Association between periprocedural myocardial injury and long-term all-cause mortality in patients undergoing transcatheter aortic valve replacement: a systematic review and meta-analysis

Wentao Chen, Yilong Han, Chunlin Wang and Wenqiang Chen

The Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education, Chinese National Health Commission and Chinese Academy of Medical Sciences, The State and Shandong Province Joint Key Laboratory of Translational Cardiovascular Medicine, Department of Cardiology, Qilu Hospital of Shandong University, Jinan, China

ABSTRACT

Objective. The purpose of this meta-analysis was to investigate the effect of periprocedural myocardial injury (PPMI) on long-term all-cause mortality in patients undergoing transcatheter aortic valve replacement (TAVR) and to explore potential factors associated with mortality risk. Design. The PubMed, Embase, and Cochrane Library databases were searched up to April 2022. Studies reporting the effect of PPMI on the risk of long-term all-cause mortality were included. The summary odds ratio (OR) was calculated using a random effects model. Additionally, meta-regression and subgroup analyses were conducted according to specific research characteristics to explore sources of heterogeneity. Results. Fourteen studies involving 6,415 patients who underwent TAVR showed that the occurrence of PPMI was associated with a higher risk of long-term mortality. Subgroup analysis showed that in the group of aged ≥82 years, men accounted for less than 50%, coronary artery disease patients accounted for more than 50%, and the proportion of patients with chronic kidney disease accounted for more than 60%, the proportion of patients with atrial fibrillation accounted for less than 30%, and the Society of Thoracic Surgeons predicted risk of mortality score was >8 points, patients with PPMI had higher long-term all-cause mortality than those without PPMI. Conclusions. Among the patients who underwent TAVR, those who developed PPMI had higher long-term all-cause mortality.

Introduction

Aortic stenosis (AS) is usually caused by the calcification of a congenitally bicuspid or trileaflet valve, and rheumatic diseases can also cause aortic stenosis. Its pathological process is mainly endothelial damage due to mechanical stress and lipid penetration leading to fibrosis, leaflet thickening, and calcification; the prevalence of AS increases with age [1]. Currently, there is a lack of effective drug treatments for this disease. Surgical aortic valve replacement is the gold standard treatment for this disease. However, with the development and progress of minimally invasive techniques, transcatheter aortic valve replacement (TAVR) has become an option for treating this disease [1]. The latest Valve Academic Research Consortium (VARC) established a standard for the diagnosis of PPMI in the context of TAVR [2]. Fourteen studies involving 6,415 patients who underwent TAVR showed that the occurrence of PPMI was associated with a higher risk of long-term mortality. Subgroup analysis showed that in the group of aged ≥82 years, men accounted for less than 50%, coronary artery disease patients accounted for more than 50%, and the proportion of patients with chronic kidney disease accounted for more than 60%, the proportion of patients with atrial fibrillation accounted for less than 30%, and the Society of Thoracic Surgeons predicted risk of mortality score was >8 points, patients with PPMI had higher long-term all-cause mortality than those without PPMI.

KEYWORDS

Aortic valve; replacement; mortality; meta-analysis; risk; myocardial injury

CONTACT Wenqiang Chen 19926200802@sdu.edu.cn The State and Shandong Province Joint Key Laboratory of Translational Cardiovascular Medicine, Department of Cardiology, Qilu Hospital of Shandong University, Jinan, China

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Materials and methods

Search strategy and eligibility criteria

This study was completed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [14]. We searched PubMed, Embase, and Cochrane Library databases for relevant studies from inception to April 15, 2022. Searches were conducted using a combination of keywords and Medical Subject Headings terms for TAVR, PPMI, troponin, and creatine kinase-myocardial bands. Retrieval was not restricted by language. References to eligible articles were also reviewed.

Studies that met the following criteria were considered eligible for inclusion. (1) Subjects were patients treated with TAVR. (2) The groups were divided according to the occurrence of PPMI. (3) Subjects were followed for 1 year or more. (4) Long-term all-cause mortality has also been reported. (5) Standardized or similar definitions of PPMI were used. (6) Articles were published. The PPMI was defined for each study using the types of biomarkers tested and biomarker elevation thresholds set by the investigators. Only heart-specific biomarkers were used in this study. Studies were included if standardized thresholds matched those defined in VARC-2 as troponin >15 × upper limit of normal (ULN) or CK-MB > 5 × ULN or VARC-3 as troponin >10 × ULN or CK-MB > 5 × ULN [5,15]. Other studies were considered if they were considered clinically significant. These standardized criteria were used in 10 of the 14 studies [4,9–13,16–19]. Different diagnostic thresholds used in the other four studies were high-sensitivity troponin T > 18.3 × ULN [7], troponin T > 3 × ULN [8], troponin T > 5 × ULN [20], and CK-MB > 7 ng/mL [21].

Data extraction

Data were independently screened and extracted by two researchers. Differences were resolved through group discussion or third-party negotiations. Data were extracted from the study source, including author name, year of publication, sample size, country, population characteristics (mean age, proportion of males, number of people between different groups, proportion of patients via transfemoral approach, Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) scores, percentage of patients with coronary artery disease (CAD), percentage of patients with diabetes (DB), percentage of patients with chronic kidney disease (CKD), percentage of patients with atrial fibrillation (AF), follow-up time, myocardial marker thresholds for the diagnosis of PPMI, and number of death events in different groups.

Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS), which is a validated scale for nonrandomized studies in meta-analyses. The NOS has three columns: study population selection, inter-group comparability, and results. The full score is 9 stars, and more than 6 stars indicate high literature quality. We graded the studies according to NOS standards.

For studies reporting the relationship between PPMI and long-term mortality using Kaplan-Meier survival curves alone, we calculated the number of deaths in the control and exposure groups according to Parmar et al.’s formula [22]. Heterogeneity between the studies was assessed using Cochran’s Q and I² tests. Cochran’s Q test with I² >50% or p < .10 indicated significant heterogeneity between studies. When statistical heterogeneity was observed, we chose a random-effects meta-analysis; otherwise, a fixed-effects model was applied [23]. In addition, a sensitivity analysis was performed to analyze sources of heterogeneity. Meta-regression was conducted according to the research characteristics to explore the possible sources of heterogeneity, including mean age, male proportion, STS-PROM scores, proportion of patients via the transfemoral approach, percentage of patients with CAD, percentage of patients with CKD, percentage of patients with AF, percentage of patients with DB, and myocardial marker thresholds for the diagnosis of PPMI. Finally, subgroup analyses for all-cause mortality were performed using the following factors: mean age (>82 vs. <82 years), male proportion (≥50% vs. <50%), STS-PROM scores (≤8 vs. >8), proportion of patients via the transfemoral approach (≥50% vs. <50%), percentage of patients with CAD (≥50% vs. <50%), percentage of patients with CKD (≥60% vs. <60%), percentage of patients with AF (≥30% vs. <30%), percentage of patients with DB (≥30% vs. <30%), and whether cardiac marker thresholds for the diagnosis of PPMI follow the new Valve Academic Research Consortium criteria [23]. Publication bias was detected using Begg and Egger test [24,25]. Trim and fill methods were used in cases in which publication bias was possible [26]. Two-sided p values <.05 were considered significant. All data analyses were performed using STATA Software version 16.0 (STATA Corporation, College Station, TX, USA). This systematic review of previous systematic reviews with meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) trial registry (CRD42022327596).

Results

Literature selection and characteristics of the included studies

Figure 1 displays the flowchart of our selection process. By searching the electronic databases, 622 studies were obtained. After removing duplicate studies and reading titles and abstracts, 28 studies were finally included for a detailed evaluation. Fourteen studies were included in this meta-analysis according to the inclusion and exclusion criteria. All studies were cohort studies with NOS scores of 7 stars, suggesting that the included studies were of high quality.

Table 1 shows the main characteristics of the data extracted from the included studies, which included a total of 6415 patients from 14 studies, with sample sizes ranging from 103 to 1333 for individual studies. Geographically, four studies were from Germany, one was a multicenter study, and the rest were from Australia, Switzerland, Italy, Japan, the Netherlands, and America. The average age of the study population ranged from 81 to 85 years. The follow-up period in each study ranged from 1 to 9 years.
The included studies analyzed 1310 deaths among 6415 participants using all-cause mortality as an outcome measure. In the random-effects model, the pooled OR of long-term all-cause mortality in patients with PPMI associated with TAVR was 1.55 (95% confidence interval [CI] 1.17–2.06) compared with patients without PPMI (Figure 2). There was moderate heterogeneity between studies (I² = 71.6%; p = 0.0). A sensitivity analysis excluding one item at a time showed little change in the pooled odds ratio (OR) and 95%CI (Figure 3). According to the Begg correlation test (p = 0.743) and Egger regression test (p = 0.842), there was no evidence of publication bias.

**Subgroup analysis**

The results of subgroup analyses are shown in Table 3. Subgroup analysis showed that in the group aged ≥82 years (OR = 2.00; 95%CI [1.22–3.27]), the male proportion was less than 50% (OR = 2.01; 95%CI [1.49–2.71]), CAD patients accounted for more than 50% (OR = 1.50; 95%CI

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**Table 1. Baseline characteristics of the included studies.**

| Study                  | Year  | Country     | Subjects (n) | Death (n) | Male (%) | Age (years) | STS-PROM | CAD (%) | TF approach (%) | Follow-up (years) | Definition of PPMI |
|------------------------|-------|-------------|--------------|-----------|----------|-------------|----------|---------|----------------|-------------------|-------------------|
| Z. Y. Yong et al       | 2012  | Netherland  | 119          | 68        | 39       | 81          | 6        | NA      | 100            | 1                 | cTnT >5 × ULN      |
| I. M. Barbash et al    | 2013  | America     | 103          | 27        | 41       | 85          | 12       | 53      | 100            | 9                 | CK-MB > 7 ng/ml    |
| H. B. Ribeiro et al    | 2015  | NA          | 1131         | 270       | 51       | 80          | 9        | 54      | 73             | 2                 | cTnT > 15 × ULN    |
| J. M. Sinning et al    | 2016  | Germany     | 276          | 63        | 55       | 81          | 7        | 65      | 95             | 1                 | cTnI ≥ 15 × ULN    |
| K. C. Koskinas et al   | 2016  | Switzerland | 577          | 143       | 54       | 82          | 6        | 64      | 80             | 2                 | cTnT > 15 × ULN    |
| W. M. Kohler et al     | 2016  | Germany     | 218          | 88        | NA       | NA          | NA       | NA      | NA             | 2                 | hsTNT > 15 × ULN   |
| A. Stundl et al        | 2017  | Germany     | 756          | 228       | 53       | 81          | 5        | 62      | 97             | 5                 | hsTNT > 15 × ULN   |
| Y. Nara et al          | 2018  | Japan       | 126          | 12        | 24       | 85          | 7        | NA      | 94             | 1                 | cTnI ≥ 1.5 ng/mL   |
| V. Sharma et al        | 2019  | America     | 510          | 151       | 56       | 81          | NA      | 59      | 58             | 3                 | cTnT > 3 × ULN     |
| M. Mirna et al         | 2020  | Germany     | 164          | 18        | NA       | 83          | NA      | NA      | 100            | 1                 | hsTNT > 15 × ULN   |
| M. Schindler et al     | 2021  | Switzerland | 1333         | 187       | 54       | 81          | 5        | 49      | 95             | 2                 | hsTNT > 18.3 × ULN |
| V. De Marzo et al      | 2021  | Italy       | 596          | 48        | 43       | 83          | NA      | 45      | 93             | 1                 | cTnI ≥ 15 × ULN    |
| D. Filomena et al      | 2021  | Rome        | 106          | 22        | 36       | 81          | NA      | NA      | NA             | 2                 | hsTNT > 15 × ULN   |
| M. Dagan et al         | 2022  | Australia   | 400          | 166       | 55       | 83          | 4.0      | 32%     | 96             | 9                 | cTnI > 15 × ULN    |

STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; TF: transfemoral; CAD: coronary artery disease; PPMI: periprocedural myocardial injury; ULN: upper limit of normal; NA: not available; CK-MB: creatine kinase-myocardial band; cTnI: cardiac troponin I; cTnT: cardiac troponin T; hsTNT: high-sensitivity troponin T.
STS-FROM score was >8 points (OR = 1.89; 95%CI [1.29–2.77]), the proportion of patients with CKD was more than 60% (OR = 2.61; 95%CI [2.04–3.33]), the proportion of patients with AF was less than 30% (OR = 2.32; 95%CI [1.87–2.87]), and patients with PPMI had higher long-term all-cause mortality compared with patients without PPMI.

Figure 2. Forest plot of PPMI and all-cause mortality in patients who undergoing TAVR. OR: odds ratio; PPMI: periprocedural myocardial injury.

Figure 3. Sensitivity analysis excluding one item at a time to evaluate the OR of the remaining studies. OR: odds ratio.
Table 2. Meta regression of PPMI and long-term all-cause mortality.

| Subgroups                          | Number of trials | Heterogeneity between trials | Effects model | Results of meta-analysis  |
|------------------------------------|------------------|------------------------------|---------------|--------------------------|
|                                    |                  | p                            | I² (%)           | OR (95%CI)     | p          |
| Age (years)                        |                  |                              |                |                          |            |
| <82                                | 7                | 0                            | 80             | Random 1.36 (0.90–2.07) | .14        |
| ≥82                                | 6                | .02                          | 64             | Random 2.00 (1.22–3.27) | .01        |
| Male proportion                    |                  |                              |                |                          |            |
| <50%                               | 6                | .41                          | 1              | Fixed 2.01 (1.49–2.71)  | .00        |
| ≥50%                               | 6                | 0                            | 85             | Random 1.35 (0.88–2.07) | .17        |
| Definition of PPMI                 |                  |                              |                |                          |            |
| troponin ≥ 15 × ULN or CK-MB ≥ 5 × ULN | 3              | .35                          | 4              | Fixed 1.87 (1.27–2.74)  | .00        |
| troponin < 15 × ULN or CK-MB < 5 × ULN | 11          | 0                            | 77             | Random 1.49 (1.07–2.07) | .02        |
| Percentage of AF                   |                  |                              |                |                          |            |
| ≥30%                               | 6                | .07                          | 50             | Random 1.12 (0.80–1.57) | .51        |
| <30%                               | 4                | .31                          | 15             | Fixed 2.32 (1.87–2.87)  | .00        |
| Percentage of CAD                  |                  |                              |                |                          |            |
| ≥50%                               | 6                | 0                            | 76             | Random 1.50 (1.01–2.23) | .04        |
| <50%                               | 7                | 0                            | 84             | Random 1.39 (0.87–2.21) | .17        |
| STS-PROM score                     |                  |                              |                |                          |            |
| ≤8                                | 2                | .24                          | 27             | Fixed 1.89 (1.29–2.77)  | .00        |
| >8                                | 10               | 0                            | 77             | Random 1.48 (1.06–2.07) | .02        |
| Percentage of transfemoral         |                  |                              |                |                          |            |
| <100%                              | 3                | .24                          | 30             | Fixed 2.22 (1.26–3.91)  | .05        |
| ≥100%                              | 10               | .03                          | 59             | Random 1.14 (0.84–1.54) | .40        |
| Male proportion                    |                  |                              |                |                          |            |
| <50%                               | 6                | .87                          | 0              | Fixed 2.61 (2.04–3.33)  | .00        |
| ≥50%                               | 4                | .04                          | 64             | Random 1.44 (0.85–2.43) | .17        |
| Percentage of DB                   |                  |                              |                |                          |            |
| ≥30%                               | 4                | 0                            | 81             | Random 1.71 (0.93–3.13) | .08        |
| <30%                               | 5                | 0                            | 81             | Random 1.71 (0.93–3.13) | .08        |

STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; TF: transfemoral; CAD: coronary artery disease; CKD: chronic kidney disease; AF: atrial fibrillation; PPMI: periprocedural myocardial injury; DB: diabetes; CI: confidence interval.

Table 3. Subgroup analyses of PPMI and long-term all-cause mortality.

| Baseline characteristics | Number of trials | Risk of all-cause mortality | p |
|--------------------------|------------------|-----------------------------|---|
| Age                      | 13               | 0.37 (0.32–1.07)            | .26 |
| Male proportion          | 12               | 0.32 (0.01–0.38)            | .74 |
| Definition of PPMI       | 14               | 0.24 (0.03–0.55)            | .52 |
| Percentage of CAD        | 9                | 0.13 (0.10–0.80)            | .76 |
| STS-PROM score           | 9                | 0.15 (0.03–1.13)            | .72 |
| Percentage of AF         | 10               | 0.83 (0.30–1.36)            | .01 |
| Percentage of CKD        | 10               | 0.74 (0.39–1.29)            | .01 |
| Percentage of DB         | 9                | 0.15 (0.05–0.73)            | .66 |
| Percentage of TF approach| 13               | 0.43 (0.07–1.34)            | .31 |

STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; TF: transfemoral; CAD: coronary artery disease; PPMI: periprocedural; CKD: chronic kidney disease; AF: atrial fibrillation; CK-MB: creatine kinase-myocardial band; DB: diabetes; CI: confidence interval.

Discussion

In this meta-analysis of 6415 patients who underwent TAVR, the occurrence of PPMI predicted a higher long-term all-cause mortality. A sensitivity analysis confirmed the reliability of our results.

Myocardial injury is commonly seen in conditions such as heart failure, pulmonary hypertension, and chronic renal failure and is associated with poor clinical outcomes [27–29]. Aortic valve stenosis is associated with microvascular dysfunction and left ventricular hypertrophy, which affect coronary flow reserve, leading to an imbalance in myocardial oxygen supply, making the myocardium susceptible to ischemia [30,31]. Therefore, patients with aortic stenosis are highly susceptible to myocardial injury when undergoing TAVR. However, there are no consistent results regarding whether the occurrence of PPMI in patients undergoing TAVR is associated with long-term all-cause mortality.

Our meta-analysis summarized 14 relevant studies and showed that the occurrence of PPMI during TAVR is associated with higher long-term all-cause mortality. This suggests that PPMI may be helpful in risk stratification of patients who have undergone TAVR. However, there is still no definitive explanation for the influence of PPMI on long-term all-cause mortality, and some studies suggest that myocardial injury may reflect broader diseases throughout the body, thus putting patients at a higher risk of death [20]. Some studies have shown that for patients who are susceptible to PPMI, β-blocker treatment, shortening of procedural duration, and prevention of deep prosthesis insertion may improve their clinical outcomes [20]. However, there are no studies showing that certain measures could improve the prognosis of patients with PPMI; nonetheless, we believe that for patients with PPMI, early treatment is necessary. Further research is required to examine this deeper link. For cardiovascular physicians, how to effectively control the occurrence of ischemic events during TAVR remains a substantial problem.

Our subgroup analysis showed that long-term all-cause mortality with PPMI was higher in the subgroup of patients ≥82 years old, the proportion of males was less than 50%, the STS-PROM score was >8 points, the percentage of CAD patients was ≥50%, the proportion of patients with CKD was more than 60%, and the proportion of patients with AF was less than 30%. This may indicate that older age, female sex, high STS-PROM scores, and the presence of coronary artery disease or chronic kidney disease be associated with a poorer prognosis after the occurrence of PPMI in patients undergoing TAVR.

The STS-PROM scores are commonly used to predict 30-day mortality after cardiac surgery such as TAVR or coronary artery bypass grafting, and a previous study showed that the STS score can also predict long-term mortality [32]. Our
study also showed that a high STS score was associated with worse prognosis, which further demonstrates the value of STS in predicting mortality in patients undergoing cardiac surgery.

In addition, PPMI was associated with long-term all-cause mortality in subgroups with a proportion of less than 30% of patients with AF, which was different from what we expected, possibly because fewer studies were included. However, further studies are required in the future. Surprisingly, PPMI was not associated with long-term all-cause mortality in any of the diabetes subgroups. Interestingly, there has been controversy as to whether diabetes is an independent predictor of long-term mortality after TAVR [33], which may involve deeper causes, such as diabetes typing. In addition, although the long-term mortality was higher in patients with PPMI than that of without in the group characterized by the percentage of patients with transfemoral approach and myocardial marker thresholds for the diagnosis of PPMI, in the subgroup of lower myocardial injury marker threshold and total transfemoral artery approaches, there was a higher correlation between the occurrence of PPMI and long-term all-cause mortality. This is consistent with previous results [8]. The Valve Academic Research Consortium 3 has a lower diagnostic threshold for PPMI than the previous one; however, it appears to provide better risk stratification in some studies that used lower thresholds [5,8,15,20]. Therefore, the threshold for the diagnosis of PPMI in patients undergoing TAVR requires further adjustments to provide better risk stratification. Many studies have shown that transapical approaches are more prone to inducing myocardial injury [8,17,18], but that they do not seem to be associated with long-term mortality risk [8,18]. Our research showed that PPMI and long-term all-cause mortality had a stronger correlation in the subgroup of patients who underwent a total transfemoral approach. This may indicate that, in patients with PPMI, the surgical approach has no independent predictive value for the risk of long-term death.

**Limitations**

Our study has some limitations. First, the diagnostic definitions of PPMI were not identical among the included studies, and three of the studies had thresholds lower than VARC-3. Our subgroup analysis showed that a lower threshold for myocardial injury increased the association with long-term all-cause death, which may have caused some bias. Second, the efficacy of hypersensitive troponin in the diagnosis of PPMI according to the VARC-3 criteria is unclear, but during this analysis, five studies used hypersensitive troponin as a myocardial marker, which may cause confounding factors to influence the results [5]. Third, most of the included studies were retrospective, which could not exclude the influence of confounding factors and had a high risk of bias. Fourth, because patient-level data were not available, we could not assess specific patient or procedural characteristics that might affect the clinical endpoints.

**Conclusion**

Our meta-analysis suggests that in patients undergoing TAVR, the occurrence of PPMI had higher long-term all-cause mortality and that the increased risk may be associated with higher age, sex, CAD, and other factors. For patients undergoing TAVR, it is necessary to take reasonable measures to prevent PPMI, and timely screening for PPMI may contribute to risk stratification and long-term prognosis.

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