Body mass index and outcomes of patients with cardiogenic shock: A systematic review and meta-analysis

Tao WX et al. BMI and outcomes of patients with cardiogenic shock

Wen-Xia Tao, Guo-Ying Qian, Hong-Dan Li, Feng Su, Zhou Wang

Abstract

BACKGROUND
Cardiogenic shock continues to be a highly morbid complication that affects around 7%-10% of patients with acute myocardial infarction or heart failure. Similarly, obesity has become a worldwide epidemic.

AIM
To analyze the impact of higher body mass index (BMI) on outcomes of patients with cardiogenic shock.

METHODS
A systematic and comprehensive search was undertaken on the electronic databases of PubMed, Embase, ScienceDirect, CENTRAL, and Google Scholar for all types of studies comparing mortality outcomes of patients with cardiogenic shock based on BMI. All studies defined overweight or obese patients based on the World Health Organization BMI criteria. The data were then extracted and assessed on the basis of the Reference Citation Analysis (https://www.referencedicationanalysis.com/).
RESULTS

Five studies were included. On pooled analysis of multivariable-adjusted ratios, we noted a statistically significantly reduced risk of mortality in overweight/obese vs normal patients (three studies; odds ratio [OR] = 0.92, 95% confidence interval [CI]: 0.85-0.98, \( I^2 = 85\% \)). On meta-analysis, we noted that crude mortality rates did not significantly differ between overweight/obese and normal patients after cardiogenic shock (OR = 0.95, 95%CI: 0.79-1.15, \( I^2 = 99\% \)). The results were not stable on sensitivity analysis and were associated with substantial heterogeneity.

CONCLUSION

Current evidence on the association between overweight/obesity and mortality after cardiogenic shock is scarce and conflicting. The obesity paradox might exist in patients with cardiogenic shock but could be confounded by the use of mechanical circulatory support. There is a need for further studies to clarify this relationship.

**Key Words:** Obese; Overweight; Myocardial infarction; Shock; Mortality


**Core Tip:** Cardiogenic shock continues to be a highly morbid complication that affects around 7%-10% of patients and similarly, obesity is now prevalent around the globe. We reviewed data from five studies to assess the impact of obesity on outcomes of cardiogenic shock. Pooled analysis of adjusted data indicated that overweight/obese was associated with a reduced risk of mortality vs normal patients but the same relationship was not noted in the analysis of crude mortality rates. Thus, current
evidence on the association between overweight/obesity and mortality after cardiogenic shock is scarce and conflicting and there is a need for further studies.

**INTRODUCTION**

Obesity is a recognized global health problem that has significantly burdened the entire healthcare system\[1\]. The epidemic of obesity has touched countries across the globe and more than 2 billion people are affected by it\[2\]. According to estimates, the prevalence of obesity has tripled since 1975 and more than 39% of adults older than 18 years were overweight in 2016\[3\]. The World Health Organization (WHO) defines obesity based on measurements of the body mass index (BMI) wherein an individual with a BMI ≥ 30 kg/m² is defined as obese while BMI ≥ 25 kg/m² is overweight\[3\]. The heightened prevalence of overweight and obesity can be attributed to the increasingly sedentary lifestyle which has affected most workplaces. Lack of physical activity and an unhealthy diet has significantly increased obesity in the past decade\[4,5\]. An important implication of high body fat is an increased risk of metabolic disorders like diabetes mellitus, coronary artery disease (CAD), cerebrovascular disorders, hypertension, and heart failure\[6\]. Despite the heightened risk of several cardiovascular diseases with obesity, recent research has uncovered the prevalence of the “obesity paradox” which suggests that patients with higher BMI have a better prognosis and lower mortality rates as compared to normal BMI patients\[7\]. Niedziela et al\[8\] in a meta-analysis of patients with acute coronary syndrome have shown that overweight, obese, and severely obese patients had significantly lower mortality rates as compared to those with normal BMI. Similar outcomes have been noted by researchers for heart failure and septic shock\[9,10\].

Cardiogenic shock continues to be a highly morbid complication that affects around 7%-10% of patients with acute myocardial infarction (AMI) or heart failure\[11,12\]. It is a complex and hemodynamically diverse state of end-organ hypoperfusion which leads to high morbidity and mortality\[11\]. While several studies have analyzed the impact of obesity on outcomes of patients with acute coronary syndrome, it is still unclear how high BMI affects outcomes of patients with cardiogenic shock. The question that needs
to be answered is: Does an obesity paradox exists in the prognosis of patients with cardiogenic shock or do obese patients have higher mortality as compared to normal BMI patients? To the best of our knowledge, this research question has been systematically analyzed by only one review to date. Meng et al[13] in a recently published meta-analysis pooled data from three studies to assess the association between high BMI and mortality after cardiogenic shock. An important limitation of their review was that two of the three studies were from the same database with a considerable overlap of data. To overcome this limitation, we hereby conducted an updated systematic review and meta-analysis to analyze the impact of high BMI on outcomes of cardiogenic shock.

MATERIALS AND METHODS

The methodology of our review was based on reporting guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[14]. The protocol of the review was prospectively registered on PROSPERO (No. CRD42021274841).

Literature search

A systematic and comprehensive search was undertaken on the electronic databases of PubMed, Embase, ScienceDirect, and CENTRAL. Google Scholar was used to search the gray literature, but only for the first 200 results of each search query. To minimize single reviewer bias, two authors separately explored the databases. The search limits were set from the time of inception of databases up to 25th August 2021. Search terms included were: "obese", “obesity”, "overweight", "body mass index", and “cardiogenic shock”. Further details of the search strategy which was common for all databases are presented in Supplementary Table 1. Research citation analysis (https://www.referencecitationanalysis.com/) was used to supplement the search. After the initial search, the results were deduplicated and the remaining articles were assessed by their titles and abstracts. We identified studies relevant to the review and
extracted their full texts. The two reviewers independently evaluated these studies for final inclusion in the review. Any discrepancies in study selection were resolved by consensus. In the end, manual scoping of the reference list of included studies was carried out for any missed references.

**Eligibility criteria**

The inclusion criteria were: (1) All types of studies comparing mortality rates of patients with cardiogenic shock based on BMI; (2) Studies that clearly defined overweight or obese patients based on the WHO BMI criteria (i.e., overweight > 25 kg/m² and obese > 30 kg/m²) and compared outcomes with normal BMI patients; and (3) Language of publication should have been English. We excluded the following studies: (1) Studies including less than 50 patients; (2) Studies not reporting mortality outcomes; (3) Non-comparative studies; and (4) Studies reporting duplicate data. If the same database was used by two studies, we judged the period of overlap. In case of partial overlap, the study was included and the strength of the results was analyzed by a sensitivity analysis.

**Data extraction and quality assessment**

Two authors independently extracted the following data: Author details, publication year, study type, study location, BMI definition, primary diagnosis, sample size, demographic details, comorbidities (diabetes mellitus, hypertension, chronic kidney disease, dyslipidemia, and cardiovascular disease), revascularization details, use of mechanical circulatory support (MCS), and study outcomes. The primary outcome of the study was early mortality defined as in-hospital or 30-d mortality. The methodological quality of studies was assessed using the Newcastle-Ottawa scale[15]. It was conducted by two authors independent of each other. Any disagreements were solved by a discussion. Studies were assessed for selection of study population, comparability, and outcomes, with each domain being awarded a maximum of four, two, and three points, respectively. The maximum score which can be awarded was
nine. Studies with a score of 9 points, 7-8 points, and 6 points and below were considered to have a low, moderate, and high risk of bias, respectively.

**Statistical analysis**

The meta-analysis was performed using “Review Manager” (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014). We extracted multivariable-adjusted odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs) on mortality rates and pooled them using the generic inverse variance function of RevMan. The final effect size was calculated as OR with 95% confidence interval (CI). Crude mortality rates were also extracted from the included studies and pooled OR was generated. All meta-analyses were conducted using the random-effects model. Heterogeneity was assessed using the $I^2$ statistic. $I^2$ values of 25%-50% represented low, values of 50%-75% medium, and more than 75% represented substantial heterogeneity. Funnel plots were not used to assess publication bias as less than ten studies were available for each meta-analysis. A sensitivity analysis was carried out to assess the contribution of each study to the pooled estimate by removing one study at a time and recalculating the pooled effect estimates for the remaining studies.

**RESULTS**

The search strategy and the number of records at each stage are presented in Figure 1. Based on the screening criteria, a total of five studies were included in this systematic review and meta-analysis\cite{16-20}. Details of included studies are presented in Table 1. Three studies\cite{16,17,20} were conducted in the United States, one in Denmark\cite{18}, and one in Pakistan\cite{19}. All, except for one\cite{19}, were retrospective cohort studies. The primary diagnosis was AMI in all studies but the study of Sreenivasan et al\cite{16} also included patients with heart failure. Two studies\cite{17,20} used the same “National Inpatient database” from the United States with a partial overlap of data. Patiolla et al\cite{17} and Chatterjee et al\cite{20} used the database from 2008 to 2017 and 2004 to 2013, respectively. Thus, an overlap of six years was noted in these studies, albeit with a minor difference.
Patolla et al[17] reported combined data of overweight and obese patients whereas Chatterjee et al[20] classified their sample as obese and non-obese only. All the studies used the WHO classification of overweight and obesity. Two studies[16,17] additionally classified obesity as mild, moderate, and severe. However, for the meta-analysis, all groups were combined into a single group of obese patients. The mean age of the patients was above 55 years in the majority of studies. The percentage of patients undergoing revascularization varied across the included studies. In the study of Hermansen et al[18], all patients underwent percutaneous coronary intervention and none underwent coronary artery bypass grafting (CABG). In general, fewer patients underwent CABG as compared to percutaneous interventions in the remaining studies across obese and non-obese groups. Two studies did not report data on the percentage of patients receiving MCS[19,20]. In the study of Sreenivasan et al[16], all patients received MCS while in the remaining two studies, the percentage varied from 15% to 49% across the study sub-groups. Two studies reported mortality outcomes within 30 d while the remaining reported in-hospital outcomes[16,18].

Meta-analysis

Amongst the included studies, three[16,17,20] reported multivariable-adjusted ratios on the relationship between overweight/obesity and early mortality. On pooled analysis, we noted a statistically significantly reduced risk of early mortality after cardiogenic shock in overweight/obese vs normal patients (OR = 0.92, 95%CI: 0.85-0.98) (Figure 2). There was significantly high heterogeneity in the meta-analysis (P = 85%). Given the high heterogeneity, we conducted a sensitivity analysis by excluding one study at a time and recalculating the effect size. Results are presented in Table 2. In the exclusion of the study of Patolla et al[17] and Chatterjee et al[20], the results indicated no difference in the risk of mortality in overweight/obese vs normal patients. Second, we also extracted crude early mortality rates and pooled them in a meta-analysis. Including data from all five studies[16–20], we noted that crude mortality rates did not significantly differ between overweight/obese and normal patients after cardiogenic shock (OR =
0.95, 95% CI: 0.79-1.15) (Figure 3). There was significantly high heterogeneity in the meta-analysis ($I^2 = 99\%$). On sensitivity analysis (Table 2), we noted that the exclusion of the study of Sreenivasan et al\textsuperscript{16} changed the significance of the results with a reduced risk of mortality in overweight/obese patients as compared to normal patients. A similar tendency was noted in the exclusion of the study of Hashmi et al\textsuperscript{19}.

We were unable to conduct any subgroup analysis to explore the source of high heterogeneity in the included studies due to the limited number of the included studies. However, a few studies conducted subgroup analysis in their respective cohorts and their results are descriptively presented in Table 3. Sreenivasan et al\textsuperscript{16} further compared outcomes of obese and non-obese patients based on the primary diagnosis (acute AMI or heart failure) and age ($< 60$ years and $\geq 60$ years). On the other hand, Chatterjee et al\textsuperscript{20} conducted a subgroup analysis based on the type of AMI (ST-elevated and non-ST elevated) and the use of revascularization.

### Risk of bias

The risk of bias analysis of included studies is presented in Table 4. Four studies\textsuperscript{16,17,19,20} received a score of 7 while one study\textsuperscript{18} received a score of 5.

### DISCUSSION

Obesity has been a well-recognized risk factor for a wide spectrum of cerebrovascular and cardiovascular diseases. Higher body fat increases the bulk of atherosclerotic plaques, which leads to plaque instability. It also generates a low-grade generalized inflammatory state which increases pro-inflammatory cytokines like C-reactive protein and interleukins\textsuperscript{23}. Indeed, recent research suggests that anti-inflammatory therapies may reduce the risk of adverse cardiovascular events in patients with CAD, lending support to the inflammation hypothesis\textsuperscript{22}. These proinflammatory cytokines have also been implicated in the pathophysiology of heart failure due to their cardio-depressant properties\textsuperscript{23}. Despite being associated with the etiology of both CAD and heart failure, the mechanism by which high BMI is associated with better outcomes in these patients,
i.e., the obesity paradox, is still incompletely understood. Lavie et al\textsuperscript{[24]} have pointed out that BMI per se does not describe the body composition and they found that patients with higher lean mass along with higher body fat had lower mortality due to CAD as compared to those with lower lean mass and lower body fat. Another aspect to consider is the cardiorespiratory fitness of the individual as poor fitness levels are associated with a poorer prognosis in CAD, independent of adiposity\textsuperscript{[25]}. While the obesity paradox is firmly established in several cardiovascular diseases, its association with outcomes of patients with cardiogenic shock is still unclear. In the previous meta-analysis of three studies, Meng et al\textsuperscript{[13]} noted no difference in all-cause mortality between obese and non-obese patients with cardiogenic shock (OR = 0.88, 95% CI: 0.71-1.08, \( P = 96\% \)). In a sub-group analysis, they found that cardiogenic shock mortality was lower in developed countries (United States), but higher in developing countries (Pakistan). In addition to the lower number of studies in this meta-analysis, several other errors make this previous review unreliable. Foremost is that the two included studies in their review used the same United States database from 2005-2014 and 2004-2013, which is a considerable overlap. Second, in their multivariable analysis, the authors included the trial of Hashmi et al\textsuperscript{[19]} which only reported unadjusted ORs.

In our updated meta-analysis of five studies, we noted that overweight/obese patients did not have an increased risk of early mortality after cardiogenic shock as compared to normal BMI patients when only crude mortality rates were pooled. However, it is important to note that the significant heterogeneity in the meta-analyses reduces the confidence of our results. Assessing the included studies individually, we noted extremely divergent results amongst the studies. The studies of Sreenivasan et al\textsuperscript{[16]} and Hashmi et al\textsuperscript{[19]} demonstrated that obese patients had significantly higher mortality as compared to normal patients after cardiogenic shock. On the other hand, Patlolla et al\textsuperscript{[17]} and Chatterjee et al\textsuperscript{[20]} who used the same United States database with a partial overlap noted that an obesity paradox existed with cardiogenic shock as they found significantly lower mortality in higher BMI patients. The lone study of Hermansen et al\textsuperscript{[18]} was neutral and they found no impact of obesity on outcomes of cardiogenic shock.
in a contemporary cohort of Danish patients. Furthermore, it needs to be pointed out that several confounders can also influence outcomes of cardiogenic shock in addition to obesity. Hence, to establish the independent role of overweight/obesity on mortality rates, a multivariable-adjusted analysis is needed. A limitation of our review is that only three studies reported such data and their results were similar to the crude mortality data, with Patlolla et al\cite{17} and Chatterjee et al\cite{20} reporting better outcomes in overweight/obese patients and Sreenivasan et al\cite{16} reporting worse outcomes in such individuals. On meta-analysis of these three studies, we noted a reduced risk of mortality in overweight/obese patients but again with high heterogeneity.

One cause of the divergent results amongst the studies could be related to the use of MCS. In the study of Sreenivasan et al\cite{16}, 100% of patients received MCS while the number was much lower in the remaining studies. In a separate cohort (for which details were unavailable), Sreenivasan et al\cite{16} noted that amongst individuals not receiving MCS, patients with mild obesity had significantly lower mortality compared with the non-obese patients (OR = 0.8, 95%CI: 0.6–0.9), but this difference was non-significant for moderately and severely obese patients. These results conform to the obesity paradox found by Patlolla et al\cite{17} and Chatterjee et al\cite{20}. Higher mortality in patients receiving MCS could be due to the increased morbidity and complications like major bleeding, thrombosis, and vascular complications associated with the invasive procedure and MCS devices\cite{16}. The study of Sreenivasan et al\cite{16} also had a significant proportion of patients with severe obesity. It is plausible that higher grades of obesity are associated with severe comorbidities like diabetes, end-organ damage, and worse hemodynamic function which requires more robust MCS support like Impella or Tandem Heart and extracorporeal membrane oxygenation as compared to intra-aortic balloon pump required for patients with mild obesity\cite{16}. This may also have contributed to the opposing results of Sreenivasan et al\cite{16}. Furthermore, the contradictory results of Hashmi et al\cite{19} and the neutral results of Hermansen et al\cite{18} need to be interpreted with caution considering the small sample size of obese patients in their cohorts.
Several diverse mechanisms have also been put forward that may explain better or even worse outcomes in obese patients with cardiogenic shock. Higher lean and fat mass in obese patients may contribute to the higher metabolic reserve in such individuals and guard them against the inflammatory cascade of cardiogenic shock\cite{26}. Lower levels of tumor necrosis factor-alpha and monocyte chemoattractant protein-1 in obese patients may attenuate the inflammatory damage associated with cardiogenic shock\cite{27}. Adipose cells secrete adiponectin which has anti-inflammatory properties. Obese patients may also have a better neurohormonal profile and reduced B-type natriuretic peptide (BNP). BNP is associated with adverse outcomes in cardiogenic shock\cite{28}. Larger coronary arteries in obese patients may also lower the extent of CAD and improve outcomes\cite{29}.

Contrastingly, obesity augments the metabolic demand of the body which requires greater blood volume and increased cardiac output. High volumes increase venous return and subsequently myocardial wall tension and cause ventricular dilation. While initial ventricular hypertrophy overcomes this process, with further increase in volume, the ventricles no longer adapt and systolic dysfunction occurs. Hypertension, arrhythmias, and CAD associated with obesity can cause several functional and structural alterations which could lead to worse outcomes in obese patients\cite{16}. Our meta-analysis has some limitations. First, only a small number of predominantly retrospective studies were available for meta-analysis. Selection bias is an important limitation of these studies which can skew the results. Furthermore, databases are also prone to errors in record keeping. Second, the sample size of the included studies varied widely with two studies including a small cohort of obese patients. As mentioned earlier, there was a partial overlap of data in another two studies. Third, overweight patients were also merged into the obese group of one study which may have influenced the results. Since separate analyses for different grades of obesity were not available from all included studies, subgroup analysis for the same could not be carried out. Fourth, the treatment modality varied across the studies and obese and non-obese groups. While we used adjusted mortality data for the pooled analysis, it was
not reported by all studies. A meta-regression based on treatment modality could not be conducted due to a scarcity of data. Fifth, BMI is not the sole indicator of obesity and may not correctly represent the relationship between obesity and outcomes. Several other factors like cardiorespiratory fitness, lean mass, and fat mass could also influence the relationship between the two entities. Lastly, data in our meta-analysis were from a limited number of countries and hence not generalizable to the world population.

CONCLUSION
Current evidence on the association between overweight/obesity and mortality after cardiogenic shock is scarce and conflicting. The obesity paradox might exist in patients with cardiogenic shock but could be confounded by the use of MCS. There is a need for further studies to clarify this relationship.
Fanhua Meng, Feiyan Guo, Burebiguli Abulimiti, Kaidi Zhao, Ying Dong, Xiang Ma, Zhenyan Fu, Yitong Ma. "Body mass index and all-cause mortality in patients with cardiogenic shock: A systematic review and meta-analysis", The American Journal of Emergency Medicine, 2021

Crossref
<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Authors</th>
<th>Journal</th>
<th>Year</th>
<th>Crossref</th>
<th>Internet</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Blood transfusions may adversely affect survival outcomes of patients with lung cancer: A systematic review and meta-analysis</td>
<td>Sukjoo Cho, Jonghanne Park, Misuk Lee, Dongyup Lee, Horyun Choi, Gahyun Gim, Leeseul Kim, Cyra Y. Kang, Young Kwang Chae</td>
<td>Cancer Research</td>
<td>2020</td>
<td></td>
<td></td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>11</td>
<td>The Efficacy of Adjuvant Corticosteroids in Surgical Management of Chronic Subdural Hematoma: A Systematic Review and Meta-Analysis</td>
<td>Guoqiang Tang, Jiabei Chen, Bin Li, Song Fang</td>
<td>Frontiers in Neurology</td>
<td>2022</td>
<td></td>
<td></td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>13</td>
<td>The effect of barberry (Berberis vulgaris L.) on glycemic indices: A systematic review and meta-analysis of randomized controlled trials</td>
<td>Zahra Safari, Amirhosein Farrokhzad, Abed Ghavami, Abdulmnannan Fadel et al.</td>
<td>Complementary Therapies in Medicine</td>
<td>2020</td>
<td></td>
<td></td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>15</td>
<td>Efficacy of Trimetazidine in Limiting</td>
<td>Chang Wang, Weiwei Chen, Ming Yu, Ping Yang</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>
Periprocedural Myocardial Injury in Patients Undergoing Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis", Angiology, 2021