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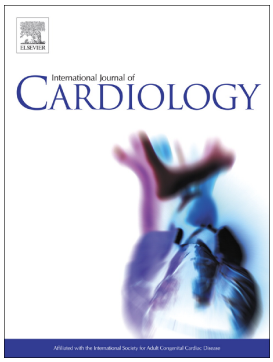

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PII: S0167-5273(22)01337-7

DOI: https://doi.org/10.1016/j.ijcard.2022.09.028

Reference: IJCA 30563

To appear in: *International Journal of Cardiology*

Received date: 22 May 2022

Revised date: 5 August 2022

Accepted date: 12 September 2022

Please cite this article as: S. Higuchi, M. Orban, M. Adamo, et al., Sex-specific impact of anthropometric parameters on outcomes after transcatheter edge-to-edge repair for secondary mitral regurgitation, *International Journal of Cardiology* (2022), https://doi.org/10.1016/j.ijcard.2022.09.028

Sex-specific impact of anthropometric parameters on outcomes after transcatheter edge-to-edge repair for secondary mitral regurgitation

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Grant support

None.

Conflicts of interest

Dr. Higuchi has received lecture fees from Medtronic Japan, Daiichi Sankyo, and Ono Pharmaceutical Company. Dr. Orban has received speaker fees from Abbott Vascular and Tomtec Imaging Systems. Dr. Adamo has received payment from Abbott and Medtronic. Dr. Melica has received consulting fee and honoraria for lectures from Abbott and honoraria for lectures from Edwards. Dr. Karam has received consultant fees from Abbott Vascular. Dr. Praz has received travel expenses from Abbott Vascular, Polares Medical and Edwards. LifesciencesDr. Kalbacher has received lecture fees and travel expenses by Abbott and proctor and lecture fees as well as travel expenses by Edwards Lifesciences. Dr. Schofer has received personal fees from Boston Scientific and travel compensation from Abbott Vascular and Edwards Lifesciences. Dr. Ludwig has received travel compensation from Abbott Vascular. Dr. Braun has received speaker honoraria from Abbott Vascular. Dr. Windecker has received grants from Abbott, Amgen, Astra Zeneca, BMS, Bayer, Biotronik, Boston Scientific, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Johnson & Johnson, Medicure, Medtronic, Novartis, Polares, OrPha Suisse, Pfizer, Regeneron, Sanofi-Aventis, Sinomed, Terumo and V-wave. Dr. Pfister has received consulting fees from Edwards Lifesciences, honoraria for lectures and financial support for attending symposia by Abbott Vascular, and honoraria for lectures from Edwards Lifesciences. Dr. von Bardeleben has received speaker fees from Abbott Vascular and Edwards Lifesciences. Dr. Lurz has received grants from Abbott Vascular, Edwards Lifesciences, and ReCor Medical. Dr. Petronio has received consulting fees and honoraria for lectures from Abbott and Medtronic, consulting fee from Boston, and honoraria fee from Daiichi Sankyo. Dr. Hausleiter has received research support and speaker honoraria from Abbott Vascular and Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Abstract

Background: Body surface area (BSA) has been reported to be the stronger predictor for prognosis than body mass index in heart failure (HF) patients. The sex-specific association of BSA with mortality has been unclear.

Methods: EuroSMR, a European multicenter registry, included patients who underwent edge-to-edge repair (TEER) for secondary mitral regurgitation (SMR). The outcome was two-year all-cause mortality.

Results: The present cohort included 1594 HF patients (age, 74 ± 10 years; male, 66%). Association of calculated BSA with two-year all-cause mortality was evaluated. Patients were classified into three BSA groups: the lowest 10% (S), the highest 10% (L), and intermediate between S and L (M). Mean BSA was 1.84 ± 0.21 m^2 (male, 1.94 ± 0.18 m^2; female, 1.73 ± 0.18 m^2). The association of BSA with the endpoint in females showed a U-shaped curve, indicating worse prognosis for both S and L. The association in males followed a linear regression, demonstrating better prognosis for L. Hazard ratio (HR) of L to S in males was 0.43 (95% confidence interval [CI], 0.25–0.74; p = 0.002), whereas HR of L to M in females was 1.76 (95% CI, 1.11–2.78; p = 0.016) (p for interaction= 0.003).

Conclusions: Sex-specific association patterns demonstrate the complex influence of anthropomorphic factors in HF patients scheduled for TEER. Further investigation beyond

simple evaluation of weight and height is needed for better comprehension of the obesity paradox and better prediction of the results of transcatheter therapy in HF patients.

Keywords: obesity paradox; heart failure; secondary mitral regurgitation; transcatheter edge-to-edge repair; sex difference

1. Introduction

Anthropometric parameters of height and body weight (BW) can influence the course of multiple diseases. The most widely applied parameters are body mass index (BMI) and body surface area (BSA). Most research has focused on the body mass index (BMI), which has been used to define obesity as ≥ 30kg/m^2[1]. Increased BMI is a risk factor for the development of cardiovascular diseases with adverse prognosis.

In stark contrast, higher BMI can be associated with better prognosis in cardiovascular patients, a phenomenon termed obesity paradox [2, 3]. As such, cardiac cachexia, defined as low BMI concomitant with metabolic or cardiovascular disorders[4], was a predictor for adverse clinical events [5]. Studies in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement have shown that the association of BMI and mortality is not linear, but U-shaped [6]. Strikingly, also in noncardiac diseases such as chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) and stroke, overweight and mild forms of obesity are associated with lower mortality rates [7-9].

This obesity paradox has also been shown in heart failure (HF) patients, which frequently present with various comorbidities [10]. In valvular heart failure, low BMI (<20 kg/m^2) is a risk factor in patients with severe mitral regurgitation treated with transcatheter edge-to-edge mitral valve repair (TEER)[11]. Such association was observed in patients with SMR, not in those with primary MR. A recent multicenter analysis of patients suffering from HF with

reduced ejection fraction (HFrEF) and secondary mitral regurgitation (SMR) found a significant association for BSA but not BMI with all-cause mortality [12]. BSA has also been reported to be the stronger predictor for prognosis than BMI in HF patients [13], although BMI and BSA indices are calculated from the same variables, namely height and BW. Whether these different effects of anthropometric parameters can be explained by sex are subject of debate[14]. Indeed, distribution and amount of fat would be different between males and females[15]; therefore, significance of physique should be complicated and carefully interpreted.

Therefore, the present study aimed to investigate the sex-specific association of BSA with long-term mortality and anatomical characteristics in HF patients with SMR undergoing mitral TEER.

2. Methods

2.1. Study population

The EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry (registered at German Clinical Trials Register; DRKS00017428) is a retrospective, multicenter registry including eleven academic centers across Europe (Germany, Switzerland, France, Italy, and Portugal). The present study collected data on the clinical characteristics and outcomes of HF patients with SMR who underwent mitral TEER between November 2008 and January 2021. This study protocol conforms to the 1975 Declaration of Helsinki and is in line with the local ethical guidelines. All patients were regarded to be at high or prohibitive surgical risk. Each recommendation for mitral TEER was made by an interdisciplinary heart team at each institute, considering SMR severity, cardiac function, symptoms, patient background, and life expectancy. Patients were treated with standard guideline-directed medical therapy and cardiac resynchronization therapy, if applicable. Patient characteristics including age, sex, height, BW, diabetes mellitus (DM), atrial fibrillation and/or flutter, COPD, history of myocardial infarction, stroke, New York Heart Association (NYHA) classification, estimated glomerular filtration rate (eGFR), device therapy, echocardiographic findings, and 2-year all-cause mortality were collected. Patients with missing data of height, BW, and sex were excluded from the present analysis. Mitral TEER was performed using either MitraClip NT, NTR or XTR (Abbott Structural Heart,

Santa Clara, California) by a standard protocol, as described previously [16].

2.2. Study Endpoint and follow-up

The present study evaluated two-year all-cause mortality. The follow-up was completed on the last medical interview date, the last examination date, or the date when an endpoint event was observed, whichever came first.

2.3. Echocardiographic analysis

Echocardiography was conducted and analyzed by experienced investigators at each institute. All patients underwent transthoracic and transesophageal echocardiography before mitral TEER. SMR severity was assessed based on an integrative approach according to the European recommendations for assessment of native valvular regurgitation [17, 18]. Each cutoff value of left ventricular dilatation (LV-Dil) was determined based on time-dependent receiver operating characteristic curve according to its discriminatory value for 2-year mortality (males, LVEDV ≥181 ml; females, LVEDV ≥129 ml). Right ventricular (RV)-pulmonary arterial (PA) coupling, which refers to the association between the RV contractility and afterload, was defined as tricuspid annular plane systolic excursion (TAPSE)-to-systolic pulmonary artery pressure (sPAP) ratio (mm/mmHg). RV dysfunction (RV-Dys) was diagnosed if TAPSE-to-sPAP ratio was <0.274 mm/mmHg, which was

determined based on receiver operator characteristic analysis using the Youden index according to its discriminatory value for 2-year mortality [19].

2.4. Definitions

BSA was calculated from height and BW according to the simplified formula by Mosteller [20], (BW [kg] x height [cm] / 3600)$^{0.5}$. BMI was defined as BW (kg) / height (m^2). Improvement in NYHA functional class was defined as at least one class improvement from baseline to follow-up.

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation if Skewness-Kurtosis test did not reject the hypothesis of normality. Otherwise, variables are displayed as median and interquartile range values. Categorical variables are expressed as absolute numbers or percentages. Continuous variables were analyzed using unpaired Student's t-tests or Mann–Whitney U tests, while Fisher's exact test or the chi-squared test was used for categorical variables. BSA were classified into three groups: the lowest 10% of patients (S), the highest 10% of patients (L), and intermediate between S and L (M), respectively (males: S, < 1.72 m^2; M, ≥ 1.72 m^2 and < 2.19 m^2; L, ≥ 2.19 m^2; females: S, < 1.50 m^2; M, ≥ 1.50 m^2 and < 1.96 m^2; L, ≥ 1.96 m^2). The cumulative incidence of two-year all-cause mortality was

assessed using Kaplan-Meier-estimated curve with log-rank test. The risk of mortality was assessed using Cox regression analysis and expressed as hazard ratio (HR) with 95% confidence interval (CI). Variables with a $p < 0.10$ in the univariate Cox regression analysis were selected for multivariable Cox regression analysis. To evaluate a possible interaction between BSA and sex, models with and without the interaction term of two variables were compared and the p value was calculated using a likelihood ratio test. In the interaction analysis, BSA was normalized and assessed as both continuous and categorical values. Normalized BSA was classified based on tertile and the aforementioned category (the lowest 10%, the intermediate 80%, and the highest 10%). The model for males included age, DM, eGFR, beta blockers, NT-proBNP, RV-Dys, and residual MR of ≤1+. The model for females included NYHA function class ≥II, renin-angiotensin-system inhibitors, NT-proBNP, RV-Dys, LVEDV, and residual MR of ≤1+. The association of BSA with anatomical characteristics (only binary variables) or improvement in NYHA function class was assessed using univariate logistic regression analyses and expressed as odds ratio (OR) and 95% CI. Statistical significance was defined as p value <0.05. All statistical analyses were carried out using Stata version 14 (Stata Corp; College Station, TX, USA).

3. Results

3.1. Patient characteristics

Of 1626 patients, 32 were excluded owing to missing data (BSA, 25; sex, 2; NYHA at baseline, 3; MR severity at baseline and post procedure, 2). Accordingly, 1594 patients (age, 74 ± 10 years; male, 66%) were analyzed. BSA was 1.87 ± 0.21 m^2 (male, 1.94 ± 0.18 m^2; female, 1.73 ± 0.18 m^2; $p < 0.001$) and BMI was 25.8 ± 4.4 kg/m^2 (male, 25.9 ± 4.1 kg/m^2; female, 25.6 ± 4.9 kg/m^2; $p = 0.237$). Patient characteristics are displayed in Table 1 and supplemental Table 1 (male BSA groups) and 2 (female BSA groups). History of myocardial infarction, CKD, DM, COPD, and stroke were observed in 311 (31%), 1080 (68%), 484 (30%), 276 (17%), and 143 (9%) patients, respectively. LVEF was 35 ± 12%. Before TEER, MR was graded 3+ in 793 (50%) and 4+ in 746 (47%) patients. After TEER, MR grade was ≤1+ in 1043 (65%), 2+ in 445 (28%), 3+ in 78 (5%), and 4+ in 28 (2%) patients, respectively. Females presented with lower prevalence of previous myocardial infarction and DM, a higher prevalence of CKD, higher LVEF, smaller LVEDV, and higher TAPSE/sPAP ratio than males.

3.2. Association of BSA with 2-year all-cause mortality

The median follow-up duration was 611 (329–1112) days and all-cause mortality at 2 years was observed in 472 patients (29.6 %). Restricted cubic spline curves demonstrated a different association pattern of BSA with mortality between males and females (Figure 1). In

females, the association showed a U-shaped curve, while in males the association followed a linear regression. A similar pattern with different sex-specific associations was also observed for BMI (supplemental Figure 1).

Kaplan Meier curves demonstrated the association of BSA with mortality in males and females for the small (S), moderate (M), and large (L) BSA groups (Figure 2). Overall, BSA was associated with a lower 2-year all-cause mortality (HR in an increase of 0.2 m^2, 0.89; 95% CI, 0.82–0.98: p = 0.012) and BMI was not (HR in an increase of 1 kg/m^2, 0.99; 95% CI, 0.97–1.01; p = 0.364). The results of univariate Cox regression analyses for the overall cohort, males or females are shown in Supplemental Table 3. Age, history of myocardial infarction, CKD, DM, beta blocker intake, and TR severity ≥2+ predicted mortality in the overall cohort or males but did not in females. History of CABG and LVEF predicted mortality in the overall cohort or females but did not in males. NYHA class IV, NT-proBNP, RAS-I intake, RV-Dys, and residual MR (resMR) ≤1+ were predictors regardless of sex.

Univariate Cox regression analysis confirmed these patterns, as males in M and L group had a lower 2-year all-cause mortality than those in S group (HR in M group, 0.70; 0.50–0.97; p = 0.030; HR in L group, 0.43; 95% CI, 0.25–0.74; p = 0.002, respectively). Contrary, in female patients, S group and L group indicated higher mortality when compared to M group (HR in S group, 1.68; 95% CI, 1.02–2.76; p = 0.042; HR in L group, 1.76; 95% CI, 1.11–2.78; p = 0.016, respectively). Multivariate Cox regression analysis for 2-year all-cause

mortality, revealed that in males, a higher BSA was protective (HR, 0.38; 95% CI, 0.15–0.94; p = 0.037), whereas in females a higher BSA was harmful (HR, 2.73; 95% CI, 1.15–6.50; p = 0.023) (Table 2).

3.3. Interaction of BSA and sex for prognosis

Comparing models with and without square term of normalized BSA and sex, the likelihood ratio test indicated a significant interaction between the two variables (p = 0.009). Such interaction was also significant when normalized BSA was categorized based on tertile (p = 0.001) or classification of the lowest 10%, the intermediate 80%, and the highest 10% (p = 0.011). However, the interaction differed based on the range of normalized BSA. The interaction was not significant in the lowest tertile of normalized BSA (p = 0.934), while significant in the higher two tertile (p = 0.0044). This different interaction was similar if category was divided by the lowest 10%, the intermediate 80%, and the highest 10% (the lowest 10%, p = 0.863; the others, p = 0.003).

3.4. Association of BSA with anatomical characteristics

Supplemental Table 4 shows the association of certain echocardiographic characteristics with BSA in both sexes. LV-Dil was significantly correlated with BSA in males, but not in females. Females in L group tended to be related to a higher prevalence of RV-Dys, while

there was no association in males. Finally, males in L group presented with a lower prevalence of TR of ≥2+ compared to S group, while females did not indicate such association.

4. Discussions

To the best of our knowledge, this is the first study investigating the sex-specific impact of BSA on mortality in HFrEF patients with SMR. BSA was a strong predictor for 2-year all-cause mortality after TEER. While in males this association showed a pattern of linear regression, we observed a U-shaped pattern in females, conferring increased mortality risk to obese females, but not to obese males. In both sexes, low BSA, in which cachexia might be included, was an independent predictor for mortality.

While the importance of BSA as the predictor for adverse clinical outcomes is evident through our study, the pathophysiology is less understood. The "obesity paradox" in the setting of HF has been established according to previous studies [2, 5, 21, 22]. The majority of such reports evaluated obesity based on BMI. Evaluation by BSA seemed to be less frequent despite being potentially more accurate for outcome prediction [13]. Both indices are calculated from height and BW. Whereas these two parameters are equally assessed in BSA, they are not in BMI due to the square of height in its formula. This difference could have different impact on outcome. In fact, the restricted cubic spline curves of BSA and BMI in each sex resembled, but BSA had a stronger association with mortality than BMI. Therefore, it may be preferrable to use BSA rather than BMI for risk prediction based on BW and height.

Currently, the mechanism of the obese paradox has been unclear. BSA seems to be a

simple and useful parameter for risk stratification, but is thought to be just an indicator, which does not sufficiently approach to pathophysiology on its own. Among individuals who have similar BSA, some individuals could for example have considerable amount of skeletal muscle whereas others might have relevant body fat. Further, fat is classified into visceral and subcutaneous fat. The former contributes to adverse cardiocerebrovascular events and the latter protects against such events [15, 23, 24]. Waist-to-hip ratio, which reflects skeletal muscle as well as fat deposition, has been reported to predict mortality more accurately than BMI in HF patients[25]. This simple evaluation would contribute to more accurate prediction. These findings imply that not quantity, but quality of BW would be essential to solve the obesity paradox. We believe that BSA contributes to patient risk stratification, but these remaining issues warrant further evaluation with a focus on the relative contribution of different tissues (e.g., skeletal muscle, visceral fat, or subcutaneous fat) and metabolic state (e.g., malnutrition and cardiac cachexia).

The specific sex-related difference in outcome based on BSA observed in our SMR patients has not been reported so far in other clinical settings. It is noteworthy that higher BSA predicted higher mortality in females, but lower mortality in males. Males are likely to gain muscle mass rather than fat with exercise compared to women due to higher level of testosterone in males [26]. Therefore, among patients with larger BSA, males might present with a higher muscle/fat ratio than females. Namely, sarcopenic obese might be observed

more frequently in females than males. A lower muscle/fat ratio could be harmful when suffering from chronic diseases. Sex-specific different distribution of fat accumulation could also contribute to the present results [27]. On the other hand, lower BSA was consistently associated with worse prognosis in both sexes in our study and others, which might be due to cardiac cachexia. As HF is a catabolic state with a high resting metabolic rate [13], more severe HF patients could be prone to progressive weight loss.

Our study shows that a more complex statistical analysis is necessary to reveal associations of BSA or BMI based on sex, as distinct association patterns can be revealed. Analyzing overall patient cohorts could lead to inaccurate conclusions for the impact of therapeutic interventions in males vs. females. Statistical methods for survival analysis such as Cox regression analysis could overlook a U-shaped association as we have seen in female patients in the present study. As such, BMI was not a significant predictor for death in our study if evaluated regardless of sex. But BMI might be a sex-specific predictor for clinical adverse events also in HF patients [28]. Physique may be related to associated cardiac anatomical features more strongly in males than females. Considering the high prevalence of LV-Dil in male patients with large BSA, it might be possible to deploy multiple edge-to-edge devices into the mitral valve to achieve more MR reduction without risking mitral stenosis.

The present study raised some important questions. Do any interventions for BW improve prognosis as this is a modifiable parameter? This would be of interest in especially

in women with high BSA and men with low BSA who had higher mortality risks. A previous study indicated that cardiopulmonary fitness attenuated the risk of HF development in individuals with obesity as well as normal weight and overweight[29]. However, this study did not assess HF patients and excluded individuals with BMI of <18.5 kg/m^2. It is unclear whether such findings are observed in fragile HF patients with SMR, some of whom may not be able to have sufficient cardiopulmonary fitness. To answer these questions, future studies within the field of valvular heart failure will have to evaluate nutrition, skeletal muscle and adipose tissue biomarkers, exercise capacity, and relative amount of muscle and fat.

4.1. Study Limitations

This study has several limitations. First, although our study adjusted potential confounders thoroughly, there might be other undetectable confounders. Second, other constitutional parameters such as visceral and subcutaneous fat accumulation may be more accurate than BSA and BMI but are very elaborate. However, it would be difficult to acquire routinely information of fat accumulation patterns in clinical practice given that abdominal computed tomography or magnetic resonance imaging is necessary to acquire them. Third, this study could not determine the number of patients with cardiac cachexia because of lack of necessary biomarkers for establishing diagnosis. Fourth, causes of death were not available in the current cohort. Finally, this cohort included mostly HFrEF patients with SMR. It is

unknown whether the findings are generalized to other cohorts, such as atrial secondary MR. However, it is plausible that analysis of BSA or BMI should be conducted separately based on males and females even in other diseases before analysis of overall cohorts. Establishment and validation of certain cutoff values of BSA are necessary in the future to enable risk prediction in the specific setting of SMR treated with TEER, but also for other cardiovascular diseases. Without a detailed anatomic analysis of the mitral valve apparatus, an explanation for the observed higher rates of lower resMR in males with high BSA is challenging.

5. Conclusions

BSA is a stronger and more differential predictor than BMI for outcome in HF patients with SMR. Sex-specific association patterns demonstrate the complex influence of anthropometric parameters in chronic diseases like SMR. Further investigation beyond simple evaluation of weight and height would be needed for the comprehension of the obesity paradox in heart failure patients.

Acknowledgement

We thank all staff at the EuroSMR registry for their support in the data acquisition.

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Figure legends

Figure 1. Different impact of BSA on 2-year all-cause mortality based on sex

Restricted cubic spline curve demonstrates the association of BSA with 2-year all-cause mortality in all patients (A), men (B), and women (C). It is noteworthy that men showed a linear regression, while women disclosed a U-shaped curve of association. Groups were formed according to BSA at baseline: the lowest 10% of patients (S), the highest 10% of patients (L), and intermediate between S and L (M).

Males: S, < 1.72 m2; M, ≥ 1.72 m2 and < 2.19 m2; L, ≥ 2.19 m2

Females: S, < 1.50 m2; M, ≥ 1.50 m2 and < 1.96 m2; L, ≥ 1.96 m2

BSA, body surface area

Figure 2. Kaplan Meier survival curves stratified by BSA

Overall, larger BSA was associated with lower 2-year all-cause mortality in all patients (A). Males (B) demonstrated a similar association with lower BSA conferring risk, but females (C) in both L and S groups were related to higher mortality than those in M group.

Males: S, < 1.72 m^2; M, ≥ 1.72 m^2 and < 2.19 m^2; L, ≥ 2.19 m^2

Females: S, < 1.50 m^2; M, ≥ 1.50 m^2 and < 1.96 m^2; L, ≥ 1.96 m^2

BSA, body surface area; TEER, transcatheter edge-to-edge repair

Supplemental Figure 1. Association of BMI with two-year all-cause mortality in males and females

Restricted cubic spline curve demonstrates the association of BMI with 2-year all-cause mortality in males (A) and females (B). As with body surface area, males showed a linear regression, while females disclosed a U-shaped curve.

Table 1. Patient characteristics

	All	Males	Females	
	n = 1594	n = 1047	n = 547	p value
Age, years	74 ± 10	72 ± 10	76 ± 9	< **0.001**
Body surface area, m^2	1.87 ± 0.22	1.94 ± 0.18	1.73 ± 0.18	< **0.001**
Body mass index, kg/m^2	26 ± 4	26 ± 4	26 ± 5	0.237
History of myocardial infarction, n (%)	500 (31)	372 (36)	128 (23)	< **0.001**
History of PCI, n (%)	516 (32)	373 (36)	143 (26)	< **0.001**
History of CABG, n (%)	306 (19)	250 (24)	56 (10)	< **0.001**
History of ICD, n (%)	218 (14)	169 (16)	49 (9)	< **0.001**
History of CRT, n (%)	362 (23)	289 (28)	73 (13)	< **0.001**
History of Afib or Aflut, n (%)	962 (60)	646 (62)	316 (58)	0.128

Ischemic mitral regurgitation, n (%)	807 (51)	572 (55)	235 (43)	< **0.001**
NYHA classification IV at baseline, n (%)	349 (22)	246 (23)	103 (19)	**0.032**
Chronic kidney disease, n (%)	1080 (68)	681 (65)	399 (73)	**0.001**
Diabetes mellitus, n (%)	484 (30)	336 (32)	148 (27)	**0.038**
Chronic obstructive pulmonary disease, n (%)	276 (17)	188 (18)	88 (16)	0.349
History of stroke, n (%)	143 (9)	98 (9)	45 (8)	0.455
NT-proBNP, pg/ml)	3018 (1232-6692)	3445 (1529-6931)	2473 (691-6033)	< **0.001**
eGFR, ml/min/1.73m2	48 ± 22	50 ± 23	44 ± 19	< **0.001**
Logistic EuroSCORE	16.5 (9.5-27.8)	16.3 (9.0-27.9)	17.0 (10.3-27.8)	0.242
RAS-I, n (%)	1024 (64)	661 (63)	363 (66)	0.202
Beta blockers, n (%)	1222 (77)	802 (77)	420 (77)	0.935
MRA, n (%)	726 (46)	509 (49)	217 (40)	< **0.001**

Echocardiography characteristics				
LVEF, %	35 ± 12	33 ± 11	39 ± 13	< **0.001**
LVEDV, ml	183 ± 79	204 ± 77	140 ± 65	< **0.001**
LV-Dil*	NA	573 (55)	245 (45)	< **0.001**
MR severity at baseline				**0.001**
moderate (2+)	55 (3)	35 (3)	20 (4)	
moderate-to-severe (3+)	793 (50)	487 (47)	306 (56)	
severe (4+)	746 (47)	525 (50)	221 (40)	
MR EROA, cm^2	0.33 ± 0.23	0.34 ± 0.25	0.29 ± 0.19	< **0.001**
MR volume, ml	43 ± 23	44 ± 24	42 ± 22	0.387
MR vena contracta, mm	5.9 ± 3.0	6.2 ± 2.9	5.4 ± 3.2	< **0.001**
TR severity at baseline moderate or severe	888 (56)	576 (55)	312 (57)	0.440

TR vena contracta, mm	5.4 ± 2.9	5.5 ± 2.9	5.3 ± 2.8	0.242
RA area, cm2	24 ± 8	25 ± 8	21 ± 7	< **0.001**
TAPSE, mm	17 ± 5	17 ± 5	18 ± 5	< **0.001**
sPAP, mmHg	47 ± 14	48 ± 14	47 ± 14	0.074
TAPSE/sPAP, mm/mmHg	0.398 ± 0.206	0.391 ± 0.215	0.414 ± 0.188	0.073
RV-Dys	274 (17)	197 (19)	77 (14)	**0.017**
MR severity post mitral TEER				0.868
none or mild (≤1+)	1043 (65)	677 (65)	366 (67)	
moderate (2+)	445 (28)	296 (28)	149 (27)	
moderate-to-severe (3+)	78 (5)	54 (5)	24 (4)	
severe (4+)	28 (2)	20 (2)	8 (1)	

Afib, atrial fibrillation; Aflut, atrial flutter; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; ICD, implantable cardioverter defibrillator; LV-Dil, left ventricular dilatation; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RA, right atrium; RAS-I, renin-angiotensin system inhibitors; RV-Dys, right ventricle dysfunction; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation

* LV-Dil in males and females were defined as LVEDV ≥181 ml and ≥129 ml, respectively.

Table 2. Multivariate Cox regression analysis for 2-year all-cause mortality

	Univariate analysis						Multivariate analysis					
	Males			Females			Males			Females		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
S Group	1.00 (reference)			1.68	1.02-2.76	**0.042**	1.00 (reference)			0.82	0.24-2.83	0.759
M Group	0.70	0.50-0.97	**0.030**	1.00 (reference)			0.58	0.33-1.00	0.056	1.00 (reference)		
L Group	0.43	0.25-0.74	**0.002**	1.76	1.11-2.78	**0.016**	0.38	0.15-0.94	**0.037**	2.73	1.15-6.50	**0.023**

Parameters with a p-value < 0.1 were included in the multivariate models.

Model for males: adjustment for age, diabetes mellitus, estimated glomerular filtration rate, NT-proBNP, beta blockers, right ventricle dysfunction, and residual mitral regurgitation of ≤1+

Model for females: adjustment for New York Heart Association functional class IV, renin-angiotensin system inhibitors, NT-proBNP, right ventricle dysfunction, left ventricular end-diastolic volume, and residual mitral regurgitation of ≤1+

Males: S Group, < 1.72 m^2; M Group, ≥ 1.72 m^2 and < 2.19 m^2; L Group, ≥ 2.19 m^2

Females: S Group, < 1.50 m^2; M Group, ≥ 1.50 m^2 and < 1.96 m^2; L Group, ≥ 1.96 m^2

BSA, body surface area; CI, confidence interval; HR, hazard ratio

Supplemental Table 1. Male patient characteristics based on BSA classification

	S group n = 109	M group n = 835	L group n = 103	p value
Age, years	72 ± 12	73 ± 10	68 ± 9	**0.001**
Body surface area, m^2	1.65 ± 0.07	1.93 ± 0.12	2.30 ± 0.11	**<0.001**
Body mass index, kg/m^2	21 ± 2	26 ± 3	32 ± 4	**<0.001**
History of myocardial infarction, n (%)	44 (40)	302 (36)	26 (25)	0.053
History of PCI, n (%)	42 (39)	303 (36)	28 (27)	0.615
History of CABG, n (%)	31 (28)	201 (24)	18 (17)	0.186
History of ICD, n (%)	14 (13)	135 (16)	20 (19)	0.698
History of CRT, n (%)	27 (25)	225 (27)	37 (36)	0.055
History of Afib or Aflut, n (%)	56 (51)	524 (63)	66 (64)	0.059

Ischemic mitral regurgitation, n (%)	69 (63)	461 (55)	42 (41)	**0.012**
NYHA classification IV at baseline, n (%)	33 (30)	189 (23)	24 (23)	0.201
Chronic kidney disease, n (%)	79 (72)	538 (64)	64 (62)	0.222
Diabetes mellitus, n (%)	27 (25)	264 (32)	45 (44)	**0.007**
Chronic obstructive pulmonary disease, n (%)	15 (14)	158 (19)	15 (15)	0.298
History of stroke, n (%)	6 (6)	82 (10)	10 (10)	0.356
NT-proBNP, pg/ml)	5008 (1441–11941)	3485 (1573–6843)	2680 (1319–5210)	0.088
eGFR, ml/min/1.73m2	44 ± 26	50 ± 22	57 ± 24	**0.036**
Logistic EuroSCORE	19.3 (9.6–33.0)	16.2 (9.2–27.6)	12.8 (5.7–25.4)	**0.012**
RAS-I, n (%)	63 (58)	520 (62)	78 (76)	**0.002**
Beta blockers, n (%)	76 (70)	640 (77)	86 (83)	**0.002**
MRA, n (%)	58 (53)	397 (48)	54 (52)	0.299

Echocardiography characteristics				
LVEF, %	34 ± 11	33 ± 11	32 ± 11	0.439
LVEDV, ml	187 ± 64	202 ± 74	237 ± 98	**<0.001**
LV-Dil*	50 (46)	458 (55)	65 (63)	**0.015**
MR severity at baseline				0.118
moderate (2+)	4 (4)	27 (3)	4 (4)	
moderate-to-severe (3+)	38 (35)	399 (48)	50 (49)	
severe (4+)	67 (61)	409 (49)	49 (48)	
MR EROA, cm^2	0.36 ± 0.29	0.35 ± 0.25	0.31 ± 0.15	**<0.001**
MR volume, ml	40 ± 19	45 ± 25	40 ± 19	**0.001**
MR vena contracta, mm	6.9 ± 2.5	6.1 ± 3.0	6.0 ± 2.5	**0.046**
TR severity at baseline moderate or severe	70 (64)	462 (55)	44 (43)	**0.003**

TR vena contracta, mm	6.0 ± 3.9	5.6 ± 2.8	4.5 ± 2.6	**0.009**
RA area, cm2	22 ± 6	26 ± 8	27 ± 8	0.086
TAPSE, mm	17 ± 4	17 ± 5	18 ± 5	0.660
sPAP, mmHg	49 ± 13	48 ± 15	47 ± 13	0.103
TAPSE/sPAP, mm/mmHg	0.387 ± 0.298	0.391 ± 0.208	0.390 ± 0.153	**<0.001**
RV-Dys	19 (17)	161 (19)	17 (17)	0.651
MR severity post mitral TEER				0.418
none or mild (≤1+)	63 (58)	537 (64)	77 (75)	
moderate (2+)	37 (34)	236 (28)	23 (22)	
moderate-to-severe (3+)	7 (6)	45 (5)	2 (2)	
severe (4+)	2 (2)	17 (2)	1 (1)	

Afib, atrial fibrillation; Aflut, atrial flutter; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; ICD, implantable cardioverter defibrillator; LV-Dil, left ventricular dilatation; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RA, right atrium; RAS-I, renin-angiotensin system inhibitors; RV-Dys, right ventricle dysfunction; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation

* LV-Dil in males was defined as LVEDV ≥181 ml.

Supplemental Table 2. Female patient characteristics based on BSA classification

	S group n = 52	M group n = 438	L group n = 57	p value
Age, years	78 ± 9	76 ± 9	72 ± 9	0.982
Body surface area, m^2	1.42 ± 0.06	1.73 ± 0.12	2.07 ± 0.09	**<0.001**
Body mass index, kg/m^2	20 ± 2	25 ± 4	34 ± 5	**<0.001**
History of myocardial infarction, n (%)	17 (33)	96 (22)	13 (23)	0.238
History of PCI, n (%)	13 (25)	114 (26)	16 (28)	0.684
History of CABG, n (%)	8 (15)	42 (10)	6 (11)	0.343
History of ICD, n (%)	3 (6)	39 (9)	7 (12)	0.631
History of CRT, n (%)	7 (13)	7 (14)	3 (5)	0.149
History of Afib or Aflut, n (%)	17 (33)	259 (59)	40 (70)	**<0.001**

Ischemic mitral regurgitation, n (%)	26 (50)	184 (42)	25 (44)	0.599
NYHA classification IV at baseline, n (%)	17 (33)	73 (17)	13 (23)	**0.019**
Chronic kidney disease, n (%)	40 (77)	316 (72)	43 (75)	0.882
Diabetes mellitus, n (%)	7 (13)	116 (26)	25 (44)	**0.001**
Chronic obstructive pulmonary disease, n (%)	11 (21)	65 (15)	12 (21)	0.252
History of stroke, n (%)	5 (10)	36 (8)	4 (7)	0.917
NT-proBNP, pg/ml)	3757 (587–10186)	2547 (865–5796)	1770 (432–3498)	0.167
eGFR, ml/min/1.73m2	41 ± 22	45 ± 19	45 ± 20	0.234
Logistic EuroSCORE	18.7 (12.7–30.5)	17.2 (10.3–27.8)	14.5 (8.7–27.3)	0.424
RAS-I, n (%)	35 (67)	285 (65)	43 (75)	0.194
Beta blockers, n (%)	39 (75)	331 (76)	50 (88)	0.079
MRA, n (%)	23 (44)	165 (38)	29 (51)	**0.021**

Echocardiography characteristics				
LVEF, %	40 ± 13	39 ± 13	40 ± 14	0.929
LVEDV, ml	120 ± 49	141 ± 66	153 ± 66	**0.041**
LV-Dil*	20 (38)	195 (45)	30 (53)	0.436
MR severity at baseline				0.052
moderate (2+)	3 (6)	17 (4)	0 (0)	
moderate-to-severe (3+)	23 (44)	243 (55)	40 (70)	
severe (4+)	26 (50)	178 (41)	17 (30)	
MR EROA, cm^2	0.30 ± 0.18	0.29 ± 0.20	0.29 ± 0.14	0.954
MR volume, ml	42 ± 24	42 ± 21	43 ± 22	0.983
MR vena contracta, mm	5.8 ± 2.9	5.5 ± 3.2	4.9 ± 3.2	0.312
TR severity at baseline moderate or severe	31 (60)	252 (58)	29 (51)	0.661

TR vena contracta, mm	5.9 ± 3.1	5.1 ± 2.7	5.8 ± 3.7	0.355
RA area, cm2	18 ± 6	22 ± 7	23 ± 9	**0.004**
TAPSE, mm	17 ± 5	18 ± 5	19 ± 5	0.351
sPAP, mmHg	46 ± 13	46 ± 14	49 ± 12	0.465
TAPSE/sPAP, mm/mmHg	0.412 ± 0.224	0.420 ± 0.188	0.370 ± 0.147	0.319
RV-Dys	9 (17)	57 (13)	11 (19)	0.110
MR severity post mitral TEER				0.772
none or mild (≤1+)	36 (69)	291 (66)	39 (68)	
moderate (2+)	13 (25)	122 (28)	14 (25)	
moderate-to-severe (3+)	1 (2)	19 (4)	4 (7)	
severe (4+)	2 (4)	6 (1)	0 (0)	

Afib, atrial fibrillation; Aflut, atrial flutter; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; ICD, implantable cardioverter defibrillator; LV-Dil, left ventricular dilatation; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RA, right atrium; RAS-I, renin-angiotensin system inhibitors; RV-Dys, right ventricle dysfunction; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation

* LV-Dil in females was defined as LVEDV ≥129 ml

Supplemental Table 3. Univariate Cox regression analysis for 2-year all-cause mortality

	All			Males			Females		
	Univariate			Univariate			Univariate		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Age (an increase of 1 year)	1.02	1.01-1.03	**0.001**	1.02	1.01-1.04	**< 0.001**	1.00	0.99-1.02	0.665
Male	1.07	0.88-1.30	0.509		NA			NA	
Body surface area (an increase of 0.2 m^2)	0.89	0.82-0.96	**0.012**	0.77	0.68-0.87	**< 0.001**		NA*	
Body mass index (an increase of 1 kg/m^2)	0.99	0.97-1.01	0.364	0.96	0.94-0.99	**0.012**		NA*	
History of myocardial infarction	1.25	1.03-1.51	**0.024**	1.29	1.03-1.62	**0.027**	1.11	0.77-1.62	0.571
History of PCI	1.01	0.82-1.24	0.946	0.91	0.70-1.17	0.447	1.26	0.86-1.84	0.237
History of CABG	1.34	1.08-1.67	**0.008**	1.26	0.98-1.62	0.073	1.68	1.06-2.64	**0.026**
History of ICD	1.16	0.87-1.53	0.311	1.08	0.77-1.50	0.665	1.44	0.85-2.44	0.181

History of CRT	1.23	1.00-1.51	0.053	1.19	0.93-1.51	0.164	1.34	0.88-2.05	0.177
History of Afib or Aflut	1.14	0.94-1.37	0.176	1.07	0.85-1.35	0.554	1.28	0.92-1.77	0.146
Ischemic mitral regurgitation	1.14	0.95-1.39	0.167	1.25	0.98-1.59	0.068	0.96	0.69-1.33	0.802
NYHA class IV	1.75	1.43-2.14	**< 0.001**	1.56	1.22-1.98	**< 0.001**	2.26	1.59-3.22	**< 0.001**
Chronic kidney disease	1.47	1.17-1.84	**0.001**	1.52	1.17-1.98	**0.002**	1.39	0.90-2.16	0.139
Diabetes mellitus	1.36	1.12-1.66	**0.002**	1.37	1.08-1.73	**0.009**	1.33	0.94-1.90	0.111
Chronic obstructive pulmonary disease	1.19	0.94-1.49	0.143	1.14	0.87-1.51	0.344	1.28	0.85-1.92	0.231
History of stroke	1.34	1.00-1.79	0.052	1.28	0.90-1.83	0.173	1.47	0.88-2.47	0.144
NT-proBNP (an increase of 1000 pg/ml)	1.01	1.00-1.01	**0.001**	1.01	1.00-1.01	**0.024**	1.04	1.02-1.07	**< 0.001**
eGFR (an increase of 10 ml/min/1.73m^2)	0.89	0.85-0.93	**< 0.001**	0.87	0.83-0.92	**< 0.001**	0.91	0.83-0.99	**0.049**
Logistic EuroSCORE (an increase of 1 point)	1.02	1.01-1.02	**< 0.001**	1.02	1.01-1.02	**< 0.001**	1.02	1.01-1.03	**< 0.001**
RAS-I	0.64	0.50-0.83	**0.001**	0.70	0.51-0.94	**0.018**	0.54	0.35-0.84	**0.006**

Beta blockers	0.56	0.42-0.74	< **0.001**	0.51	0.36-0.73	< **0.001**	0.66	0.40-1.10	0.111
MRA	0.82	0.65-1.04	0.103	0.79	0.59-1.05	0.101	0.90	0.60-1.36	0.626
MR severity before procedure (an increase of a stage)	1.19	1.01-1.41	**0.041**	1.20	0.98-1.47	0.080	1.16	0.86-1.56	0.333
LVEF (an absolute increase of 10%)	0.90	0.84-0.97	**0.008**	0.93	0.84-1.03	0.157	0.86	0.76-0.98	**0.022**
LVEDV (an increase of 1 ml)	1.00	0.99-1.01	0.798	0.99	0.98-1.01	0.417	1.02	1.00-1.05	0.070
LV-Dil†	1.14	0.94-1.38	0.172	1.11	0.86-1.43	0.435	1.26	0.90-1.77	0.185
MR EROA (an increase of 0.1 cm^2)	1.00	0.96-1.04	0.956	1.00	0.95-1.05	0.921	1.00	0.92-1.08	0.938
MR volume (an increase of 1 ml)	1.00	0.99-1.00	0.993	1.00	1.00-1.01	0.637	1.00	0.99-1.01	0.482
MR vena contracta (an increase of 1 mm)	1.05	1.00-1.09	**0.047**	1.04	0.98-1.10	0.211	1.06	0.99-1.13	0.119
TR severity at baseline of 2+ or more	1.31	1.08-1.58	**0.006**	1.31	1.14-1.50	< **0.001**	1.16	0.95-1.42	0.138
TR vena contracta (an increase of 1 mm)	1.09	1.04-1.14	< **0.001**	1.09	1.03-1.15	**0.003**	1.09	1.01-1.17	**0.027**
RA area (an increase of 1 cm^2)	1.02	1.00-1.03	**0.011**	1.02	1.00-1.03	0.083	1.02	0.99-1.05	0.126

TAPSE (an increase of 1mm)	0.95	0.93-0.97	**< 0.001**	0.95	0.92-0.97	**< 0.001**	0.95	0.91-0.99	**0.010**
sPAP (an increase of 1 mmHg)	1.01	1.00-1.02	**0.005**	1.01	1.00-1.02	**0.006**	1.01	0.99-1.02	0.333
TAPSE/sPAP ratio (an increase of 0.1mm/mmHg)	0.89	0.83-0.95	**0.001**	0.90	0.82-0.98	**0.015**	0.86	0.76-0.97	**0.015**
RV-Dys	2.04	1.62-2.56	**< 0.001**	2.03	1.54-2.68	**< 0.001**	2.08	1.37-3.15	**0.001**
Residual MR of ≤1+	0.70	0.58-0.84	**< 0.001**	0.78	0.62-0.98	**0.033**	0.56	0.40-0.77	**< 0.001**

Afib, atrial fibrillation; Aflut, atrial flutter; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; ICD, implantable cardioverter defibrillator; LV-Dil, left ventricular dilatation; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RA, right atrium; RAS-I, renin-angiotensin system inhibitors; RV-Dys, right ventricle dysfunction; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation

*NA due to the fact that association of BSA and BMI with mortality in females did not follow linear regression.

†LV-Dil in males and females were defined as LVEDV ≥181 ml and ≥129 ml, respectively.

Supplemental Table 4. Association of BSA with anatomical characteristics

	Males			Females		
	OR	95% CI	p value	OR	95% CI	p value
LV-Dil*						
S Group	1.00 (reference)			1.00 (reference)		
M Group	1.61	1.07-2.41	**0.022**	1.33	0.73-2.44	0.354
L Group	2.25	1.28-3.95	**0.005**	1.68	0.77-3.67	0.193
RV-Dys						
S Group	1.00 (reference)			1.68	0.74-3.81	0.219
M Group	1.22	0.71-2.11	0.472	1.00 (reference)		
L Group	0.98	0.46-2.07	0.950	1.96	0.91-4.24	0.086
TR ≥2+ at baseline						
S Group	1.00 (reference)			0.98	0.54-1.76	0.942
M Group	0.71	0.47-1.09	0.118	1.00 (reference)		
L Group	0.39	0.23-0.69	**0.001**	0.77	0.43-1.36	0.365

All other echocardiographic characteristics were not associated with BSA.

Males: S, < 1.72 m^2; M, ≥ 1.72 m^2 and < 2.19 m^2; L, ≥ 2.19 m^2; Females: S, < 1.50 m^2; M, ≥ 1.50 m^2 and < 1.96 m^2; L, ≥ 1.96 m^2

In females, the lowest prevalence of RV-Dys and the highest prevalence of TR ≥2+ at baseline were observed in M group, followed by S group and L group. Therefore, M group was selected as the reference concerning these variables.

BSA, body surface area; CI, confidence interval; HR, hazard ratio; LV-Dil, left ventricle dilatation; OR, odds ratio; RV-Dys, right ventricle dysfunction

* LV-Dil in males and females were defined as LVEDV ≥181 ml and ≥129 ml, respectively.

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Manuscript Title:
Sex-specific impact of anthropometric parameters on outcomes after transcatheter edge-to-edge repair for secondary mitral regurgitation

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This statement is to certify that all authors have seen and approved the manuscript
being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology.*

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On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are

no conflicts of interest, the COI should read: “The authors report no relationships that could be construed as a conflict of interest”.

Highlights

BSA was a strong predictor for 2-year mortality after mitral TEER.

Such relationship demonstrated a pattern of linear regression in males.

The association of BSA with mortality indicated a U-shaped pattern in females.

In both sexes, low BSA was an independent predictor for mortality.

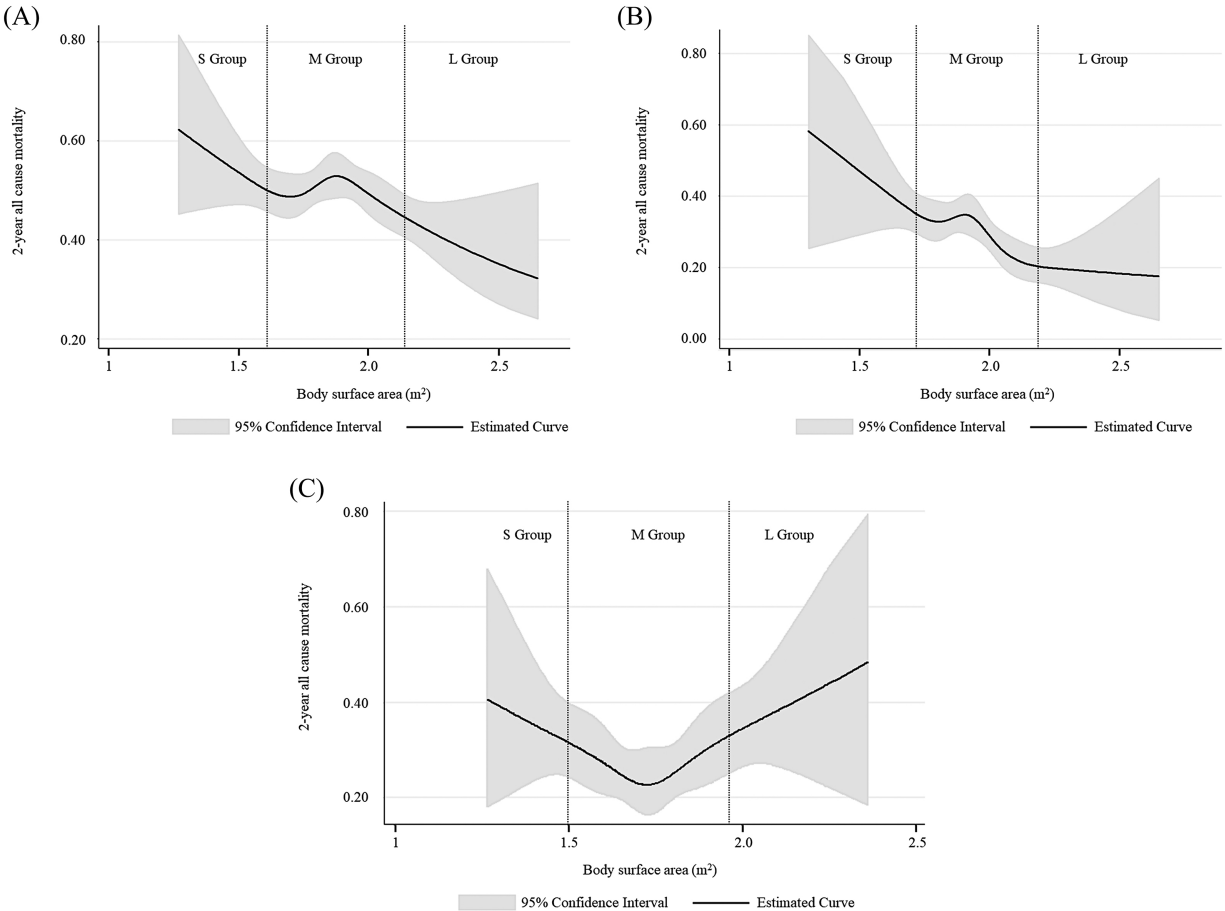
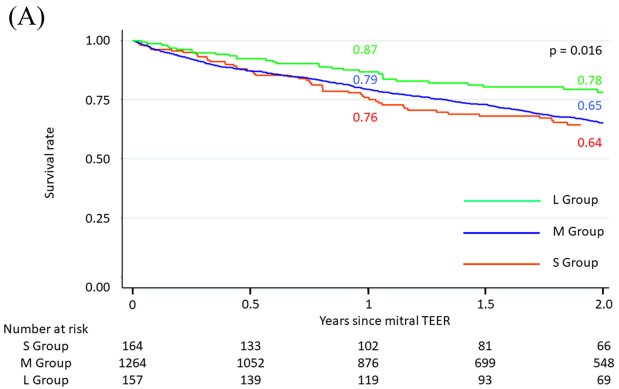
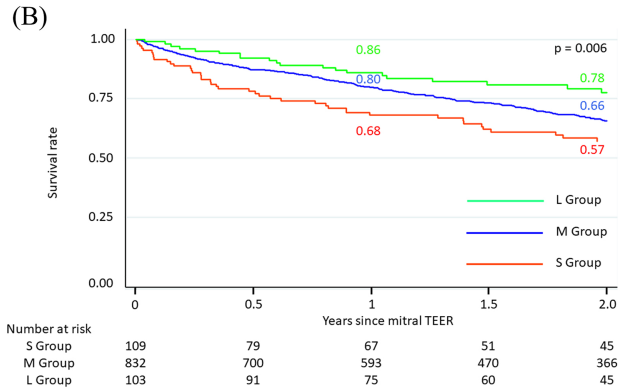

(A)
S Group
M Group
L Group
2-year all cause mortality
0.80
0.60
0.40
0.20
1
1.5
2.0
2.5
Body surface area (m²)
95% Confidence Interval
Estimated Curve
(B)
S Group
M Group
L Group
2-year all cause mortality
0.80
0.60
0.40
0.20
0.00
1
1.5
2.0
2.5
Body surface area (m²)
95% Confidence Interval
Estimated Curve
(C)
S Group
M Group
L Group
2-year all cause mortality
0.80
0.60
0.40
0.20
1
1.5
2.0
2.5
Body surface area (m²)
95% Confidence Interval
Estimated Curve

Figure 1


(A)
1.00
0.75
0.50
0.25
0.00
Survival rate
0.87
0.79
0.76
p = 0.016
0.78
0.65
0.64
L Group
M Group
S Group
0
0.5
1
1.5
2.0
Years since mitral TEER
Number at risk
S Group 164 133 102 81 66
M Group 1264 1052 876 699 548
L Group 157 139 119 93 69


(B)
1.00
0.75
0.50
0.25
0.00
Survival rate
0.86
0.80
0.68
p = 0.006
0.78
0.66
0.57
L Group
M Group
S Group
0
0.5
1
1.5
2.0
Years since mitral TEER
Number at risk
S Group 109 79 67 51 45
M Group 832 700 593 470 366
L Group 103 91 75 60 45

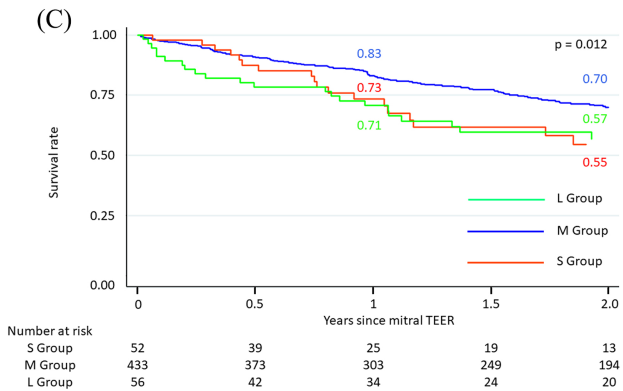

(C)
1.00
0.75
0.50
0.25
0.00
Survival rate
0.83
0.73
0.71
p = 0.012
0.70
0.57
0.55
L Group
M Group
S Group
0
0.5
1
1.5
2.0
Years since mitral TEER
Number at risk
S Group 52 39 25 19 13
M Group 433 373 303 249 194
L Group 56 42 34 24 20

Figure 2