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Outcomes of Mitral Valve Transcatheter Edge-To-Edge Repair In Patients With Chronic Kidney Disease: A Systematic Review And Meta-Analysis

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Abstract: Background: Transcatheter edge-to-edge repair of the mitral valve (M-TEER) improves outcomes in patients with chronic severe symptomatic mitral valve regurgitation who are at high risk for surgical mitral valve repair or replacement. This systematic review and meta-analysis aimed to describe the outcomes of M-TEER in patients with moderate-to-severe (stage III; Group 1) chronic kidney diseases (CKD) and end-stage kidney disease (stages IV-V; Group 2) in comparison with those with normal kidney function or mild CKD (stages I-II; Group 3). **Methods:** A systematic literature search of PubMed, Scopus, and Embase was conducted from inception to December 10th, 2023. The odds ratio (OR) with a 95% confidence interval (CI) was pooled using the random-effects model. **Results:** We screened 6,090 articles of which 40 citations were reviewed in full texts. Eight cohort observational studies met the eligibility criteria. Group 1 versus Group 3: short-term and long-term mortality were significantly higher in Group 1 [(OR 1.73, CI: 1.30-2.29) and (OR 1.78, CI: 1.38-2.29), respectively]. The shock was significantly higher (OR 1.95, CI: 1.45-2.63), and vascular complications were significantly lower (OR 0.51, CI: 0.26-0.99) in Group 1. The incidence of stroke, cardiac tamponade, or conversion to open surgery did not differ between groups [OR 0.87, CI: 0.34-2.23), (OR 1.52, CI: 0.62-2.75), or (OR 0.53, 95% CI: 0.12-2.24), respectively]. Group 2 versus Group 3: long-term mortality was significantly higher in Group 2 (OR 3.56, CI: 2.53-5.02) without a difference in short-term mortality (OR 4.92, CI: 0.91-26.72) or conversion to open surgery (OR 0.92, CI: 0.45-1.91) between groups. **Conclusion:** In patients who are undergoing M-TEER, impaired kidney function may be associated with increased odds of mortality in comparison with absence or mild kidney impairment.

Keywords: Symptomatic mitral valve, Transcatheter, Edge-To-Edge Repair, Chronic Kidney Disease, Systematic Review, Outcomes of M-TEER

1. Introduction

Transcatheter edge-to-edge repair of the mitral valve (M-TEER) has evolved tremendously over the past two decades, particularly following the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) I trial which has proven its safety and efficacy [1]. The EVEREST-II trial and the REALISM registry showed a significant reduction in the severity of mitral regurgitation with clinical improvement in high-risk surgical patients and real-world outcomes data, respectively [2] [3] [4]. Based on that, M-TEER was approved in 2013 for degenerative mitral valve regurgitation (MR) for high-surgical risk patients [5]. Following the publication of the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trials, M-TEER was approved by the Food and Drug Administration (FDA) for functional moderate-to-severe and severe MR after maximizing the guideline-directed medical therapy as it was found to improve rehospitalization and all-cause mortality outcomes within two years of follow-up [6] [7]. Chronic kidney disease (CKD) commonly co-exists in patients with heart failure as well as those with functional MR [8] as was noted in the COAPT trial, where 71.6% and 75.2% of the population in the MitraClip® device and the control groups had creatinine clearance of ≤ 60 mL/hour, respectively [6]. CKD has its own burden and it is become more prevalent over the last few decades with a rate of 13.4% [9]. As a result, we reviewed the literature and aimed to evaluate the outcomes of M-TEER in patients with CKD.

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2. Methodology

2.1. Search Strategy

We conducted a systematic literature search using three different databases: Embase, PubMed, and Scopus, from inception to December 10, 2023. We identified studies that reported the outcomes of patients who underwent M-TEER with concomitant CKD. The search was limited to human subjects and articles in the English language. The keywords used for the systematic search included chronic kidney disease, renal failure, transcatheter mitral valve repair, M-TEER, MitraClip, and percutaneous mitral valve repair.

2.2. Inclusion and Exclusion Criteria

We allowed any study design including randomized and observational studies. For the observational design, we included cohort studies reporting the outcomes of M-TEER in patients with CKD. We excluded patients on dialysis, articles published in non-English languages, abstracts, reviews, single-arm studies, case reports/series and correspondence/commentaries.

2.3. Study selection and data Extraction.

The search records were examined at the titles and abstract levels by three authors. Then potential studies were retrieved in full text. An independent author solved the conflicts regarding the inclusion of any study. The extracted data of the included studies were compiled into tables. The extracted data included study characteristics, patient characteristics, and outcome measures. Our outcomes of interest included mortality, shock, and safety measures. The outcomes analysis at specific follow-up (i.e., short- and longer-term) was performed according to data availability.

2.4. Quality assessment

We assessed the methodological strength of the included studies using the Newcastle Ottawa Scale. The scale is a composite scoring scale that assesses the quality of cohort and case-control studies. It utilizes a "star system" to rate each included study on three broad perspectives, i.e., selection, comparability, and outcome. Nine stars represent the highest level of quality [10].

2.5. Statistical Analysis

The meta-analysis was performed using an aggregate data approach. Odds ratio (OR) with 95% confidence interval (CI) were reported for binary outcomes. A mean difference with 95% CI was reported for the continuous data. The median (interquartile range) was converted into mean (standard deviation) if was reported by a study. Sensitivity analysis was considered when there was an inconsistency in outcome follow-up duration. The Q statistic p-value of < 0.1 or I^2 value of $> 50\%$ should indicate significant heterogeneity. [11] Publication bias was visually inspected using funnel plots. The R software (RStudio 2023) was used to perform the meta-analysis.

3. Results

3.1. Search results

Our systematic literature search yielded 6,090 citations, of which 6,050 articles were excluded at the title and abstract levels. Forty articles were reviewed in full text. We selected eight observational cohort studies to be included (Figure S1) [12] [13] [14] [15] [16] [17] [18] [19]. However, three studies derived their data from the National Readmission Database (11) (16) and the National Inpatient Database (18). When these studies reported similar outcomes, and to avoid potential overlapping and double counting of the patients, we only included the study reporting homogenous outcomes with other studies. Otherwise, the priority was for the study with a bigger sample size. The comparisons were categorized into two groups based on the CKD stages: moderate-to-severe CKD (stage III; Group 1) and end-stage kidney disease (stages IV-V; Group 2) in comparison with normal kidney function or mild CKD (stages I-II; Group 3) each.

3.2. Study characteristics

We included eight observational cohort studies from seven countries. There were four multi-centre studies, one single-centre study, and three nationwide studies. The total sample size was 32,928 with 12,413 CKD patients undergoing M-TEER (Table S1). The studies' quality according to the Newcastle Ottawa Scale ranged from six to eight stars indicating studies of good quality (Table S2).

Table 1: Study characteristics

Study	Recruitment period	Country	Number of sites	Sample size	CKD group	Comparator group
Shah et al.	November 2013 – June 2016	USA	204 centers	5,059	3,856	1,203
Sawalha et al.	January 2016 – December 2016	USA	National Readmission Database	4,645	1,433	3,212
Panchal et al.	January 2010 – December 2016	USA	National inpatient database	9,228	2,574	6,654

Ohno et al.	August 2008 – May 2014	Italy	Single center	240	113	101
Beohar et al.	December 2012 – June 2017	USA and Canada	78 centers	606	467	139
Sisinni et al.	October 2008 – May 2018	Italy and Switzerland	Three centers	565	369	196
Estévez-Loureiro et al.	August 2009 – November 2012	UK, Denmark, and Sweden	Three centers	173	98	75
Raheja et al.	January 2014 – December 2017	USA	National Readmission Database	13,653	4,152	8,935

UK: United Kingdom; USA: United States of America

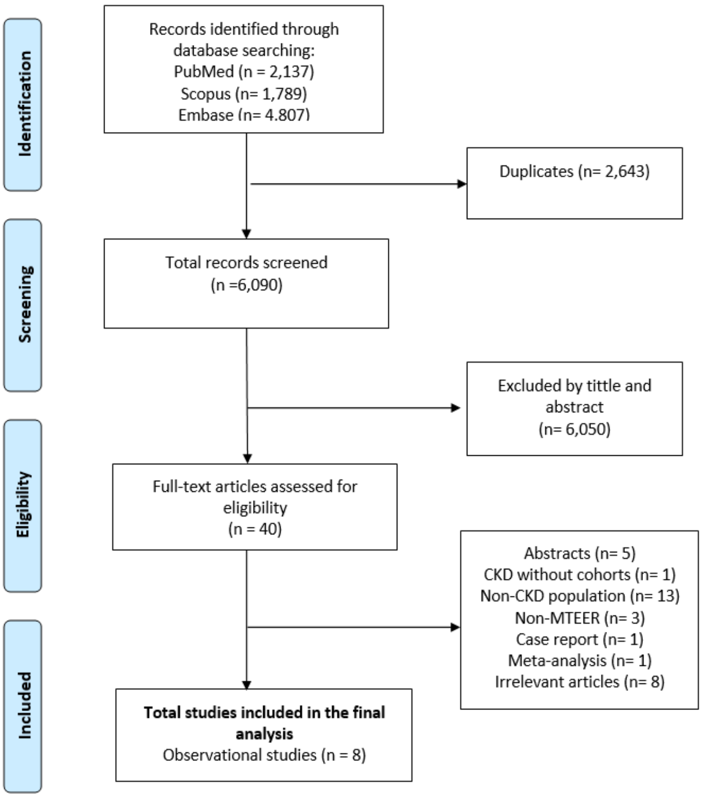


Figure 1: Flow chart from the literature search.

3.3. Patient characteristics

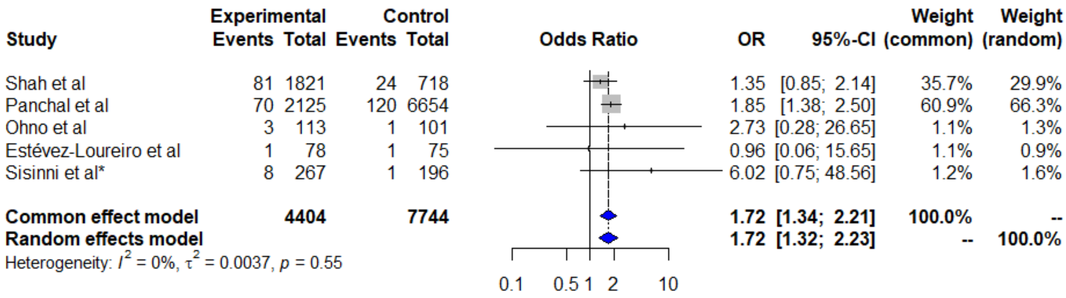
The age range of the patients with stage I-II CKD was 55–88.8, while that of those with CKD stage III-V was 63.7 – 92.0. Females accounted for 20.7% of patients. Three studies reported the type of MR, in groups 1 and 2; 752 subjects had functional MR and 3513 had primary MR. Atrial fibrillation was present in 53.7%, and the percentages of coronary artery disease, diabetes, and hypertension were 18.7%, 26.4%, and 25.2, respectively, among groups 1 and 2.

3.4. Outcomes

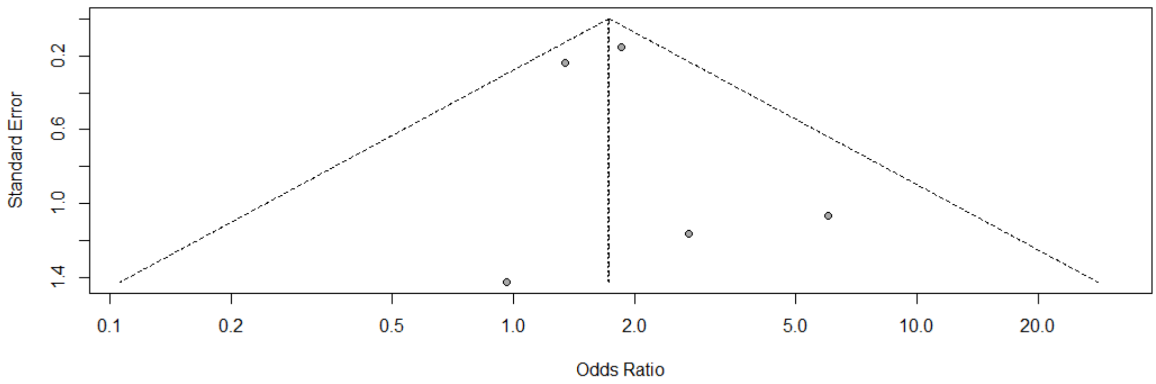
3.4.1. Group 1 versus Group 3

The pooled analysis of moderate-to-severe CKD (Group 1) in comparison with normal kidney function or mild CKD (Group 3) showed a significant increase in short-term (in-hospital or 30-day: OR 1.72, 95% CI: 1.32 – 2.23, $p < 0.0001$; $I^2 = 0\%$) and long-term mortality (OR 1.78, 95% CI: 1.38 – 2.29, $p < 0.0001$; $I^2 = 25\%$) (Figure 1). Sensitivity analysis for short-term mortality, i.e., removing, Sisinni et. al. study, which reported in-hospital mortality [14], yielded consistent results (Figure S3; Panel A). Similarly, when the study that reported two-year mortality [15] was removed from the long-term mortality outcome, the result remained significant (Figure S2; Panel B). The pre-and post-procedure mean gradient pressure did not differ between the two groups (Figure S3). Two studies [12] [18] reported the need for renal replacement therapy post-procedure with significantly more events occurring in Group 1 (OR 2.68, 95% CI: 1.64 – 4.38, $p < 0.0001$; $I^2 = 0\%$) (Figure S4). There were no differences between the groups in terms of stroke, cardiac tamponade, conversion to surgical procedure or vascular complications (Figure S5 – S8). Interestingly, the length of hospital stay was significantly longer in Group 1 by 1.7 days (mean difference 1.68 days, 95% CI: 0.10 – 3.27, $p = 0.038$; $I^2 = 96\%$) (Figure S9).

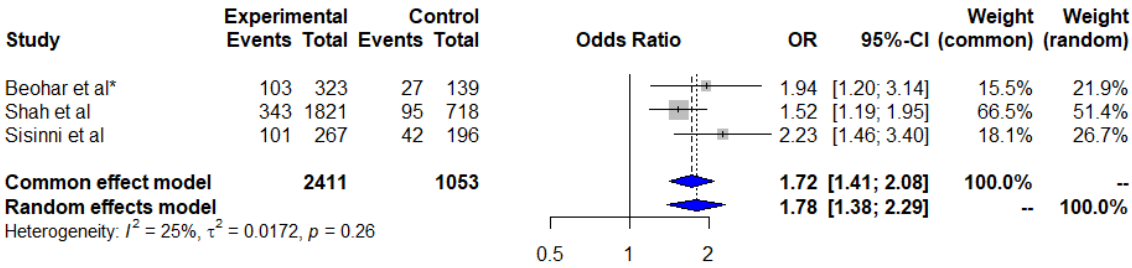
A. Short-term mortality (In-hospital or at 30-day)



*In-hospital mortality (1 study)



B. Long-term mortality (1- and 2-year)



*2-year mortality (1 study)

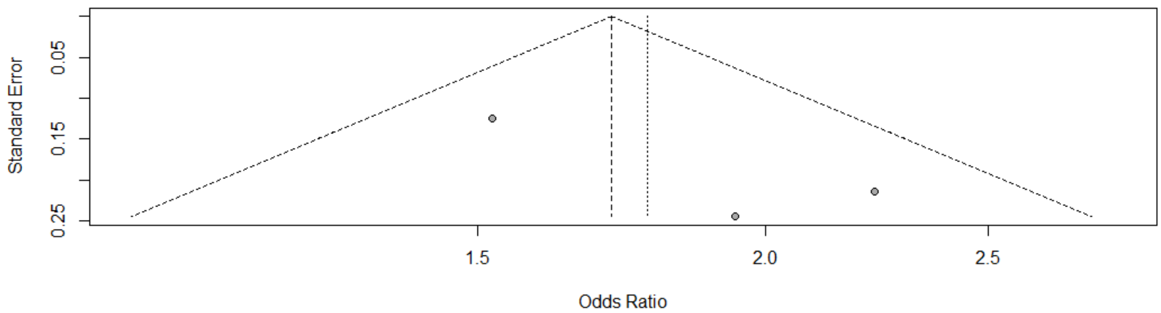


Figure 2. Forest plots for mortality outcomes (Group 1 versus Group 3)

3.4.2. Group 2 versus Group 3

End-stage kidney disease (Group 2), in comparison with Group 3, showed a statistically significant more deaths at short- (in-hospital or 30-day: OR 11.09, 95% CI: 1.32 – 93.09, p = 0.027; I^2 = 99%) and long-term (OR 3.56, 95% CI: 2.53 – 5.02, p < 0.0001; I^2 = 47) follow-up (Figure 2). However, when excluding the study that reported 30-day mortality from short-term mortality outcome, (12) there was only a trend for a higher in-hospital mortality in Group 2 (Figure S10). There was no difference in the rate of conversion to surgical procedure (Figure S11).

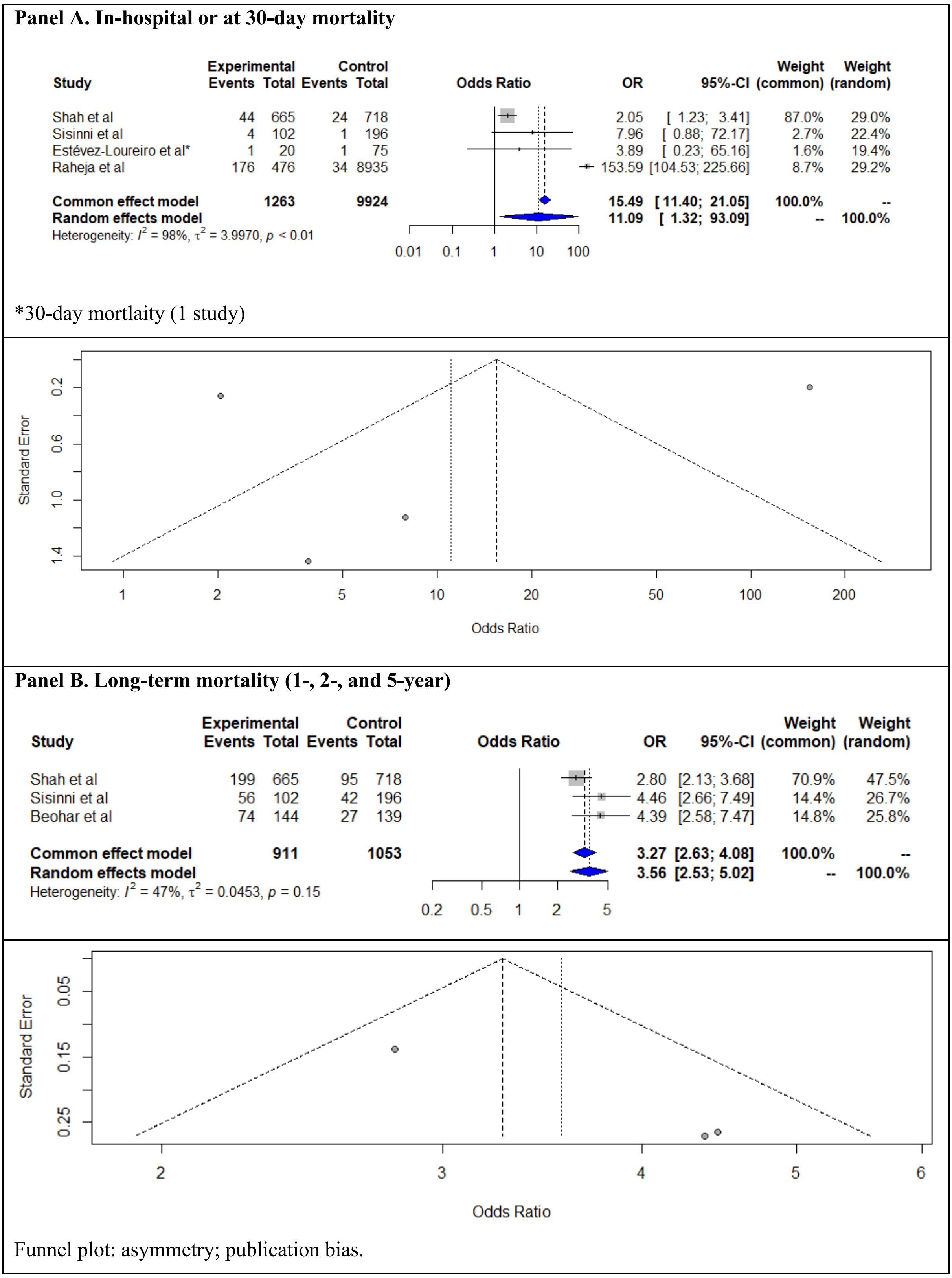


Figure 3: Forest plots for mortality outcomes (Group 2 versus Group 3)

4. Discussion

The present meta-analysis pooled eight observational cohort studies that evaluated the impact of the presence of CKD in patients who underwent M-TEER procedure. The key findings of the pooled data show that CKD stage III and CKD stage IV-V are associated with higher incidence of short and long-term mortality. In CKD stage IV-V, the in-hospital mortality was noted to be insignificant in the sensitivity analysis upon omitting Estévez's article which reported the 30-day mortality. The incidence of stroke, cardiac tamponade, or conversion to open surgery was found to be low across the three groups.

The M-TEER procedure had a swift evolution over the past decade [20]. Patients with heart failure and functional MR tend to suffer from multiple co-morbidities, particularly CKD [21], which is well described in the literature and found to be associated with worse outcomes [22]. Decreased cardiac output in heart failure secondary to left ventricular failure, decrease in the left ventricular ejection fraction, and functional MR might lead to recurrent prerenal acute renal failure, which is also worsened by the increased pre-load and venous congestion. Moreover, neurohormonal mechanisms increase systemic vascular resistance hypertension and worsen renal functions [23].

In M-TEER, the outcomes have been associated and linked to a variety of co-morbiditie**s** [24]**. O**f those, acute renal failure and CKD were consistently associated with worse outcomes [12] [19]**.** Sawalha et al. reported nationwide data on patients with renal failure who had a significant rate of hospital re-admissions; however, renal function improved in some patients on that index hospitalization [17]**.** In our study, the findings concurred with the conclusion of worsened outcomes in CKD. Additionally, Doulamis et al. (24) highlighted in their meta-analysis of six studies that renal functions are found to be vulnerable due to different reasons and the development of acute kidney injury is a marker for worse clinical outcomes and mortality.

The limitation of our article is that cohorts in this study were mostly from observational studies, which might not be as robust as pooling the data from randomized clinical trials. Moreover, the underlying etiology of CKD was not mentioned, which might impact the results. Thus, the outcomes of this meta-analysis should be interpreted carefully.

In conclusion, in patients who underwent M-TEER, impaired kidney function may be associated with increased odds of short and long-term mortality in comparison with the absence or mild kidney impairment.

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