



Rapetto, F., Bruno, V. D., King, M., Benedetto, U., Caputo, M., Angelini, G. D., ... Vohra, H. A. (2018). Impact of body mass index on outcomes following mitral surgery: Does an obesity paradox exist? *Interactive Cardiovascular and Thoracic Surgery*, 26(4), 590-595.  
<https://doi.org/10.1093/icvts/ivx383>

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**Impact of body mass index on outcomes following mitral surgery: does an obesity paradox exist?**

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**Abstract****OBJECTIVES**

This study was conducted to clarify the relationship between body mass index and mitral valve (MV) surgery and to determine whether an ‘obesity paradox’ exists in the context of surgery for degenerative MV disease.

**METHODS**

In this retrospective single-centre study, we analysed data from 715 patients who underwent mitral surgery for degenerative disease from 2000 to 2015. Patients were classified according to body mass index: underweight ( $<20$  kg/m<sup>2</sup>), normal weight (20–24.99 kg/m<sup>2</sup>), overweight (25–29.99 kg/m<sup>2</sup>) and obese ( $\geq 30$  kg/m<sup>2</sup>). Early and long-term results were investigated.

Multivariable analysis was conducted to identify risk factors for long-term mortality.

**RESULTS**

Mean follow-up was  $67 \pm 44$  months (range 0–190 months). There were no differences between groups regarding 30-day mortality ( $P = 0.35$ ), stroke ( $P = 0.45$ ), reoperation for bleeding ( $P = 0.9$ ) and length of hospital stay ( $P = 0.31$ ). Obese patients were at increased risk of acute kidney injury when compared with normal weight patients (17% vs 5%;  $P = 0.03$ ) but not when compared with the other groups; this was confirmed within the subgroup with depressed ejection fraction (42% vs 10%,  $P = 0.02$ ). No differences in long-term survival were found across groups for all patients ( $P = 0.62$ ) and for patients with depressed ejection fraction ( $P = 0.6$ ), with a trend towards worse survival in obese patients undergoing MV repair ( $P = 0.06$ ). Survival in obese patients undergoing repair was significantly worse than that in obese patients undergoing replacement ( $P = 0.04$ ).

**CONCLUSIONS**

An ‘obesity paradox’ was not demonstrated after surgery for degenerative MV disease. Obese patients are more prone to acute kidney injury and have worse late survival after MV repair.

## Introduction

Obesity is an increasingly relevant medical and socioeconomic problem in developed countries, with well-documented impact on healthcare systems [1, 2]. The estimated costs for overweight and obesity was \$113.9 billion in the USA in 2008, representing 4.8% of healthcare expenditure that year [3]. Also, obesity is known to be a strong risk factor for cardiovascular disease including hypertension, coronary artery disease (CAD) and heart failure [4, 5]. On the other hand, the relationship between body mass index (BMI) and outcomes following adult cardiac surgery is less clear. Obesity has been associated with worse clinical outcomes following open heart surgery, with higher mortality and increased incidence of postoperative complications including respiratory failure, prolonged intensive care unit stay and sternal wound infection [6–9]. Nevertheless, this relationship was not observed in a number of studies with several series demonstrating an ‘obesity paradox’, defined as an association between obesity and improved postoperative results [10–14]. The obesity paradox in cardiac surgery has been investigated mainly in patients undergoing coronary artery bypass grafting (CABG). The evidence with regard to valve surgery is limited, and the impact of the BMI on mitral valve (MV) surgery to the best of our knowledge has not been specifically analysed. Using a single-centre cohort, we conducted a retrospective study to clarify the relationship between the BMI and postoperative morbidity and mortality after isolated or combined surgery for degenerative MV disease at our institution.

## Materials and Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki. The local audit committee approved the study, and the requirement for individual patient consent was waived. Standard data are collected prospectively for all patients at our institution. The data collection form includes 5 sections that are filled in consecutively by an anaesthetist, a surgeon, a perfusionist and nurses; data are entered into a database (Patient Analysis & Tracking System, Dendrite Clinical Systems, Henley-on-Thames, UK). For this study, data for 1742 consecutive patients who had undergone MV surgery between April 2000 and March 2015 were obtained from the database. After extracting patients with degenerative MV disease, our sample was composed of 863 consecutive patients who underwent isolated or combined MV surgery during the aforementioned time period. All the operations were performed through a vertical median sternotomy approach.

The logistic EuroSCORE [15] was calculated for all patients. BMI was obtained using Quetelet's formula [16]. One hundred and forty-eight patients were excluded from the analysis because of incomplete BMI data, and therefore our final sample included 715 patients. The study population was divided into 4 groups based on the BMI: underweight ( $<20 \text{ kg/m}^2$ ), normal weight ( $20\text{--}24.99 \text{ kg/m}^2$ ), overweight ( $25\text{--}29.99 \text{ kg/m}^2$ ) and obese ( $>30 \text{ kg/m}^2$ ). These are in close accordance with the definitions of the World Health Organization (WHO) excluding the underweight category, where a  $<20 \text{ kg/m}^2$  cut-off was used instead of  $<18.5 \text{ kg/m}^2$ , as this has been widely used in the literature and therefore allowed for comparison. Early (30-day) mortality, median postoperative length of hospital stay, incidence of acute kidney injury (AKI), incidence of cerebrovascular accident, incidence of reoperation for bleeding and late survival were used as indicators of postoperative outcomes. The AKI was determined using pre- and postoperative serum creatinine and estimated glomerular filtration rate; the variable was dichotomized with a  $\geq 2$  times increase in creatinine or  $>50\%$  decrease in estimated glomerular filtration rate, which reflects Stage 2 AKI from the risk, injury, failure, loss, end-stage (RIFLE) criteria, defining the presence of AKI [17].

#### Statistical analysis

Continuous variables are reported as mean  $\pm$  standard deviation. Categorical variables are reported as percentage frequencies. When comparing preoperative characteristics, operative characteristics and postoperative outcomes across groups, the Kruskal–Wallis test was used for continuous variables. The  $\chi^2$  comparisons were used for categorical variables, with the Bonferroni *posthoc* tests. The Fisher's exact test was used when appropriate. *P*-value  $\leq 0.05$  was taken as conferring a significant difference. Long-term survivals for each group are presented as the Kaplan–Meier survival curves, and the log-rank test was used to compare the curves. Effects of the clinical variables on long-term survival were assessed using the Cox proportional hazard models and are reported as hazard ratios (HRs, 95% confidence interval and *P*-value). A *P*-value of  $<0.05$  was considered statistically significant. After conducting univariable analysis testing for main preoperative and operative variables, a multivariable Cox model was fitted including both the potential confounding factors and the variables that proved to be significantly associated with late mortality in the univariable model [age, gender, BMI, preoperative atrial fibrillation, history of CAD, extracardiac arteriopathy, hypertension, insulin-dependent diabetes mellitus, high preoperative New York Heart Association class, depressed left ventricular ejection fraction (LVEF), history of lung disease,

history of smoke, urgent/emergent surgery, isolated mitral procedure and mitral valve repair (MVR) were entered in the multivariable model]. Age and BMI were modelled as continuous variables using restricted cubic spline functions with 5 knots to avoid potential biases that can originate from categorization as previously described [18]. Associations between continuous predictors and long-term survival are reported as interquartile range HRs [19]. Assumption of proportionality was tested with the scaled Schoenfeld residuals, and it was met.

A subanalysis was also conducted with regard to early- and long-term outcomes in patients with depressed LVEF, defined as <50%.

Statistical analysis was performed with RStudio, version 1.0.136 (RStudio: Integrated Development for R. RStudio, Inc., Boston, MA, USA).

## Results

Of the 715 patients in the study population, 64 (9%) were classified as underweight, 292 (41%) as normal BMI, 263 (37%) as overweight and 96 (13%) as obese. Baseline characteristics are listed in Table 1. Patients in the lower BMI groups were significantly less likely to be male ( $P = 0.002$ ). When compared with the overweight group (74% male), there was a significantly lower proportion of men in both the underweight (50%;  $P < 0.001$ ) and normal weight (65%;  $P = 0.02$ ) groups. Obese patients showed significantly higher rates of hypertension ( $P = 0.009$ ) and New York Heart Association Class III/IV ( $P < 0.001$ ) when compared with the lower BMI groups. In contrast, the proportion of patients with a history of smoking was significantly higher in the lower BMI groups ( $P < 0.001$ ). Operative characteristics are listed in Table 2. Similar proportions of urgent/emergent procedures, reoperations and isolated MV operations were performed in each group. Cardiopulmonary bypass (CPB) and aortic cross-clamp (AoX) times were significantly longer in the higher BMI groups. The analysis of early postoperative outcomes did not demonstrate any statistically significant difference between groups with regard to 30-day mortality ( $P = 0.35$ ), cerebrovascular accident ( $P = 0.45$ ), reoperation for bleeding ( $P = 0.89$ ) and median postoperative length of hospital stay ( $P = 0.31$ ), as listed in Table 3. Overall incidence of AKI was significantly different across groups ( $P = 0.05$ ), with obese patients being at increased risk of AKI when compared with normal BMI patients (17% vs 5.2%;  $P = 0.03$ ) but not when compared with the other groups.

Early outcomes were also analysed considering patients with preoperative LVEF <50%. No statistically significant differences were found across BMI groups with regard to 30-day mortality ( $P = 0.93$ ), reoperation for bleeding ( $P = 0.82$ ), cerebrovascular accident ( $P = 0.79$ ) and postoperative length of hospital stay ( $P = 0.23$ ). The overall occurrence of AKI was not different across groups ( $P = 0.05$ ), but obese patients had a significantly increased incidence of AKI when compared with other patients in this subgroup with depressed LVEF (42% vs 10% in normal weight patients,  $P = 0.02$ ).

Regarding long-term survival, follow-up was 100% complete; mean follow-up was  $67 \pm 44$  months (range 0–190 months). The Kaplan–Meier curves were stratified according to the BMI groups as shown in Fig. 1. The log-rank test was conducted to compare the various Kaplan–Meier curves, and no statistically significant difference was found. The Kaplan–Meier curves were also derived considering patients with depressed LVEF (Fig. 2) and patients who underwent MVr (Fig. 3A), and no differences in the overall long-term survival were found across BMI groups in these subsets of patients ( $P = 0.6$  and  $P = 0.06$ , respectively). Nevertheless, a trend towards worse late survival was observed in obese patients undergoing MVr when compared with other BMI groups, and late survival in obese patients undergoing MVr was significantly worse than in obese patients undergoing mitral valve replacement (MVR,  $P = 0.04$ , Fig. 3B), whereas the trend within the other BMI groups was in favour of MVr.

When modelled as a continuous variable, BMI was not associated with long-term mortality on univariable (interquartile HR 1.12; 0.75–1.67) or multivariable (interquartile HR 1.08; 0.70–1.68) Cox analysis (Table 4, Fig. 4A and B) for long-term survival. Age, preoperative atrial fibrillation, CAD, hypertension, insulin-dependent diabetes mellitus, high New York Heart Association class, depressed LVEF, lung disease, smoke and urgency/emergency were found to be risk factors for late mortality on univariable analysis; age, smoke and preoperative atrial fibrillation remained significantly associated with late adverse outcomes in the multivariable model (Table 4).

## Discussion

In this study, we analysed the outcomes of MV surgery for degenerative MV disease with relation to different BMI categories across 15 years at our institution. As obesity is widely recognized to be a risk factor for atherosclerosis, the impact of BMI on adult cardiac surgery

has been traditionally investigated in the context of CABG [7, 8, 20], and published series analysing valve surgery mainly focused on aortic valve procedures [8, 11, 13, 14, 21]. To our knowledge, this is the first study specifically concentrating on MV surgery. We included patients undergoing combined procedures, but the majority of patients had isolated MV surgery, and this proportion was similar across BMI groups.

This study has 3 main findings. First, a trend towards a higher risk for postoperative AKI in obese patients was observed, when compared with normal weight patients; this was also confirmed by a subanalysis in patients with depressed LVEF. This finding has not been replicated by other previously published series [10, 11]. Wigfield *et al.* [22] found extreme obesity ( $BMI \geq 40$ ) to be a risk factor for postoperative AKI; in their series focused on valvular surgery, Thourani *et al.* [21] also found obese patients ( $BMI \geq 36$ ) to be at higher risk of postoperative AKI. Pathogenesis of AKI following cardiac surgery is multifactorial, and prolonged CPB and AoX times have been found to be risk factors for renal injury [23]. CPB and AoX times were longer in obese patients in our sample, and therefore this may account for our results in terms of AKI. Moreover, the higher incidence of hypertension in our obese group may be a marker of more advanced underlying renal disease, even though this was not highlighted by preoperative creatinine and estimated glomerular filtration rate levels. Our data indicate no clear correlation between BMI and postoperative morbidity and mortality other than AKI.

Second, MV surgery can be performed with good long-term results in patients with both high and low BMI. Overall postoperative survival up to 10 years in our series was consistent with previous reports [24, 25], and it was similar across BMI groups. This was confirmed even after conducting survival analysis in patients with depressed LVEF and in patients who underwent MVr. Nevertheless, when considering the MVr subgroup, obese patients seemed to have a slightly worse long-term prognosis when compared with other BMI groups. Interestingly, we are the first group to report that long-term survival is better in obese patients undergoing MVR compared with MVr. This is not entirely unexpected in the challenging group of obese patients which can lead to longer operative times (mainly because of difficult access) and longer CPB and AoX times in MVr when compared with MVR. Even though the preoperative risk profile of these patients seemed to be homogeneous, our obese group was composed of 96 patients, and analyses on a larger number of individuals are needed to further



explain this effect. If this finding is confirmed, a technically less demanding and shorter MVR might be preferable in high-BMI patients.

Third, an obesity paradox, defined as a protective effect of obesity against early postoperative complications and late mortality, could not be demonstrated in our study. Multiple previous articles reported a U- or J-shaped relationship between BMI and postoperative outcomes, with better results in mildly obese patients when compared with underweight and severely obese patients [12, 14, 26]. Several reasons have been hypothesized for this, including smaller coronary arteries, implantation of smaller valves and more severe CPB-related haemodilution in the underweight group on the one hand and more aggressive, evidence-based medical therapy given to obese patients on the other hand [11, 27, 28]. However, previously published studies generally reported a higher risk profile in underweight patients (higher preoperative risk scores, older age and more valve procedures compared with those of overweight/obese patients [11, 21]), which may partially account for worse outcomes. This was not the case in this study: all patients underwent MV surgery, and BMI groups were overall well matched, with significant differences being only found in terms of gender, smoking history, hypertension and New York Heart Association class. In this sample of patients undergoing mitral surgery, we did not demonstrate a protective effect of mild obesity or a negative effect of low BMI on early or long-term outcomes. Regarding late survival, even after adjusting for confounding factors and modelling BMI as a continuous variable to avoid the potential bias deriving from categorization, a U- or J-shaped relationship between BMI and late mortality was not found. Long-term outcomes after mitral surgery have been investigated by Badhwar *et al.* [29] in a large series of patients undergoing isolated MVR: BMI was not related to late mortality even though obesity was found to be a risk factor for nonfatal outcomes including late readmission for congestive heart failure.

In our opinion, the lack of correlation between BMI and most postoperative outcomes found in our series might be explained by the characteristics of the patient population included in this study. Our sample was mainly composed of patients with isolated MV disease, and associated conditions such as CAD were equally distributed across groups. Obesity is known to play a strong role in the pathogenesis of CAD [5] and, for this reason, an impact of BMI on CABG outcomes might be expected; the fact that in CABG cohorts obese patients are usually younger is in accordance with this prediction and indicates a more aggressive CAD. On the other hand, the influence of obesity on the development of MV disease is less clear and

probably less strong; as an indirect proof, in our sample of patients with MV disease, age was not significantly different across BMI groups. According to our findings, other factors such as AF might be more closely related to the disease process in this cluster of patients, thus reducing the role of BMI in determining postoperative results.

### Limitations

The absence of data on sternal wound infection is a significant limitation of our study; sternal wound infection is a major complication, which has been related to BMI by other groups [12, 26]. Furthermore, we focused our survival analysis on the association between BMI and late mortality; however, BMI has been found to be related to non-fatal late adverse events, which we did not take into account [29]. Finally, this study is limited by its non-randomized, single-centre, retrospective nature; our findings must be confirmed by other surgical experiences, and multicentre studies are needed.

This work was supported by the NIHR Bristol Biomedical Research Centre.

**Conflict of interest:** none declared.

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**Table 1:**

Baseline patient characteristics

Variables	Underweigh t ( <i>n</i> = 64)	Normal weight ( <i>n</i> = 292)	Overweight ( <i>n</i> = 263)	Obese ( <i>n</i> = 96)	<i>P</i> - value
Age (years)	66.3 ± 15.7	68.6 ± 10.6	68.3 ± 10.0	66.9 ± 10.4	0.54
Male, <i>n</i> (%)	32 (50)	189 (65)	194 (74)	63 (66)	<b>0.002</b>
Hypertension, <i>n</i> (%)	25 (39)	128 (44)	132 (50)	59 (61)	<b>0.009</b>
Smoking history, <i>n</i> (%)	47 (73)	197 (67)	135 (51)	45 (47)	<b>&lt;0.001</b>
NYHA Class III– IV, <i>n</i> (%)	27 (42)	144 (49)	128 (49)	69 (72)	<b>&lt;0.001</b>
LVEF (%)	50.5 ± 7.4	50.3 ± 8.1	50.3 ± 8.2	50.3 ± 8.2	0.99
Lung disease, <sup>a</sup> <i>n</i> (%)	5 (8)	29 (10)	30 (11)	15 (16)	0.37
Neur dysf, <sup>a</sup> <i>n</i> (%)	2 (3)	8 (3)	3 (1)	0	0.22
Previous MI, <sup>a</sup> <i>n</i> (%)	2 (3)	26 (9)	27 (10)	11 (11)	0.59
IDDM, <i>n</i> (%)	3 (5)	2 (1)	6 (2)	1 (1)	0.1
Extracardiac arteriopathy, <sup>a</sup> <i>n</i> (%)	4 (6)	17 (6)	11 (4)	5 (5)	0.95
AF, <i>n</i> (%)	27 (42)	111 (38)	89 (34)	35 (36)	0.74
CAD, <i>n</i> (%)	11 (17)	72 (25)	88 (33)	27 (28)	0.08
Creatinine (μmol/l)	96.5 ± 28.8	100.2 ± 23.3	108.9 ± 61.6	97.5 ± 21.4	0.37
LogEuroSCORE	7.5 ± 9.1	7.0 ± 7.4	6.4 ± 6.7	6.7 ± 6.3	0.88

*P*-values <0.05 reported in bold are considered statistically significant.

a

Defined according to the logistic EuroSCORE model.

AF: atrial fibrillation; CAD: coronary artery disease; IDDM: insulin-dependent diabetes mellitus; LVEF: left ventricular ejection fraction; MI: myocardial infarction; Neur dysf: neurological dysfunction; NYHA: New York Heart Association.

**Table 2:**

Operative characteristics

<b>Variables</b>	<b>Underweigh t (<i>n</i> = 64)</b>	<b>Normal weight (<i>n</i> = 292)</b>	<b>Overweigh t (<i>n</i> = 263)</b>	<b>Obese (<i>n</i> = 96)</b>	<b><i>P</i>- value</b>
<b>Urgency/emergency, <i>n</i> (%)</b> )	15 (23)	69 (24)	61 (23)	20 (21)	0.95
<b>Redo surgery, <i>n</i> (%)</b>	5 (8)	21 (7)	22 (8)	11 (11)	0.62
<b>CPB time (min)</b>	110 ± 33	123 ± 51	137 ± 58	136 ± 53	<b>&lt;0.001</b>
<b>AoX time (min)</b>	77 ± 28	87 ± 35	92 ± 35	95 ± 35	<b>&lt;0.001</b>
<b>Isolated mitral surgery, <i>n</i> (%)</b>	53 (83)	223 (76)	184 (70)	73 (76)	0.11

*P*-values <0.05 reported in bold are considered statistically significant.

AoX: aortic cross-clamp; CPB: cardiopulmonary bypass.

**Table 3:**

Early postoperative outcomes

<b>Variables</b>	<b>Underweight (n = 64)</b>	<b>Normal weight (n = 292)</b>	<b>Overweight (n = 263)</b>	<b>Obese (n = 96)</b>	<b>P- value</b>
<b>30-day mortality, n(%)</b>	2 (3)	9 (3)	16 (6)	4 (4)	0.35
<b>CVA, n (%)</b>	1 (2)	9 (3)	3 (1)	2 (2)	0.45
<b>AKI,<sup>a</sup> n (%)</b>	2 (7) <sup>a</sup>	9 (5) <sup>a</sup>	12 (9) <sup>a</sup>	9 (17) <sup>a</sup>	0.06
<b>Reoperation for bleeding, n (%)</b>	3 (5)	16 (5)	11 (4)	4 (4)	0.9
<b>LOS (days), median (IQR)</b>	8 (6–12)	8 (6–12)	9 (6–13)	9 (7–14)	0.31

a

Because information on kidney function prior to February 2009 was not available, data for AKI were calculated on 393 patients.

AKI: acute kidney injury; CVA: cerebrovascular accident; IQR: interquartile range; LOS: length of hospital stay.

**Table 4:**

Univariable and multivariable Cox model analyses for overall survival

Variables	Univariable			Multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	3.25	2.09– 5.04	<b>&lt;0.001</b>	3.23	1.98– 5.29	<b>&lt;0.001</b>
BMI	1.12	0.75– 1.67	0.8	1.04	0.67– 1.61	0.84
Male sex	0.79	0.58– 1.07	0.13	0.78	0.54– 1.13	0.2
Hypertension	1.41	1.04– 1.89	<b>0.02</b>	0.80	0.57– 1.14	0.22
Smoking history	1.54	1.14– 2.07	<b>0.005</b>	1.47	1.04– 2.06	<b>0.03</b>
AF	2.12	1.58– 2.85	<b>&lt;0.001</b>	1.90	1.34– 2.69	<b>0.003</b>
NYHA Class III–IV	1.71	1.26– 2.32	<b>0.006</b>	1.08	0.76– 1.54	0.67
LVEF <50%	1.95	1.45– 2.63	<b>&lt;0.001</b>	1.32	0.91– 1.90	0.14
CAD	1.44	1.06– 1.95	<b>0.02</b>	1.16	0.71– 1.90	0.55
Lung disease	1.64	1.06– 2.53	<b>0.02</b>	1.24	0.75– 2.06	0.40
IDDM	2.29	1.07– 4.90	<b>0.03</b>	1.89	0.85– 4.18	0.12
Extracardiac arteriopathy	1.74	0.99– 3.06	0.06	1.70	0.89– 3.24	0.11
Isolated mitral	0.78	0.57– 1.07	0.12	1.34	0.83– 2.16	0.23
Repair	1.079	0.78– 1.49	0.64	1.14	0.77– 1.68	0.50
Urgency/emergency	1.75	1.29– 2.39	<b>0.004</b>	1.42	0.97– 2.10	0.07

P-values <0.05 reported in bold are considered statistically significant.

AF: atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; CI: confidence interval; HR: hazard ratio; IDDM: insulin-dependent diabetes mellitus; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association.



## Figure Legend

Figure 1. The Kaplan–Meier curves stratified for BMI groups for overall population. BMI: body mass index.

Figure 2. The Kaplan–Meier curves stratified for BMI groups in patients with depressed ejection fraction. BMI: body mass index.

Figure 3. (A) The Kaplan–Meier curves stratified for BMI groups in patients undergoing mitral valve repair. (B) The Kaplan–Meier curves for obese patients undergoing mitral valve replacement and mitral valve repair. BMI: body mass index.

Figure 4. The relationship between BMI-restricted cubic spline function and hazard ratio for late mortality on unadjusted univariable (A) and adjusted multivariable (B) analyses. BMI: body mass index.