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SPECIAL ISSUE: EVIDENCE-BASED IMAGING

ORIGINAL RESEARCH

Impact of Prosthesis-Patient Mismatch After Transcatheter Aortic Valve Replacement

Meta-Analysis of Kaplan-Meier–Derived Individual Patient Data

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ABSTRACT

BACKGROUND It remains controversial whether prosthesis-patient mismatch (PPM) (in general considered moderate if indexed effective orifice area is 0.65-0.85 cm^2/m^2 and severe when <0.65 cm^2/m^2) affects the outcomes after transcatheter aortic valve replacement (TAVR).

OBJECTIVES The purpose of this study is to evaluate the time-varying effects and association of PPM with the risk of overall mortality.

METHODS Study-level meta-analysis of reconstructed time-to-event data from Kaplan-Meier curves of studies published by December 30, 2021.

RESULTS In total, 23 studies met our eligibility criteria and included a total of 81,969 patients included in the Kaplan-Meier curves (19,612 with PPM and 62,357 without PPM). Patients with moderate/severe PPM had a significantly higher risk of mortality compared with those without PPM (HR: 1.09 [95% CI: 1.04-1.14]; $P < 0.001$). In the first 30 months after the procedure, mortality rates were significantly higher in the moderate/severe PPM group (HR: 1.1 [95% CI: 1.05-1.16]; $P < 0.001$). In contrast, the landmark analysis beyond 30 months yielded a reversal of the HR (0.83 [95% CI: 0.68-1.01]; $P = 0.064$), but without statistical significance. In the sensitivity analysis, although the authors observed that severe PPM showed higher risk of mortality in comparison with no PPM (HR: 1.25 [95% CI: 1.16-1.36]; $P < 0.001$), they did not observe a statistically significant difference for mortality between moderate PPM and no PPM (HR: 1.03 [95% CI: 0.96-1.10]; $P = 0.398$).

CONCLUSIONS Severe PPM, but not moderate PPM, was associated with higher risk of mortality following TAVR. These results provide support to implementation of preventive strategies to avoid severe PPM following TAVR. (J Am Coll Cardiol Img 2023;16:298–310) © 2023 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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The concept of prosthesis-patient mismatch (PPM), first proposed by Rahimtoola et al[1] and reintroduced by Pibarot et al,[2] provided the logical framework to select the proper prosthesis based on the indexed effective orifice area (iEOA) needed, which is derived from the effective orifice area (EOA) of the prosthesis and the patient's body surface area (BSA). Pibarot et al[3] proposed avoiding an iEOA lower than 0.85 cm^2/m^2 (lower cut point in obese patients; <0.70 cm^2/m^2)[4] to prevent PPM, because the consequence of using prostheses with a small EOA relative to the BSA would be the obstruction of the outflow of the left ventricle (LV), which would not favor the reverse remodeling of the hypertrophied LV.[5] PPM is considered moderate when the iEOA is between 0.65 and 0.85 cm^2/m^2 and severe when <0.65 cm^2/m^2.[2,3]

A previous meta-analysis[6] evaluating the impact of PPM on the risk of perioperative and early-, mid-, and long-term mortality rates after surgical aortic valve replacement (SAVR) showed increases in mortality of 49%, 46%, 36%, and 53%, respectively. The incidence of severe PPM was lower with transcatheter aortic valve replacement (TAVR) compared with SAVR in a meta-analysis of randomized controlled trials.[7] The association of severe PPM with clinical outcomes occurs after SAVR and TAVR but was generally less significant with TAVR.[8,9] Hence, it has been suggested that PPM may have less impact on outcomes following TAVR vs SAVR.[8] In the present study, we aimed to assess the impact of PPM on mortality after transcatheter aortic valve replacement (TAVR). We designed a pooled analysis of Kaplan-Meier-estimated individual patient data (IPD) from studies comparing patients with and without PPM after TAVR to evaluate its effect on the all-cause mortality risk, also analyzing its potential time-varying effect.

METHODS

ELIGIBILITY CRITERIA, DATABASES, AND SEARCH STRATEGY. This study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) reporting guideline.[10] Using the PICOS (Population, Interventions, Comparison, Outcome, and Study design) strategy, studies were included if the following criteria were fulfilled: 1) the population comprised patients who underwent TAVR and had an echocardiogram after the procedure to measure the iEOA for PPM assessment; 2) there was a group with PPM after TAVR; 3) there was a second group without PPM after TAVR; 4) outcomes studied included survival and/or mortality (with Kaplan-Meier curves); and 5) the study design was retrospective/prospective, randomized/nonrandomized, monocentric/multicentric, with matched/unmatched populations.

The following sources were searched for papers meeting our inclusion criteria and published by December 30, 2021: PubMed/MEDLINE, EMBASE, SciELO, LILACS, CENTRAL/CCTR (Cochrane Controlled Trials Register), Google Scholar, and the reference lists of relevant papers. We searched for the following terms: "mismatch OR PPM OR patient-prosthesis mismatch OR prosthesis-patient mismatch" AND "AVR OR aortic valve replacement" AND "percutaneous OR transcatheter OR transluminal OR transarterial OR transapical OR transaortic OR transcarotid OR transsubclavian OR transaxillary OR transiliac OR transfemoral." The following steps were taken for study selection: 1) identification of titles of records through database search; 2) removal of duplicates; 3) screening and selection of abstracts; 4) assessment for eligibility through full-text papers; and 5) final inclusion in study. Studies were selected by 2 independent reviewers (X.J., J.V.E.). When there was disagreement, a third reviewer (M.P.S.) made the decision to include or exclude the study. Ethical approval was not applicable for this study, as it consisted of a systematic review and meta-analysis. There were no language restrictions.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BSA = body surface area

EOA = effective orifice area

iEOA = indexed effective orifice area

IPD = individual patient data

PPM = prosthesis-patient mismatch

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

ViV-TAVR = valve-in-valve transcatheter aortic valve replacement

ASSESSMENT OF RISK OF BIAS. The ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) tool was systematically used to assess included studies for risk of bias.[11] The studies and their characteristics were classified into low, moderate, and serious risk of bias. Two independent reviewers (P.S., A.D.) assessed risk for bias. When there was a disagreement, a third reviewer (M.P.S.) checked the data and made the final decision.

STATISTICAL ANALYSIS. Time-to-event outcomes do not lend themselves easily to traditional meta-analyses. In the past, several authors have attempted to pool median survival times, event rates estimated from survival estimates at given time-points, or direct estimates of the HRs across the studies. All of these approaches have been shown to be limiting and unsatisfactory, as they fail to recognize some of the central tenets of survival analysis, such as censoring and the proportional hazards assumption.[12] In response to inconsistent reporting that resulted from these diverging approaches, the "curve approach" has emerged as the current gold

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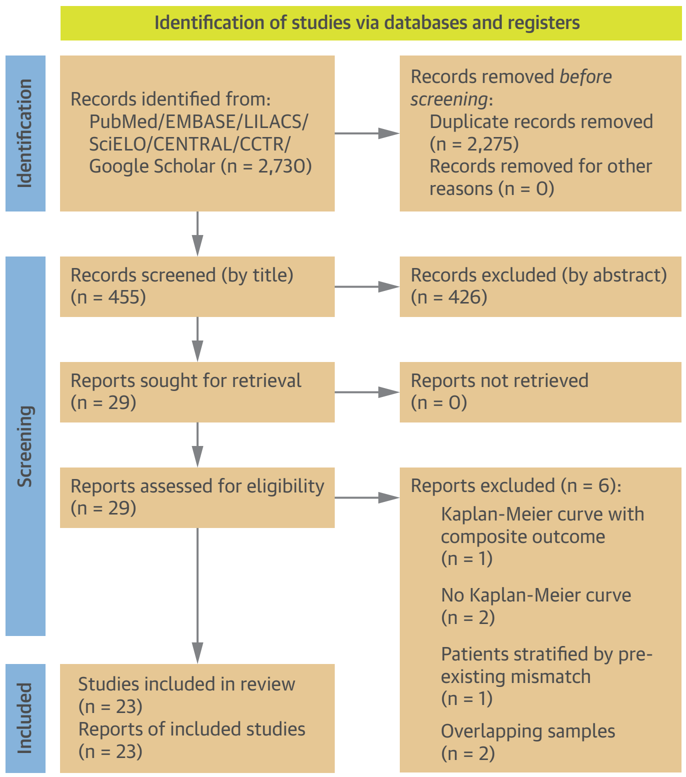
FIGURE 1 Flow Diagram of Studies Included in Data Search



CCTR = Cochrane Controlled Trials Register.

standard for meta-analysis of aggregated time-to-event data.[13] This approach reconstructs individual patient data (IPD) based on the published Kaplan-Meier graphs from the included studies. In this meta-analysis, we used the 2-stage approach as described by Liu et al.[14] based on the R package "IPDfromKM" version 0.1.10 (R Foundation for Statistical Computing). In the first stage, raw data coordinates (time, survival probability) were extracted from each treatment arm in each of the Kaplan-Meier curves. In the second stage, the data coordinates were processed based on the raw data coordinates from the first stage in conjunction with the numbers at risk at given timepoints, and IPD were reconstructed.

Finally, the reconstructed IPD from all studies were merged to create the study data set. The cumulative incidence of all-cause mortality at follow-up in both arms (with and without PPM) were visually assessed using Kaplan-Meier estimates with the R packages "survival" version 3.2-13 and "survminer" version 0.4.9. HRs with 95% CIs for the difference between both treatment arms were calculated using a Cox regression model with the R package "coxphw" version 4.0.2. The proportionality of the hazards of the Cox model was checked with the Grambsch-Therneau test and diagnostic plots based on Schoenfeld residuals.[15] Our protocol stated that flexible parametric survival models with B-splines and landmark analysis would be performed in case the proportional hazards assumption was violated, as apparent either from these tests or from visual inspection of the Kaplan-Meier curves.

Much like Cox regression models, flexible parametric survival models (also known as Royston-Parmar models or generalized survival models) with B-splines provide HRs with 95% CIs as a measure of association between exposures and outcome, with the addition that they allow the time effect(s) to be smooth.[16,17] As a result, they do not depend on proportional hazards and can capture a wide range of hazard shapes. In the present study, we modeled the baseline hazard rate based on a spline with 4 degrees of freedom (df) (df; 3 intermediate knots and 2 knots at each boundary, placed at quartiles of distribution of events), using the R package "rstpm2" version 1.5.2. Interactions between treatment arm and time were added to the model using a second spline function. The resulting output estimates time-varying HRs with 95% CIs for every given timepoint during follow-up.

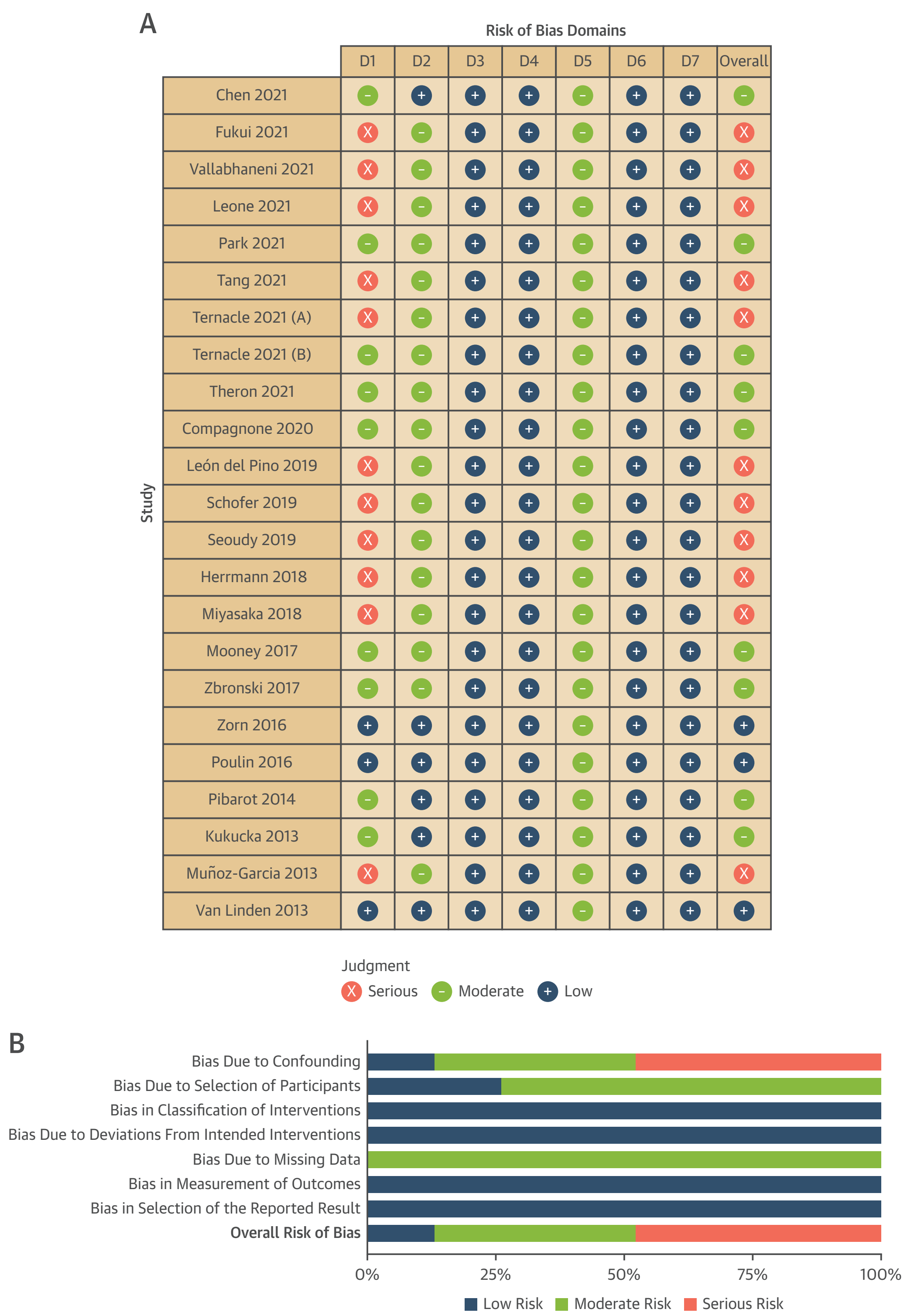
In the landmark analysis of time-to-event data,[18] a timepoint occurring during the follow-up period (referred to as the landmark time) is designated, after which only those subjects are analyzed who have survived until the landmark time. In the present study, we designated the landmark timepoints to delineate the regions on flexible parametric survival modeling. This allowed us to estimate HRs with 95% CIs for each of these regions.

All analyses were completed with R Statistical Software version 4.1.1.

RESULTS

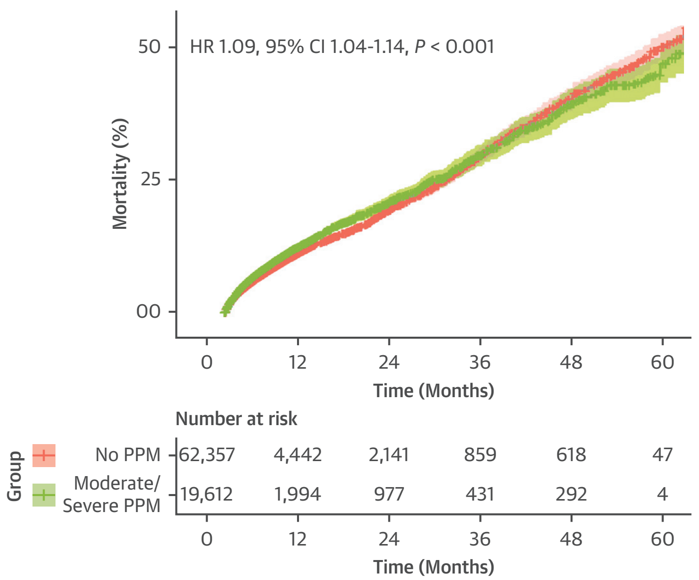
STUDY SELECTION AND CHARACTERISTICS. After excluding duplicates and non-eligible studies, 23 studies (Supplemental Reference List) met our eligibility criteria (**Figure 1**). All of the studies were non-randomized (although some of them had data extracted from randomized studies, such as PARTNER [Placement of AoRTic TraNscathetER Valve Trial]-1, PARTNER-2, CoreValve US High Risk Pivotal Trial), 10 studies were multicentric, and 7 studies were prospective (Supplemental Table 1). A total of 81,969 patients were included in the Kaplan-Meier curves (19,612 with PPM and 62,357 without PPM). The overall incidence of any PPM after TAVR was

FIGURE 2 Risk of Bias Summary: ROBINS-I Tool With Traffic Lights and Summary Plot



Risk of bias summary-ROBINS-I tool with traffic lights **(A)** and summary plot **(B)**. D1 = bias due to confounding; D2 = bias due to selection of participants; D3 = bias in classification of interventions; D4 = bias due to deviations from intended interventions; D5 = bias due to missing data; D6 = bias in measurement of outcomes; D7 = bias in selection of the reported result; ROBINS-I = Risk of Bias in Non-Randomized Studies of Interventions.

FIGURE 3 Pooled Kaplan-Meier Curves Showing the Cumulative Risk of Mortality



Pooled Kaplan-Meier curves showing the cumulative risk of mortality following transcatheter aortic valve replacement (TAVR) in patients with moderate/severe prosthesis-patient mismatch (PPM) vs no PPM measured by echocardiography.

23.9%. Considering the studies that reported the incidence of moderate and severe PPM after TAVR separately, we found incidences of 24.1% for moderate PPM and 10.9% for severe PPM (bear in mind that some studies reported only "any PPM," so that they are not considered in these calculations). Only 5 studies included patients who underwent valve-in-valve (ViV)-TAVR (ranging from 3%-10%) (Supplemental Refs. 5,7,10,14,20). Patients' mean age, sex distribution, and transcatheter heart valves (THVs) are shown in Supplemental Table 1. In summary, patients were around 80 years of age with good representation of women in both groups and the studies presented a mix of balloon-expandable valves (BEV) and self-expandable valves (SEV). Figure 2 shows the qualitative assessment of the studies with the ROBINS-I tool. There are several concerns regarding confounding factors and selection bias in the studies because of important differences between the groups regarding age, risk score, obesity, BSA, body mass index (BMI), previous CAD, and previous coronary bypass graft.

ANALYSIS OF ALL-CAUSE MORTALITY (INCLUDING ALL STUDIES). Figure 3 depicts the pooled Kaplan-Meier curve for the cumulative risk of mortality in all included studies reporting PPM using echocardiography. The data of 81,969 patients (no PPM: 62,357 patients; moderate/severe PPM: 19,612 patients) from 23 studies were pooled. Patients with moderate/severe PPM had a significantly higher risk of mortality compared with those without PPM (HR: 1.09 [95% CI: 1.04-1.14]; $P < 0.001$).

There was evidence of strong violation of the proportional hazards assumption, underscored by crossing of the curves around 30 months of follow-up and the Schoenfeld residuals, and the Grambsch-Therneau test for time-invariant effect ($P < 0.001$). The effect estimation based on Cox proportional hazards regression for this cohort might therefore be misleading. To account for a possible time-varying effect of PPM, we proceeded with flexible parametric survival models with B-splines and landmark analysis within this subgroup.

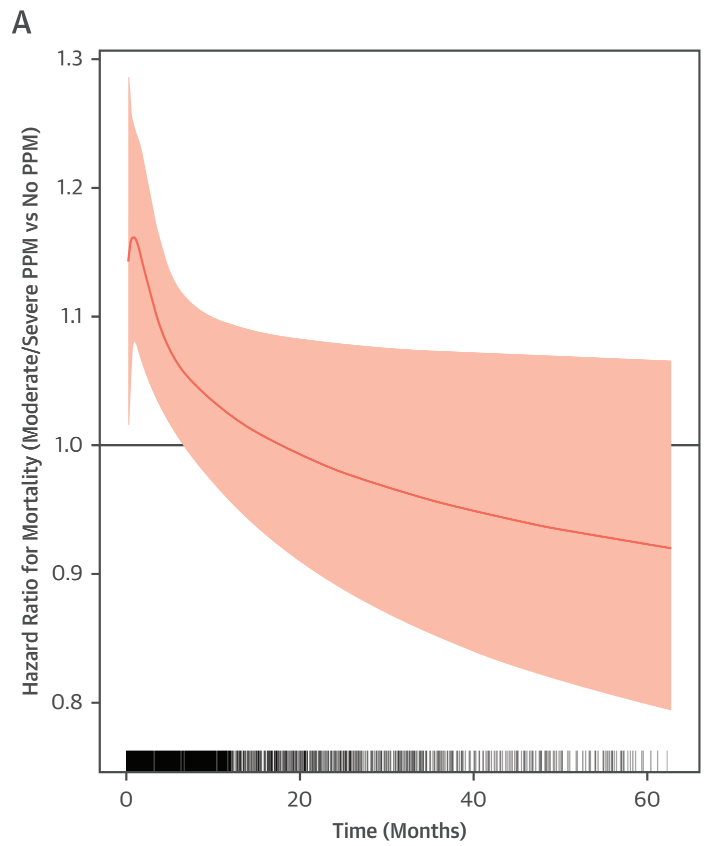
The analysis of time-varying HRs based on flexible parametric survival models with B-splines within the subgroup of PPM is presented in Figure 4A. In the first 30 months after the procedure (the landmark timepoint at which the curves crossed in Figure 3), mortality rates were significantly higher in the moderate/severe PPM group (HR: 1.1 [95% CI: 1.05-1.16]; $P < 0.001$) (Figure 4B). In contrast, the landmark analysis beyond 30 months yielded a reversal of the HR (0.83 [95% CI: 0.68-1.01]; $P = 0.064$), but without statistical significance (Figure 4B).

SENSITIVITY ANALYSIS (MODERATE OR SEVERE PPM VS NO PPM). The same procedures described previously were repeated including only those studies which compared moderate and severe PPM vs no PPM separately (Figure 3). Although we did not observe a statistically significant difference for mortality in the comparison between the groups with moderate PPM and no PPM (HR: 1.03 [95% CI: 0.96-1.10]; $P = 0.398$) (Figure 5A), severe PPM showed a higher risk of mortality compared with no PPM (HR: 1.25 [95% CI: 1.16-1.36]; $P < 0.001$) (Figure 5B). Because no evidence of strong violation of the proportional hazards assumption was found for these analyses (Grambsch-Therneau test: $P > 0.05$), extra landmark analyses were not necessary.

SENSITIVITY ANALYSIS (1-STUDY-REMOVED ANALYSES). Besides having disproportionally larger sample sizes in comparison with the other studies included, 2 studies (Supplemental Refs. 6,14) have the same source (STS/ACC TVT [Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy] Registry). Although they were deemed eligible to be included during the systematic review, we identified a short time overlap between them that might cause introduction of overlap samples. Therefore, we decided to carry out analyses of the total sample in 2 ways to investigate how much these specific studies might have affected our overall results: first, omitting only Supplemental Ref. 6 (to avoid a possible overlap with the sample included in Supplemental Ref. 14); and, sequentially, omitting both Supplemental Refs. 6 and 14 concomitantly (to avoid excessive impact of 2 disproportionately larger samples over the rest of the samples). Because there was evidence of strong violation of the proportional hazards assumption, underscored by crossing of the curves during the follow-up and the Schoenfeld residuals and the Grambsch-Therneau test for time-invariant effect ($P < 0.001$), landmark analyses were performed for all these analyses (**Figures 6 and 7**).

The statistically significant difference between the groups (observed in **Figure 4B**) maintained its statistical significance (**Figures 6 and 7**, respectively), confirming the negative impact of PPM on the outcomes in the first 30 months. The landmark analyses beyond 30 months for these 2 sensitivity analyses yielded a reversal of the HR, but without statistical significance (exactly as in **Figure 4B**).

FIGURE 4 **Landmark Analyses**



(A) Time-varying HRs with 95% CIs for all-cause mortality in moderate/severe PPM compared with no PPM at every given time during follow-up; these are derived from flexible parametric survival models with B-splines. **(B)** Landmark analysis of all-cause mortality in moderate/severe PPM compared with no PPM, designating 30 months of follow-up as the landmark time. Abbreviation as in Figure 3.

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DISCUSSION

SUMMARY OF EVIDENCE. To the best of our knowledge, this is the first pooled meta-analysis of reconstructed time-to-event data analyzing the impact of PPM on outcomes after TAVR. Our main findings were the following (**Central Illustration**):

1. Moderate/severe PPM is associated with higher risk of mortality;
2. Moderate/severe PPM is associated with higher risk of mortality for the first 30 months after TAVR but not thereafter, suggesting a time-varying risk for PPM; and
3. When analyzing the different degrees of PPM severity, we found that severe PPM but not moderate PPM was associated with an increased and constant risk of mortality compared with no PPM over time.

COMMENTS. There is discordant evidence on the impact of PPM on clinical outcomes after TAVR, probably because of methodological differences across the studies, patient populations with non-balanced baseline characteristics, and type of THV.[19,20] Although there is consistent evidence of the negative impact of PPM on outcomes after SAVR,[6] the evidence of association between PPM and poor outcomes after TAVR has been conflicting.[21-23] What is the rationale behind this "PPM conundrum" between SAVR and TAVR? Does it really make sense?

For example, although Tang et al[21] did not find a relationship between severe PPM and mortality in patients who received supra-annular THVs in the STS/ACC TVT Registry, Herrmann et al[22] observed in the same registry that patients with severe PPM had significantly higher mortality ($P < 0.001$). This discrepancy in the findings could be explained by the inclusion of TAVR patients treated with all commercially approved THVs in the latter, including both intra-annular and supra-annular devices. Another aspect is that, whereas both Tang et al[21] and Herrmann et al[22] used the iEOA measured at discharge echocardiogram to define severe PPM (iEOA <0.65 cm^2/m^2) following TAVR, only Tang et al[21] used adjusted thresholds of iEOA in obese patients (ie, iEOA <0.55 cm^2/m^2 if BMI is >30 kg/m^2) as

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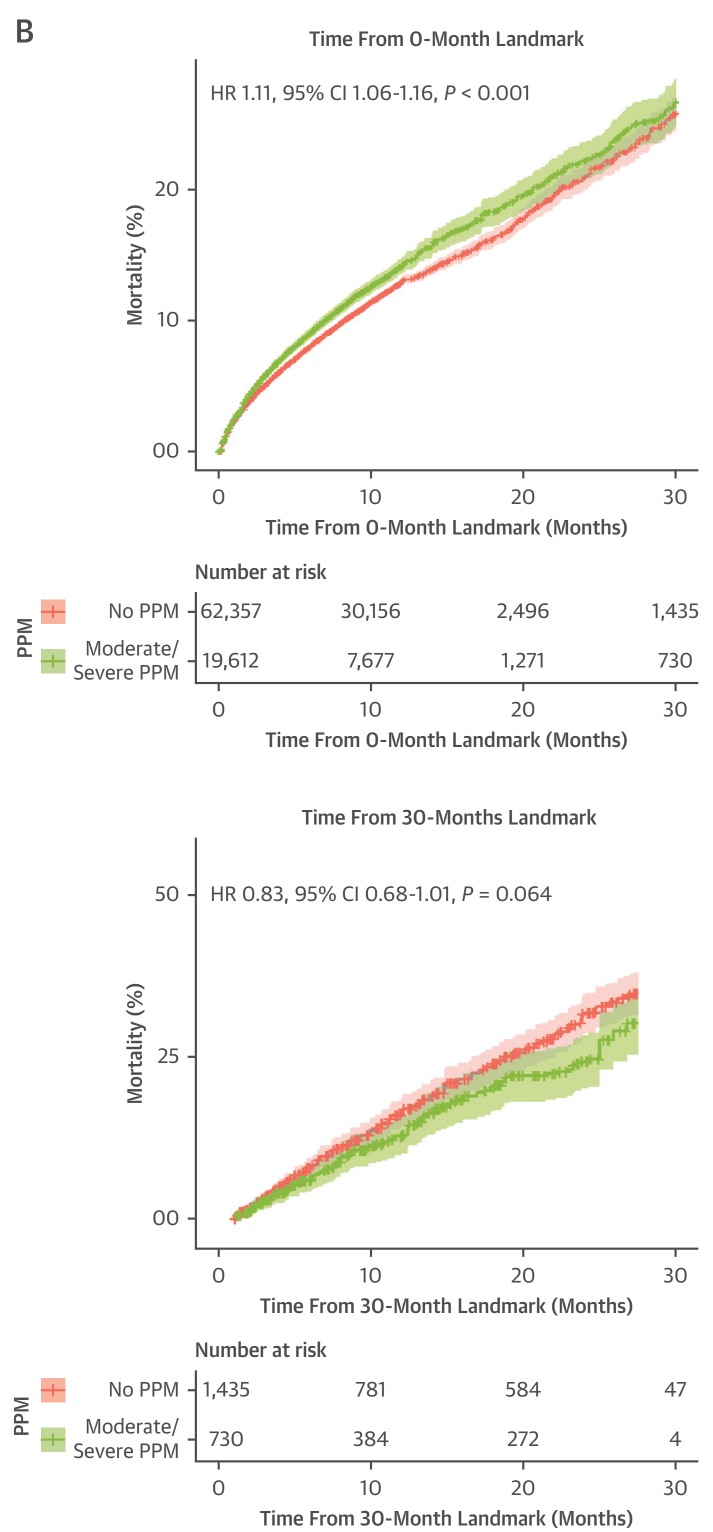
FIGURE 4 Continued



recommended by the Valve Academic Research Consortium 3.[24]

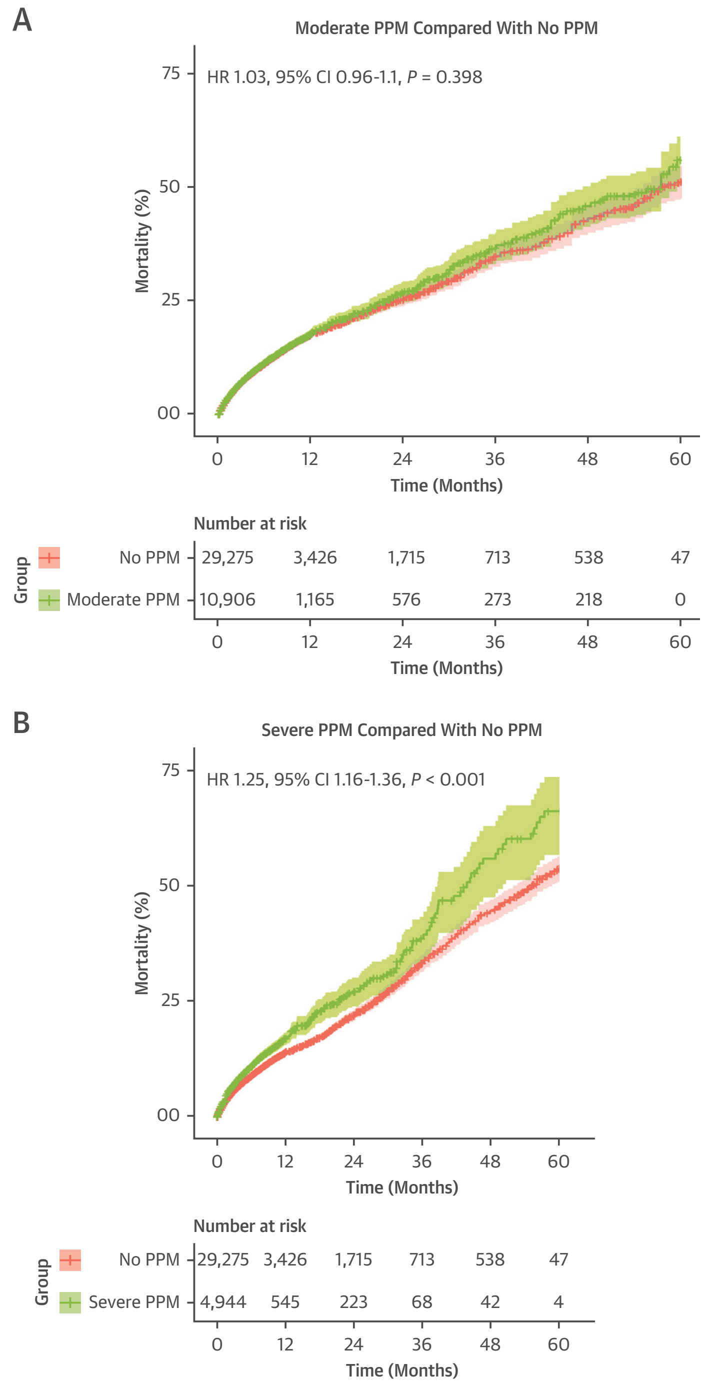
One aspect that we should discuss further is the diagnosis of PPM by echocardiogram immediately after TAVR procedures. In a study of patients undergoing TAVR recently published by Ternacle et al,[25] the use of the predicted iEOA (normal reference value of the EOA for the prosthesis model and size indexed to the body surface area) instead of the measured iEOA resulted in a dramatic reduction in the incidence of severe PPM from 17% to 1%. The iEOA measured by Doppler echocardiography following TAVR (and after SAVR) has inherent limitations and generally overestimates the incidence and severity of PPM caused by flow-dependency.[26] In the presence of a low-flow state, the EOA can decrease below its normal value even if the THV function is normal. Because of this flow-induced reduction in EOA, the iEOA is falsely measured and overestimates the severity of PPM,[26] making patients who would belong to the group without PPM jump to the group with PPM (which in turn could "hide" the negative impact of PPM on outcomes in the survival analyses). Furthermore, there is evidence[27] showing that exercise Doppler echocardiography (not at rest) should be used to complete the assessment of PPM, especially in patients with a low-flow state. Unfortunately, most studies included in our meta-analysis do not report the stroke volumes (so that we could not include this aspect in our analyses) and, indeed, patients with PPM had mostly higher means of BSA and/or BMI, which might also lead to pseudosevere PPM. To overcome this issue of PPM overestimation by the measured iEOA, Ternacle and Pibarot[26] propose the use of predicted iEOA, which is the normal reference value of EOA reported in the literature for each given model and size of THVs divided by patient's BSA. On the other hand, Bleiziffer and Rudolph[28] affirm that echocardiography remains the main imaging tool to assess PPM following TAVR, but they point out the importance of excluding potential measurement errors of the continuous and pulse wave Doppler signal and how crucial it is to measure the LV outflow tract diameter at the inferior edge of the THV stent and from outer-edge to outer-edge, because there are 2 areas of flow acceleration: first at the level of the inferior edge of the stent, and second at the level of the cusps. Bleiziffer and Rudolph[28] also underscore the role played by the phenomenon of pressure recovery, which affects Doppler-derived gradients across the THV, emphasizing that this should be considered while assessing hemodynamics of the THV.

In most of our analyses, the negative effect of PPM is more pronounced in the first 30 months after TAVR. The rationale behind this phenomenon may lie in the fact that it takes some time for the hypertrophied LV to go through the process of reverse remodeling. At first, the LV remains under the influence of diastolic dysfunction with high filling pressures, and the presence of PPM "adds insult to injury" functioning as an obstruction to the outflow, which is even more pronounced in patients with severe PPM. These patients, differently from those with moderate PPM, die more frequently at early timepoints and are at a constant higher risk over time, which is in accordance with the findings by Leone et al[29] in the TAVR-SMALL (International Multicenter Registry to Evaluate the Performance of Self-Expandable Valves in Small Aortic Annuli) registry. Previous studies also showed an association between PPM after TAVR and reduced LV mass regression, with reduced post-procedural functional class improvement[30,31] and increased risk of rehospitalization for heart failure.[32] Therefore, there is no reason for us to believe that severe PPM would be harmful in patients undergoing SAVR while innocuous in patients undergoing TAVR.

Some studies have suggested that post-TAVR computed tomography angiography (CTA) evaluation of PPM might improve our understanding of this phenomenon.[33,34] Fukui et al[33] investigated this aspect and, even though post-TAVR CTA substantially downgraded the prevalence of PPM compared with echocardiography in their study, they concluded that CTA- and echo-defined PPM were both associated with the composite of death and heart failure rehospitalization. Mooney et al[34] sought to determine if iEOA using LVOT measured from CTA reclassified PPM compared with conventional echocardiogram-defined measurements and found that CTA downgrades frequency and severity of PPM in patients after TAVR; however, it was not associated with less LV mass regression or mortality 1 year after TAVR. Therefore, the value of CTA in this context remains to be further investigated.

Although outside the scope of our work, some comments on strategies to avoid PPM after TAVR may be valuable. If we learn from the experience with SAVR,[35] which showed that supra-annular valves (compared with intra-annular valves) are associated

FIGURE 5 **Sensitivity Analysis (According to PPM Severity) With Pooled Kaplan-Meier Curves Showing the Cumulative Risk of Mortality Following TAVR**



Cumulative risk of mortality following TAVR is shown in patients with moderate PPM vs no PPM **(A)** and severe PPM vs no PPM **(B)** according to echocardiography. Abbreviations as in Figure 3.

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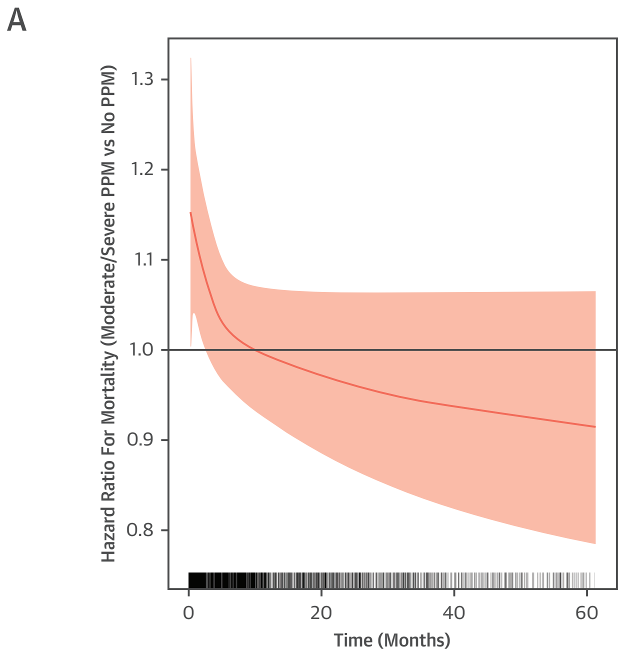
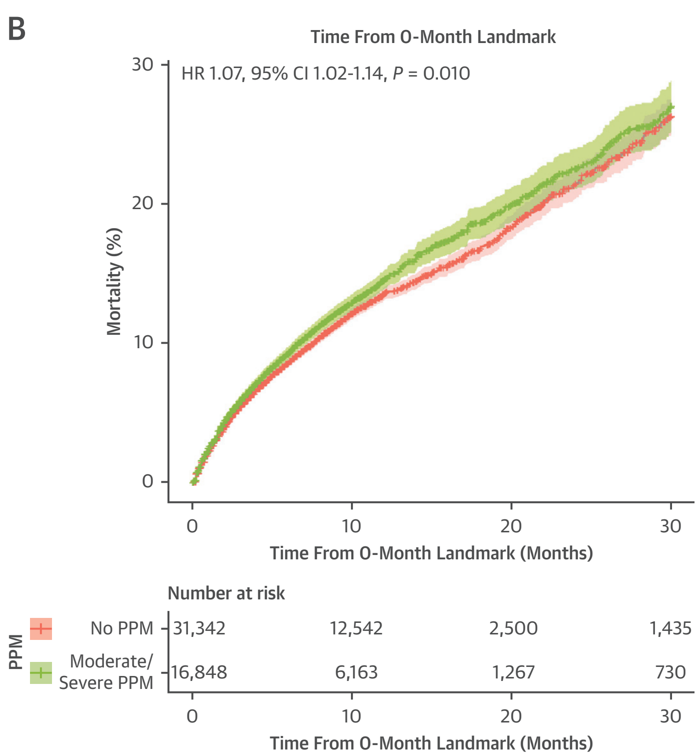
FIGURE 6 Sensitivity Analysis (1-Study-Removed) With Pooled Kaplan-Meier Curve After Removal of the Largest Database





(A) Sensitivity analysis (1-study-removed) with **(B)** pooled Kaplan-Meier curve showing the cumulative risk of mortality following TAVR in patients with moderate/severe PPM vs no PPM according to echocardiography after removal of the largest database. Abbreviations as in Figure 3.

with larger postoperative EOA and iEOA, lower transaortic peak velocity, and mean pressure gradient with better LV mass regression over time, we suggest the preference for supra-annular THVs over intra-annular devices (especially in those patients with small aortic annulus and/or with large BSA) as a strategy to avoid PPM after TAVR. Additionally, data published by Leone et al[29] suggest postdilatation and valve oversizing as further strategies associated with lower risk of PPM after TAVR in patients with small annuli.

Another aspect deserving some attention—although it represents a very small fraction of the overall population in our meta-analysis—is the scenario of ViV-TAVR, which carries a higher risk of severe PPM in comparison with its surgical counterpart (redo SAVR).[36] The incidence of PPM after ViV-TAVR is highly dependent on the size of the surgical valve implanted at the time of the index SAVR. Therefore, cardiac surgeons should master techniques of aortic annulus/root enlargement which enable the implantation of larger surgical valves[37-39] not only to avoid PPM after the index SAVR, but also to set up patients for ViV-TAVR without PPM in the future (when structural valve deterioration of the index bioprosthetic valves takes place).

WHAT DOES OUR STUDY ADD TO THE LATEST META-ANALYSIS? Lim et al[40] recently published a meta-analysis showing that all-cause mortality was significantly affected in severe PPM compared with nonsevere cases, whereas this excess mortality was not observed between those with any degree of PPM and those without. Although we recognize the value of our colleagues' work, our meta-analyses differ in some aspects to be considered:

1. Whereas Lim et al[40] compared severe PPM vs nonsevere PPM (which includes patients with no PPM and also with moderate PPM in the same group), we only established separate comparisons between moderate and severe PPM with no PPM as basis, so that we had comparisons between "moderate AND severe PPM" vs "no PPM" or "only moderate OR only severe PPM" vs "no PPM," but never "no PPM together with moderate PPM" vs "severe PPM"—merging "no PPM and moderate PPM" into 1 group contaminates the control group with some degree of PPM, which may create a false comparison.
2. Despite having included 22 studies in their systematic review, Lim et al[40] combined the data of only 11 studies to calculate the pooled risk for all-cause mortality, whereas we pooled the Kaplan-

Meier-derived data of all 23 studies we had included, which gave us a much larger sample size to analyze in the follow-up.

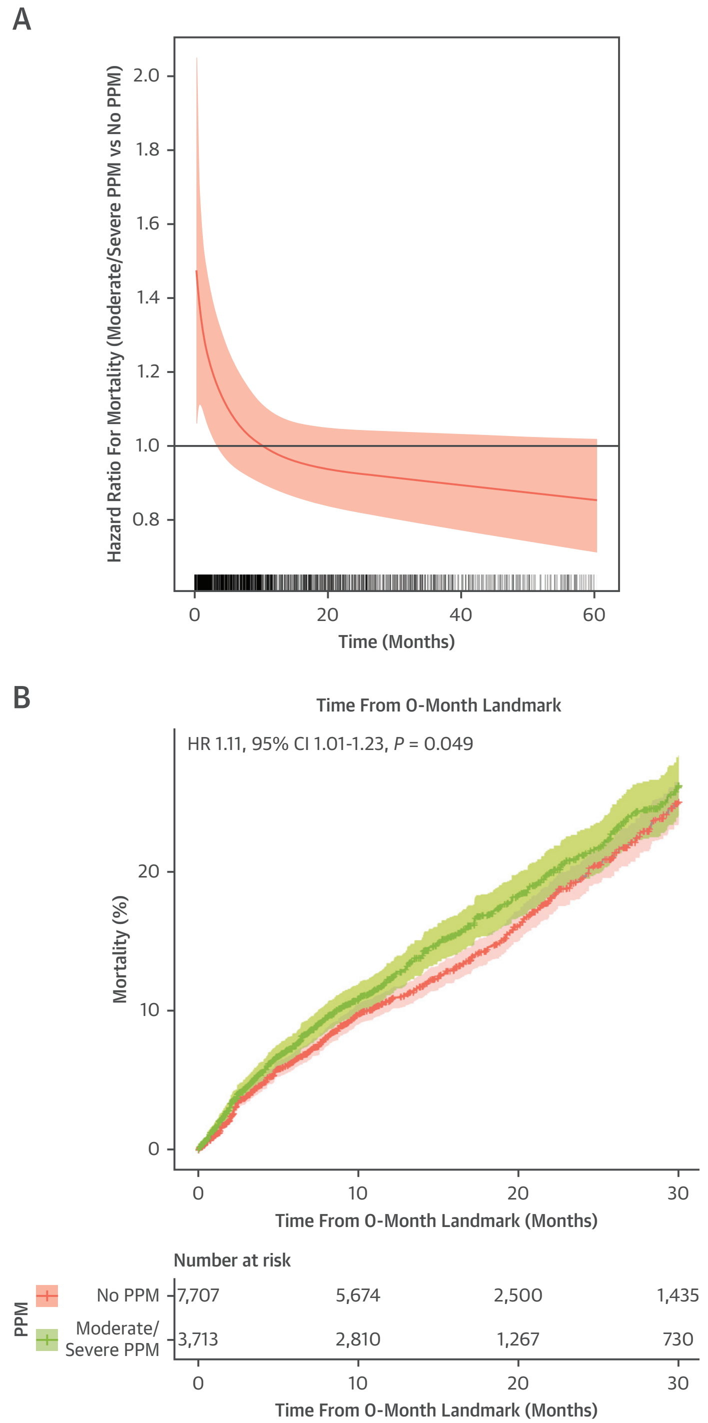
3. Instead of merging the HRs of the studies into a single summary measure as done by Lim et al,[40] we used reconstructed time-to-event data based on the Kaplan-Meier curves, respecting the central tenets of survival analysis and considering the populations over time—this is not done when authors merge HRs produced with different follow-ups collected at different timepoints as if they had been measured at the same timepoint with the same follow-up;
4. Whereas Lim et al[40] presented the usual forest plots for meta-analyses, we present Kaplan-Meier curves and landmark analyses for all-cause mortality, which enable us to visualize the mortality rate over time and also appreciate the time-varying risk of death with landmark analyses (highlighting the importance of PPM more pronounced in an early phase after TAVR).

STUDY LIMITATIONS. All-cause mortality was the sole outcome reported in all studies with Kaplan-Meier curves, whereas other outcomes (such as cardiovascular death, valvular-related death, rehospitalization, stroke, myocardial infarction, reintervention for SVD) that might affect quality of life and life expectancy were not available in most studies for us to be able to carry out more thorough and comprehensive analyses. The original studies included early- and new-generation devices together, while also mixing BEVs and SEVs.

Very few studies attempted to minimize the impact of some confounders (such as, age, sex, diabetes, smoking, BMI, LV ejection fraction, renal insufficiency, concomitant coronary artery disease, and so on) using propensity score matching. Even when this method is applied, although useful to reduce the impact of selection and treatment biases, it does not consider all baseline factors that may differ between the groups and, thus, may have not achieved a perfectly well-balanced comparison of the groups. For example, we should also bear in mind that the populations in the studies are of advanced age (around 80 years) (Supplemental Table 1) and it is highly likely that the "frailty" factor was not captured in the studies and, consequently, in our analyses.

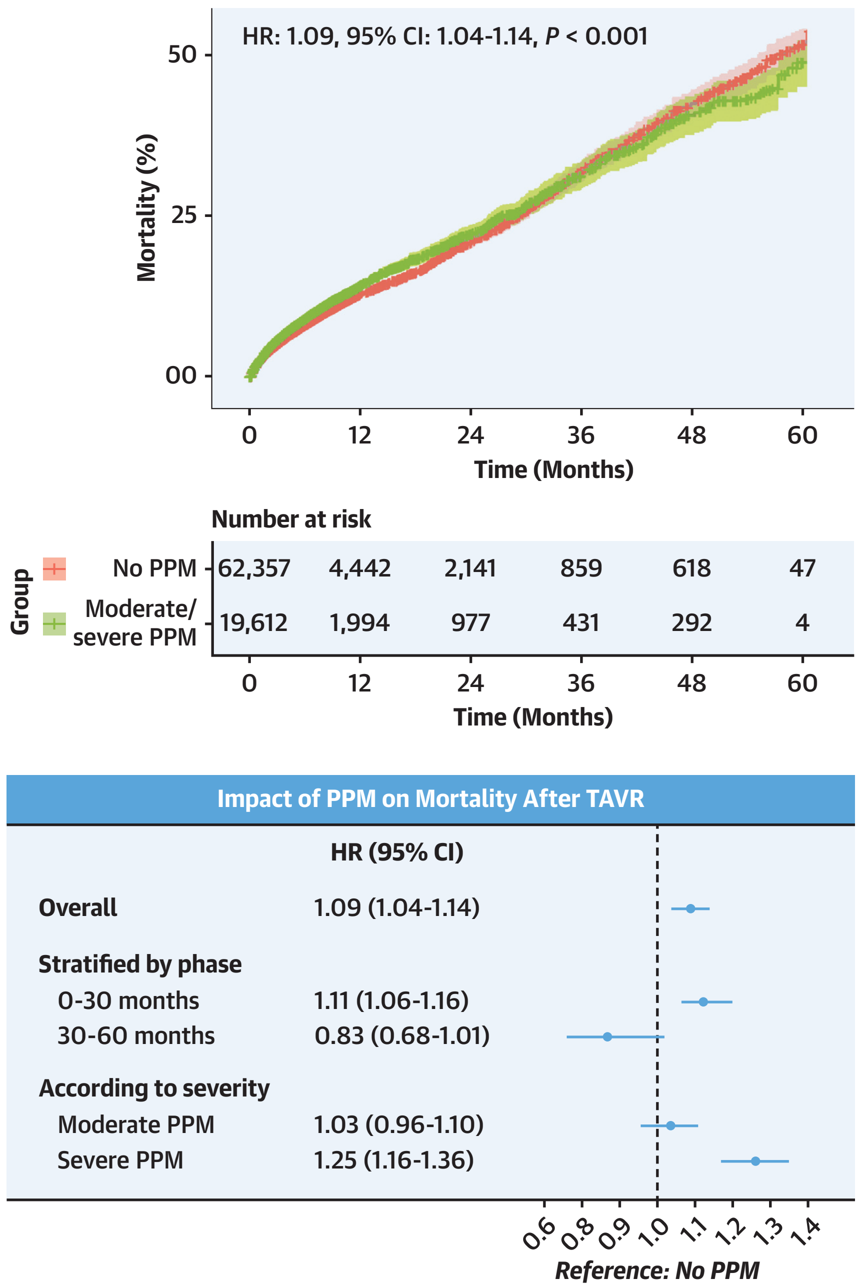
In this study, we used PPM defined with the use of the indexed EOA measured by echocardiography at 30 days or predischarge echocardiography, because this is the method that has been used in the vast majority of TAVR studies. On the other hand, several

FIGURE 7 **Sensitivity Analysis (1-Study-Removed) With Pooled Kaplan-Meier Curve After Removal of the First and Second Largest Database Simultaneously**



(A) Sensitivity analysis (1-study-removed) with **(B)** pooled Kaplan-Meier curve showing the cumulative risk of mortality following TAVR in patients with moderate/severe PPM vs no PPM according to echocardiography after removal of the first and second largest database simultaneously. Abbreviations as in Figure 3.

CENTRAL ILLUSTRATION Severe Prosthesis-Patient Mismatch, but not Moderate Prosthesis-Patient Mismatch, Is Associated With Higher Risk of Mortality Following TAVR



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PPM = prosthesis-patient mismatch; TAVR = transcatheter aortic valve replacement.

SAVR studies and meta-analyses have used the predicted indexed EOA to define PPM.[6] Another aspect to be highlighted is the fact that some studies used lower cutoffs of iEOA in obese patients (ie, <0.70 cm^2/m^2 for moderate PPM and <0.55 cm^2/m^2 for severe PPM) as recommended,[4] whereas others did not apply any adjustment to BMI ≥30 kg/m^2.

CONCLUSIONS

The results of the present study suggest that severe PPM, but not moderate PPM, is associated with higher risk of mortality following TAVR. These results provide support to implementation of preventive strategies to avoid severe PPM following TAVR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Severe PPM defined by echocardiography after TAVR is associated with worse survival. Overall mortality seems to be affected only by severe PPM, but not moderate PPM.

TRANSLATIONAL OUTLOOK: Further studies to develop strategies to prevent PPM are warranted.

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APPENDIX For supplemental references and a table, please see the online version of this paper.