Early and Long-Term Outcomes of Transcatheter Aortic Valve Replacement for Selected Nonagenarians in Japan

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Background: Transcatheter aortic valve implantation (TAVI) is increasingly being performed in very elderly patients, although its efficacy and validity remain unclear. This study evaluated real-world TAVI outcomes in Japanese nonagenarians with severe aortic stenosis.

Methods and Results: This single-center study retrospectively assessed the early and long-term clinical outcomes of TAVI in nonagenarians (n=35) and in patients aged <90 years (group Y; n=171). There were no in-hospital deaths in either group. The device success rate and early safety were comparable between the 2 groups. The 5-year rates of freedom from cardiac events and deaths were equivalent in both groups. The cumulative survival rate at 5 years was non-significantly lower in nonagenarians (32.6% in nonagenarians vs. 57.5% in patients aged <90 years, P=0.49). There were no differences in the 5-year survival between nonagenarians after TAVI and the sex- and age-matched populations (P=0.18). The Cox regression model revealed that lower hemoglobin levels were associated with all-cause mortality (P=0.02), and age ≥90 years was not associated with all-cause mortality.

Conclusions: The early and long-term clinical outcomes of TAVI for selected Japanese nonagenarians were comparable to those in patients aged <90 years. Nonagenarians who underwent TAVI achieved an acceptable prognosis compared to the sex- and age-matched population; thus, TAVI appears to be effective for treating aortic stenosis in Japanese nonagenarians.

Key Words: Aortic valve stenosis; Elderly patients; Japan; Nonagenarians; Transcatheter aortic valve implantation

According to the 2020 World Health Organization report, Japanese people have the longest life expectancy worldwide.¹ The latest report from the Japanese Ministry of Health, Labour and Welfare stated that life expectancy has reached 81.2 years for men and 87.3 years for women, with the population including 438,000 people who are >90 years old.² Unfortunately, this age group has an increased prevalence of aortic stenosis and is likely to have comorbid conditions, which pose a dilemma to cardiologists and cardiac surgeons when selecting conservative or interventional treatment. Eight years ago, surgical aortic valve replacement (SAVR) was the only treatment for severe aortic stenosis patients in Japan, although Japanese national health insurance began covering transcatheter aortic valve implantation (TAVI) in 2013 as a less invasive alternative to SAVR.^{3,4} Thus, TAVI has been rapidly adopted, as previously seen in European coun-

tries.⁵ The Japanese Association for Thoracic Surgery reported that TAVI accounted for 30.2% of all aortic valve replacement procedures in Japan during 2017 and increased up to 38.4% during 2018.^{6,7}

The widespread use of TAVI in the aging Japanese population has led to an increase in the number of TAVI procedures performed in very elderly patients. Some Western studies have reported the outcomes of TAVI in nonagenarians,⁸⁻¹⁰ although few reports have evaluated TAVI in nonagenarians from Asian countries.¹¹ This study aimed to clarify the outcomes and validity of TAVI in Japanese nonagenarians with severe aortic stenosis.

Methods

This single-center retrospective study was approved by the Institutional Review Board of Yamaguchi University Hospital

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Variables	Overall (n=206)	Age ≥90 years (n=35)	Age <90 years (n=171)	P value
Age, years	85.1±5.2	91.4±2.2	83.7±4.5	<0.0001
[range]	[69–97]	[90–97]	[69–89]	
Female gender, n (%)	138 (67.0)	28 (80.0)	111 (64.9)	0.07
Height, cm	149±9	146±8	150±9	<0.05
Weight, kg	49.9±9.6	45.7±6.5	50.7±9.9	<0.05
BSA, kg/m ²	1.41±0.19	1.35±0.12	1.43±0.19	<0.05
Medical history				
Hypertension, n (%)	182 (88.3)	33 (94.3)	149 (87.1)	0.38
Dyslipidemia, n (%)	111 (53.9)	21 (60.0)	90 (52.6)	0.71
Diabetes mellitus, n (%)	54 (26.2)	6 (17.1)	48 (28.1)	0.21
Cerebral vascular disease, n (%)	47 (22.8)	7 (20.0)	40 (23.3)	0.82
Ischemic heart disease, n (%)	77 (37.4)	8 (22.9)	69 (40.4)	0.06
Previous cardiac surgery	13 (6.3)	1 (2.9)	12 (7.0)	0.70
Permanent pacemaker, n (%)	13 (6.3)	4 (17.1)	9 (5.3)	0.24
Atrial fibrillation, n (%)	27 (13.1)	6 (17.1)	21 (1.2)	0.41
COPD, n (%)	6 (2.9)	0	6 (3.5)	0.60
Malignancy, n (%)	7 (3.4)	1 (2.9)	6 (3.5)	0.99
Calculated risk scores				
JapanSCORE, %	7.2±6.0	5.7±4.8	7.5±6.2	0.13
STS-PROM, %	7.5±4.2	8.0±2.8	7.4±4.4	0.32
EuroSCORE II, %	4.9±4.2	5.3±2.8	4.8±4.4	0.58
Clinical frailty scale ≥4, n (%)	131 (63.6)	22 (62.9)	109 (63.7)	1.00
NYHA class III/IV, n (%)	69 (33.5)	15 (42.9)	54 (31.5)	0.23
Echo parameters (Pre-TAVI)				
Aortic valve area, cm ²	0.63±0.16	0.60±0.15	0.64±0.16	0.18
Aortic valve mean PG, mmHg	50.3±15.3	53.9±17.0	49.5±15.2	0.13
Peak systolic velocity, m/s	4.6±0.7	4.7±0.7	4.6±0.7	0.22
LVEF, %	63.2±12.3	66.9±9.1	62.5±12.7	0.06
AR ≥ moderate, n (%)	24 (11.7)	6 (17.1)	18 (10.5)	0.25
Laboratory data				
eGFR, mL/min/1.73 m ²	47.9±9.6	48.8±13.7	47.7±15.9	0.70
Hemoglobin, g/dL	11.4±0.6	10.3±1.3	11.6±9.4	0.42
Albumin, g/dL	3.6±0.4	3.6±0.4	3.6±0.4	0.67
BNP, pg/mL	303±309	299±188	304±329	0.93

AR, aortic regurgitation; BSA, body surface area; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PG, pressure gradient; STS-PROM, Society of Thoracic Surgeons predictive risk of mortality.

(Study ID: H2020-149). The center used an opt-out consent process, and all procedures complied with the Declaration of Helsinki.

Study Patients and TAVI Procedure

The study included 206 patients who were treated at our institution for severe aortic stenosis between April 2014 and July 2021. All patients were assessed by a multidisciplinary cardiac team that included cardiac surgeons, cardiologists, cardiac anesthesiologists, and physical therapists to determine the appropriate treatment strategy. TAVI was performed under general anesthesia with endotracheal intubation. A temporary right ventricle pacing lead wire was inserted through the right jugular vein and used when needed. The approach to deploy the transcatheter prosthetic valve was discussed by a cardiac team. The transfemoral approach was considered the first choice, although other approaches were used if the femoral approach was not

feasible. The type and size of the prosthetic valve were determined according to the findings concerning the aortic valve complex after preoperative enhanced cardiac computed tomography. The balloon-expandable valves were the Edwards Sapien XT and Sapien 3 devices (Edwards Lifesciences, Irvine, CA, USA), and the self-expandable valves were the Core Valve, Evolut R, Evolut PRO, and Evolut PRO+ devices (Medtronic Inc., Minneapolis, MN, USA).

Assessments of Clinical Outcomes and Statistical Analysis

We retrospectively assessed the early and long-term clinical outcomes after TAVI in nonagenarian patients (n=35) and in patients aged <90 years (n=171). Early clinical outcomes were assessed according to the Valve Academic Research Consortium 2 (VARC-2) criteria.¹² Cardiac events were defined as cardiac death, re-admission due to heart failure, reintervention for the aortic valve, newly required pace-

Variables	Overall (n=206)	Age ≥90 years (n=35)	Age <90 years (n=171)	P value
Clinical Frailty Scale, n (%)				
1	0	0	0	
2	3 (1.4)	0	3 (1.8)	
3	72 (35.0)	13 (37.2)	59 (34.5)	
4	67 (32.5)	9 (25.7)	58 (33.9)	
5	42 (20.4)	10 (28.6)	32 (18.8)	
6	17 (8.3)	3 (8.5)	14 (8.1)	
7	5 (2.4)	0	5 (2.9)	
8.9	0	0	0	0.67
5-meter walk test, seconds	8.4±6.3	7.8±4.8	8.5±6.7	0.59
Grip strength, kg				
Men	25.5±6.1	22.4±5.0	25.8±6.0	0.22
Women	15.0±4.5	14.1±3.4	15.2±4.7	0.27
Knee extensor strength, N				
Men	199±71	266±81	196±72	0.77
Women	142±49	146±42	141±51	0.63
Psoas muscle volume, cm ³				
Men	235±58	214±21	236±61	0.36
Women	146±35	142±31	147±36	0.59

Grip strength, knee extensor strength, and psoas muscle volume are separately presented according to sex because those baseline statuses are obviously different between sexes. Knee extensor strength is calculated as the average of the values of the right and left knee strengths. Data of the Clinical Frailty Scale and psoas muscle volume are available for all 206 participants. Data for the 5-meter walk test, grip strength, and knee extensor strength are available for only 175 participants (age ≥90 years: 28 patients; age <90 years: 147 patients).

Variables	Overall (n=206)	Age ≥90 years (n=35)	Age <90 years (n=171)	P value
Transcatheter heart valve, n (%)				
Sapien XT	57 (27.7)	13 (37.1)	44 (25.7)	0.21
Sapien3	76 (36.9)	9 (25.7)	67 (39.2)	0.23
CoreValve	15 (7.3)	4 (11.4)	11 (6.4)	0.29
Evolut R	21 (10.2)	3 (8.6)	18 (10.5)	1.00
Evolut PRO	25 (12.1)	4 (11.4)	21 (12.3)	0.53
Evolut PRO+	12 (5.8)	2 (5.7)	10 (5.8)	1.00
Approach site, n (%)				
Femoral	158 (76.7)	28 (80.0)	130 (76.0)	0.82
Iliac	6 (2.9)	1 (2.9)	5 (2.9)	1.00
Subclavian	7 (3.4)	1 (2.9)	6 (3.5)	1.00
Apical	28 (13.6)	4 (11.4)	24 (14.0)	0.61
Aorta	7 (3.4)	1 (2.9)	6 (3.5)	1.00
Device success, n (%)	183 (88.8)	32 (91.4)	150 (88.3)	0.77

"Device success" was defined according to composite endpoints of Valve Academic Research Consortium (VARC)-2 criteria.

maker implantation, and cardiogenic stroke. Cardiac death was defined as death due to cardiac disease and sudden death. All study participants were followed up until the end of study period. The mean follow-up period was 2.3±1.8 years (2.8±2.1 years in nonagenarians and 2.2±1.7 years in non-nonagenarians). Continuous data were expressed as mean±standard deviation and evaluated using a Student's t-test. Categorical data were evaluated using the chi-squared test or Fisher's exact test, as appropriate. Time-to-event analyses were performed using Kaplan-Meier

estimates and log-rank tests. Independent predictors of mortality after TAVI were determined using Cox regression analysis. The multivariable models included covariates with a P value of <0.1 in the univariate analyses. Statistical analyses were performed using StatView software (version 5.0; SAS Institute, Cary, NC, USA), and differences were considered statistically significant at P values <0.05. Predicted survival was calculated from sex- and age-matched Japanese populations based on the Japanese abridged life tables published by the Ministry of Health, Labour and

Table 4. Early Clinical Outcomes

Variables	Overall (n=206)	Age ≥90 years (n=35)	Age <90 years (n=171)	P value
30-day outcome, n (%)				
In-hospital death	0	0	0	1.00
All-cause mortality	1 (0.4)	0	1 (0.5)	1.00
Cardiovascular mortality	0	0	0	1.00
Peri-procedural MI	1 (0.4)	0	1 (0.5)	1.00
Stroke	6 (2.9)	1 (2.8)	5 (2.9)	1.00
Disabling stroke	3 (1.4)	1 (2.8)	2 (1.1)	0.42
Life-threatening bleeding	9 (4.3)	0	9 (5.2)	0.36
Acute kidney injury – stage 2 or 3	0	0	0	1.00
Major vascular complication	4 (1.9)	2 (5.7)	2 (1.1)	0.13
New pacemaker implantation	20 (9.7)	5 (14.2)	15 (8.7)	0.34
Conversion to open surgery	1 (0.4)	0	1 (0.5)	1.00
Unplanned use of cardiopulmonary bypass	2 (0.9)	0	2 (1.1)	1.00
Coronary obstruction	2 (0.9)	1 (2.8)	1 (0.5)	0.31
Cardiac tamponade	2 (0.9)	0	2 (1.1)	1.00
TAVI in TAVI deployment	2 (0.9)	1 (2.8)	1 (0.5)	0.31
Prosthetic aortic valve stenosis – ≥ moderate	0	0	0	1.00
Prosthetic aortic valve regurgitation – ≥moderate	23 (11.1)	3 (8.5)	20 (11.6)	0.77
Early safety, n (%)	186 (90.2)	31 (88.5)	155 (90.6)	0.75
Hospital stay after procedure, days	12.2±14.1	14.6±26.8	11.7±9.9	0.28
ICU stay, days	1.7±1.1	1.8±0.8	1.7±1.1	0.82

"Early safety" was defined according to composite endpoints Valve Academic Research Consortium (VARC)-2 criteria. ICU, intensive care unit; MI, myocardial infarction; TAVI, transcatheter aortic valve implantation.

Welfare in Japan (<http://www.mhlw.go.jp/toukei/list/list54-57.html>). A statistically significant difference between the estimated survival curve and the predicted survival curve was assessed by calculating the z value from cumulative survival rates and its standard error, as calculated by using the Greenwood method.¹³ Finally, the P value between the estimated survival curve and the predicted survival curve was calculated from the z value.

Results

Baseline Characteristics and Frailty

Baseline patient characteristics are shown in **Table 1**. The 206 patients (138 females [67%]; mean age 85.1±5.2 years) were evaluated and divided into 2 groups according to their age at TAVI; nonagenarians (age ≥90 years, n=35) and non-nonagenarians (age <90 years, n=171). Nonagenarians included a slightly greater number of female patients (P=0.07). Nonagenarians were shorter and lighter than non-nonagenarians in terms of their physical characteristics. The medical history and calculated risk factors were not significantly different between the 2 groups. The prevalence of clinical frailty scale ≥4 and New York Heart Association (NYHA), functional class III/IV, cardiac echo parameters, and laboratory data were not significantly different between the 2 groups.

Details regarding baseline frailty are shown in **Table 2**. Distributions of clinical frailty scale scores, 5-meter walk test, grip strength, knee extensor strength, and psoas muscle volume results were all similar between the 2 groups.

Procedural Characteristics of TAVI

The TAVI characteristics are presented in **Table 3**. A balloon expandable valve was implanted in 133 patients

(64.6%), and a self-expandable valve was implanted in 73 patients (35.4%), and the transfemoral approach was performed in 158 patients (76%). The types of prosthetic valves and approach sites were not significantly different between the 2 groups. The device's success, according to the VARC-2 criteria, was recorded in 32 nonagenarians (91.4%) and 150 non-nonagenarians (88.3%), and there were no significant differences between the 2 groups. Two patients required a second prosthetic valve implantation, comprising 1 patient in each group. The device was not successful where there was paravalvular leakage.

Early and Long-Term Clinical Outcomes

Early clinical outcomes are summarized in **Table 4**. No in-hospital deaths occurred in either group. The 30-day outcomes according to the VARC-2 criteria were not significantly different between the two groups. One patient died 26 days after TAVI. He developed sudden paraplegia and renal failure of unknown cause after discharge. He refused further examination and medical treatment, including hemodialysis, so he passed away. This patient may have experienced onset of acute aortic dissection after discharge. The duration of hospital stay after TAVI and ICU did not differ between the 2 groups.

The overall 5-year survival rates were 48.9% in all patients (**Figure 1A**), 36.6% in nonagenarians, and 57.5% in non-nonagenarians (P=0.26, **Figure 1B**). The 5-year rates of freedom from cardiac events were 69.4% in all patients (**Figure 1C**), 60.2% in nonagenarians, and 71.5% in non-nonagenarians (P=0.40; **Figure 1D**). The 5-year rates of freedom from cardiac death were 88.0% in all patients (**Figure 1E**), 73.7% in nonagenarians, and 91.9% in non-nonagenarians (P=0.18; **Figure 1F**).

Fifteen late deaths were observed in nonagenarians. The

Figure 1. Time-to-event data. (A) Curves for cumulative survival in all patients. (B) Curves for cumulative survival stratified by the age at procedure. (C) Curves for freedom from cardiac events rate in all patients. (D) Curves for freedom from cardiac events stratified by age at procedure. (E) Curves for freedom from cardiac death rate in all patients. (F) Curves for freedom from cardiac death rate stratified by the age at procedure.

causes of late death in nonagenarians were chronic heart failure in 2 patients, sudden death in 2, pneumonia in 5, other infectious diseases in 2, malignancy in 2, and senility in 2.

Comparison With the Japanese General Population and Predictors for Mortality

We compared the 5-year survival of nonagenarians who underwent TAVI in this study, to that of the sex- and age-matched Japanese population calculated from the Japanese abridged life tables. Five-year survival of nonagenarians in this study was similar to that of the general Japanese population of nonagenarians (32.6% vs. 37.0, $P=0.18$, **Figure 2**). We also analyzed the predictors of mortality after TAVI using the Cox regression models (**Table 5**). Univariate analysis revealed that preoperative serum albumin level, hemoglobin concentration, and clinical frailty scale ≥ 4 might be associated with mortality. Multivariate analysis

revealed that preoperative hemoglobin concentration was the sole predictor of mortality (hazard ratio: 0.81, 95% confidence interval: 0.68–0.98, $P=0.02$). Age ≥ 90 years was not associated with mortality after TAVI.

Discussion

TAVI is becoming an increasingly common procedure in geriatric patients. In this study, we elucidated whether clinical outcomes of TAVI for Japanese nonagenarians are acceptable. Healthcare systems and life expectancy values vary across countries. For example, Japan has a universal and compulsory health insurance system that creates a unique healthcare delivery environment, relative to countries without compulsory health insurance systems. There are several reports regarding the outcomes of TAVI in nonagenarians from Western countries.^{8–10} Yokoyama et al investigated the clinical outcomes after TAVI among Japanese nonagenarians.¹¹ They reported that early safety and 3-year mortality in nonagenarians were similar to those in patients aged <90 years. These findings match the results of this study. This study elucidated further long-term outcomes (5 years), and nonagenarians who underwent TAVI had an acceptable 5-year survival comparable to that of the general nonagenarian population in Japan. Severe aortic stenosis is a life-threatening heart valvular disease, and elderly patients with severe aortic stenosis are supposed to have a poor prognosis; however, nonagenarians treated with TAVI have an acceptable prognosis compared to the general nonagenarian population. Takeji et al reported that the current in-hospital mortality rate for TAVI is 1.3% in Japan, which suggests that it has a high success rate and is being performed safely with very low mortality.³ This study also revealed that TAVI in Japanese nonagenarians provided excellent short- and long-term outcomes. For example, the in-hospital mortality rates were identical for nonagenarian and non-nonagenarian patients (0% vs. 0%). Early outcomes in nonagenarians were comparable to those in non-nonagenarians, which indicates that TAVI can be safely performed even in very elderly patients. Studies from Western countries have also shown that TAVI can achieve acceptable in-hospital outcomes in nonagenarians, and that age alone should not

Table 5. Prediction of Patient Mortality After TAVI

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥ 90 years	1.23 (0.67–2.26)	0.49		
Female sex	0.67 (0.39–1.15)	0.15		
STS-PROM	1.00 (0.95–1.05)	0.92		
EuroSCORE II	0.94 (0.86–1.02)	0.17		
JapanSCORE	0.97 (0.92–1.02)	0.25		
NYHA class III/IV	1.27 (0.75–2.15)	0.36		
Clinical frailty scale ≥ 4	1.71 (0.96–3.06)	0.06	1.58 (0.86–2.88)	0.13
LVEF	1.01 (0.99–1.03)	0.14		
BNP	1.00 (0.15–0.89)	0.39		
Albumin	0.46 (1.00–1.01)	<0.05	0.74 (0.35–1.54)	0.42
Hemoglobin	0.79 (0.63–0.95)	<0.01	0.81 (0.68–0.98)	0.02
eGFR	1.01 (0.98–1.05)	0.37		
COPD	0.82 (0.89–9.49)	0.74		

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

exclude patients from this treatment,^{8–10} which agrees with our findings.

A decade ago, SAVR was the only effective therapy for aortic valve stenosis, although the development of TAVI has dramatically changed the surgical treatment of aortic valve stenosis. Previous studies with nonagenarian cohorts revealed early mortality rates of 11–17% after SAVR,^{14,15} whereas recent observational studies have revealed noticeably lower in-hospital or 30-day mortality rates after TAVI in nonagenarians (0–8.7%).^{8–10} Furthermore, we did not detect any in-hospital or 30-day mortality among our nonagenarian patients. We also revealed acceptable long-term outcomes of TAVI in nonagenarians, which appears to be a useful therapeutic option and a reasonable alternative to SAVR in nonagenarians, based on their relatively short life expectancy.

The 5-year survival rate of nonagenarian patients in this study was 32.6%, which was similar to that of the Japanese nonagenarian population (37.0%). The causes of late death in our nonagenarian group were cardiac death (including sudden death) in 4 patients, pneumonia in 5 patients, other infectious diseases in 2 patients, malignancy in 2 patients, and senility in 2 patients. The Japanese Ministry of Health, Labour and Welfare has reported that the top five causes of mortality in nonagenarians are cardiac disease, pneumonia, senility, cerebrovascular disease, and malignancy.¹⁶ The cases of late death also seem to be unsurprising and comparable to the Japanese nonagenarian population.

The widespread adoption of TAVI and population aging has led to an increase in the number of TAVI procedures performed worldwide. Thus, it is essential to identify prognostic factors that can guide patient selection and stratification in the TAVI era. The reported predictors of postprocedural mortality after TAVI include anemia, intraoperative or postoperative blood transfusion, psoas muscle area, and appetite immediately before discharge.^{17–20} The present study revealed that lower preoperative hemoglobin concentrations were associated with poor long-term outcomes ($P=0.02$). Thus, hemoglobin concentration may be a potential predictor of TAVI outcomes. The present study also revealed that age ≥ 90 years did not predict prognosis, despite age being an important prognostic factor for mortality. In this context, older patients have more comorbidities and a higher operative risk, and older age is considered an independent risk factor for major operative risk scores, including the Society of Thoracic Surgery, EuroSCORE, and JapanSCORE systems.^{21–23} However, there were few differences in the baseline characteristics between nonagenarians and non-nonagenarians in this study (**Table 1**). Furthermore, clinical frailty scale scores in this study were almost similar between the 2 groups (**Table 2**). Thus, the nonagenarian patients might have been more carefully selected and in better condition, relative to the <90 age group. We believe that careful evaluation of patients before TAVI is essential to achieve excellent clinical outcomes.

Stehli et al reported that impairment of activities of daily living (ADL) after TAVI was more common in older patients, and that 25% of nonagenarian patients transitioned to aged-care facilities within 1 year after TAVI.⁹ We believe that this points to a disadvantage of TAVI, which is specific to very elderly patients. We evaluated frailty assessment data for 28 of 35 nonagenarian patients, as these assessments were not routinely performed during the early study period, and we found the deterioration of their grip strength in the early phase after TAVI (**Supplementary**

Table). However, these data are insufficient for assessing possible changes in ADL and quality of life. Further investigations are needed to understand the long-term ADL outcomes of patients with TAVI.

This study has several limitations. First, the retrospective observational study design was prone to selection bias. Second, the sample size was limited because our hospital is not a high-volume center. Third, data regarding the outcomes of conservative medical therapy for nonagenarian patients with aortic stenosis were not available.

Conclusions

The early and long-term clinical outcomes of TAVI in select Japanese nonagenarians were comparable to those in patients aged <90 years. Furthermore, nonagenarians who underwent TAVI had acceptable 5-year survival rates. Therefore, TAVI may be an effective treatment for aortic stenosis, even in nonagenarian patients.

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Disclosures

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IRB Information

The Institutional Review Board of Yamaguchi University Hospital (Study ID: H2020-149) approved this study.

Author Contributions

H.K., R.S.: data analysis and drafting the article. A.M., T. Okamura: study conception and design. B.S., Y.M., H.T., T. Oda: data collection. M.Y., K.H.: approval of the article.

Data Availability

The data generated from this study may be shared upon reasonable request through the corresponding author.

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Supplementary Files

Please find supplementary file(s);
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