Obesity paradox among elderly patients with coronary artery disease undergoing non-cardiac surgery

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Abstract

Background High body mass index (BMI) is a risk factor for chronic cardiac disease. However, mounting evidence supports that high BMI is associated with less risk of cardiac morbidity and mortality compared with normal BMI, also known as the obesity paradox. Therefore, we sought to determine the existence of the obesity paradox in regard to perioperative 30-day cardiac events among elderly Chinese patients with known coronary artery disease undergoing non-cardiac surgery.

Methods A post-hoc analysis of a prospective, multi-institutional cohort study was performed. Patients aged > 60 years with a history of coronary artery disease and undergoing non-cardiac surgery were grouped according to BMI: underweight (< 18.5 kg/m\textsuperscript{2}), normal weight (18.5–24.9 kg/m\textsuperscript{2}), overweight (25–29.9 kg/m\textsuperscript{2}) and obese (≥ 30 kg/m\textsuperscript{2}). Demographic information, perioperative clinical variables and incidence of 30-day postoperative cardiac adverse event were retrieved from a research database.

Results We identified 1202 eligible patients (BMI: 24.3 ± 3.8 kg/m\textsuperscript{2}). Across BMI groups, a U-shaped distribution pattern of incidence of 30-day postoperative major cardiac events was observed, with the lowest risk in the overweight group. When using the normal-weight group as a reference, no difference was found in either the obesity or overweight groups in terms of a major cardiac adverse event (MACE). However, risk of a 30-day postoperative MACE was significantly higher in the underweight group (odds ratio [OR] 2.916, 95% confidence interval [CI]: 1.072–7.931, \( P = 0.036 \)).

Conclusion Although not statistically significant, the U-shaped relation between BMI and cardiac complications indicates the obesity paradox possibly exists.

Keywords: Body mass index; Major cardiac event; Non-cardiac surgery; The elderly

1 Introduction

Obesity has emerged as a critical public health issue in China.\cite{1} According to Global Health Observatory (GHO) data from World Health Organization (WHO), mean body mass index (BMI) of China is on the rise for the past four decades and reached 23.8 (23.5–24.2) kg/m\textsuperscript{2} in the year 2016.\cite{2} Consequences of high body mass index (BMI), including increased risk of coronary artery disease (CAD), diabetes, hypertension, dyslipidemia and atherosclerosis, have been well recorded in the literature.\cite{3} However, a recent series of studies have reported obesity as being a survival benefit in long-term prognosis of cardiovascular disease.\cite{4,5} Some studies have even discovered a paradoxical U-shaped relationship between BMI and long-term cardiovascular outcomes.\cite{6,7,8} This phenomenon has been termed “obesity paradox”, suggesting that patients with higher BMI have similar or lower mortality rates compared with normal BMI, while patients with extremely low BMI have worse outcomes. In surgical settings, overweight and obesity have been found to be associated with less cardiac mortality in peripheral artery surgery,\cite{9} as well as percutaneous coronary intervention.\cite{10,11} However, conflicting results do exist\cite{4,10} and evidence in non-cardiac surgery is scarce.

With changing lifestyle and dietary structure, Asian populations are facing a shifting pattern of BMI distribution.\cite{12} An increasing number of patients complicated with obesity-related disease, especially coronary artery disease will require surgery and anesthesia management. Postoperative morbidity and mortality are most frequently a direct result of an adverse cardiac event. Incidence of postoperative cardiac complications in cardiac patients remains high, ranging from 3.9% to 10%.\cite{13,14,15} Elderly patients are even more vulnerable to postoperative cardiac events. China is
highly different from western countries in terms of life expectancy, demographic profiles, as well as environmental and genetic risk factors. Considering that BMI is differently distributed across ethnic groups, whether or not the obesity paradox described in previous studies conducted in Europe and North America apply to Chinese elderly patients remains unclear.

Thus, examining the association between BMI and cardiovascular adverse events in Chinese coronary artery disease patients undergoing non-cardiac surgery is important.

2 Method

2.1 Study population

We performed a post-hoc analysis using data from a multicenter prospective study. The original study enrolled consecutive patients diagnosed with coronary artery disease who were over 60 years of age undergoing non-cardiac surgery between March 1, 2008 and February 28, 2010, at five university-affiliated tertiary care hospitals in China. The details of the original study have been described previously.\[16\] This study was approved by a local medical ethics committee. Inclusion criteria were patients with a history of CAD undergoing intermediate-to-high-risk non-cardiac surgery based on the American College of Cardiology/American Heart Association guidelines. Original exclusion criteria included: (1) patients who underwent emergency surgery or low-risk surgery; (2) patients with American Society of Anesthesiologists (ASA) classification of V or VI; and (3) patients with congenital heart disease or cardiomyopathy. For the present study, we further excluded patients with incomplete data necessary to extrapolate BMI. The analyzed preoperative variables including patient demographics, co-morbid conditions, and laboratory values were all extracted from the original database. Intraoperative variables were also analyzed. The primary outcome measure was occurrence of a postoperative adverse cardiac event within 30 days postoperatively. Major cardiac adverse events included: cardiac death, nonfatal myocardial infarction, nonfatal cardiac arrest, and heart failure (Table 1).

2.2 BMI definition

BMI is defined as body weight in kilograms divided by height in meters squared. Applying the World Health Organization’s (WHO’s) BMI cutoff points directly to the Asian population has been questioned.\[17\] A WHO expert consultation suggests that, among Asian populations, associations between BMI, percentage of body fat, and health risks differ from that among European populations and that interpretation of population-specific BMI should be considered.\[18\] However, an agreed consensus was never reached. The purpose of a BMI cut-off point is to identify, within each population, the proportion of people who are at high risk of an undesirable health state that warrants public health or clinical intervention. Therefore, we deemed that keeping the cutoff value in line with the original WHO value for research purposes was the best course of action. Furthermore, we incorporated new cutoff points of 23 kg/m² and 27.5 kg/m² for reporting purposes with a view to facilitate international comparisons as recommended by the WHO. For the reasons stated above, in this study, BMI was categorized into the following six groups: (1) < 18.5 kg/m² (underweight); (2) 18.5–22.9 kg/m² (normal I); (3) 23–24.9 (normal II); (4) 25–27.4 kg/m² (Overweight I); (5) 27.5–29.9 kg/m² (overweight II); and (6) BMI ≥ 30 kg/m²(obese).

2.3 Statistical analysis

Continuous variables were compared across BMI classes using analysis of variance (ANOVA) or Kruskal–Wallis equality-of-populations rank test. Categorical variables were compared across BMI classes using chi-square test. The influence of BMI class on the risk of morbidity and mortality was assessed using odds ratios from logistic regression analyses, with normal BMI class as the reference. \(P < 0.05\) was considered to indicate statistical significant.

3 Results

3.1 Baseline comparisons

According to WHO’s BMI classification, among the 1202 included patients, 57 (4.74%) were underweight, 632 (52.58%) were normal weight, 450 (37.44%) were overweight, and 63 (5.24%) were obese. Patient variables were stratified by BMI obesity group, as described in the methods section (Table 1). Demographic covariates demonstrated that overweight and obese patients were more likely to be younger and female. As expected, more patients with higher BMI were diabetic and hypertensive \(P < 0.05\). Lower BMI was associated with lower preoperative hemoglobin and creatinine levels \(P < 0.05\). No significant differences were observed across BMI groups with regard to risk factors that are particularly relevant to patients with known ischemic heart disease undergoing non-cardiac surgery, such as: history of previous myocardial infarction, history of heart failure, history of PCI, and smoking status.

A total of 52 (4.3%) patients experienced postoperative cardiac complications (Table 2). The BMI classification associated with the highest rates of a major adverse cardiac event (MACE) was underweight (10.5%). Additionally, a
| Table 1. Patient characteristics according to BMI classification. |
|-----------------|-----------|-----------|-----------|-----------|-----------|
|                  | Under weight | Normal weight | Overweight | Obese | P        |
|                  | (n = 57)     | (n = 361)   | (n = 271)   | (n = 305) | (n = 145) | (n = 63) |
| **BMI, kg/m²**   | < 18.5      | 18.5–22.9  | 23–24.9     | 25–27.4   | 27.5–29.9 | ≥30      |
| **Demographic**  |             |            |            |         |          |          |
| Age, yrs         | 70.8 ± 6.8  | 70.6 ± 6.4 | 68.9 ± 6.4 | 69.2 ± 6.0 | 68.8 ± 5.6 | 67.5 ± 6.6 | < 0.01 |
| Male             | 29 (50.9%)  | 209 (57.9%)| 162 (59.8%)| 145 (47.5%)| 75 (51.2%) | 23 (36.5%) | 0.02   |
| Education        | 7 (12.3%)   | 75 (20.8%) | 52 (19.9%) | 71 (23.3%) | 35 (24.1%) | 15 (23.8%) | 0.39   |
| Social supported | 6 (10.5%)   | 37 (10.2%) | 23 (8.5%)  | 32 (10.5%) | 13 (8.9%)  | 3 (4.8%)   | 0.75   |
| **Risk factor**  |             |            |            |         |          |          |
| DM               | 5 (8.8%)    | 63 (17.4%) | 67 (24.7%) | 73 (23.9%) | 35 (24.1%) | 22 (34.9%) | 0.02   |
| Insulin dependent DM | 2 (3.5%) | 22 (6.1%) | 30 (11.1%) | 29 (9.5%) | 19 (13.1%) | 10 (15.9%) | 0.02   |
| Hypertension     | 15 (26.2%)  | 167 (46.3%)| 146 (53.9%)| 196 (64.3%)| 108 (74.5%)| 48 (76.2%) | < 0.01 |
| History of smoking | 26 (45.6%) | 140 (38.9%)| 109 (40.5%)| 95 (31.1%) | 51 (35.1%) | 18 (28.6%) | 0.06   |
| History of CHF   | 2 (3.5%)    | 4 (1.1%)   | 6 (2.2%)   | 3 (1.0%)  | 4 (2.8%)   | 3 (4.8%)   | 0.21   |
| History of myocardial infarction | 7 (12.3%) | 39 (10.8%) | 41 (15.1%) | 37 (12.1%) | 22 (15.2%) | 11 (17.5%) | 0.47   |
| History of stroke | 7 (12.3%) | 36 (10.0%) | 30 (11.1%) | 39 (12.8%) | 15 (10.3%) | 8 (12.7%) | 0.89   |
| History of PCI   | 3 (5.3%)    | 25 (6.9%)  | 36 (13.3%) | 29 (9.5%) | 11 (7.6%)  | 8 (12.7%) | 0.07   |
| **Laboratory parameter** |             |            |            |         |          |          |
| Hemoglobin, g/L  | 120 ± 19    | 124 ± 22   | 129 ± 21   | 130 ± 21  | 133 ± 18   | 130 ± 20  | < 0.01 |
| HDL-C, mmol/L    | 1.29 ± 0.49 | 1.13 ± 0.35| 1.04 ± 0.32| 1.09 ± 0.33| 1.14 ± 0.54| 1.15 ± 0.30| 0.05*  |
| Creatine, μmol/L | 66.7 ± 21.9 | 77.6 ± 25.8| 78.1 ± 24.9| 76.9 ± 23.7| 79.2 ± 20.6| 81.4 ± 22.7| < 0.01*|
| **Intraoperative** |             |            |            |         |          |          |
| High surgical risk | 12 (21.1%) | 75 (20.8%) | 67 (24.7%) | 60 (19.7%) | 24 (16.5%) | 8 (12.7%) | 0.23   |
| Intraoperative hypotension | 17 (29.8%) | 110 (30.5%)| 70 (25.9%) | 89 (29.2%) | 33 (22.8%) | 18 (28.6%) | 0.54   |
| Operative time > 2.5 h | 12 (21.1%) | 75 (20.8%) | 67 (24.7%) | 60 (19.7%) | 24 (16.5%) | 8 (12.7%) | 0.23   |
| **Outcome**      |             |            |            |         |          |          |
| MI               | 4 (7.0%)    | 8 (2.2%)   | 8 (2.9%)   | 6 (1.9%)  | 2 (1.4%)   | 1 (1.6%)  | 0.25   |
| CHF              | 2 (3.5%)    | 8 (2.2%)   | 3 (1.1%)   | 3 (1.0%)  | 7 (4.8%)   | 1 (1.6%)  | 0.10   |
| MACE             | 6 (10.5%)   | 14 (3.8%)  | 10 (3.7%)  | 10 (3.3%) | 9 (6.2%)   | 3 (4.8%)  | 0.17   |

Data are shown as n (%) or as mean ± SD. *Kruskal–Wallis equality-of-populations rank test. Social support: represented by marital status, socially supported (married, remarried), socially uns supported (divorced, widowed or separated); education: number of patients with a college degree or higher; surgical risk: high-risk surgery defined in compliance with the 2014 America College of Cardiology/American Heart Association guidelines on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery.\(^{134}\) BMI: body mass index; CHF: congestive heart failure; DM: diabetes mellitus; HDL-C: high-density lipoprotein; MACE: major adverse cardiac event; MI: myocardial infarction; PCI: percutaneous coronary intervention.

| Table 2. Number of patients with MACE. |
|---------------------------------------|
| **MACE**                              | **N** | **Percentage (%)** |
| Cardiac death                         | 6    | 0.5                 |
| Nonfatal myocardial infarction        | 29   | 2.4                 |
| Nonfatal cardiac arrest               | 1    | 0.1                 |
| Congestive heart failure              | 24   | 2.0                 |
| Total                                 | 52   | 4.3                 |

\(N = 1202.\) Eight patients experienced more than one MACE. Cardiac death: any death, unless an unequivocal non-cardiac cause could be established. Non-fatal cardiac arrest: an absence of cardiac rhythm or presence of chaotic rhythm requiring any component of basic or advanced cardiac life support. Non-fatal myocardial infarction: increase and gradual decrease in troponin level or a faster increase and decrease of creatine kinase isoenzyme as markers of myocardial necrosis in the company of at least one of the following: ischemic symptoms, abnormal Q waves on the ECG, ST-segment elevation or depression; or coronary artery intervention or a typical decrease in an elevated troponin level detected at its peak after surgery in a patient without a documented alternative explanation for the troponin elevation. Congestive heart failure: new in-hospital signs or symptoms of dyspnea or fatigue, orthopnea, paroxysmal nocturnal dyspnea, increased jugular venous pressure, signs of cardiomegaly or pulmonary congestion. MACE: major cardiac adverse event.
Figure 1. Distribution of cardiac events across BMI subgroups. Underweight: < 18.5 kg/m²; Normal I: 18.5–22.9 kg/m²; Normal II: 23–24.9; overweight I: 25–27.4 kg/m²; Overweight II: 27.5–29.9 kg/m²; Obese: ≥ 30 kg/m². BMI: body mass index; MACE: major cardiac adverse event.

Table 3. Odds ratio of when compared with normal weight group.

|                      | Crude OR  | 95% CI       | P value | Adjusted OR* | 95% CI       | P value |
|----------------------|-----------|---------------|---------|--------------|---------------|---------|
| Underweight          | 2.916     | 1.072–7.931   | 0.036   | 3.739        | 1.294–10.801  | 0.014   |
| Normal weight II     | 0.950     | 0.415–2.172   | 0.902   | 1.053        | 0.441–2.517   | 0.906   |
| Overweight I         | 0.840     | 0.368–1.920   | 0.679   | 0.818        | 0.340–0.340   | 0.652   |
| Overweight II        | 1.640     | 0.694–3.878   | 0.259   | 1.800        | 0.715–4.536   | 0.213   |
| Obesity              | 1.239     | 0.346–4.443   | 0.742   | 0.990        | 0.250–3928    | 0.988   |

*After adjusting for age, creatinine level, comorbidities including hypertension, diabetes, atrial fibrillation, and operation related risk factor including operation time longer than 2.5 h and intraoperative hypotension.

BMI range of 25–27.4 kg/m² was observed to be associated with the lowest rates of MACE (Table 1).

The distribution of MACE across different BMI groups demonstrated no statistical difference but appeared to resemble a reversed U-shaped pattern (Figure 1). When considering 30-day postoperative myocardial infarction independently, a clear U-shaped pattern can be observed, with lowest incidence in the overweight group. Meanwhile, 30-day postoperative heart failure also demonstrated a similar pattern with lowest incidence in the overweight group.

When compared with the normal-weight group, the underweight group (< 18.5 kg/m²) was at higher risk of developing 30-day postoperative cardiac events (OR = 2.916, 95% CI: 1.072–7.931, P = 0.036). However, no statistical significance was demonstrated between the normal-weight group and either the overweight I group, or the overweight II group, or the obese group in terms of postoperative cardiac risks (Table 3). Multivariate logistic regression showed that after adjusting for age, creatinine level, comorbidities including hypertension, diabetes, atrial fibrillation, and operation related risk factor including operation time longer than 2.5 h and intraoperative hypotension, underweight remained an independent risk factor of MACE (OR = 3.739, 95% CI: 1.294–10.801, P = 0.014), while the other BMI group did not (Table 3).

4 Discussion

Numerous studies worldwide have demonstrated that overweight and obese patients have better prognoses compared with leaner patients.[19] In perioperative settings, the obesity paradox has been proposed as applied to both the Western population and among Chinese patients undergoing PCI.[10] In this study, we demonstrated a U-shaped pattern between BMI and perioperative cardiac morbidity and mortality in elderly patients with coronary artery disease. The risk of a 30-day postoperative major cardiac event is nearly three fold in the underweight group compared with the normal-weight group. Although not statistically significant, risk of MACE tended to be higher in the obese and overweight.
groups when compared with the normal-weight group. Incidence of both MACE and heart failure were lowest in the slightly overweight group (BMI 25–27.4 kg/m²), while incidence of myocardial infarction was lowest in the heavier group (BMI 27.5–29.9 kg/m²). This pattern is similar to that found in previous studies investigating western populations in terms of longer-term cardiac prognosis, suggesting that the obesity paradox exists across ethnic groups.

Many hypotheses underlying the obesity paradox in cardiovascular disease have been made. Excessive accumulation of adipose tissue can lead to significant neuro-hormonal changes and adaptations in the cardiovascular system.[20] Activation of the renin-angiotensin-aldosterone system, altered levels of pro-inflammatory cytokines, and activation of the sympathetic nervous system can contribute to increased heart rate, renal sodium retention, circulating blood volume, ventricular end-diastolic volume, cardiac output, and eventually cardiac remodeling.[21–23] Additionally, obesity is well known to be associated with a chronic inflammatory state. These chronic changes possibly play a protective role during a stressful perioperative period, and remain as an active area of investigation.

Additionally, the size of the coronary arteries has been suggested to increase with BMI.[24] Better coronary perfusion may account for the observed lower cardiac mortality rate among the overweight and obese patients. Furthermore, more medical attention is usually given to overweight and obese patients than to normal-weight patients. As a result, cessation of smoking, cardiac rehabilitation, and counseling about blood glucose and diet are more frequently enforced than in normal-weight patients. Such enforced actions could lead to early detection and prompt management of chronic disease and lower complication rate.

In the elderly population, low BMI often indicates malnutrition. Better nutritional status and New York Heart Association functional class have been found in elderly patients with higher BMI.[25] One study demonstrated that having better functional status was associated with higher BMI values, even in BMIs ≥ 30 kg/m².[26] The ideal BMI range for elderly surgical candidates with known coronary artery disease should be further studied and incorporated into a preoperative optimization strategy. In cardiac surgery, obesity has been demonstrated as not being an independent cause of short- and long-term mortality, while it has been shown to be beneficial for older patients. However, obese patients have been revealed to have lower MACE-free survival because of an increased incidence of rehospitalization for congestive heart failure.[27] In this study, we demonstrated that overall, both MACE and myocardial infarction were highest in the underweight elderly population, while congestive heart failure incidence was highest in the overweight group. These findings suggest a unique correlation between obesity and the progression of heart failure.[28]

Overall, the obesity paradox is possibly an end result of the complex nature of the interaction between several potential relevant mechanisms, such as energy reserve, nutritional status, earlier presentation of cardiovascular symptoms, more prompt medical intervention, chronic oxidative stress and inflammatory state. Previous studies have reported on the survival benefit of obesity in cardiovascular disease at a younger age.[4,5] However, in our study, both obesity and overweight showed no statistical difference compared with the normal-weight group with regard to risks of MACE both before and after adjusting for age and gender, thus suggesting that BMI itself is involved.

Obesity is known to be associated with metabolic syndrome (Met-S). One meta-analysis concluded that metabolic syndrome was associated with increased risks of MACE in patients after revascularization.[29] Additional evidence indicates that a component of metabolic syndrome is associated with increased risk of myocardial infarction.[30] However, the correlation of BMI and true metabolic disturbance has been questioned.[31] Furthermore, subgroups within the obese group that do not display the typical metabolic disorders associated with obesity are hypothesized to experience a lower risk of complications. This metabolically healthy obese population may represent the overweight group with better cardiovascular prognosis in the obesity paradox. In our study, higher BMI was also found to more likely occur among patients who were hypertensive, were insulin resistant and had a lower high-density lipoprotein cholesterol level. Nonetheless, due to a lack of data on waist circumference in the original research database, proper diagnosis of Met-S remains unclear and therefore how Met-S affects perioperative MACE in this study remains unclear. Additionally, BMI may not be a perfect surrogate for the beneficial effect of obesity over cardiac prognosis demonstrated in clinical research. Evidence suggests that muscle mass and strength are the major determinants of the prognostic implications of obesity in cardiovascular disease.[32] This evidence means that both leaner and obese people may benefit from increased muscle mass regardless of adipose tissue. The role of metabolic deregulation in the obesity paradox is unclear and warrants further investigation in the future.

Despite a large body of evidence showing that postoperative mortality is not increased in the majority of obese patients undergoing surgery, a negative attitude towards obesity as a comorbid condition remains. Concern regarding known obesity-associated risky cardiovascular changes attracts the attention of anesthesiologists during preoperative
visits while underweight patients are overlooked. Although counterintuitive, we must recognize that obesity is not an independent risk factor for perioperative cardiac morbidity and mortality and may even be beneficial, just as indicated by the present study results.

To summarize, we conducted a multi-center prospective study investigating elderly patients with coronary artery disease undergoing non-cardiac surgery. Among this population, the underweight groups were at higher risk of MACE compared with the normal-weight group, while no difference was found in the obese group. The phenomenon of the obesity paradox may exist in elderly Chinese patients with coronary artery disease undergoing non-cardiac surgery. Patients with a low BMI should receive more attention than they currently do during preoperative preparation and risk stratification. Additionally, a higher than normal BMI may be more ideal for the elderly population in terms of cardiovascular complications. The interrelation between aging, obesity, cardiovascular disease and inflammation should be a key research topic in the near future.

Although the original study is a multicenter study, a limited number of patients were allocated to both extreme high and low BMI groups, which may have undermined the statistical power. Due to a naturally low baseline BMI in this elderly Chinese population, few people met the current WHO’s criteria (BMI > 30 kg/m²) for inclusion in the obesity group. This may have resulted in inaccurate results. Furthermore, in this study, the original database lacked parameters such as body fat content and muscle mass waist circumference, which could have provided insight into the relationship between metabolism and a cardiac event. The relation between socioeconomic status and obesity is also important. The extent to which obesity or body mass are influenced by an individual’s income varies across countries. For example, in developed countries, obesity is associated with poverty. However, the situation may be more complicated in China. A major portion of underweight Chinese patients likely suffer from poverty and face inequalities of medical opportunities. Conversely, for patients in a better economic status, a low BMI may be the result of intentional weight reduction for better functional status. Therefore, socioeconomic background should be considered in future studies.

Acknowledgments

LX, LC, MYW, and YGH participated in the study design and acquisition of participants and data. LX obtained funding for the study. LC and MYW provided support in the statistical analyses and interpretation of results. LC drafted and edited the manuscript. YGH and LX provided guidance on final manuscript editing and approval. All authors approved the final report for submission. None of the authors have potential conflicts of interest to disclose. We thank Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

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