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Is there an obesity paradox in cardiovascular outcomes for patients undergoing Transcatheter Edge-to-Edge Repair? A pilot meta-analysis

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ABSTRACT

Background: The impact of body mass index (BMI) on Transcatheter Edge-to-Edge Repair (TEER) outcomes remains uncertain, with studies showing conflicting results. Some suggest an 'obesity paradox' exists, favoring better outcomes for obese patients and worse outcomes for underweight patients, while others report no significant impact of BMI.

Methodology: We systematically searched major databases for studies on baseline BMI and post-procedural outcomes in TEER patients. Patients were grouped by BMI: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2). Data were pooled using a random-effects model, with risk ratios (RRs) and their 95 % confidence intervals (CIs) as effect measures. Statistical significance was set at $p < 0.05$.

Results: Our study, analyzing five observational studies with 7580 obese and 74,717 non-obese patients, found no significant difference in in-hospital mortality between the groups (RR: 0.85; p = 0.427). Subgroup analysis indicated a higher mortality risk for underweight patients compared to overweight (RR: 1.48; p = 0.006) and obese patients (RR: 1.40; p = 0.036), though the difference between underweight and normal-weight patients was not significant (RR: 1.18; p = 0.216). The risks of myocardial infarction (RR: 1.10; p = 0.592) and stroke (RR: 0.43; p = 0.166) were also similar between obese and non-obese patients.

Conclusions: In conclusion, our analysis found no significant difference in in-hospital mortality, myocardial infarction or stroke risk between obese and non-obese patients undergoing TEER. However, underweight patients may have a higher risk of in-hospital mortality compared to overweight and obese individuals, highlighting the potential impact of BMI on outcomes in TEER patients.

1. Introduction

Mitral regurgitation (MR) and tricuspid regurgitation (TR) are common valvular heart diseases that can arise from either primary structural abnormalities of the valve itself (e.g., leaflet degeneration causing poor leaflet coaptation) or from conditions like infective endocarditis that damage the valve, leading to regurgitation without coaptation failure. Alternatively, these diseases can develop from secondary

Abbreviations: MR, Mitral regurgitation; TR, tricuspid regurgitation; TEER, Transcatheter Edge-to-Edge Repair; BMI, body mass index; CVD, cardiovascular diseases.

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causes related to ventricular dysfunction, both of which result in incomplete valve closure and the backflow of blood into the atria [1–3]. While the severity of these disorders varies, they may lead to adverse cardiovascular events and heart failure if left untreated [4]. Surgical valve replacement or repair has long been the available treatment option; however, they may not be accessible to patients with high surgical risks and comorbidities [4,5]. Percutaneous interventions are therefore considered appropriate for such patients, and various transcatheter techniques have emerged in recent years [6–8].

Transcatheter Edge-to-Edge Repair (TEER) is a minimally invasive procedure effective in treating MR and TR [9–12]. The MitraClip system is the most widely used device for TEER, and its implantations are increasing worldwide [11,13,14]. Studies have shown its effectiveness in improving clinical outcomes, reducing patients' symptoms, and lowering rehospitalization rates, as well as being associated with reduced rates of adverse events [11,13,15]. However, patient selection for TEER remains a point of debate, and certain characteristics, such as the body mass index (BMI) of the patients, have been shown to influence the success of the procedure [16,17]. Despite obesity being a known risk factor for cardiovascular diseases (CVD), several studies have demonstrated better prognosis in obese patients, especially suffering from coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) as compared to their normal or underweight counterparts [17,18]. This is referred to as the 'obesity paradox.' However, the literature provides conflicting results in valvular conditions (such as MR or TR) about the impact of BMI on MitraClip procedural outcomes with some studies showing no discernible effect to others demonstrating the obesity paradox [16,19,20].

Considering the significant literature gap about this paradox, our *meta*-analysis aims to evaluate the impact of BMI categories: underweight, normal-weight, overweight, and obesity, on short-term and long-term clinical outcomes in patients undergoing TEER using the MitraClip system.

2. Material and methods

Our *meta*-analysis was conducted according to the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21]. The study protocol was formally registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD42024578749.

2.1. Literature search and study selection

We conducted an extensive electronic search on August 12, 2024, across multiple databases, including PubMed, Embase, Scopus, Cochrane and Web of Science from inception to August 2024. The aim was to identify all studies examining the relationship between baseline BMI status and post-procedural outcomes in patients undergoing TEER. Our search strategy utilized medical subject headings (MeSH) terms and

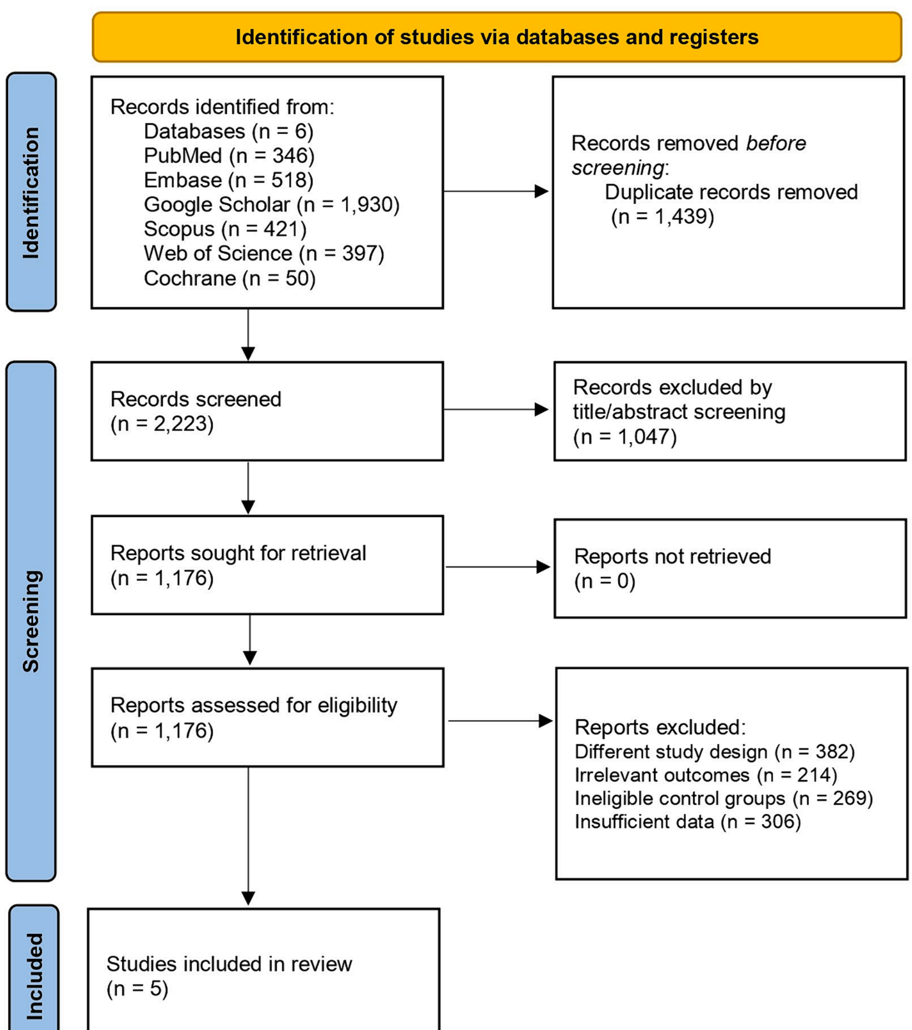

Fig. 1. The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flowchart.

free text keywords: “Body Mass Index” OR “BMI” OR “Underweight” OR “Overweight” OR “Overweight” OR “Obese” OR “MitraClip” OR “Transcatheter mitral valve repair” OR “TEER” OR “Transcatheter edge-to-edge repair” OR “Tricuspid regurgitation” OR “Mitral regurgitation”. Boolean operators such as “AND” and “OR” were used to create a search strategy in combination with keywords. These terms were employed in various combinations using Boolean operators such as “AND” and “OR” to optimize the search results. Additionally, we manually reviewed the reference lists of all identified articles to ensure that no relevant studies were overlooked in the initial search. A detailed description of the search strategy is available in Supplementary Table 1.

The studies identified through the literature search were imported into EndNote X9 (Clarivate Analytics, USA), where duplicates were removed. Two authors (A.G. and M.D.T.) independently screened the studies by reviewing the titles and abstracts, followed by a full-text review of the selected articles. In cases of disagreement, a third author (S. M.) was consulted to reach a consensus.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

The inclusion criteria for the studies were based on the PECO framework (Population, Exposure, Comparison, and Outcome) commonly used in systematic reviews and *meta*-analyses. In this framework, ’P’ represents patients undergoing TEER for MR or TR, ’E’ refers to obese patients, ’C’ refers to non-obese patients, and ’O’ includes in-hospital mortality, myocardial infarction, and stroke as outcomes. Thus, the inclusion criteria included: [1] studies involving patients undergoing TEER for MR or TR, [2] studies comparing post-procedural outcomes according to the baseline BMI of patients, and [3] studies reporting any of the pre-specified outcomes.

2.2.2. Exclusion criteria

The exclusion criteria included studies that did not provide data on the association between baseline BMI and post-procedural outcomes in TEER patients or had overlapping populations. We also excluded non-peer-reviewed articles, non-English publications, case reports, case series, commentaries, editorials, review articles and *meta*-analyses.

2.3. Data extraction

Data extraction from the included studies was performed by two authors (S.M. and M.D.T.) using a pre-tested Excel sheet, capturing details such as the first author’s name, publication year, country of origin, study design, sample size and reported outcomes. Data was extracted by categorizing patients into four BMI groups: underweight (BMI<18.5 kg/m2), normal-weight (BMI 18.5–24.9 kg/m2), overweight (BMI 25–29.9 kg/m2) and obese (BMI≥30 kg/m2). Underweight, normal-weight and overweight patients were included in the non-obese group.

2.4. Quality assessment of the included studies

The quality of the non-randomized studies included in this systematic review and *meta*-analysis was evaluated using the Newcastle Ottawa Scale (NOS) [22]. This scale assesses studies based on several criteria, including the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, evidence of outcome absence at the study’s outset, cohort comparability, outcome assessment, and follow-up adequacy. The risk of bias was categorized into low risk (7–10points), moderate risk (4–6 points), and high risk (0–3 points). Two reviewers (A.M.K and M.D.T.) independently carried out this assessment.

2.5. Statistical analysis

Statistical analyses were conducted using R software version 4.4.1

Table 1
Baseline characteristics of included studies.

Study	Study design	Country of origin	Participants, n				Sex (Females), n				Age (years), Mean ± SD			
			Underweight	Normal weight	Overweight	Obese	Underweight	Normal weight	Overweight	Obesity	Underweight	Normal weight	Overweight	Obesity
Agarwal 2023	Observational study	USA	NR	23,289	NR	3,176	NR	10,503	NR	1673	NR	78.4 ± 13.735	NR	71.35 ± 15.85
Keller 2020	Observational study	Germany	NR	12,546	NR	1,017	NR	4,959	NR	462	NR	76.67 ± 6.67	NR	73.67 ± 7.42
Kalbacher 2020	Observational study	Germany	49	293	296	132	39	107	97	58	78.8 ± 7.4	76.5 ± 8.1	75.0 ± 8.2	71.9 ± 9.8
Keller 2022	Observational study	Germany	12	220	237	80	10	135	104	43	79.47 ± 10.90	80.23 ± 7.09	78.83 ± 6.86	74.30 ± 7.04
Shamaki 2023	Observational study	USA	NR	37,775	NR	3,175	NR	16,583	NR	1,606	NR	76.5 ± 77.743	NR	70.7 ± 45.078

Abbreviations: NR: Not reported; SD: standard deviation using the “meta” package. The analysis included the calculation of pooled risk ratios (RRs) and 95 % confidence intervals (CIs) for dichotomous outcomes, utilizing the Mantel-Haenszel random effects model for pooling results from the studies. Forest plots were generated to visually present the results. A p-value of less than 0.05 was considered statistically significant. Heterogeneity among the studies was assessed using the Higgins I2 test [23]. Sensitivity analyses, using a leave-one-out approach, were performed to explore the sources of potential heterogeneity by excluding one study at a time, thereby assessing each study’s impact on the overall estimate. Publication bias was assessed by visually inspecting the funnel plots.

3. Results

3.1. Study selection and characteristics

A total of 3,662 records were identified from various databases. After removing 1,439 duplicates, 2,223 studies were further screened based on title and abstract. A total of 1,176 studies were assessed using their full texts after removing studies that did not meet our inclusion criteria. Further text screening resulted in the exclusion of 382 studies due to different study designs, 214 studies for reporting irrelevant outcomes, 269 studies with ineligible control groups, and 306 studies due to insufficient data. Ultimately, five studies (16,19,24–26) met the inclusion criteria and were included in the final analysis. This selection process is depicted in the PRISMA flowchart (Fig. 1).

Our *meta*-analysis included 82,297 participants, with 7,580 in the obese group and 74,717 in the non-obese group, with the female percentages of 44 % and 51 %, respectively. The mean age of participants ranged from 70 to 80 years across the studies. Hypertension was reported in 44 % of non-obese and 53 % of obese patients, while 26 % and 49 % were diabetic in the two groups, respectively. Two studies reported functional mitral valve regurgitation in 66 % of non-obese and 73 % of obese patients. All included studies involved patients undergoing TEER for MR. None of the studies included patients undergoing TEER in TR, as no study met our inclusion criteria. Approximately 13 % of non-obese and 15 % of obese patients had a prior history of myocardial infarction, whereas a history of prior stroke was present in 5 % of patients in both groups. The detailed baseline characteristics of the studies and the demographic details of the patients are summarized in Tables 1 and 2, respectively.

3.2. Endpoints

3.2.1. In-hospital mortality

Five studies reported the outcome of in-hospital mortality [16,19,24–26]. The pooled analysis revealed no statistically significant difference between the obese and non-obese patients (RR: 0.85; 95 % CI: 0.57 to 1.27; p = 0.427; I2 = 87 %) (Fig. 2-A). High heterogeneity was observed among the studies. Upon performing the leave-one-out sensitivity analysis, the heterogeneity was reduced to 30 % by excluding Keller et al. 2020 [16]) (Supplementary Fig. 1. The subgroup analysis showed a significantly higher risk of in-hospital mortality for underweight patients compared to overweight (RR: 1.48; 95 % CI: 1.12 to 1.95; p = 0.006) (Fig. 2-B) and obese patients (RR: 1.40; 95 % CI: 1.02 to 1.92; p = 0.036) (Fig. 2-C). However, the comparison between underweight and normal-weight patients did not show statistical significance (RR: 1.18; 95 % CI: 0.91 to 1.55; p = 0.216) (Fig. 2-D).

3.2.2. Myocardial infarction

The outcome of myocardial infarction was reported by four studies [16,19,25,26]. According to the pooled analysis, the risk of MI was comparable between the two groups (RR: 1.10; 95 % CI: 0.77 to 1.58; p = 0.592; I2 = 73 %) (Fig. 3) and the difference was not statistically insignificant. Moderate heterogeneity was observed among the studies, which reduced to 61 % after excluding Agarwal et al. 2023 [25] from the analysis (Supplementary Fig. 2).

3.2.3. Stroke

Three studies reported data on the outcome of stroke [16,19,25]. Based on the pooled analysis, there was no statistically significant difference between the two groups (RR: 0.43; 95 % CI: 0.13 to 1.42; p = 0.166; I2 = 81 %) (Fig. 4). High heterogeneity was observed among the studies. The leave-one-out sensitivity analysis reduced the heterogeneity

Table 2
Demographic details of participants in the included studies.

Study	Hypertension, n (%)				Diabetes mellitus, n (%)				Coronary artery disease, n (%)				Prior MI, n (%)			
	Underweight	Normal weight	Overweight	Obese	Underweight	Normal weight	Overweight	Obese	Underweight	Normal weight	Overweight	Obese	Underweight	Normal weight	Overweight	Obese
Agarwal 2023	NR	19353 (83.1)	NR	2848 (89.6)	NR	5682 (24.4)	NR	1528 (48.1)	NR	NR	NR	NR	NR	3843 (16.5)	NR	537 (16.9)
Keller 2020	NR	7269 (57.9)	NR	600 (59.0)	NR	3657 (29.1)	NR	524 (51.5)	NR	8441 (67.3)	NR	690 (67.8)	NR	356 (2.8)	NR	24 (2.4)
Kalbacher 2020	37 (76.1)	229 (78.2)	225 (76.2)	110 (83.6)	9 (18.4)	67 (22.9)	108 (36.6)	59 (45.0)	40 (81.8)	225 (76.8)	245 (82.7)	95 (71.9)	7 (14.3)	75 (25.5)	94 (31.7)	39 (29.5)
Keller 2022	8 (66.7)	200 (81.3)	244 (90.0)	78 (97.5)	0	40 (16.3)	85 (31.4)	59 (73.7)	5 (41.7)	154 (62.6)	172 (63.5)	65 (81.25)	NR	NR	NR	NR
Shamaki 2023	NR	5704 (15.1)	NR	422 (13.3)	NR	NR	NR	NR	NR	1058 (2.8)	NR	86 (2.7)	NR	5552 (14.7)	NR	524 (16.5)

Study	Prior stroke, n (%)				Atrial fibrillation, n (%)				Prior PCI, n				Functional mitral valve regurgitation, n (%)			
	Underweight	Normal weight	Overweight	Obese	Underweight	Normal weight	Overweight	Obese	Underweight	Normal weight	Overweight	Obese	Underweight	Normal weight	Overweight	Obese
Agarwal 2023	NR	2981 (12.8)	NR	309 (9.7)	NR	NR	NR	NR	NR	559 (2.4)	NR	69 (2.17)	NR	NR	NR	NR
Keller 2020	NR	122 (1.0)	NR	9 (0.9)	NR	8061 (64.3)	NR	702 (69.0)	NR	1118 (8.9)	NR	84 (8.2)	NR	NR	NR	NR
Kalbacher 2020	NR	NR	NR	NR	21 (42.9)	131 (44.7)	124 (42.0)	61 (46.5)	NR	NR	NR	NR	29 (58.7)	192 (65.7)	216 (73)	98 (74)
Keller 2022	0	30 (12.2)	31 (11.4)	11 (13.7)	7 (58.3)	181 (73.6)	191 (70.5%)	69 (86.2)	NR	NR	NR	NR	4 (33.3)	139 (56.5)	155 (57.2)	57 (71.2)
Shamaki 2023	NR	718 (1.9)	NR	44 (1.4)	NR	NR	NR	NR	NR	1095 (2.9)	NR	67 (2.1)	NR	NR	NR	NR

Abbreviations; NR: Not reported; MI: Myocardial infarction; PCI: Percutaneous coronary intervention

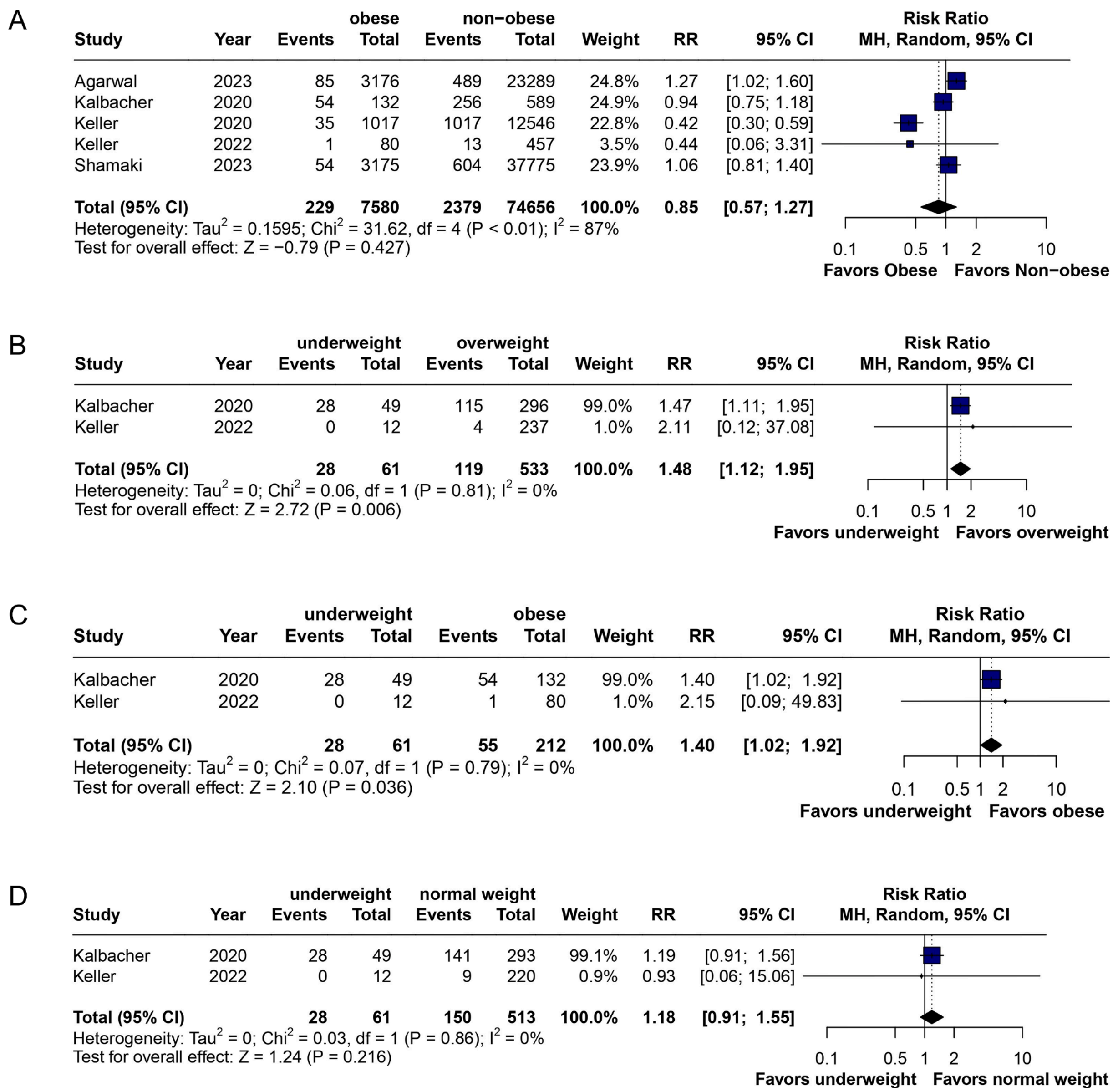

Fig. 2. Forest plots for the comparison of in-hospital mortality between **(A)** obese and non-obese patients, **(B)** underweight and overweight patients, **(C)** underweight and obese patients, and **(D)** underweight and normal weight patients undergoing Transcatheter Edge-to-Edge Repair (TEER).

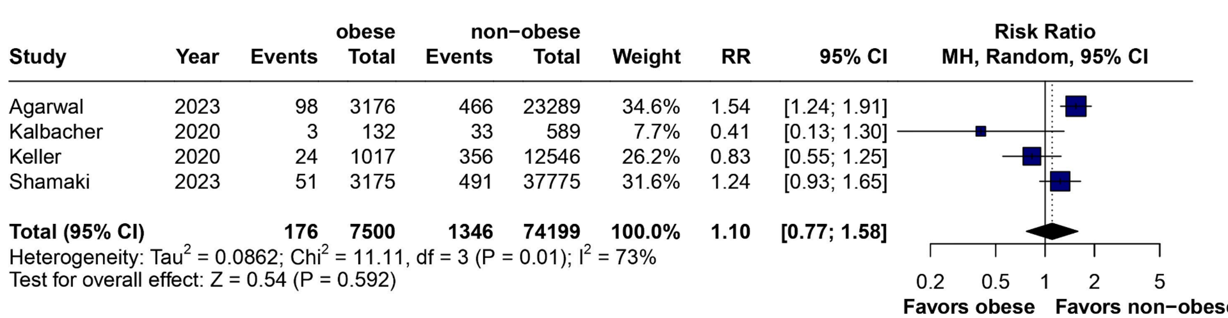

Fig. 3. Forest plot for the comparison of myocardial infarction between obese and non-obese patients undergoing Transcatheter Edge-to-Edge Repair (TEER).

to 39 % after excluding Kalbacher et al. 2020 [19] (Supplementary Fig. 3).

3.2.4. *Quality assessment and publication bias*

According to the Newcastle-Ottawa Scale, the risk of bias for all included studies was rated as 'low' (Supplementary Table 2). Visual inspection of the funnel plots showed a symmetrical appearance, indicating no to low risk of publication bias (Supplementary Fig. 4).

4. Discussion

Our study aimed to investigate the impact of BMI on the outcomes of

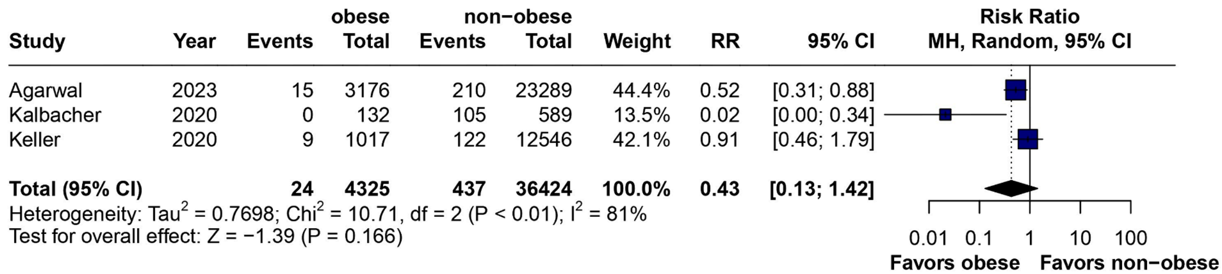

Fig. 4. Forest plot for the comparison of stroke between obese and non-obese patients undergoing Transcatheter Edge-to-Edge Repair (TEER).

TEER procedures in patients with both TR and MR by categorizing the patients into four distinct BMI groups (underweight, normal-weight, overweight, and obese). Our *meta*-analysis included five observational studies and a substantial cohort of 82,297 patients. Previous studies have established both underweight and overweight statuses as significant predictors of mortality in CVDs [27]. Our study included 7580 in the obese group and 74,717 in the non-obese group. Both groups had a similar mean age range of 70 to 80 years, with prior stroke affecting 5 % of patients in each group. Additionally, the prevalence of prior myocardial infarction was 13 % to 15 % across the two groups.

A multitude of studies have indicated a potential protective effect of overweight and obesity against mortality in patients with pre-existing heart conditions, including coronary artery disease, atrial fibrillation, and heart failure, as well as those undergoing interventional procedures such as transcatheter aortic valve replacement (TAVR) and TEER for symptomatic MR [19,28–34]. Although these studies primarily defined obesity as a BMI of 30 kg/m2 or higher, the consistency and underlying mechanisms of this paradoxical finding remain a subject of ongoing debate within the scientific community. To our knowledge, this *meta*-analysis is the first of its kind to comprehensively study the impact of BMI on TEER outcomes. Our analysis did not reveal a significant difference in mortality rates between obese and non-obese patients ($p = 0.427$). However, upon conducting a subgroup analysis, a nuanced picture emerged. Notably, underweight patients demonstrated a significantly elevated risk of in-hospital mortality compared to both overweight ($p = 0.006$) and obese ($p = 0.036$) patients. Our results corroborate the findings of the MIVNUT registry study by Caneiro-Queija et al., which demonstrated a significant link between moderate-severe malnutrition and adverse outcomes following TEER, including increased mortality and heart failure readmission [35]. Although the comparison between underweight and normal-weight individuals did not reach statistical significance ($p = 0.216$), the trend suggests a potentially increased risk, warranting further investigation in larger studies. These findings emphasize the importance of considering the entire BMI spectrum when evaluating patient risk and informing the development of tailored management strategies.

The "obesity paradox" refers to the unexpected finding that individuals who are overweight or obese, despite being at increased risk of developing heart disease, often exhibit better outcomes and lower mortality rates compared to normal-weight individuals once they have been diagnosed with a heart condition. Excess weight may serve as a protective factor in certain populations. This is particularly relevant for older, frail individuals with multiple health conditions, as increased body mass can potentially act as a nutritional reserve [36]. Furthermore, overweight and obese individuals might be better equipped to withstand the metabolic stress of acute cardiovascular events, surgeries, or interventions [36–40]. A recent systematic review by El-Andari et al. demonstrated a similar trend in heart valve surgery, where patients with higher BMI showed either favorable or comparable mortality rates at various timepoints compared to those with normal or low BMI, with the latter group tending to have worse outcomes [41]. Additionally, elevated BMI might confer protection against inflammation by influencing lipoprotein production [37]. It is important to note that BMI, while commonly used, may not be an ideal measure of adiposity. BMI does not distinguish between excess fat and lean muscle mass, meaning that individuals with higher BMI may have increased muscle mass rather than increased adiposity. This limitation may contribute to the observed 'obesity paradox,' as patients with greater muscle mass could experience better outcomes independent of their fat levels [42]. Some researchers have even proposed that normal weight in older populations with CVD may be an indicator of underlying, undetected health issues rather than a protective factor [37,43,44].

Approximately half of patients undergoing TEER procedures exhibit frailty [45], a condition characterized by decreased physical function and nutritional decline [46]. Frail patients are at significantly elevated risk of mortality and heart failure hospitalization compared to their counterparts [45]. Malnutrition, a core component of frailty assessment, likely contributed to the adverse outcomes observed in a substantial portion of the study population. Consequently, malnutrition, independent of MR treatment efficacy, may be a critical determinant of CVD outcomes in this patient cohort. Conversely, it is crucial to acknowledge that TEER procedures can effectively treat patients with both malnutrition and frailty [45]. Recognizing the heightened in-hospital mortality risk among underweight patients undergoing TEER necessitates a paradigm shift in patient care. Comprehensive preoperative evaluations, including nutritional assessment and risk stratification, are essential for identifying vulnerable individuals. Existing research supports the beneficial impact of nutritional interventions on hospitalized patients, with potential reductions in length of stay and readmission rates [47].

While myocardial infarction rates remained consistent across BMI groups, a non-significant trend toward decreased stroke risk was observed in obese patients. This potential protective effect against stroke might be attributed to factors such as altered metabolic or coagulation profiles associated with obesity. However, the absence of statistical significance precludes definitive conclusions.

5. Limitations

This study provides a thorough review of the literature; however, it has some limitations. First, the observational nature of the included studies increases the risk of bias due to confounding factors. Second, the relatively small number of studies, combined with underpowered outcomes, could affect the reliability of the effect estimate. Third, we observed high heterogeneity in all outcomes, which we attempted to address via sensitivity analyses. However, this could introduce variability and affect the reliability of the results. Fourth, no studies were found that examined the effect of BMI on procedural outcomes of TEER in patients with TR, which limits the generalizability of our results to this population. Lastly, our study did not stratify patients based on prevailing co-morbidities, which may influence the outcomes.

6. Conclusion

In conclusion, our study found no significant association between obesity and in-hospital mortality when comparing obese and non-obese groups. However, subgroup analyses indicated a potential increased risk of in-hospital mortality among underweight individuals compared to overweight and obese patients. These findings suggest that underweight status may pose a greater risk than obesity for in-hospital mortality. Additionally, we found no substantial differences in myocardial infarction or stroke rates between obese and non-obese individuals. Further research is needed to investigate the factors linking increased hospital mortality to underweight status and the impact of BMI on long-term outcomes in TEER patients.

CRediT authorship contribution statement

Aman Goyal: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Surabhi Maheshwari:** Writing – review & editing, Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Muhammad Daoud Tariq:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Eeshal Zulfiqar:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis. **Abdul Moiz Khan:** Writing – original draft, Methodology, Formal analysis, Data curation. **Humza Saeed:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Mohamed Daoud:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Gauranga Mahalwar:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical considerations

No ethical approval was required for this study design, as all data were obtained from publicly available sources.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101519.

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