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Impact of arm circumference on clinical outcomes in patients undergoing transcatheter aortic valve replacement

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ABSTRACT

Background: Although Arm circumference (AC) is considered to be a predictor of clinical outcomes of transcatheter aortic valve replacement (TAVR), limited data are available on the impact of this anthropometric measurement. This study aimed to investigate the clinical impact of AC on the outcomes of patients who underwent TAVR.

Methods: AC was investigated in consecutive patients who underwent TAVR between March 2014 and May 2018. Patients were divided into low AC (n = 220) and high AC (n = 127) groups by a classification and regression tree (CART) survival model, and their baseline characteristics and mortality were compared. The correlations of AC with other frailty markers were also evaluated.

Results: One-year clinical follow-up was completed in 100% of cases, and 89 patients (31 men, 58 women) died during the median follow-up period of 825 days. The low AC group was more fragile than the high AC group, and the AC value was significantly correlated with each frailty marker (all $p < 0.05$). The Cox regression analysis demonstrated the independent association of mortality with low AC (HR: 2.56, 95% confidence interval [CI]: 1.47–4.46, $p < 0.001$). When AC was compared to conventional prediction models of survival, the net reclassification improvement and the integrated discrimination improvement analysis showed significant improvements in predicting outcomes after including the AC with other frailty markers (all $p < 0.05$).

Conclusions: The AC is related to frailty markers and is an important surrogate marker for predicting worse clinical outcomes after TAVR. Assessment of AC may be considered when deciding on TAVR.

1. Introduction

Anthropometry is an essential tool in geriatric assessment for evaluating malnutrition, functional decline, and chronic health conditions, which are important risk factors for geriatric frailty, disability, and mortality [1–3]. Arm circumference (AC) is recommended as one of the tools to measure body conditions [4], such as nutritional status [2], and muscle mass [5]. AC reflects subcutaneous fat and body muscle mass, which is affected by both energy balance and local muscle activity. This simple anthropometric measurement has been shown to have the ability to predict morbidity and follow-up mortality risk [6,7]. In addition, frailty, which is not captured in the traditional surgical risk model, is considered highly prevalent in elderly fragile patients and can be characterized by several phenotypes to better define the patient's status. Frailty markers such as muscle mass [8], muscle function [9], gait speed [10], and nutritional status [11,12] have been reported to be associated

Abbreviations: TAVR, transcatheter aortic valve replacement; AC, arm circumference; NRI, net reclassification improvement; IDI, integrated discrimination improvement; GNRI, Geriatric Nutritional Risk Index; CFS, clinical frailty scale.

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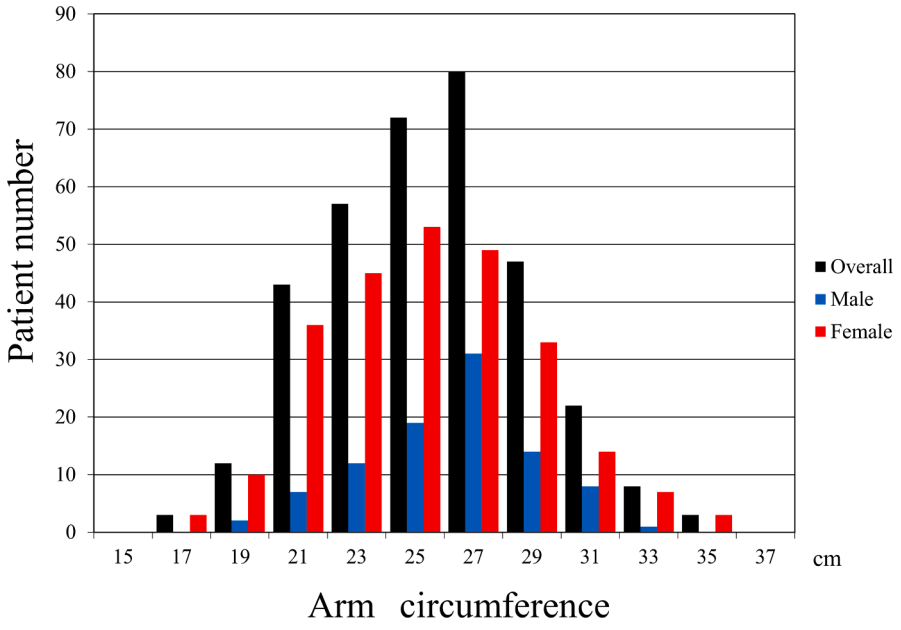

Fig. 1. Distributions of arm circumference in the overall, male, and female populations.

with clinical outcomes after transcatheter aortic valve replacement (TAVR) in Japanese people. However, limited data are available on the impact of anthropometric measurements on the outcomes of patients who underwent TAVR. The present study therefore aimed to investigate the clinical impact of AC on the outcomes of patients who underwent TAVR.

2. Methods

This was a prospective cohort study of 391 consecutive patients undergoing TAVR between March 2014 and May 2018 at Nagoya Heart Center and Toyohashi Heart Center, Japan. The decisions regarding the indications for TAVR were made after reaching a consensus through discussions within the local heart team when considering the open heart surgical risk for patients with multiple comorbidities. Transthoracic echocardiography was performed to evaluate the degree of aortic stenosis (AS). All patients with aortic valve area (AVA) < 1.0 cm^2 and mean pressure gradient > 40 mmHg or peak velocity > 4.0 m/s were diagnosed as having severe AS. Low-flow, low-gradient AS was defined based on both a stroke volume index < 35 mL/m^2 and a mean aortic gradient < 40 mmHg. The anthropometric data of 44 patients were missing. Thus, the remaining 347 patients were analyzed in this study. Clinical data, patients' characteristics, laboratory data, echocardiographic data, procedural variables, and in-hospital and all-cause mortality rates before and after TAVR were examined.

The detailed TAVR procedures were described previously [10,11]. The Edwards SAPIEN-XT/SAPIEN-3 (Edwards Lifesciences, Irvine, CA) balloon-expandable prosthesis and the Medtronic CoreValve/Evoult-R System (Medtronic, Minneapolis, MN) self-expandable prosthesis were used during the study period. The size of the bioprosthesis was determined primarily using computed tomography and echocardiographic findings. Information regarding the occurrence and/or causes of death was obtained from the treating hospital or patients' family member(s). The study protocol complied with the principles expressed in the Declaration of Helsinki. This study was approved by the Research Ethics Committee of the Nagoya Heart Center (Approval No. NHC2021-0401-01).

AC was measured to the nearest 1 mm by trained physiotherapists using a plastic measuring tape at the point midway between the lateral projection of the acromion process and the lateral epicondyle of the humerus with the elbow fully extended. The mean of the left and right AC measurements was used for the analyses [6]. The cut-off value of the AC for predicting mortality was determined by a classification and regression tree (CART) survival model [10]. The cut-off value of the AC was 25.9 cm, and the prognostic value of the AC was assessed for the entire cohort using this cut-off value.

All statistical analyses were performed using Stata 15 (Stata Corporation, College Station, TX) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) [13]. Continuous variables are expressed as means ± standard deviation (SD) and as medians with interquartile ranges (IQRs). Baseline characteristics were compared using Student's *t*-test or one-way analysis of variance, chi-squared tests, or Fisher's exact tests, as appropriate. The relationships between AC and frailty markers were assessed using Spearman's correlation analysis. The Kaplan-Meier method was used to generate event-free survival curves, and differences in mortality were assessed with the log-rank test. Univariate Cox regression analysis was performed to obtain the hazard ratio (HR) for all-cause mortality during the follow-up period. Multivariate analysis was then performed using the baseline clinical characteristics and other variables with a univariate p value of < 0.1 to examine the independent associations of AC with all-cause mortality. Improvements in the predictive accuracy of AC compared to conventional prediction and frailty markers of survival were determined by calculating the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI). In addition, we analyzed differences in mortality by propensity score matching. Propensity score for individuals were determined by logistic regression analysis based on age; sex; clinical frailty scale (CFS); New York Heart Association (NYHA) class III/IV; B-type natriuretic peptide (BNP). The area under the receiver operating characteristic curve was calculated to evaluate the discrimination capability of this propensity score model.

Potential effect modification was assessed by subgroup analyses across age (stratified at 85 years), sex, body mass index (BMI) (stratified at 22 kg/m^2), serum albumin (stratified at 3.5 g/dL), gait speed (stratified at 0.8 m/sec), CFS (stratified at 4), BNP (stratified at the median), and chronic kidney disease (CKD). The p-values for interactions between groups were calculated. All tests with two-sided p-values of < 0.05 were considered significant.

Table 1
Baseline characteristics of study patients.

	Overall, n = 347	Low AC, n = 220	High AC, n = 127	*P* value
Baseline clinical characteristics				
Age, years	84.1 ± 5.0	84.9 ± 5.0	82.7 ± 4.8	<0.001
≥85 years, n	163 (47.0%)	119 (54.1%)	44 (34.6%)	0.001
Male, n	94 (27.1%)	49 (22.3%)	45 (35.4%)	0.009
Height, cm	149.5 ± 8.7	147.9 ± 8.5	152.3 ± 8.3	<0.001
Weight, kg	49.2 ± 9.7	44.6 ± 7.2	57.4 ± 7.9	<0.001
Body mass index, kg/m^2	22.0 ± 3.5	20.4 ± 2.7	24.7 ± 2.8	<0.001
NYHA class, III or IV	130 (37.5%)	96 (43.6%)	34 (26.8%)	0.002
Other frailty markers				
Clinical frailty scale	4.0 ± 1.4	4.3 ± 1.4	3.6 ± 1.2	<0.001
≥4, n	194 (55.9%)	144 (65.5%)	50 (39.4%)	<0.001
5 m walk gait speed, (m/s, n = 312)	0.81 ± 0.31	0.77 ± 0.30	0.86 ± 0.30	0.008
Peak grip strength, (kgf, n = 324)	18.5 ± 6.6	17.1 ± 6.0	20.9 ± 6.8	<0.001
GNRI	96.9 ± 10.3	93.5 ± 9.5	102.7 ± 8.8	<0.001
MMSE, (n = 341)	24.3 ± 4.3	23.5 ± 4.6	25.6 ± 3.5	<0.001
Preprocedural laboratory data				
Creatinine, mg/dL	1.1 ± 0.7	1.1 ± 0.7	1.0 ± 0.3	0.091
Estimated glomerular filtration rate, ml/min	49.8 ± 17.8	49.0 ± 18.8	51.0 ± 15.8	0.309
Hemoglobin, g/dL	11.3 ± 1.6	11.0 ± 1.6	11.7 ± 1.6	0.001
B-type natriuretic peptide, pg/mL	286.9 (137.0–722.8)	379.5 (190.1–822.1)	185.0 (91.8–399.0)	<0.001
Comorbidities				
Peripheral artery disease, n	107 (30.8%)	77 (35.0%)	30 (23.6%)	0.03
Diabetes mellitus, n	91 (26.2%)	48 (21.8%)	43 (33.9%)	0.016
Hypertension, n	292 (84.1%)	175 (79.5%)	117 (92.1%)	0.002
Chronic kidney disease, n	230 (66.3%)	154 (70.0%)	76 (59.8%)	0.06
Chronic obstructive pulmonary disease, n	44 (12.7%)	24 (10.9%)	20 (15.7%)	0.241
Echocardiographic data				
LVEF, %	59.3 ± 13.6	58.2 ± 14.3	61.1 ± 12.2	0.061
AVA, cm^2	0.59 ± 0.19	0.56 ± 0.19	0.63 ± 0.19	0.003
Indexed AVA, cm^2/m^2	0.42 ± 0.12	0.42 ± 0.12	0.41 ± 0.12	0.753
Peak velocity, m/sec	4.5 ± 0.7	4.6 ± 0.7	4.5 ± 0.7	0.74
Peak gradient, mmHg	84.7 ± 26.1	86.0 ± 26.2	82.3 ± 25.9	0.273
Body measurement data				
arm circumference, cm	24.8 (22.0–26.8)	22.9 (20.8–24.6)	27.8 (26.7–29.1)	<0.001

Values are numbers (%) or mean ± SD, median with interquartile range. AVA = aortic valve area; GNRI = Geriatric Nutritional Risk Index; LVEF = left ventricle ejection fraction; MMSE = Mini-Mental State Examination; NYHA = New York Heart Association.

Table 2
Relationships between AC and nutritional markers / frailty markers / age.

Variable	ρ	*P* value
BMI, kg/m^2	0.76	<0.01
Albumin, g/dL	0.14	0.014
GNRI	0.43	<0.01
Clinical Frailty Scale	−0.30	<0.01
Peak grip strength, kgf	0.12	0.035
Age, years	−0.26	<0.01

AC = arm circumference; BMI = body mass index; GNRI = Geriatric Nutritional Risk Index.

3. Results

Distributions of AC in the overall, male, and female populations are shown in Fig. 1, and the baseline characteristics of the study patients are presented in Table 1. The average age of the 347 patients was 84.1 ± 5.0 years, and 72.9% of the patients were women. One-year clinical follow-up was completed in 100% of cases, and 89 patients (31 men, 58 women) died during the median follow-up period of 825 days (IQR: 541–1181 days). The low AC and high AC groups had several differences in baseline characteristics, prevalence of NYHA class III/IV, peripheral artery disease (PAD), diabetes mellitus (DM), hypertension (HT), and CKD (all $p < 0.05$). The low AC group was more fragile than the high AC group based on the frailty markers, such as CFS, gait speed, grip strength, Geriatric Nutritional Risk Index (GNRI) [14], and the Mini-Mental State Examination (MMSE).

The relationships between AC and clinical variables are presented in Table 2. AC was positively correlated with BMI ($p < 0.05$). In addition, there were significant correlations with each frailty marker (all $p < 0.05$).

The Kaplan-Meier survival rates according to AC are presented in Fig. 2. The Kaplan-Meier analysis indicated that the 1-year mortality rates were 4.7% and 14.7% for patients in the high AC and low AC groups, respectively ($p < 0.01$). In terms of the Kaplan-Meier analysis for all-cause mortality, the survival rate was significantly lower for patients in the low AC group (log-rank test $p < 0.001$). After propensity score matching, there were no differences in frailty markers other than BMI and GNRI between high AC group and low AC group (n = 99 pairs, a total of 198 patients) (**Supplementary Table S1**). The Kaplan-Meier analysis for all-cause mortality, the survival rate was significantly lower for patients in the low AC group after propensity score matching (log-rank test $p = 0.043$) (**Supplementary Figure S1**). The area under the receiver operating characteristic curve of this propensity score model was 0.63 (95% CI, 0.56–0.70).

The results of the Cox regression analysis are presented in Table 3. On univariate analysis, the clinical variables of low AC, male, NYHA class III/IV, albumin, eGFR, BNP, and PAD were significant risk factors for increased mortality after TAVR. In the multivariate model, adjustments for the above variables along with age were made. Low AC was significantly associated with an increased risk of mortality (HR: 2.56, 95% confidence interval [CI]: 1.47–4.46, $p < 0.001$). The results of the NRI and IDI analyses of the incremental value of the AC when added to conventional risk factors and other frailty markers are presented in Table 4. Both the NRI and IDI showed significant improvements in predicting outcomes after adding the AC to conventional risk factors (NRI: 0.427, 95% CI: 0.215–0.638, $p < 0.001$; IDI: 0.028, 95% CI: 0.011–0.046, $p = 0.001$, respectively). Furthermore, a significant improvement in predicting outcomes after TAVR was seen after adding AC to other frailty markers. The associations between AC and outcomes were similar regardless of age, sex, BMI, serum albumin, gait speed, CFS, BNP, and CKD (Fig. 3).

4. Discussion

The primary findings of our study were as follows: 1) AC was

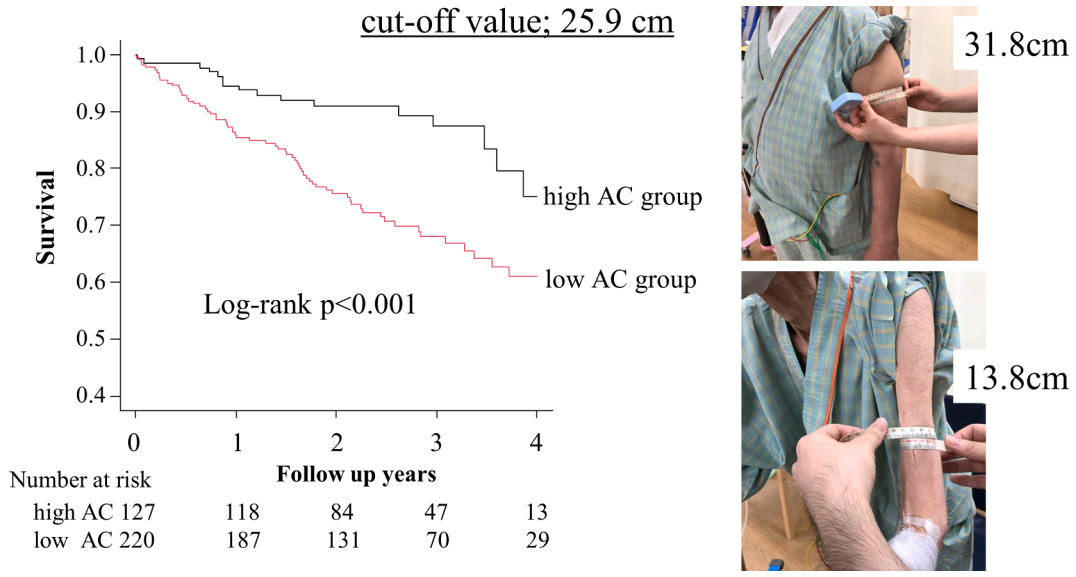

Fig. 2. The Kaplan-Meier survival rates according to arm circumference. AC = arm circumference.

Table 3
Cox regression analysis for the association between all-cause mortality and clinical findings.

	Univariate analysis			Multivariate analysis		
Explanatory variables	HR	95% CI	p value	HR	95% CI	p value
anthropometric data						
Low AC (for high)	2.42	1.44–4.06	<0.001	2.56	1.47–4.46	<0.001
Adjusting factors						
Age (per 1 year increase)	1.03	0.99–1.08	0.13	1.02	0.97–1.07	0.44
Male (for female)	1.59	1.02–2.45	0.038	1.81	1.15–2.85	0.01
NYHA class III/IV (for I/II)	1.56	1.03–2.38	0.037	0.86	0.53–1.40	0.55
Albumin (per 1.0 g/dL increase)	0.29	0.19–0.44	<0.001	0.28	0.17–0.46	<0.001
eGFR (per 1 mL/min/1.73 m^2 increment)	0.98	0.96–0.99	<0.001	0.98	0.97–0.99	0.001
BNP (per 1-SD increment)	1.27	1.07–1.51	0.007	0.99	0.80–1.24	0.96
Peripheral artery disease	1.89	1.23–2.89	0.004	1.58	0.98–2.52	0.059
Diabetes mellitus	1.14	0.71–1.85	0.58	–	–	–
Hypertension	1.01	0.56–1.83	0.97	–	–	–
COPD	0.98	0.51–1.9	0.96	–	–	–
LVEF (per 1% increase)	0.99	0.97–1.00	0.14	–	–	–
Transfemoral (for non-transfemoral)	0.65	0.23–1.82	0.41	–	–	–

AC = arm circumference; BNP = B-type natriuretic peptide; CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = Estimated glomerular filtration rate; HR = hazard ratio; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association.

Table 4
Net reclassification improvement and Integrated discrimination improvement for comparison among frailty markers.

	NRI	95% CI	p value	IDI	95% CI	p value
Model	Reference			Reference		
+ AC	0.427	0.215–0.638	<0.001	0.028	0.011–0.046	0.001
+ BMI vs + AC	0.298	0.058–0.539	0.015	0.02	0.0046–0.035	0.011
+ Clinical frailty scale vs + AC	0.419	0.204–0.634	<0.001	0.03	0.012–0.049	0.001
+ 5 m walk gait speed vs + AC	0.443	0.202–0.684	<0.001	0.025	0.0051–0.045	0.014
+ Peak grip strength vs + AC	0.424	0.197–0.651	<0.001	0.022	0.0049–0.04	0.012
+ GNRI vs + AC	0.357	0.131–0.583	0.002	0.018	0.0045–0.032	0.01
+ MMSE vs + AC	0.375	0.151–0.599	0.001	0.029	0.011–0.048	0.002

AC = arm circumference; BMI = body mass index; CI = confidence interval; GNRI = Geriatric Nutritional Risk Index; IDI = integrated discrimination improvement; MMSE = Mini-Mental State Examination; NRI = net reclassification improvement.
Model; Adjusted for age, Male, NYHA class III/IV, PAD, Albumin, eGFR, B-type natriuretic peptide.

independently associated with outcomes in patients who underwent TAVR; and 2) AC showed complementary prognostic capability to frailty and nutritional markers. This study highlights the importance of anthropometric measurements that can be easily taken in addition to quantitative measures of physical function and nutritional status. Routine anthropometric measurements should be effectively used not only for strategic planning of TAVR, but also for risk stratification of patients undergoing TAVR.

Previous reports have shown that AC is associated with fat-free mass in patients with chronic obstructive pulmonary disease [5] and with mortality risk in elderly persons [1]. Kamiya et al [6,7] have also shown AC to be an independent predictor of physical function in patients with

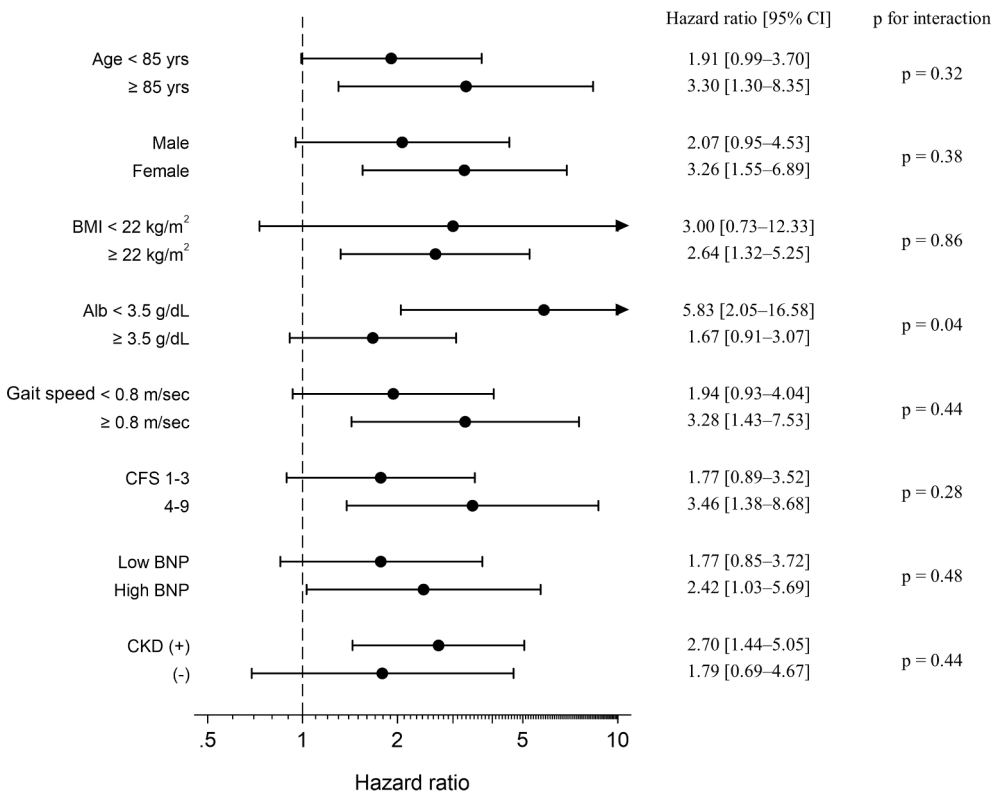

Fig. 3. Arm circumference and outcomes among subgroups. Alb = serum albumin; BNP = B-type natriuretic peptide; CFS = clinical frailty scale; CKD = chronic kidney disease.

heart disease. These reports show that patients with lower AC have worse clinical outcomes, which is consistent with the results of the present study. The reason for AC affecting all-cause mortality is unclear, but the relationships between AC and frailty markers may be a possible explanation. AC was significantly correlated with general nutritional indicators, such as serum albumin and GNRI, and with general physical function (CFS, peak grip strength) in the present study. Inflammation causes pathologies associated with frailty and induces a catabolic state, which leads to loss of muscle mass and worsening prognosis [15]. Low AC may be associated with a poor prognosis by reflecting the presence of inflammation as a cause of frailty.

Another possible explanation is that AC may be a composite reflection of muscle mass and subcutaneous fat mass [4]. Muscle mass [8,16,17] and subcutaneous fat [18,19] have been reported to be associated with a poor prognosis after TAVR, and it is possible that a single anthropometric measurement may combine the characteristics of both parameters. Furthermore, skeletal muscle mass is correlated with cardiopulmonary fitness [20,21], which has been reported to be an important prognostic factor [22–26], and the integration of multiple indicators by AC in the present study may have enabled more accurate risk stratification. In addition, AC was very strongly correlated with BMI. A meta-analysis of patients who underwent TAVR identified the paradoxical survival benefits of a higher BMI in patients defined as obese [27]. However, BMI alone can lead to misclassification in conditions such as heart failure, which can be affected by weight. In the present study, the addition of AC to BMI was shown to significantly improve prognostic value, allowing for more accurate classification of patients with edema that would be misclassified by BMI alone. Therefore, AC was shown to be a very useful index for predicting prognosis after TAVR.

The strong point of the AC is that it can be easily obtained in routine clinical practice using a simple measuring tape, at no cost. In addition, the AC can be measured in a resting sitting position and is useful even in patients with symptoms of heart failure who have difficulty standing or walking. The reproducibility of the AC measurement has been shown to be exceptionally good, with intraclass correlation coefficients of 0.98 for between-observer variation and 0.99 for within-observer variation, with the patient in either the sitting or standing position [28]. Currently, there is a lack of data on the serial changes in anthropometric data after TAVR, so changes in the AC due to nutritional and exercise interventions and their impact on prognosis need to be investigated.

Several limitations of this study should be discussed. First, this was a relatively small retrospective study with limited follow-up. Therefore, the long-term protective effect of high AC is unclear in this population. Second, direct measurement of muscle mass and body fat (e.g., using magnetic resonance imaging or computed tomography) was not performed. However, this was also a strength of the study, because the utility of a metric that can be measured easily in daily clinical practice was demonstrated. Third, the study population was comprised of a homogeneous group of Japanese elderly patients. The distributions of muscle mass and body fat in this cohort were likely different from those of the general population. Again, the age- and race-specific differences should be confirmed by further studies. Fourth, several confounding factors were considered in the Cox regression model, but some potentially important variables were not included in the current model.

5. Conclusions

AC is a useful predictor of short-term and midterm mortality in patients undergoing TAVR. AC is a simple tool to assess a patient's nutritional status and muscle mass and can be used by nongeriatric specialists, thereby increasing its clinical utility. Assessing AC before TAVR will positively affect the clinical care and improve postoperative outcomes of the patients.

Disclosures

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CRediT authorship contribution statement

Kenichi Shibata: Data curation, Conceptualization, Methodology, Writing – review & editing. **Masanori Yamamoto:** Formal analysis, Methodology, Supervision. **Masataka Kameshima:** Data curation, Methodology. **Hiroaki Fujiyama:** Data curation, Methodology. **Taisei Sano:** Data curation, Methodology. **Ai Kagase:** Data curation. **Takahiro Tokuda:** Data curation. **Yuya Adachi:** Data curation. **Ryo Yamaguchi:** Data curation. **Tetsuro Shimura:** Data curation. **Naoki Iritani:** Data curation, Methodology. **Kazuma Murase:** Data curation, Methodology. **Yutaka Koyama:** Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101049.

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