures, such as mitral valve replacement or CABG.

Limited data are currently available on detailed clinical events in patients with severe AS, especially among those who underwent SAVR.[17] Our study elucidated the breakdown of cardiovascular events during the follow-up period less optimistically. In fact, admission for HF was the leading adverse event in both groups and was markedly different at 3 years. However, during the entire follow-up period, the admission rate for HF in the SAVR group reached 36%, which corroborated the non-SAVR group (38%). The findings of a few previous studies[12] are consistent with this study, although almost 55% of our population was symptomatic and there was a delay between the diagnosis and SAVR along with a possible baseline characteristics imbalance between the two groups. These remarkable findings of high readmission rates in SAVR patients may be explained by two primary

factors: increases in valve-related events and established myocardial damage affecting postoperative outcomes. There are clinical issues with valve deterioration and durability and increased risk of valve-related events such as prosthetic valve endocarditis and thrombosis. Andrew and colleagues[18] reported that patients with AS with severe diastolic dysfunction have more diffuse myocardial fibrosis detected on equilibrium contrast cardiovascular MRI, indicating that the regression of left ventricular hypertrophy 6 months following SAVR is due to cellular rather than fibrosis resolution. Therefore, we can speculate that a complete reversible change in the cardiac function before and after SAVR cannot be expected in patients with AS in whom myocardial damage has completely developed. Further studies are warranted to explore the potential mechanisms of HF in patients undergoing SAVR.

Additionally, our subgroup analysis with created PS-matched samples added new findings that these positive correlations remained substantial among patients aged ≥80 years, even in symptomatic patients or those with a history of HF admission. Likewise, this study revealed that a correlation between SAVR and survival decreased among asymptomatic patients and those with renal insufficiency. It is typically accepted from the current guidelines that the symptom development is a vital indication for intervention, whether surgical or transcatheter. A recent comprehensive study using the Japanese population recommended early intervention in selected asymptomatic subjects with AS because long-term outcomes of symptomatic patients were worse than those of asymptomatic patients.[19] In fact, some groups of patients with AS processed the decompensation without any complaints at daily practice because of frailty, cognitive disorder or workload avoidance. Of note, an appropriate assessment of the symptomatic status can be challenging, especially
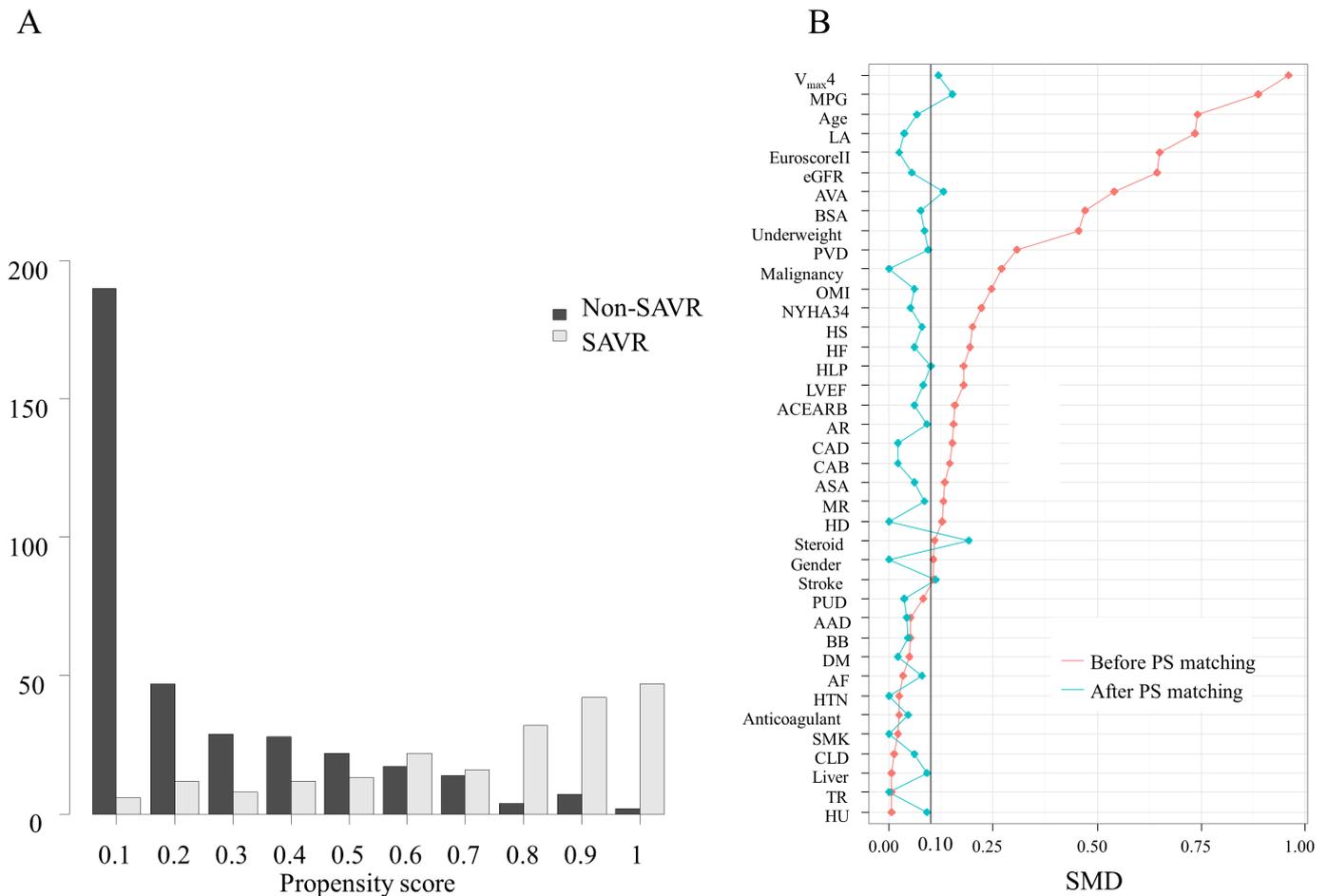
A

B

Figure 3 Distributions of PS between the non-SAVR (n=360) and SAVR (n=210) groups (A). The SMD of the 39 selected baseline variables before and after PS matching (B). AAD, aortic aneurysm or dissection; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AF, atrial fibrillation; AR, aortic regurgitation; ASA, antiplatelet; AVA, aortic valve area; BB, β-blocker; BMI, body mass index; BSA, body surface area; CAB, calcium channel blocker; CAD, coronary artery disease; CLD, chronic lung disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HD, haemodialysis; HTN, hypertension; HLP, hyperlipidaemia; HF, heart failure; HS, prior history of cardiac surgery, HU, hyperuricaemia; LA, limited activity; LVEF, left ventricular ejection fraction; MPG, mean aortic gradient; MR, mitral regurgitation; NYHA34, New York Heart Association class III or IV; OMI, old myocardial infarction; PVD, peripheral vascular disease; PS, propensity score; PUD, peptic ulcer disease; SAVR, surgical aortic valve replacement; SMD, standardised mean differences; SMK, current smoker; TR, tricuspid regurgitation; $V_{max}4$, peak aortic velocity >4.0 m/s.

in elderly patients who commonly have impaired physical mobility and cognitive impairment.[20] Thus, a systematic strategy to assess symptoms among elderly patients with AS is warranted to avoid underestimation. Moreover,

Figure 4 Cumulative event-free survival curves between the non-SAVR (n=101) and SAVR (n=101) groups in the PS-matched population regarding (A) all-cause mortality, (B) all-cause mortality and heart failure hospitalisation and (C) all-cause mortality and cardiovascular events. PS, propensity score; SAVR, surgical aortic valve replacement.

some studies reported that patients with AS and preoperative renal dysfunction exhibited an increased operative risk for SAVR,[21] with acute kidney injury following SAVR occurring in 3.4%–43% of SAVR cases. Reportedly, the 30-day mortality for these patients was 5.5%–46%.[22] In patients with pre-existing renal dysfunction, valve replacement with mechanical prostheses poses a higher risk for anticoagulation-related complications, whereas bioprosthetic replacement might be complicated by acceleration in structural valve deterioration.[23] Hence, further studies are warranted to elucidate the appropriate indications, methods and timing of intervention for patients with severe AS and renal dysfunction.
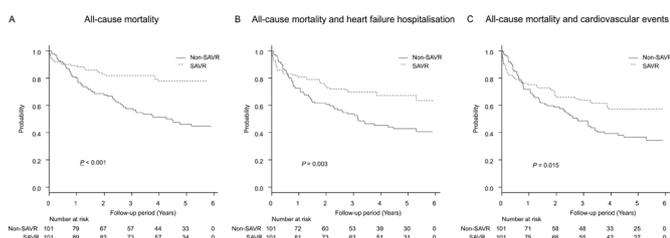
Study limitations
This relatively large cohort study holds several limitations. First, selection bias should be considered in this non-randomised study which could account for massive

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Table 3 Correlation between SAVR and the three types of clinical events in the selected subgroups of the propensity score-matched population

Subgroup	Non-SAVR	SAVR	Death HR (95% CI)	P value	Death and HF HR (95% CI)	P value	Death and cardiovascular events HR (95% CI)	P value
All matched patients	101	101	0.35 (0.21 to 0.59)	<0.001	0.53 (0.34 to 0.82)	0.004	0.62 (0.42 to 0.92)	0.02
Over 80 years	46	42	0.13 (0.05 to 0.34)	<0.001	0.31 (0.16 to 0.60)	<0.001	0.42 (0.23 to 0.77)	0.01
Symptomatic	56	62	0.19 (0.10 to 0.37)	<0.001	0.34 (0.20 to 0.59)	<0.001	0.37 (0.23 to 0.62)	<0.001
Asymptomatic	45	39	0.83 (0.38 to 1.84)	0.66	0.99 (0.48 to 2.03)	0.97	1.17 (0.60 to 2.28)	0.65
Renal insufficiency	49	37	0.60 (0.33 to 1.07)	0.09	0.72 (0.42 to 1.24)	0.24	0.74 (0.44 to 1.25)	0.26
Prior HF admission	34	38	0.38 (0.19 to 0.78)	0.01	0.44 (0.23 to 0.82)	0.01	0.42 (0.23 to 0.76)	0.004

HF, heart failure; SAVR, surgical aortic valve replacement.

confounding by indication between both groups. Thus, besides a crude comparison, we applied the PS-mediated analysis to adjust for selection bias and potential confounding factors rigorously, although a room still remains for discussion regarding the variable selection and manipulation for a fairer comparison of the process of obtaining these findings. Second, the matching method, while attaining a more well-balanced matching, decreased the matched sample population by almost 50% in the SAVR group, that might affect its generalisability. Finally, being a single-centre, retrospective, observational study, our findings might, therefore, not be generalised to other facilities within or outside of Japan. However, our heart centre is the only largest cardiovascular facility in the area, and almost all patients with diseased valves potentially warranting surgical intervention are referred to us for the comprehensive examination and follow-up without much selection. Consequently, a relatively large number of patients with severe AS were successfully reviewed in a short period along with comprehensive records of patients' characteristics.

CONCLUSION

This study establishes a correlation between SAVR and a lower incidence of both all-cause mortality and adverse cardiovascular events during the total follow-up period of 3.9 years in the 570 patients with severe AS and the PS-matched population. The patients with severe AS undergoing SAVR and concomitant surgical procedures were related to a 65% risk reduction of mortality and 38% risk reduction of adverse cardiovascular events compared with the medically treated cohort following rigorous adjustment for baseline characteristics. Notwithstanding, sufficient room exists to consider surgical indications, procedure types and timing for severe AS in asymptomatic patients. These findings have significant implications for informed decision-making during the management of patients with severe AS.

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