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Effect of Elevated Body Mass Index on Outcomes of Transcatheter Aortic Valve Replacement for Severe Aortic Stenosis

ORIGINAL INVESTIGATION

ABSTRACT

Background: The association of body mass index (BMI) and an "obesity paradox" with cardiovascular risk prediction is controversial. This study aimed to evaluate the impact of elevated BMI on the outcome of transcatheter aortic valve replacement (TAVR) for aortic stenosis.

Methods: This retrospective study included 1019 patients with a BMI of ≥18.5 kg/m^2 divided into 3 groups: 1) normal BMI (18.5-24.9 kg/m^2), 2) overweight (25-29.9 kg/m^2), and 3) obese (≥30 kg/m^2). Propensity score matching was used to compare normal BMI with overweight and normal BMI with obese.

Results: The median age of the cohort was 82 years, and 348 patients had a normal BMI, while 319 and 352 patients were overweight and obese, respectively. After 1 : 1 propensity score matching, 258 and 192 pairs between normal BMI and overweight, and normal BMI and obese patients, respectively, were analyzed. Both overweight and obese patients had higher post-transaortic mean gradients and lower indexed effective orifice areas compared to normal BMI patients. During a median follow-up of 25 (range: 0.1-72) months, all-cause mortality was similar between overweight or obese patients and patients with a normal BMI. However, in a subgroup analysis of patients with moderate/severe chronic lung disease, all-cause mortality was significantly higher in obese patients compared with normal BMI patients (hazard ratio = 3.49, 95% confidence interval, 1.21-10.0, P = .021).

Conclusions: In this study, the "obesity paradox" was not observed in patients undergoing TAVR; rather, in patients with significant lung disease, obesity may be associated with worse mid-term outcomes after TAVR.

Keywords: Aortic stenosis, aortic valve replacement, valve disease

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INTRODUCTION

Overweight and obesity, often defined by body mass index (BMI), are known cardiovascular risk factors and are associated with several systemic metabolic disorders such as dyslipidemia and diabetes, as well as decreased life expectancy in the general population.[1] However, being overweight or obese may be associated with improved survival and clinical outcomes in certain clinical settings, which is known as the "obesity paradox."[2,3] There are several possible explanations for this phenomenon: increased production of soluble tumor necrosis factor-α receptors in adipose tissue, which neutralizes the adverse effects of an inflammatory cytokine, tumor necrosis factor-α,[4] increased lean or fat-free body mass,[5] increased clinical attention to obesity-related comorbidities,[6] earlier onset of symptoms and earlier seeking medical care,[7] and the comorbidities associated with low BMI such as cachexia and frailty.[8] There are conflicting data regarding the relationship between BMI and clinical outcomes of aortic stenosis. In patients with initially asymptomatic aortic stenosis enrolled in the SEAS (Simvastatin Ezetimibe in Aortic Stenosis) study,[9] both overweight and obesity were associated with increased mortality, while Rossi et al[10] observed a protective effect of higher BMI for all-cause mortality in patients with severe aortic stenosis.

Transcatheter aortic valve replacement (TAVR) is a well-established treatment option for symptomatic severe aortic stenosis with comparable or superior outcomes to surgical aortic valve replacement in patients at any surgical risk.[11,12] Transcatheter aortic valve replacement volumes have increased rapidly worldwide, and with the expansion of TAVR to lower risk cohorts, the impact of multiple risk factors should be closely examined. There have been several studies investigating the effect of BMI on TAVR outcomes, showing contradicting results. In the French Aortic National CoreValve and Edwards 2 (FRANCE-2) registry (n = 3072), Yamamoto et al[13] observed superior survival at 1 year in overweight and obese patients compared with normal weight patients. Conversely, Corcione et al[14] found no paradoxical effects of elevated BMI on short- or mid-term mortality in the Registro Italiano GISE sull'impianto di Valvola Aortica Percutanea (RISPEVA) study (n = 3075). In addition, there are few studies that have examined the long-term association between BMI and TAVR outcomes with follow-up beyond 1 year. Given its potential implications for optimizing patient risk stratification and management to improve postoperative outcomes, there is growing interest in understanding whether the obesity paradox truly exists in TAVR outcomes. This study aims to investigate the effect of elevated BMI on clinical outcomes of TAVR for aortic stenosis.

METHODS

Patients and Methods

This retrospective observational study included 1045 consecutive TAVR with newer generation transcatheter heart valves for severe native aortic stenosis performed between January 2018 and December 2022 at our institution. To evaluate the effect of elevated BMI compared to normal BMI, 26 patients with a BMI of <18.5 were excluded, resulting in a total of 1019 patients analyzed. These patients were divided into 3 BMI groups according to the World Health Organization (WHO) classification: 1) normal BMI (18.5-24.9 kg/m^2), 2) overweight (25-29.9 kg/m^2), and 3) obese (≥ 30 kg/m^2).

Primary outcome was all-cause mortality, and other outcomes of interest included periprocedural outcomes and the composite of all-cause mortality, stroke, and rehospitalization for heart failure. Definitions, terminology, and reported outcomes were consistent with the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies (STS/ACC TVT) Registry and the VARC-3 (Valve Academic Research Consortium 3) criteria.[15] Only the Sapien (Edwards Lifesciences, Irvine, CA, USA) and Evolut (Medtronic Inc., Minneapolis, MN, USA) valves were used during the study period, and the Sapien 3/3 Ultra and Evolut Pro/Pro+/FX were considered newer generation valves. The decision for TAVR was made by a dedicated cardiac team based primarily on age and surgical risk according to the STS Predicted Risk of Mortality (STS-PROM). In addition, patient anatomy and specific factors such as frailty were considered in the decision-making process. Artificial intelligence–assisted technologies, such as large language models, chatbots, or image creators, were not used in the production of submitted work in this study.

Statistical Analysis

Since all continuous values analyzed in this study were not normally distributed, as determined by the Shapiro–Wilk test, they are presented as median (interquartile range). In addition to the crude analysis across 3 groups, a propensity score matching procedure was used to control for confounding in the comparison between normal BMI and overweight patients and between normal BMI and obese patients. For continuous variables, the Kruskal–Wallis test was used to compare 3 groups for crude analysis, and the Mann–Whitney *U* test was used to compare 2 groups after propensity score matching. Categorical variables are reported as numbers (percentages), and comparisons between groups were made using the chi-squared test or Fisher's exact test, as appropriate. When significant differences between the 3 groups were observed, post hoc tests with Bonferroni correction were used to determine specific group differences.

Nearest neighbor matching was performed based on the calculated propensity scores. Specifically, a 1 : 1 matching ratio with a margin of 0.1 SDs of the logit of the propensity score was used without replacement. Propensity scores were calculated using the 24 variables listed in Supplementary Table 1. Aortic valve area and indexed aortic valve area were not included in the propensity score calculation because these measures are significantly influenced by BMI. The goodness of fit of the variables was assessed using the absolute standardized mean difference, with values less than 0.1 indicating an ideal fit. Kaplan–Meier curves were constructed to estimate the incidence of late outcomes of interest up to 5 years, including all-cause mortality and the composite of all-cause mortality, stroke, and rehospitalization for heart failure. A Cox proportional hazards model was used to report hazard ratios. Eight subgroups of patients were prespecified and all-cause mortality was compared between the matched groups. The subgroups were defined by age (≥ 80 years or < 80 years), sex (male or female), diabetes (presence or absence), moderate/severe chronic lung disease (presence or absence), creatinine (≥ 1.5 mg/dL or < 1.5 mg/dL), anemia (presence or absence), albumin (≥ 3.5 g/dL or < 3.5 g/dL), and left ventricular ejection fraction (≥ 40% or < 40%). Anemia was defined as hemoglobin <13.5 g/dL for men and <12 g/dL for women. All *P* values were 2-sided, and a 5% level was considered significant. All analyses were conducted using the R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

HIGHLIGHTS

- Approximately one-third of patients undergoing transcatheter aortic valve replacement (TAVR) for aortic stenosis were overweight and another one-third were obese.
- Overweight and obese patients had different baseline characteristics, including younger age and lower surgical risk, compared with patients with normal body mass index (BMI).
- After adjustment, mid-term outcomes after TAVR were similar except for higher mortality in obese patients with moderate/severe chronic lung disease compared to normal BMI patients with the same condition.

RESULTS

Prior to Propensity Score Matching

Baseline and procedural characteristics, as well as periprocedural outcomes across the 3 groups before propensity score matching, are shown in Table 1. The median age of the entire cohort was 82 years, and 954 patients (94%) were of white race. Among the cohort, 348 patients (34%) had a normal BMI, 319 patients (31%) were overweight, and 352 patients (35%) were obese. Compared to normal BMI patients, elevated BMI (both overweight and obese) patients were younger, had lower STS-PROM scores, lower indexed aortic valve area and hemoglobin levels, higher rates of diabetes, and lower rates of moderate/severe mitral regurgitation. In addition, obese patients had lower rates of moderate/severe tricuspid regurgitation compared to normal BMI patients and were younger and had more diabetes compared to overweight patients.

The overall periprocedural mortality was 1.9% with no significant differences between the 3 groups. Postprocedural transaortic mean gradient was highest and indexed effective orifice area was lowest in obese patients. Supplementary Figure 1 shows crude Kaplan—Meier curves for all-cause mortality and the composite of all-cause mortality, stroke, and rehospitalization for heart failure between the 3 groups. The median follow-up was 25 (15-42) months with a range of 0.1-72 months, and the overall 1-year and 3-year survival rates were 88% and 67%, respectively. All-cause mortality was significantly lower in obese patients compared to normal BMI patients with a hazard ratio of 0.76 (95% confidence interval, 0.59-0.98, $P = .037$). There was no significant difference in the composite outcome between the 3 groups.

Normal Body Mass Index Versus Overweight After Propensity Score Matching

The propensity score C-statistic was 0.66 (95% confidence interval, 0.62-0.70). Propensity score matching resulted in 258 matched patient pairs for analysis (Table 2). Similar baseline and procedural characteristics were observed for all variables with an absolute standardized mean difference <0.1 between the 2 groups. Supplementary Figure 2 shows the distribution of propensity scores and love plots of the absolute standardized mean difference before and after matching.

The postprocedural transaortic mean gradient was significantly higher in the overweight group compared to the normal BMI group. In addition, while the effective orifice area was comparable, the indexed effective orifice area was significantly lower in the overweight group. Other major periprocedural outcomes were comparable between groups (Table 2). During follow-up, all-cause mortality (hazard ratio = 0.97, 95% confidence interval, 0.72-1.31) and the composite outcome (hazard ratio = 1.13, 95% confidence interval, 0.84-1.47) were similar between the normal BMI and overweight groups. In addition, no subgroup analyses showed significant differences in all-cause mortality (Figure 1).

Normal Body Mass Index Versus Obese After Propensity Score Matching

The propensity score C-statistic was 0.79 (95% confidence interval, 0.76-0.82). Propensity score matching resulted in 192 matched patient pairs for analysis (Table 3). Again, similar baseline and procedural characteristics were observed after matching (Supplementary Figure 3).

The postprocedural transaortic mean gradient was significantly higher in the obese group compared to the normal BMI group. The rate of mean gradient ≥20 mm Hg was also higher in the obese group. In addition, the indexed effective orifice area was significantly lower in the obese group. Other major periprocedural outcomes were comparable between groups (Table 3). During follow-up, all-cause mortality (hazard ratio = 0.87, 95% confidence interval, 0.62-1.24) and the composite outcome (hazard ratio = 0.98, 95% confidence interval, 0.72-1.34) were similar between the normal BMI and obese groups. However, in a subgroup analysis of patients with moderate/severe chronic lung disease, all-cause mortality was significantly higher in obese patients compared with normal BMI patients (hazard ratio = 3.49, 95% confidence interval, 1.21-10.0, $P = .021$) (Figure 2).

DISCUSSION

The main findings of this study were as follows: 1) approximately one-third of patients with severe aortic stenosis undergoing TAVR at our institution in the United States were overweight, and another one-third were obese according to the WHO BMI classification, 2) these patients have different baseline characteristics, mainly being younger, with lower STS-PROM scores, and higher prevalence of diabetes, 3) an unadjusted analysis showed that obesity was associated with lower all-cause mortality compared with normal BMI, 4) however, after adjustment for confounders, there were no significant differences in early and late outcomes after TAVR, except for echocardiographic hemodynamics, between normal BMI and overweight or between normal weight and obese groups, 5) in patients with moderate/severe chronic lung disease, obesity was associated with higher all-cause mortality compared with normal BMI. The prevalence of overweight and obesity in our cohort aligns with a previous report from the STS/ACC TVT registry,[16] with a prevalence of overweight and obesity of 34% and 30%, respectively, but the prevalence of obesity is slightly higher than in the FRANCE-2 registry (19%)[13] and RISPEVA registry (18%).[14]

Several studies have examined the impact of BMI on TAVR outcomes, yielding mixed results. The methodology for examining the obesity paradox is also debated. While the issue is still contentious, numerous studies have observed worse clinical outcomes after TAVR in underweight patients.[16-18] Given the potential heterogeneity of TAVR outcomes in underweight patients, the small number of underweight patients in our cohort (n = 26), and the focus of this study on the impact of elevated BMI compared with normal BMI, we excluded the underweight cohort. Furthermore, BMI can be analyzed as either a categorical or continuous variable.[19] Some studies have observed a non-linear relationship between BMI and survival after TAVR,[20] forming a "J-shaped" curve in which, overweight patients have the lowest mortality rate, whereas normal-weight and obese patients have higher mortality rates.[21,22] Therefore, we examined the effect

Table 1. Baseline and Procedural Characteristics and Procedural Outcomes Before Propensity Score Matching

	Normal BMI 18.5-24.9 kg/m² n = 348	Overweight 25-29.9 kg/m² n = 319	Obese ≥30 kg/m² n = 352	*P**
Baseline characteristics				
Age, years	85 (79-89)	82 (78-87)*	79 (73-83)*†	<.001
Female	171 (49)	136 (43)	179 (51)	.083
Height, m	1.68 (1.60-1.75)	1.68 (1.60-1.78)	1.68 (1.60-1.78)	.825
Weight, kg	62 (56-71)	77 (68-85)*	98 (86-109)*†	<.001
New York Heart Association III/IV	169 (49)	161 (50)	193 (55)	.236
STS-PROM	4.0 (2.8-6.5)	3.3 (2.1-5.6)*	3.3 (2.1-4.5)*	<.001
Hypertension	316 (91)	290 (91)	324 (92)	.814
Dyslipidemia	313 (90)	287 (90)	312 (89)	.808
Diabetes	80 (23)	103 (32)*	164 (47)*†	<.001
Chronic lung disease ≥ moderate	29 (8.3)	69 (10)	18 (13)	.107
Liver disease	10 (2.9)	12 (3.8)	15 (4.3)	.611
Creatinine, mg/dL	1.1 (0.8-1.5)	1.1 (0.9-1.4)	1.1 (0.9-1.6)	.259
Creatinine ≥ 1.5 mg/dL	89 (26)	61 (19)	105 (30)†	.006
Dialysis	13 (3.7)	14 (4.4)	14 (4.0)	.911
Cerebrovascular accident	39 (11)	43 (13)	14 (13)	.670
Peripheral artery disease	78 (22)	83 (26)	69 (20)	.139
Coronary artery disease	159 (46)	168 (53)	160 (45)	.107
Atrial fibrillation	140 (40)	116 (36)	127 (36)	.454
Prior pacemaker/defibrillator	46 (13)	45 (14)	49 (14)	.939
Hemoglobin, g/dL	11.9 (10.4-13.1)	12.5 (11.1-13.6)*	12.7 (11.1-14.8)*	<.001
Anemia	235 (68)	185 (58)*	184 (52)*	<.001
Albumin, g/dL	3.7 (3.4-4.0)	3.8 (3.5-4.0)	3.8 (3.5-3.9)	.448
Albumin < 3.5 g/dL	92 (26)	79 (25)	72 (20)	.160
Left ventricular ejection fraction, %	61 (55-68)	63 (55-68)	63 (54-68)	.870
Left ventricular ejection fraction < 40%	43 (12)	33 (10)	35 (9.9)	.551
Aortic valve area, cm²	0.70 (0.60-0.80)	0.71 (0.60-0.84)	0.80 (0.67-0.90)*†	<.001
Indexed aortic valve area, cm²	0.41 (0.35-0.49)	0.38 (0.33-0.45)*	0.37 (0.31-0.43)*†	<.001
Transaortic mean gradient, mm Hg	41 (35-50)	41 (35-50)	42 (37-48)	.672
Mitral regurgitation ≥ moderate	66 (19)	36 (11)*	28 (8.0)*	<.001
Tricuspid regurgitation ≥ moderate	55 (16)	45 (14)	33 (9.4)*	.033
Procedural characteristics				
Non-elective procedure	40 (11)	29 (9.0)	26 (7.4)	.171
Non-transfemoral access	32 (9.2)	29 (9.1)	21 (6.0)	.207
Transcatheter heart valve				NA
Sapien 20 mm	1 (0.3)	0	0	
23 mm	44 (13)	35 (11)	38 (11)	
26 mm	78 (22)	87 (27)	90 (26)	
29 mm	50 (14)	57 (18)	76 (22)	
Evolut 23 mm	8 (2.3)	6 (1.9)	6 (1.7)	
26 mm	65 (19)	47 (15)	60 (17)	
29 mm	83 (24)	62 (19)	62 (18)	
34 mm	19 (5.5)	25 (7.8)	20 (5.7)	
Procedural outcomes				
Mortality‡	5 (1.4)	7 (2.2)	8 (2.3)	.682
Major cardiac structural complication	5 (1.4)	4 (1.3)	1 (0.3)	.250
Major vascular complication	5 (1.4)	7 (2.2)	8 (2.3)	.682
Minor vascular complication	16 (4.6)	14 (4.4)	17 (4.8)	.964

(*Continued*)

Table 1. Baseline and Procedural Characteristics and Procedural Outcomes Before Propensity Score Matching (*Continued*)

	Normal BMI 18.5-24.9 kg/m^2 n = 348	Overweight 25-29.9 kg/m^2 n = 319	Obese ≥30 kg/m^2 n = 352	*P**
Overt bleeding	17 (4.9)	20 (6.3)	20 (5.7)	.736
Need for second valve	1 (0.3)	3 (0.9)	0	.079
Acute stroke	9 (2.6)	7 (2.2)	6 (1.7)	.724
Acute kidney injury ≥ stage 2	7 (2.0)	4 (1.3)	9 (2.6)	.476
New permanent pacemaker implantation‡	43 (14)	42 (15)	57 (19)	.283
Transaortic mean gradient, mm Hg‡	8.0 (6.0-11)	9.7 (7.0-13)*	11 (8.0-14)*†	<.001
Transaortic mean gradient ≥ 20 mm Hg‡	6 (1.7)	10 (3.2)	27 (7.7)*	<.001
Effective orifice area, cm^{2}‡	1.83 (1.48-2.24)	1.80 (1.45-2.22)	1.80 (1.44-2.13)	.525
Indexed effective orifice area, cm^2/m^{2}‡	1.07 (0.86-1.35)	0.96 (0.77-1.17)*	0.83 (0.67-1.03)*†	<.001
Aortic regurgitation ≥ moderate‡	9 (2.6)	4 (1.3)	4 (1.1)	.257

Median (interquartile range), or n (%).*P < .05 versus normal BMI group with post hoc test.†P < .05 versus overweight group with post hoc test.‡30-day data or in-hospital data if 30-day data is not available. BMI, body mass index; NA, not applicable; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 2. Baseline and procedural characteristics and procedural outcomes after 1:1 propensity score matching, normal BMI versus overweight

	Normal BMI 18.5-24.9 kg/m^2 n = 258	Overweight 25-29.9 kg/m^2 n = 258	*P*
Baseline characteristics			
Age, years	84 (78-88)	83 (79-88)	.644
Female	117 (45)	121 (46)	.791
Height, m	168 (160-175)	168 (160-178)	.671
Weight, kg	63 (56-71)	76 (68-85)	<.001
New York Heart Association III/IV	127 (49)	129 (50)	.930
STS-PROM	3.7 (2.4-6.0)	3.5 (2.2-5.9)	.393
Hypertension	232 (90)	235 (91)	.764
Dyslipidemia	231 (90)	230 (89)	>.999
Diabetes	72 (28)	75 (29)	.845
Chronic lung disease ≥ moderate	21 (8.1)	20 (7.8)	>.999
Liver disease	9 (3.5)	10 (3.9)	>.999
Creatinine, mg/dL	1.0 (0.8-1.4)	1.1 (0.9-1.4)	.218
Creatinine ≥ 1.5 mg/dL	58 (23)	49 (19)	.385
Dialysis	8 (3.1)	14 (5.4)	.276
Cerebrovascular accident	30 (12)	34 (13)	.689
Peripheral artery disease	60 (23)	65 (25)	.681
Coronary artery disease	131 (51)	132 (51)	>.999
Atrial fibrillation	97 (38)	95 (37)	.927
Prior pacemaker/defibrillator	30 (12)	36 (14)	.510
Hemoglobin, g/dL	12.0 (10.7-13.3)	12.1 (10.7-13.4)	.977
Anemia	170 (66)	162 (63)	.520
Albumin, g/dL	3.8 (3.5-4.0)	3.7 (3.4-4.0)	.757
Albumin < 3.5 g/dL	63 (24)	66 (26)	.839
Left ventricular ejection fraction, %	63 (55-68)	63 (55-68)	.701
Left ventricular ejection fraction < 40%	33 (13)	27 (11)	.492
Aortic valve area, cm^2	0.70 (0.60-0.80)	0.72 (0.60-0.84)	.216
Indexed aortic valve area, cm^2	0.42 (0.35-0.48)	0.38 (0.33-0.45)	.001
Transaortic mean gradient, mm Hg	42 (35-50)	41 (35-50)	.925
Mitral regurgitation ≥ moderate	37 (14)	34 (13)	.798

(*Continued*)

Table 2. Baseline and procedural characteristics and procedural outcomes after 1:1 propensity score matching, normal BMI versus overweight (*Continued*)

Tricuspid regurgitation ≥ moderate	39 (15)	38 (15)	>.999
Procedural characteristics			
Non-elective procedure	22 (8.5)	27 (11)	.548
Non-transfemoral access	23 (8.9)	25 (9.7)	.880
Procedural outcomes			
Mortality*	2 (0.8)	7 (2.7)	.179
Major cardiac structural complication	3 (1.2)	4 (1.6)	>.999
Major vascular complication	4 (1.6)	5 (1.9)	>.999
Minor vascular complication	12 (4.7)	17 (6.6)	>.999
Overt bleeding	14 (5.4)	17 (6.6)	.711
Need for second valve	0	3 (1.2)	.247
Acute stroke	9 (3.5)	5 (1.9)	.416
Acute kidney injury ≥ stage 2	5 (1.9)	4 (1.6)	>.999
New permanent pacemaker implantation*	30 (13)	35 (16)	.514
Transaortic mean gradient, mm Hg*	8.0 (6.0-11)	9.0 (6.8-13)	.021
Transaortic mean gradient ≥ 20 mm Hg*	4 (1.6)	5 (2.0)	.991
Effective orifice area, cm^2*	1.84 (1.48-2.28)	1.80 (1.48-2.25)	.881
Indexed effective orifice area, cm^2/m^2*	1.07 (0.87-1.36)	0.97 (0.77-1.19)	<.001
Aortic regurgitation ≥ moderate*	6 (2.3)	4 (1.6)	.754

Median (interquartile range), or n (%). *30-day data or in-hospital data if 30-day data is not available. BMI, body mass index; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

of BMI according to the simple and standardized WHO BMI classification.

Two large studies using the United States National Inpatient Sample reported conflicting results regarding BMI and in-hospital outcomes. Alharbi et al[23] found no significant difference in mortality among different BMI groups in 77 319 TAVR cases, while Patel et al[24] found lower mortality in overweight, obese, and morbidly obese patients in 42 315 cases. However, the remarkably high prevalence of obesity (81% and 82%) raises questions about the accuracy and generalizability of their findings. In studies that examined

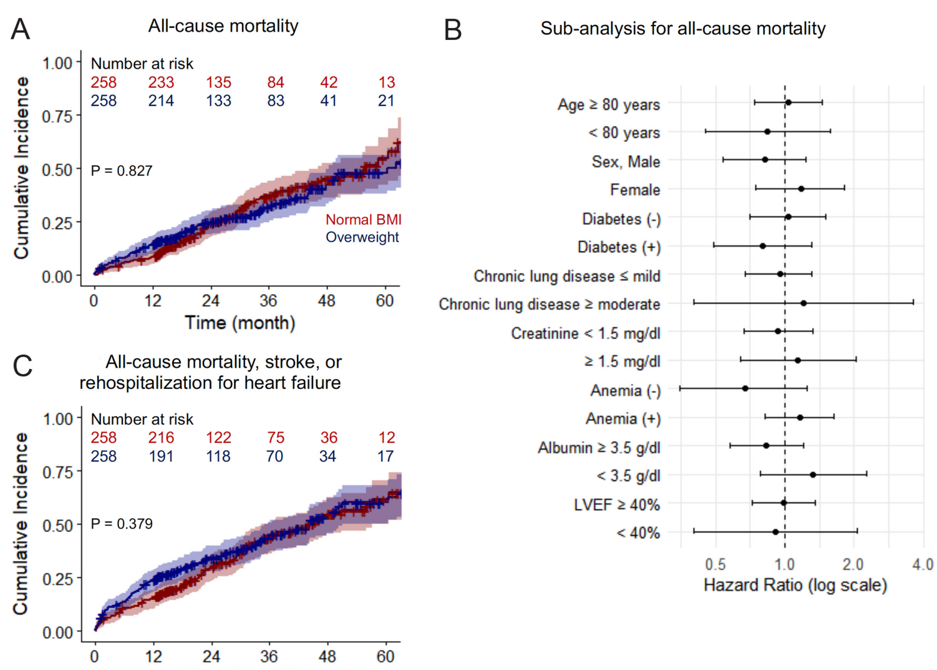

Figure 1. Kaplan–Meier curves for (a) all-cause mortality and (b) the composite of all-cause mortality, stroke, or rehospitalization for heart failure between patients with normal BMI and overweight patients after propensity score matching. (c) Forest plots for subgroup analysis of all-cause mortality. BMI, body mass index; LVEF, left ventricular ejection fraction.

Table 3. Baseline and procedural characteristics and procedural outcomes after 1:1 propensity score matching, normal BMI versus obesity

	Normal BMI 18.5-24.9 kg/m² n = 192	Obese ≥ 30 kg/m² n = 192	*P*
Baseline characteristics			
Age, years	82 (77-86)	82 (77-86)	.193
Female	99 (52)	98 (51)	>.999
Height, m	168 (160-175)	168 (160-175)	.791
Weight, kg	62 (56-71)	94 (86-107)	<.001
New York Heart Association III/IV	96 (50)	96 (50)	>.999
STS-PROM	3.6 (2.4-5.6)	3.3 (2.3-4.6)	.893
Hypertension	178 (93)	177 (92)	>.999
Dyslipidemia	173 (90)	171 (89)	.867
Diabetes	62 (32)	66 (34)	.745
Chronic lung disease ≥ moderate	18 (9.4)	15 (7.8)	.716
Liver disease	9 (4.7)	8 (4.2)	>.999
Creatinine, mg/dL	1.0 (0.8-1.4)	1.1 (0.9-1.5)	.421
Creatinine ≥ 1.5 mg/dL	43 (22)	55 (29)	.198
Dialysis	8 (4.2)	7 (3.6)	>.999
Cerebrovascular accident	20 (10)	25 (13)	.526
Peripheral artery disease	40 (21)	36 (19)	.701
Coronary artery disease	90 (47)	91 (47)	>.999
Atrial fibrillation	76 (40)	70 (37)	.599
Prior pacemaker/defibrillator	23 (12)	24 (13)	>.999
Hemoglobin, g/dL	12.2 (10.9-13.4)	12.3 (10.8-13.3)	.923
Anemia	116 (60)	113 (59)	.835
Albumin, g/dL	3.8 (3.5-4.0)	3.7 (3.5-3.9)	.379
Albumin < 3.5 g/dL	44 (23)	41 (21)	.806
Left ventricular ejection fraction, %	63 (58-69)	63 (55-68)	.655
Left ventricular ejection fraction < 40%	21 (11)	20 (10)	>.999
Aortic valve area, cm²	0.71 (0.60-0.80)	0.80 (0.69-0.90)	<.001
Indexed aortic valve area, cm²	0.42 (0.35-0.49)	0.38 (0.32-0.44)	<.001
Transaortic mean gradient, mm Hg	42 (35-49)	42 (36-48)	.628
Mitral regurgitation ≥ moderate	21 (11)	19 (9.9)	.868
Tricuspid regurgitation ≥ moderate	20 (10)	22 (12)	.870
Procedural characteristics			
Non-elective procedure	14 (7.3)	18 (9.4)	.580
Non-transfemoral access	14 (7.3)	15 (7.8)	>.999
Procedural outcomes			
Mortality*	3 (1.6)	4 (2.1)	>.999
Major cardiac structural complication	2 (1.0)	1 (0.5)	>.999
Major vascular complication	3 (1.6)	4 (2.1)	>.999
Minor vascular complication	6 (3.1)	8 (4.2)	.785
Overt bleeding	9 (4.7)	10 (5.2)	>.999
Need for second valve	0	0	NA
Acute stroke	5 (2.6)	2 (1.0)	.446
Acute kidney injury ≥ stage 2	3 (1.6)	6 (3.1)	.500
New permanent pacemaker implantation*	23 (14)	35 (21)	.107
Transaortic mean gradient, mm Hg*	8.0 (6.0-11)	10 (7.9-13)	<.001
Transaortic mean gradient ≥ 20 mm Hg*	2 (1.0)	15 (7.8)	.003
Effective orifice area, cm²*	1.87 (1.48-2.22)	1.80 (1.50-2.12)	.607
Indexed effective orifice area, cm²/m²*	1.07 (0.89-1.32)	0.83 (0.70-1.04)	<.001
Aortic regurgitation ≥ moderate*	4 (2.1)	2 (1.0)	.681

Median (interquartile range), or n (%).*30-day data or in-hospital data if 30-day data is not available. BMI, body mass index; NA, not applicable; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

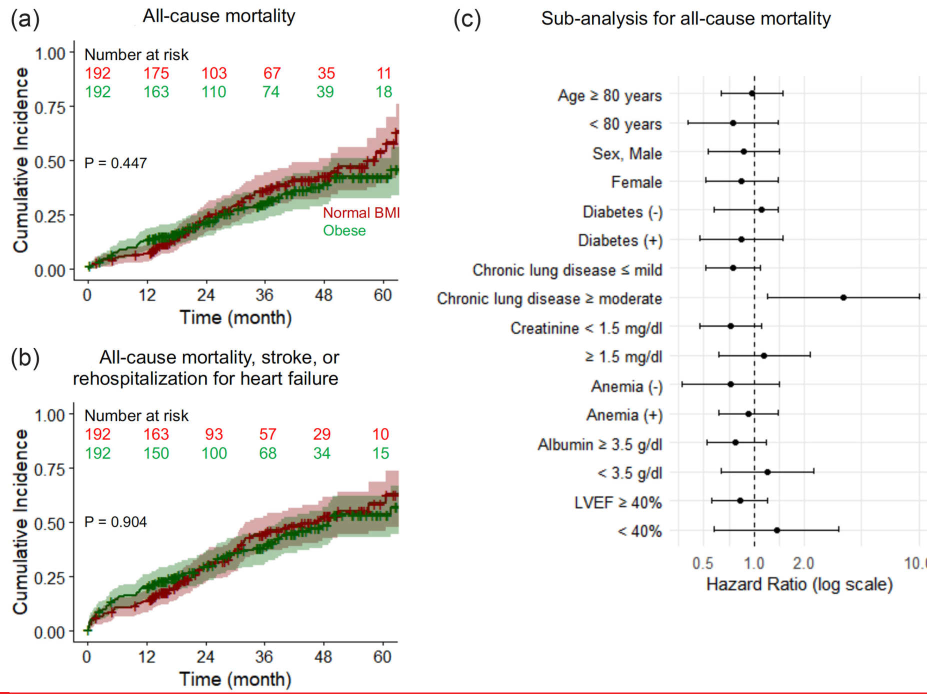

Figure 2. Kaplan–Meier curves for (a) all-cause mortality and (b) the composite of all-cause mortality, stroke, or rehospitalization for heart failure between patients with normal BMI and obese patients after propensity score matching. (c) Forest plots for subgroup analysis of all-cause mortality. BMI, body mass index; LVEF, left ventricular ejection fraction.

both short- and mid-term outcomes, the RESPIVA study[14] and a study by Boukhris et al[17] (n = 412) found no association between overweight/obesity and survival rates compared with normal weight. In contrast, Sharma et al[16] analyzed data from 31929 patients who underwent TAVR between 2011 and 2015 from the STS/ACC TVT Registry, and found that overweight patients [hazard ratio = 0.88 (0.81-0.95)] and those with class I obesity [0.84 (0.72-0.98)] and class II obesity [0.80 (0.72-0.89)] had a decreased risk of mortality at 1 year. Similarly, the FRANCE-2 registry[13] observed superior survival at 1 year in overweight and obese patients. In addition, a recent meta-analysis showed that obese patients had a lower rate of 30-day mortality, and both overweight and obese patients had lower rates of 1-year mortality compared with normal-weight patients, while the incidence of post-procedural acute kidney injury was higher in obese patients, and overweight and obese patients were more likely to require permanent pacemaker implantation. The results of our study are inconsistent with these studies, which support the existence of an "obesity paradox" in mortality. These discrepancies may be explained in part by changes in TAVR outcomes over time. For example, in the aforementioned STS/ACC TVT registry and FRANCE-2 registry, 30-day and 1-year mortality rates were 4.9-7.4% and 18-26%, and 7.0-11% and 13-20%, respectively, in patients with a normal or higher BMI. In contrast, the RESPIVA study, a more recent study, showed a 30-day mortality rate of 1.3-2.8%, and during a mean follow-up of approximately 11 months, the mortality rate was 12-15%, which is consistent with our results. In fact, overall survival after TAVR has improved due to improvements in techniques and devices, as well as expansion of the indication to lower-risk cohorts.[25] Similarly, the validity of the aforementioned study-level meta-analysis for current practice would be weakened by several factors: the lack of patient-level data, which hinders the assessment of baseline heterogeneity among BMI groups; non-standardized definitions of obesity and BMI groups with varying cutoffs; and the inclusion of only high-risk cohorts and older-generation devices in some studies. Despite the relatively small sample size and potential issues with statistical power, our study found no statistical trends in mortality after propensity score adjustment between normal and elevated BMI groups, which may actually reflect current real-world practice. On the other hand, in patients with moderate/severe chronic lung disease, we found increased all-cause mortality with obesity compared with normal BMI. Indeed, increased BMI has been suggested to be associated with decreased forced vital capacity and forced expiratory volume in 1 second,[26] which may adversely affect patients with significant chronic lung disease undergoing TAVR for severe aortic stenosis. Further research is needed to update knowledge of the obesity paradox in TAVR outcomes and to examine potential effect modification by comorbidities. This will help refine optimal risk stratification and improve patient management and potentially clinical outcomes for patients undergoing TAVR.

Study Limitations

This study has several important limitations. First, it is a single-center retrospective study with a modest sample size, especially after propensity score matching, and a relatively short observation period. Despite efforts to reduce confounding by propensity score matching, unmeasured confounders such as frailty, central or peripheral obesity,[27,28] and muscle/fat mass balance[29] may still affect the results. In addition, the majority of patients (94%) in this cohort were Caucasian, which limits the generalizability of the findings to other ethnic groups. The WHO classifies obesity into 3 categories (Class I-III) based on BMI. However, due to the limited number of patients in each category, the impact of these obesity classifications was not examined and warrants further research.

CONCLUSION

In conclusion, approximately one-third of the patients undergoing TAVR for severe native aortic stenosis were overweight and one-third were obese. In this study, the "obesity paradox" was not observed in patients undergoing TAVR; rather, in patients with significant lung disease, obesity may be associated with worse mid-term outcomes after TAVR.

Ethics Committee Approval: The study protocol was approved by the Main Line Health Hospitals Institutional Review Board (IRB 45CFR164.512) on November 11/2020.

Informed Consent: Individual patient consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – B.R.; Design – S.S.; Supervision – W.A.G., S.M.G.; Resource – B.R.; Materials – S.M.G., W.A.G., B.R.; Data Collection and/or Processing – Y.Y., M.B., M.Z., R.R., E.M.G., P.M.C., Analysis and/or Interpretation – Y.Y., S.S., M.Z., B.R.; Literature Review – E.M.G., P.M.C.; Writer – Y.Y.; Critical Review – W.A.G., S.M.G.

Declaration of Interests: Basel Ramlawi is a consultant for Medtronic, Boston Scientific, AtriCure, Schockwave and Corcym. The other authors have no conflict of interest to declare.

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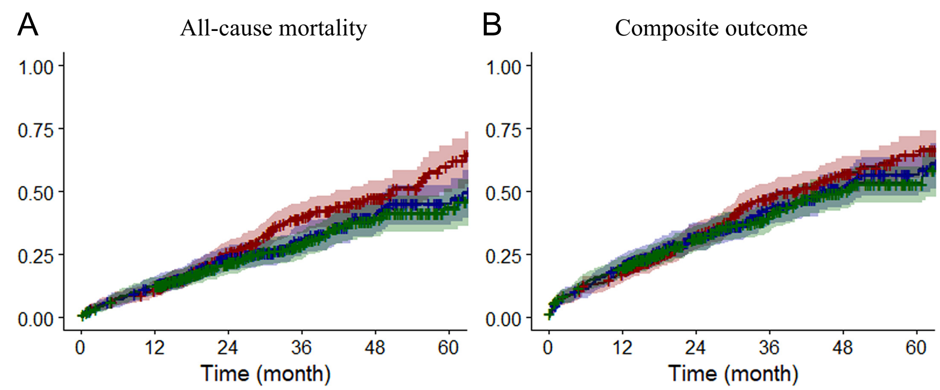
Supplementary Table 1.	Variables Used to Calculate the Propensity Score
Continuous variables	Age (years), height (m), STS-PROM, creatinine (mg/dl), hemoglobin (g/dl), albumin (g/dl), left ventricular ejection fraction (%), transaortic mean gradient (mm Hg)
Dichotomous variables	Sex (male/female), New York Heart Association III/IV, hypertension, dyslipidemia, diabetes, moderate/severe chronic lung disease, liver disease, cerebrovascular accident, peripheral artery disease, coronary artery disease, atrial fibrillation, prior pacemaker/defibrillator, moderate/severe mitral regurgitation, moderate/severe tricuspid regurgitation, non-elective procedure, non-transfemoral access

STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality



Number at risk

348	304	180	107	55	18	348	281	163	95	46	17
319	272	169	106	56	25	319	247	152	90	47	21
352	302	190	124	64	25	352	275	170	105	52	21

Hazard ratio, 95% confidence interval

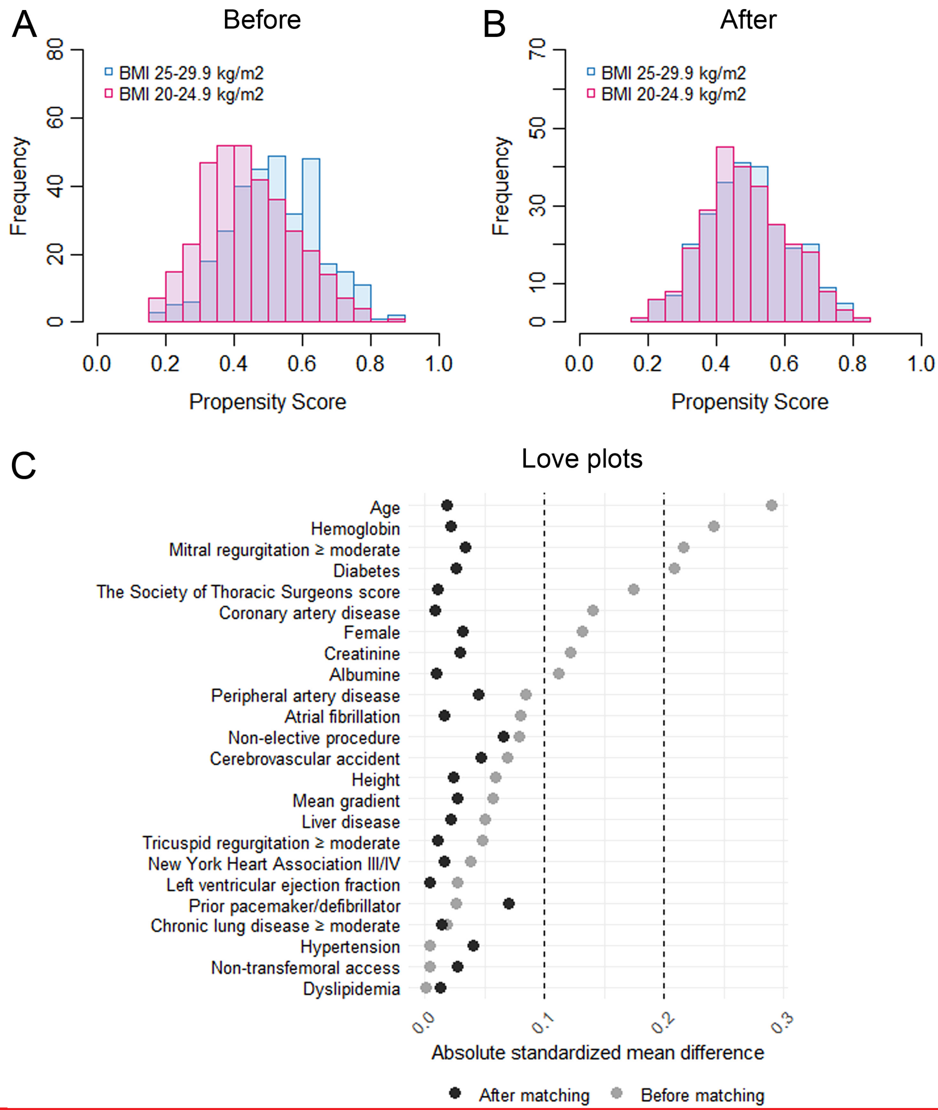
Overweight versus normal BMI

All-cause mortality: 0.79, 0.61-1.03, p=0.084; Composite outcome: 0.92, 0.73-1.16, p=0.484

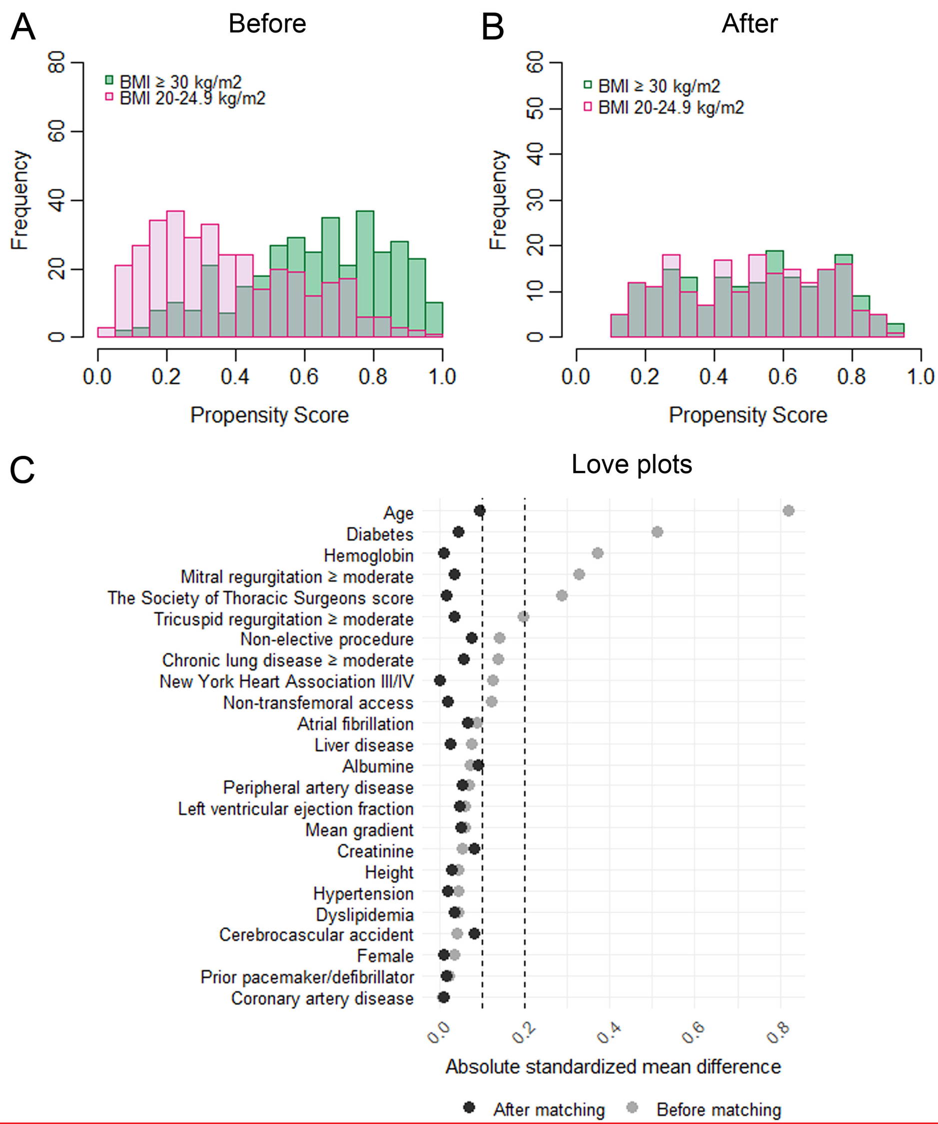
Obese versus normal BMI

All-cause mortality: 0.76, 0.59-0.98, p=0.037; Composite outcome: 0.89, 0.71-1.12, p=0.305

Supplementary Figure 1. Crude Kaplan-Meier curves for (a) all-cause mortality and (b) the composite of all-cause mortality, stroke, and rehospitalization for heart failure between normal BMI (red), overweight (blue), and obese (green) groups. BMI, body mass index.



Supplementary Figure 2. Distribution of propensity score (a) before and (b) after matching, and (c) love plots for absolute standardized mean differences before and after propensity score matching. Normal BMI vs. overweight. BMI, body mass index.



Supplementary Figure 3. Distribution of propensity score (a) before and (b) after matching, and (c) love plots for absolute standardized mean differences before and after propensity score matching. Normal BMI vs. obese. BMI, body mass index.