Outcomes After Aortic Valve Replacement for Asymptomatic Severe Aortic Regurgitation and Normal Ejection Fraction

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We investigated long-term outcomes following aortic valve replacement (AVR) in asymptomatic patients with severe aortic regurgitation (AR) and normal left ventricular (LV) function. We reviewed 268 patients who underwent isolated AVR for chronic severe AR from 1991 to 2010 and enrolled 162 asymptomatic patients with normal LV ejection fraction (≥50%) preoperatively. They were divided into 2 groups according to LV dimension at surgery, the early stage C group (indexed LV end-systolic diameter ≤25 mm/m^2 and LV end-diastolic diameter ≤65 mm, $n = 61$), and late stage C group (indexed LV end-systolic diameter >25 mm/m^2 and/or LV end-diastolic diameter >65 mm, $n = 101$). Survival was compared with that of an age- and gender-matched Japanese general population using a one-sample log-rank test. Subgroup analysis was performed for patients who survived >10 years after AVR. The mean age of all patients was 59 ± 14 years and mean follow-up period was 10 ± 5 years. Survival after AVR for the early and late stage C groups was not statistically different ($P = 0.57$). Furthermore, survival for both groups was not statistically different from that of the general population (early stage C, $P = 0.63$; late stage C, $P = 0.14$). However, subgroup analysis showed that survival >10 years after AVR was significantly worse for the late stage C group as compared to that of the general population ($P < 0.001$). Long-term survival following AVR for asymptomatic AR with normal LV ejection fraction was excellent. However, survival more than 10 years after surgery might be dependent on LV dimension at surgery.

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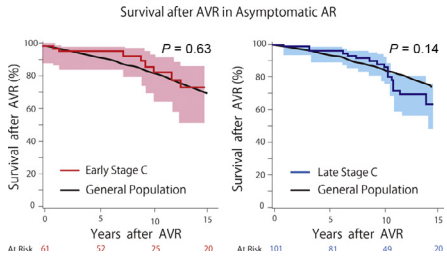
Keywords: Aortic insufficiency, Aortic valve replacement, Clinical outcome, Survival



Survival after AVR in asymptomatic AR was excellent, especially with smaller LV dimension.

Central Message

Long-term survival after AVR for asymptomatic AR with normal LVEF was excellent, although survival beyond 10 years after surgery might be dependent on the preoperative LV dimensions.

Perspective Statement

The appropriate timing for AVR for asymptomatic patients with severe AR and normal LVEF remains controversial, and information regarding long-term survival after AVR in these patients is limited. This retrospective study revealed excellent long-term survival, especially in patients with smaller LV dimension, and provide incentives for further investigations regarding earlier surgical intervention.

Abbreviations: AR, aortic regurgitation; AVR, aortic valve replacement; EDD, end-diastolic diameter; ESD, end-systolic diameter; ESDI, indexed end-systolic diameter; LV, left ventricular; LVEF, left ventricular ejection fraction

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INTRODUCTION

Surgery timing for asymptomatic patients with chronic severe aortic regurgitation (AR) and normal left ventricular ejection fraction (LVEF) remains controversial.[1–3] With recent improvements in surgical techniques and outcomes, the trend is earlier intervention.[4,5]

The 2014 American College of Cardiology/American Heart Association (ACC/AHA) guidelines[4] note that aortic valve replacement (AVR) is reasonable for asymptomatic patients with severe AR with normal LVEF (LVEF ≥50%), but with severe LV dilation (end-systolic dimension [ESD] >50 mm or indexed ESD [ESDI] >25 mm/m^2) (class IIa). Furthermore, AVR may be considered for asymptomatic patients with severe AR and normal LV systolic function at rest but with progressive severe LV dilation (end-diastolic dimension [EDD] >65 mm) if surgical risk is low (class IIb). On the other hand, periodic monitoring is recommended for asymptomatic patients with normal LV systolic function and mild-to-moderate LV dilation (ESD ≤ 50 mm or ESDI ≤ 25 mm/m^2 and EDD ≤ 65 mm).

We investigated long-term outcomes after AVR in asymptomatic patients with severe AR and normal LVEF, as well as the influence of surgery timing on survival according to LV dimension and age at surgery. Furthermore, since information regarding long-term outcomes for such patients, especially more than 10 years after surgery, is limited,[6–8] we performed a subgroup analysis of 10-year survivors.

METHODS

Study Population

Between January 1991 and December 2010, 268 consecutive patients underwent isolated AVR for severe chronic pure AR at Osaka University Hospital and 4 affiliated institutions. Of those, we enrolled patients who were asymptomatic with no history of hospitalization for heart failure, and showed LVEF ≥50% and ESD ≤55 mm at rest. Patients with aortic stenosis, mitral regurgitation or stenosis, significant coronary artery stenosis, infectious endocarditis, or aortitis were excluded, as were 24 with missing data regarding preoperative echocardiographic findings or symptoms.

Enrolled patients were divided according to the 2014 ACC/AHA guidelines (Fig. 1).[4] The early stage C group included patients with ESDI ≤25 mm/m^2 and EDD ≤65 mm (recommended for periodic monitoring), while the late stage C group included those with ESDI >25 mm/m^2 and/or EDD >65 mm (class IIa or IIb indication for AVR).

Endpoint and Follow-Up

The study endpoint was death from all causes. Follow-up analyses were performed using data obtained from medical charts, correspondence with their doctors, or a telephone call to the patient or family member, and continued until January 2013. Ethical approval was obtained from Osaka Rosai Hospital Institutional Review Board and the need for individual patient consent was waived for this retrospective analysis.

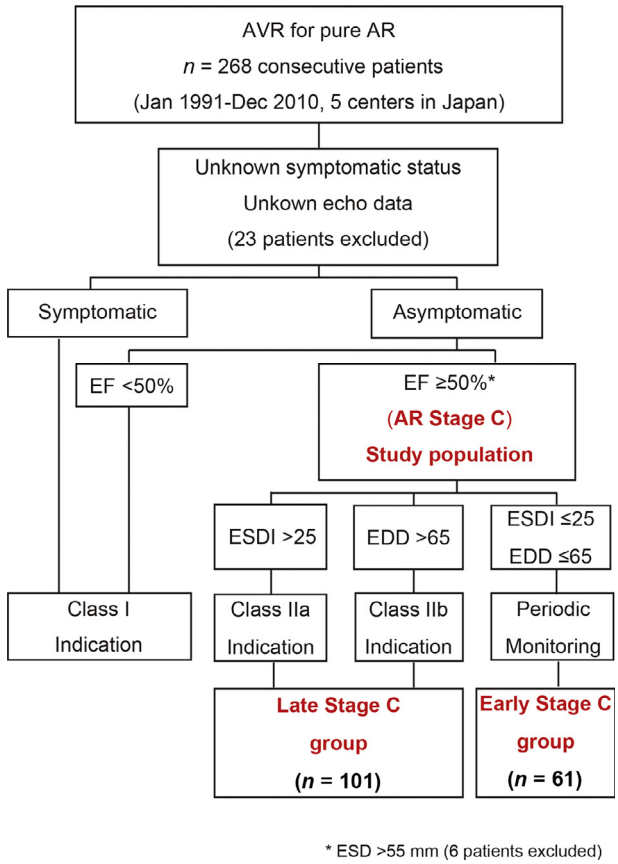


Figure 1. Algorithm for patient selection based on 2014 ACC/AHA Guidelines. The study population included 162 asymptomatic patients with EF ≥50% and ESD ≤55 mm. The early stage C group was comprised of patients with ESDI ≤25 mm/m^2 and EDD ≤65 mm, while the late stage C group was those with ESDI >25 mm/m^2 or EDD >65 mm. AR, aortic regurgitation; AVR, aortic valve replacement; EDD, end-diastolic diameter; EF, ejection fraction; ESD, end-systolic diameter; ESDI, indexed end-systolic diameter.

Statistical Analysis

Continuous variables are summarized as means with standard deviations and were compared using Welch's *t* test. Categorical variables are summarized as frequencies with percentages, and were compared using Fisher's exact test. These variables are also summarized as standardized mean differences.

Survival distribution of the study population was estimated using Kaplan-Meier product limit method and was also plotted by an event-chart to provide quantitative information about when follow-up was conducted if it was periodic.[9] Associations of preoperative factors with late death were also examined using multivariable analysis with the use of Cox proportional hazards model including the group factor (ie, early or late stage C group) as well as the factors that are clinically considered to affect survival (ie, age, sex, diabetes mellitus [DM] and chronic kidney disease [CKD]).

Survival distribution of an age- and gender-matched general Japanese population at the median year of operation was also estimated, then compared with the study population using the Finkelstein-Muzikansky-Schoenfeld method including a one-sample log-rank test.[10] For data regarding general population survival, we downloaded an Excel macro file from the Massachusetts General Hospital Biostatistics Center (http://hedwig.mgh.harvard.edu/biostatistics/node/30) and then modified that using Japanese annual survival data. As a landmark analysis, the aforementioned survival analysis was repeated for the subgroup who survived >10 years after surgery, for which the corresponding average age- and gender-specific annual mortality of the general Japanese population at the median year of the operation plus 10 years was used. We set the landmark at 10 years because information regarding long-term survival more than 10 years after surgery in asymptomatic patients with severe AR and normal LVEF is limited.[6–8] In addition, subgroup analysis for patients aged ≤50 vs >50 years was performed in the same way as the above analysis. We divided patients according to the age of 50 years because patients aged >50 years with severe AR might be considered indicated for surgery earlier than the guidelines recommend from the viewpoint of the natural history.[11]

All P values were 2-sided and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP Pro11 (SAS Institute, Cary, NC).

RESULTS

Clinical Results

We enrolled 162 asymptomatic patients (123 males) with chronic severe AR and normal LVEF, whose mean age at surgery was 59 ± 14 years (patient characteristics in Table 1). Follow-up ranged from 0 to 23 years (mean 9.9 ± 5.3 years). There were 1 (0.6%) hospital death and 31 late deaths. Seven patients were lost to follow-up, thus 96% completed follow-up rate. Follow-up quality was assessed using an event chart[9] (Fig. E1). Long-term overall survival after AVR for all 162 patients was not statistically different from that of the age- and gender-matched Japanese general population (5 years [95% confidence interval {CI}]: 96% [91–98%] vs 93%, 10 years: 87% [80–92%] vs 84%, 15 years: 67% [55–77%] vs 72%; $P = 0.42$).

Effect of AR Clinical Stage on Survival

Of the present population, 61 patients were stratified as the early stage C and 101 as the late stage C group. Overall survival in the early stage C and late stage C groups was not statistically different (5 years: 95% [86–98%] vs 96% [89–98%], 10 years: 86% [71–94%] vs 88% [79–94%], 15 years: 73% [54–86%] vs 64% [49–76%], $P = 0.57$; Fig. 2A). Multivariable analysis showed that the late stage C group was not associated with late death (hazards ratio [HR], 2.0; 95% CI, 0.9–4.6;

Table 1. Baseline Characteristics: Early vs Late Stage C

	All Patients				Ten-Year Survivors			
	Early Stage C ($n = 61$)	Late Stage C ($n = 101$)	P Value	SMD	Early Stage C ($n = 25$)	Late Stage C ($n = 49$)	P Value	SMD
Age, y	58 ± 15	59 ± 14	0.62	0.08	53 ± 17	56 ± 13	0.54	0.16
Gender (male)	52 (85)	71 (70)	0.04	0.37	21 (84)	31 (63)	0.11	0.49
BSA	1.70 ± 0.16	1.59 ± 0.21	<0.01	0.58	1.75 ± 0.17	1.58 ± 0.20	<0.01	0.88
HT	41 (67)	64 (63)	0.73	0.08	17 (68)	25 (51)	0.22	0.35
DM	8 (13)	5 (5)	0.08	0.28	3 (12)	2 (4)	0.33	0.3
CKD	20 (33)	39 (39)	0.5	0.13	8 (32)	15 (31)	1	0.02
Af	4 (7)	8 (8)	1	0.04	1 (4)	4 (8)	1	0.17
EF, %	68 ± 8	62 ± 8	<0.01	0.74	65 ± 8	63 ± 8	0.17	0.35
EDD, mm	59 ± 5	65 ± 7	<0.01	1.1	58 ± 6	66 ± 7	<0.01	1.2
EDD >65 mm	0 (0)	59 (58)	<0.01	1.7	0 (0)	32 (65)	<0.01	1.9
ESD, mm	38 ± 4	44 ± 5	<0.01	1.5	38 ± 4	45 ± 5	<0.01	1.6
ESDI, mm/m^2	22 ± 2	28 ± 4	<0.01	2.2	22 ± 2	29 ± 4	<0.01	2.2
ESDI > 25 mm/m^2	0 (0)	86 (85)	<0.01	3.4	0 (0)	43 (88)	<0.01	3.8
Year of Op								
1991–1995	9 (15)	15 (15)	0.47	0.3	6 (24)	11 (22)	0.75	0.19
1996–2000	8 (13)	22 (22)			8 (32)	20 (41)		
2001–2005	18 (30)	31 (31)			11 (44)	18 (37)		
2006–2010	26 (43)	33 (33)			0 (0)	0 (0)		
Mechanical prosthesis	40 (66)	61 (60)	0.62	0.12	22 (88)	38 (78)	0.36	0.27

Af, atrial fibrillation; AVR, aortic valve replacement; BSA, body surface area; CKD, chronic kidney disease; DM, diabetes mellitus; EDD, end-diastolic diameter; EF, ejection fraction; ESD, end-systolic diameter; ESDI, indexed end-systolic diameter; HT, hypertension; Op, operation; SMD, standardized mean difference.

Continuous and categorical variables are summarized as means ± standard deviations and frequencies with percentages in parentheses, respectively.

CKD = eGFR <60 mL/min/1.73 mm^2.

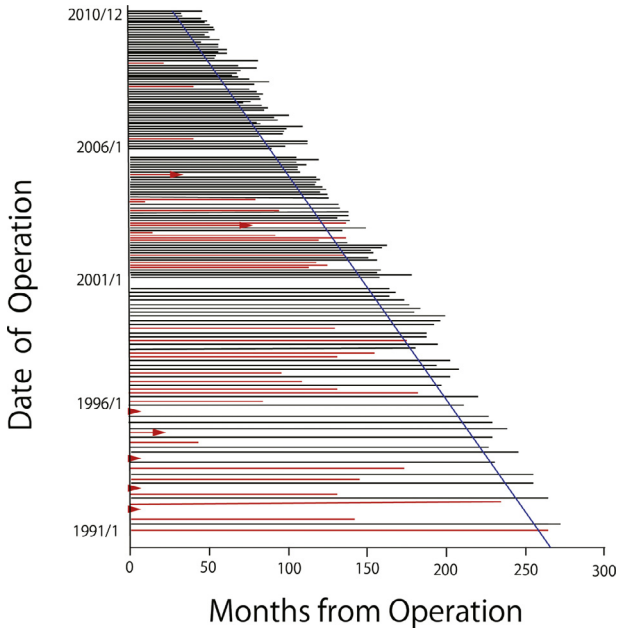


Figure E1. Events after operation. Horizontal lines represent individual patient time courses. Red line, time of death; red line with arrowhead; time of loss to follow-up; black line, time of last follow-up for living patient beyond January 2013, also indicated by blue diagonal line. (Color version of figure is available online at http://www.semthorcardiovascsurg.com.)

Table 2. Risk Factors for Late Death

Variables	Adjusted HR (95% CI)	*P* Value
Age	1.09 (1.04–1.14)/y	<0.01
Gender (male)	2.14 (0.94–5.30)	0.07
DM	3.89 (1.34–9.86)	0.02
CKD	2.08 (0.95–4.77)	0.07
Late stage C	1.99 (0.92–4.61)	0.08

CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; HR, hazard ratio.

P = 0.08), though age (HR, 1.09/year; 95% CI, 1.04–1.14/year; *P* < 0.01) and DM (HR, 3.9; 95% CI, 1.3–9.9; *P* = 0.02) were independent risk factors for late death (Table 2).

A landmark analysis for patients who survived >10 years after AVR (10-year survivors) showed that overall survival in the early stage C and late stage C groups was not statistically different (15 years: 85% [62–95%] vs 72% [56–84%], *P* = 0.28; Fig. 2B). Multivariable analysis showed the late stage C group was not associated with late death (HR, 2.7; 95% CI, 0.9–10.4; *P* = 0.09).

Overall survival in the early stage C and late stage C groups was not statistically different from that of the age- and gender-matched general population, respectively (early stage C, *P* = 0.63; late stage C, *P* = 0.14; Fig. 3A and B). Subgroup analysis of patients who survived >10 years after AVR (10-year survivors) showed that overall survival in the early stage C group was not statistically different from that of the general

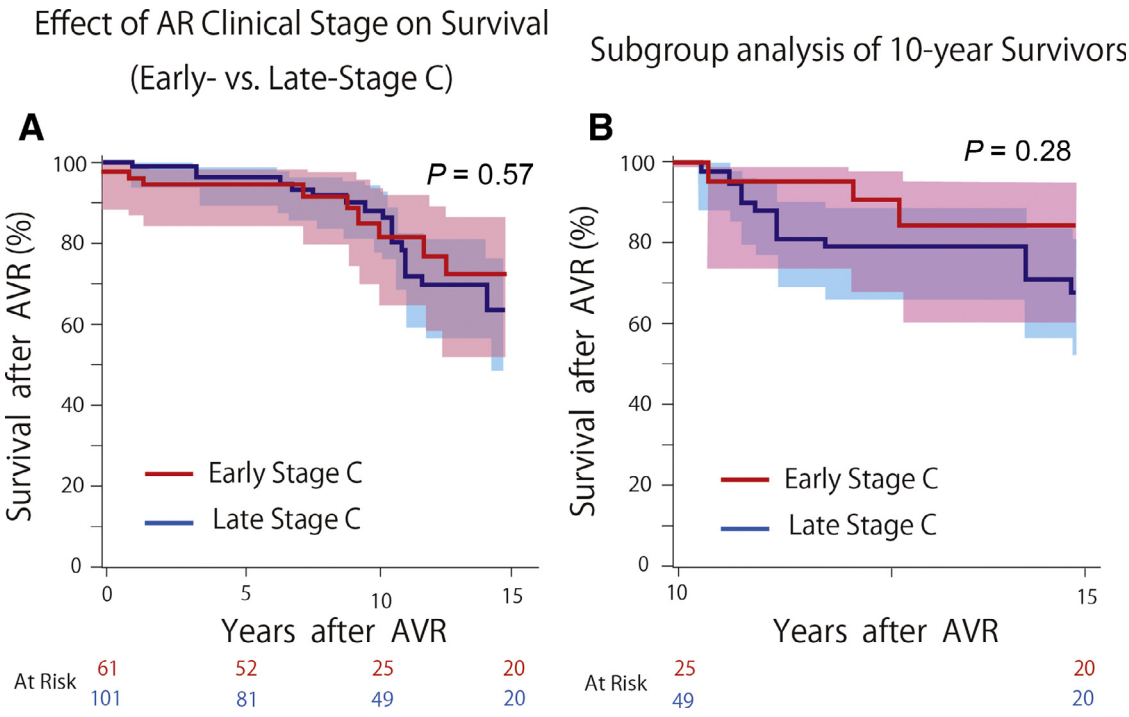


Figure 2. Effect of AR clinical stage on long-term survival after AVR. (A) Overall survival after AVR was not statistically different between the early and late stage C groups. (B) Subgroup analysis of patients who survived >10 years after AVR for early and late stage C groups showed the same results. AR, aortic regurgitation; AVR, aortic valve replacement.

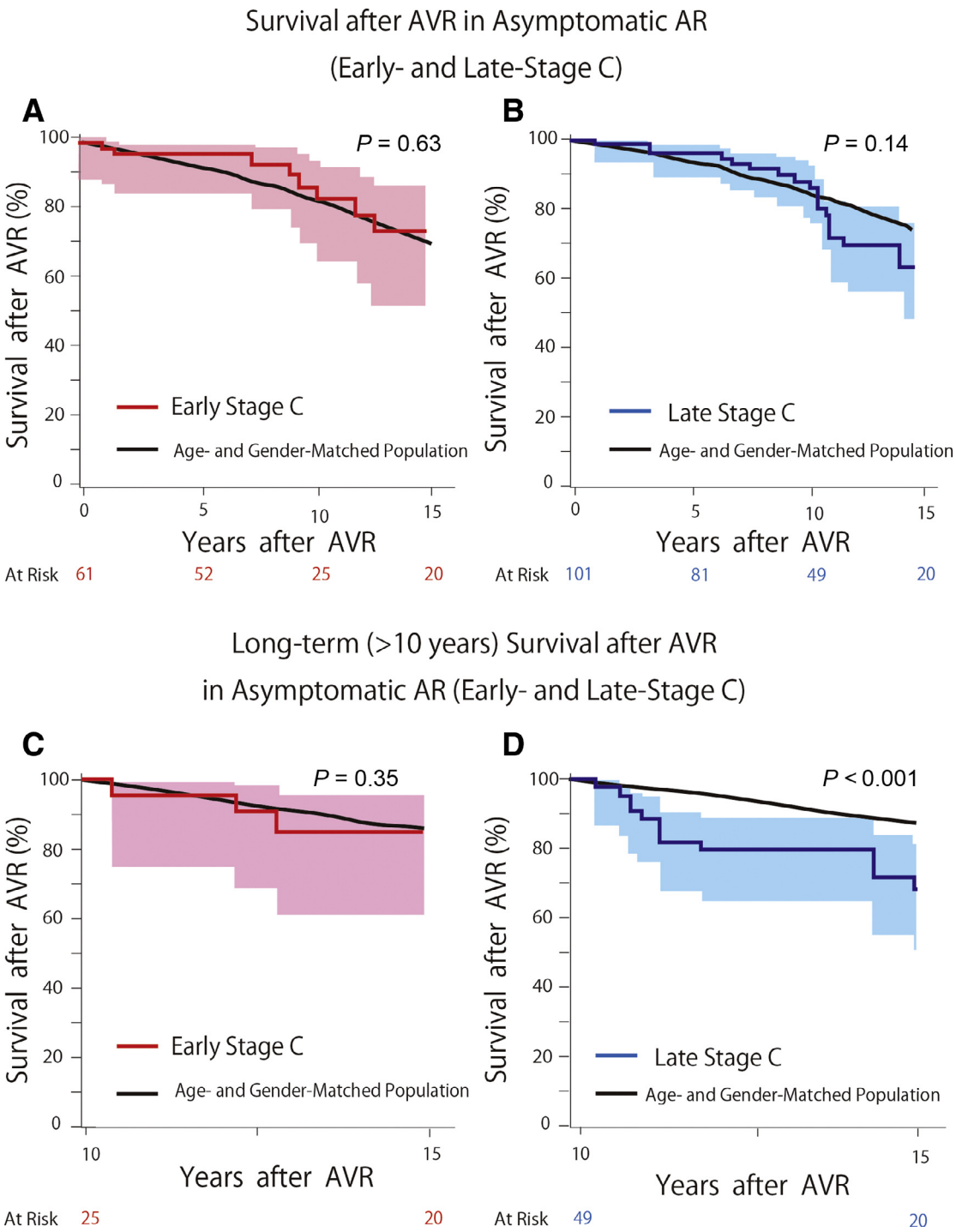


Figure 3. Survival after AVR was compared with that of an age- and gender-matched general population according to AR clinical stage. Overall survival after AVR for (A) early and (B) late stage C groups was not statistically different from that of the age- and gender-matched general population. Subgroup analysis of 10-year survivors showed that overall survival in the (C) early stage C group was not statistically different from that of the general population, while that in the (D) late stage C group was significantly worse. AR, aortic regurgitation; AVR, aortic valve replacement.

population (15 years: 85% [62–95%] vs 87%, $P = 0.26$), while that in the late stage C group was significantly worse (15 years: 72% [56–84%] vs 90%, $P < 0.001$; Fig. 3C and D).

Effect of Age at Surgery on Survival

The effect of age at time of surgery on postoperative survival was analyzed by stratifying the patients into younger

Table 3. Baseline Characteristics: Age ≤50 vs >50 Years

	Age ≤50 (n = 42)	Age >50 (n = 120)	P Value	SMD
Age, y	39 ± 9	66 ± 8	<0.01	3.2
Gender (male)	36 (86)	87 (73)	0.1	0.33
BSA	1.75 ± 0.17	1.59 ± 0.19	<0.01	0.92
HT	19 (45)	86 (72)	<0.01	0.57
DM	2 (5)	11 (9)	0.52	0.16
CKD	7 (17)	52 (43)	<0.01	0.59
Af	0 (0)	12 (10)	0.04	0.47
EF, %	62 ± 7	65 ± 8	0.12	0.27
EDD, mm	66 ± 6	62 ± 7	<0.01	0.65
EDD >65 mm	22 (52)	37 (31)	0.02	0.44
ESD, mm	44 ± 5	41 ± 6	<0.01	0.56
ESDI, mm/m^2	25 ± 4	26 ± 4	0.36	0.17
ESDI >25 mm/m^2	21 (50)	65 (54)	0.72	0.08
Year of Op				
1991–1995	13 (31)	11 (9)	<0.01	0.68
1996–2000	8 (19)	22 (18)		
2001–2005	13 (31)	36 (30)		
2006–2010	8 (19)	51 (43)		
Mechanical prosthesis	42 (100)	59 (49)	<0.01	1.66

Abbreviations as in Table 1.
Continuous and categorical variables are summarized as means ± standard deviations and frequencies with percentages in parentheses, respectively.

(≤50 years; mean 39 ± 9 years) and older (>50 years; mean 66 ± 8 years) subgroups (characteristics in Table 3). Overall survival for the younger group was not statistically different from that of the general population (5 years: 100% vs 99%, 10 years: 100% vs 98%, 15 years: 96% [76–99%] vs 95%; P = 0.75; Fig. 4A), nor was that for the older group (5 years: 94% [88–97%] vs 91%, 10 years: 83% [73–90%] vs 79%, 15 years: 53% [39–67%] vs 64%; P = 0.45; Fig. 4B).

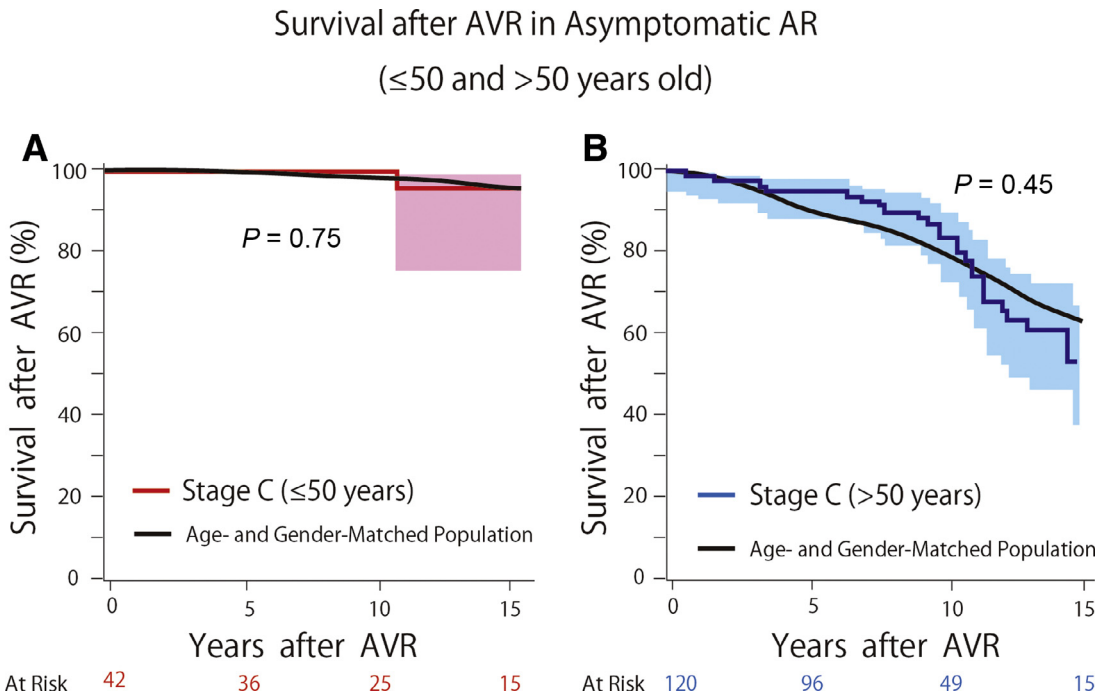


Figure 4. Effect of age on long-term survival after AVR. Overall survival after AVR in patients (A) ≤50 and (B) >50 years old was not statistically different from that of the age- and gender-matched general population, respectively. AR, aortic regurgitation; AVR, aortic valve replacement.

DISCUSSION

The major findings of the present study are as follows. (1) Survival after AVR for asymptomatic patients with severe AR and normal LVEF was excellent regardless of clinical stage. (2) Survival >10 years after AVR for patients with ESDI >25 mm/m^2 and/or EDD >65 mm was significantly worse than that of the general population, though survival >10 years after AVR in that group of patients as compared to those with a smaller LV dimension was not significantly different.

Recent studies[11,12] have shown that asymptomatic severe AR patients with preserved LVEF have a much higher rate of cardiac events when treated conservatively than noted in previous reports.[13–22] Detaint et al[11] investigated asymptomatic severe AR patients (average LVEF 68%, average ESDI 18 mm/m^2), and reported rates of AVR-free survival and cardiac events of 38% and 47%, respectively, at 5 years after diagnosis. Among asymptomatic patients with similar characteristics (average LVEF 65%, average ESDI 18 mm/m^2), Pizarro et al[12] found a cardiac events rate greater than 25% within 3–4 years after diagnosis. Those higher cardiac event rates as compared to previous studies may be explained by study cohort age differences.[1] Therefore, we considered it important to explore the possibility of earlier intervention, especially for older patients. Our results suggest the need for reassessment of surgery timing for asymptomatic patients with severe AR and normal LVEF.

No known randomized trial has investigated postoperative survival in asymptomatic AR patients with normal LVEF, thus surgery timing for asymptomatic severe AR remains controversial.[1–3,6–8] Some have insisted delaying surgery until guideline recommendations are reached, because of the generally excellent postoperative survival following onset of mild symptoms or mild LV dysfunction.[23,24] However, Brown et al[25] reported that ESDI ≥20 mm/m^2 was associated with greater mortality, though their cohort included symptomatic patients. For our patients, long-term survival >10 years in patients with ESDI >25 mm/m^2 and/or EDD >65 mm was worse than that of the general population, even with AVR performed prior to onset of symptoms or LV dysfunction. Earlier surgical intervention may improve this, though classical echocardiographic parameters, such as LVEF, ESD, and EDD, may not be sufficient to determine earlier surgical intervention for asymptomatic AR.[11,12]

Although patient age is important for decisions regarding surgical intervention, few have investigated the effect of age at surgery on long-term survival after AVR for AR. Detaint et al[11] reported low mortality for patients aged <50 years and conservatively treated, though that was not seen for those ≥50 years old. In another study of older AR patients (mean 60 years), AVR was independently associated with increased survival in patients with LVEF ≥50%, ESD <50 mm, and EDD <70 mm.[26] With those 2 studies in mind, we examined whether earlier surgery for patients aged ≥50 years is reasonable and our results suggest such a choice should be considered.

Limitations

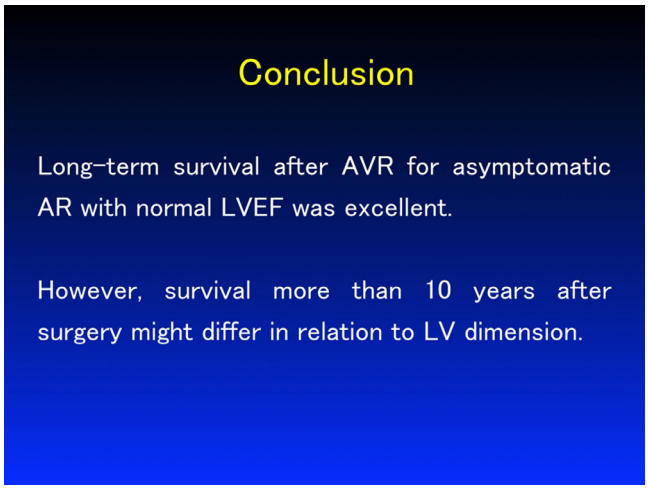
This was a retrospective study and included patients who underwent surgery over a 20-year period at 5 different centers. AR quantitation was not performed in most cases. Neither objective exercise capacity nor symptom status was assessed. Cause of death, rate of reoperation, cardiac events, postoperative symptoms, and valve gradients were not precisely surveyed, thus are not presented. The excellent survival of our patients, especially within 10 years after AVR, may be explained by selection bias (eg, exclusion of coronary artery disease cases) or the positive influence of regular clinical follow-up. The abrupt decline in survival after 10 years may be an artifact of follow-up or reflect better treatment for those who underwent surgery between 2004 and 2010, who were not included in the >10-year follow-up analysis. Our finding obtained by comparing with an age- and gender-matched general population might have been different if factors influencing mortality, such as socioeconomic or clinical history, were matched. Additionally, the number of patients in the subgroup analyses of the early stage C group was small.

CONCLUSIONS

Long-term survival following AVR for asymptomatic AR with normal LVEF was excellent regardless of clinical stage. However, survival >10 years after surgery might vary, as it can depend on LV dimension at surgery, though that was not consistently seen in all analyses. The present results provide incentive for further investigations regarding the value of surgical intervention for asymptomatic AR performed earlier than noted in current guidelines, especially for older patients.

SUPPLEMENTARY MATERIAL

The following is the supplementary data to this article:



Video 1. The timing of surgery for asymptomatic patients with chronic severe AR and normal left ventricular systolic function remains controversial. With recent improvements in surgical techniques and outcomes, there is a trend toward earlier intervention for asymptomatic patients. Here are the 2017 ACC/AHA guidelines used for indication of AVR in

asymptomatic patients with AR and normal left ventricular function. For those with normal ejection fraction and mild-to-moderate left ventricular dilation, periodic monitoring is recommended. However, we questioned whether it is adequate for such patients to undergo follow-up examinations alone without surgical intervention. In 2006, Tornos et al reported long-term outcomes of 170 patients with ejection <50% and/or an end-systolic diameter >50 mm who underwent surgical treatment for AR. In that study, they compared survival of 2 groups according to AR clinical stage, with the earlier surgery group showing better long-term survival. However, no study that compared such a population with patients who underwent surgery at an earlier clinical stage has been presented. The aim of the present study was to examine long-term outcomes following AVR in asymptomatic patients with severe AR and normal left ventricular function. We divided those patients into 2 groups according to LV dimension. The early stage C group included patients with ESDI ≤25 mm/m^2 and EDD ≤65 mm, who were recommended for periodic monitoring according to the guidelines. Overall survival for both groups was not statistically different from that of an age- and gender-matched general population. However, subgroup analysis of patients who survived for more than 10 years after AVR showed that overall survival >10 years after AVR in the early stage C group was not statistically different from that of the age- and gender-matched general population, whereas that of the late stage C group was significantly worse. We concluded that long-term survival after AVR for asymptomatic AR with normal LVEF was excellent. However, survival more than 10 years after surgery might differ depending on LV dimensions at the time of surgery. We believe that findings of this retrospective study provide incentive for further investigations regarding earlier surgical intervention for asymptomatic patients with AR.

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