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Transcatheter aortic valve replacement in patients with severe aortic stenosis and active cancer: a systematic review and meta-analysis

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ABSTRACT

Background Patients with severe aortic stenosis and concomitant active cancer (AC) are considered high-risk patients and usually are not allowed to undergo surgical valve replacement. Transcatheter aortic valve replacement (TAVR) may be an attractive option for them; however, little is known about the outcomes of TAVR in this subset of complex patients.

Methods and results In this meta-analysis, Medline, Cochrane Library and Scopus databases were searched (anytime up to April 2019) for studies evaluating the outcomes of TAVR in patients with or without AC. We assessed pooled estimates (with their 95% CIs) of the risk ratio (RR) for the all-cause mortality at the 30-day and 1-year follow-ups, a 4-point safety outcome (any bleeding, stroke, need for a pacemaker and acute kidney injury) and a 2-point efficacy outcome (device success and residual mean gradient (mean difference)). Three studies (5162 patients) were included. Of those patients, a total of 368 (7.1%) had AC. Apart from a significantly higher need for a postprocedural pacemaker (RR 1.29, 95% CI 1.06 to 1.58, p=0.01), TAVR in patients with AC resulted in similar outcomes for safety and efficacy at the 30-day follow-up compared with those without AC. Patients with AC experienced similar rates of the all-cause mortality at the 30-day follow-up compared with those without (RR 0.92, 95% CI 0.53 to 1.59, p=0.76); however, the all-cause mortality was significantly higher in patients with AC at the 1-year follow-up (RR 1.71, 95% CI 1.26 to 2.33, p=0.0006). This mortality difference was independent of cancer stage (advanced or limited) at the 30-day follow-up but not at the 1-year follow-up; only patients with limited cancer stages showed similar all-cause mortality rates compared with those without cancer at the 1-year follow-up (RR 1.22, 95% CI 0.79 to 1.91, p=0.37).

Conclusion TAVR in patients with AC is associated with similar 30-day and potentially worse 1-year outcomes compared with those in patients without AC. The 1-year all-cause mortality appears to be dependent on the cancer stage. Involving a specialised oncologist who usually considers cancer stage in the decision-making process and applying additional preoperative scores such as frailty indices might refine the risk assessment process among these patients.

PROSPERO registration number CRD42019120416.

Key questions

What is already known about this subject?

- The coexistence of severe aortic stenosis (AS) and active cancer (AC) is uncommon yet a clinically relevant entity. Patients with AS and AC are considered as high-risk patients and are usually not allowed to undergo surgical valve replacement. Transcatheter aortic valve replacement (TAVR) may be an attractive option for them. However, patients with cancer were largely excluded from pivotal TAVR trials, and very little is known about the outcomes of TAVR among these patients.

What does this study add?

- In a meta-analysis that pooled data from three studies (5162 patients), of which 368 patients (7.1%) had AC, TAVR was associated with similar all-cause mortality, safety and postprocedural efficacy outcomes at the 30-day follow-up in patients with AC compared with those without. One-year all-cause mortality was similar between those with 'limited' cancer stages and those without AC. However, patients with 'advanced' cancer stages showed a significantly higher all-cause mortality at the 1-year follow-up.

How might this impact on clinical practice?

- This meta-analysis reaffirms the findings from individual studies with a higher degree of evidence and statistical power, giving clinicians a chance to make better informed decisions. Considering that AC is not represented in the currently used preoperative risk scores, involving a specialised oncologist who usually considers cancer stage in the decision-making process and applying additional preoperative scores such as frailty indices might refine the risk assessment process for making individualised decisions for this complex subset of patients.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is becoming an acceptable alternative to surgical valve replacement in patients with severe valvular aortic stenosis (AS), regardless of their surgical risks.[1–3] However,

the outcomes of TAVR among specific patients' categories are still questionable, and one of these categories is patients with active cancer (AC). The coexistence of severe AS and AC is uncommon yet a clinically relevant entity that could be viewed as a misfortune.[4] Despite data favouring valve replacement among these patients for a better long-term overall survival,[5] they are usually not allowed to undergo surgery in regard to 'real' clinical life due to concerns related to a higher risk of postoperative complications such as infections and bleeding and the inevitable perioperative withholding of cancer therapeutics.[6–8] On the other hand, according to current guidelines for preoperative evaluation before non-cardiac surgery,[9] the presence of uncorrected severe AS interferes with some necessary high-risk oncological surgeries. Even if they were treated with chemotherapy alone, a 2016 European Society of Cardiology position paper on cancer treatments and cardiovascular toxicity recommends that patients with cancer need to be on afterload-reducing agents (using ACE inhibitors or angiotensin II receptor blockers) to mitigate the untoward effects of anthracyclines and other chemotherapeutics on left ventricular function.[10] In the case of coexistent AS, afterload reduction is only possible through valve intervention. Adding to the above-mentioned barriers to surgical valve replacement among those patients, balloon valvotomy (as a surgical alternative) has clearly failed in many clinical studies.[11] If we imagine that in an era of dizzying advances in oncology therapeutics and improved life expectancy of some patients with cancer,[12] the problem becomes worse for those with concomitant severe AS as they might succumb to their valvular disease (if left uncorrected) rather than cancer itself.

This clearly sets the stage for TAVR as a very promising outlet for this group of patients, since TAVR is less invasive and associated with less risk of infections and bleeding, allowing the patient with cancer to benefit from more optimal and aggressive cancer therapeutic modalities (including oncological surgeries) early after the procedure. However, patients with cancer were largely excluded from the pivotal TAVR trials due to concerns about the relatively short and unpredictable life expectancy among them.[13–15] The net result is that this subset of patients is left with very ambiguous treatment decisions and that oncologists, interventionalists and cardio-oncologists are forced to depend on weak assumptions of survival and quality of life (QoL) to individualise management options.

Considering that data on TAVR outcomes in patients with or without AC are very few and heterogeneous (with some investigators reporting similar all-cause mortality rates[16] at the 1-year follow-up while others did not),[17 18] we conducted this systematic review and meta-analysis to provide information for improving the clinical decisions.

METHODS

This meta-analysis was conducted according to available statements for design, analysis and reporting of meta-analyses of studies.[19] The protocol was registered in PROSPERO. No ethics committee approval was required because this is a meta-analysis of already published papers that does not involve contact with any patients and the identities of them remained anonymous.

Search strategy and selection criteria

We searched Medline, Cochrane Library and Scopus databases for studies (published anytime up to April 2019) comparing outcomes in patients with or without AC undergoing TAVR. We used search terms that provide the highest attainable sensitivity in detecting studies exploring this issue. We used the following terms: 'Transcatheter Aortic Valve Replacement' AND 'Cancer', 'Transcatheter Aortic Valve Replacement' AND 'Malignancy', 'Transcatheter Aortic Valve Replacement' AND 'Oncology', 'Transcatheter Aortic Valve Implantation' AND 'Cancer', 'Transcatheter Aortic Valve Implantation' AND 'Malignancy' and 'Transcatheter Aortic Valve Implantation' AND 'Oncology'. Medical Subject Headings terms were used whenever possible.

Eligibility criteria (PICOS) and exclusions

Population: Patients with severe AS[1] undergoing TAVR after multidisciplinary heart team discussion.

Exposure: AC.

Control: Patients with severe AS undergoing TAVR but without having AC.

Main outcome: All-cause mortality (at 30-day and 1-year follow-ups).

Additional outcomes: The 4-point safety outcome (any bleeding, any stroke, need for a pacemaker and acute kidney injury (AKI)) and 2-point efficacy outcome (device success and residual mean gradient), according to the Valve Academic Research Consortium-2 definitions, measured at the 30-day follow-up.[20]

Studies' design: Randomised and non-randomised (prospective and retrospective observational) studies.

We excluded studies not written in English.

Screening and data extraction

EndNote was used for the removal of duplications; after that, two independent reviewers performed the screenings to include records that meet inclusion criteria (excluding irrelevant records by titles and abstracts). The full-text screening was done after that to include only relevant records that met the inclusion criteria. Divergences were resolved by consensus. Search results are summarised using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. Two independent reviewers did the data extraction according to the predefined form list; then, a third reviewer was included to resolve any discrepancies if a consensus could not be reached. Plot Digitizer software (V.2.6.8) was used

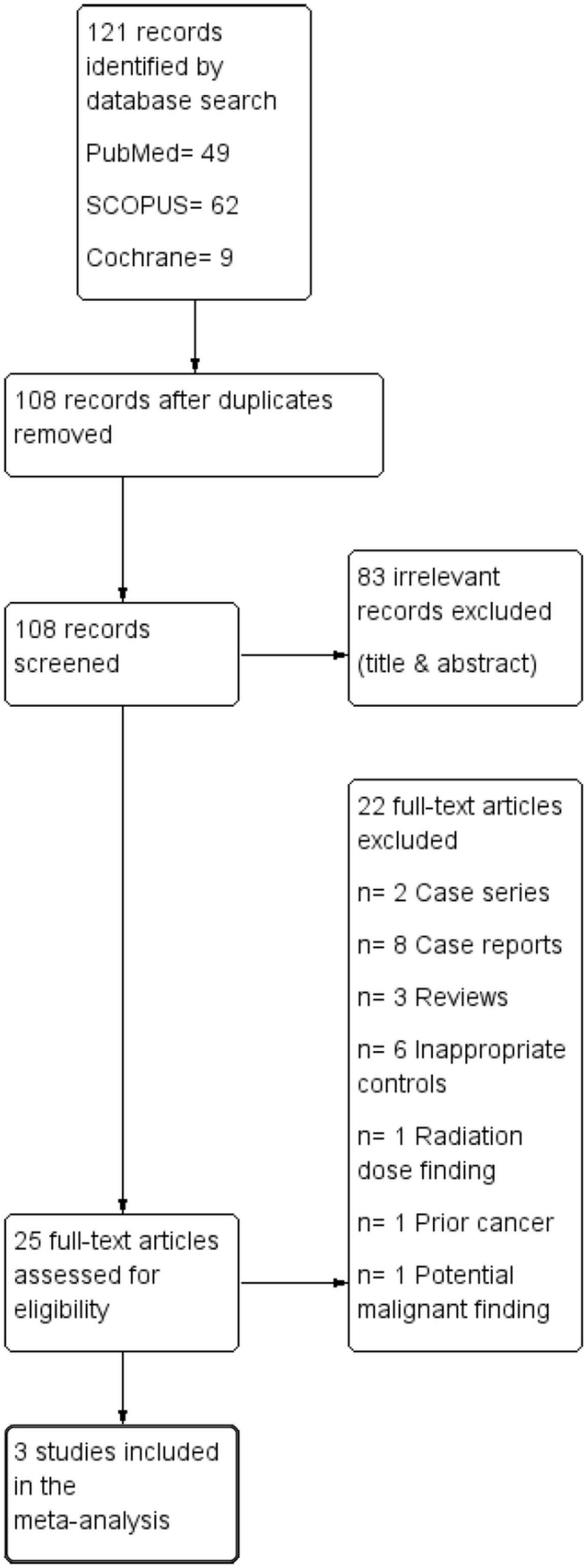

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study selection.

to extract necessary data whenever they were only available through figures.

Risk of bias assessment

The risk of bias in the included studies was evaluated independently by two reviewers using the 'Newcastle-Ottawa Scale' assessment tool,[21] which assesses the selection, comparability and outcome assessment biases. The reviewers assigned a score for each category.

Statistical analysis

Statistical analyses and graphs were performed using Review Manager (RevMan V.5.3 (computer program), Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For changes in the residual mean gradient outcome, an analysis was done using the inverse variance method to calculate mean differences (MD) with their 95% CIs. For all other outcomes, the Mantel-Haenszel method was used to determine risk ratios (RR) with their 95% CIs. Data for the residual mean gradient (reported in one study using the median and range) have been transformed to the mean and SD in order to facilitate data pooling in a consistent format.[22 23] Whenever possible, a fixed effect model was used except when there was a significant heterogeneity; in those cases, a random effects model was employed as it considers the variability between studies.[24] Assessment of heterogeneity was done first by a rough visual inspection of forest plots; evidence of heterogeneity was considered to exist if the $\chi 2$ p value (using the Cochran's Q test) was <0.1. Heterogeneity extent across trials was measured using the I^2 measurement, with values interpreted as follows: 0% means no observed heterogeneity; 25%, 50% and 75% indicate low, moderate and high heterogeneity, respectively.[25] In case of considerable heterogeneity, we performed a sensitivity analysis by excluding the study thought to be the cause of such heterogeneity.

RESULTS

Search results

Our search retrieved 121 unique articles. After screening the abstract from these articles, only 25 studies were eligible for full-text screening. In total, three studies[16–18] (all observational) with a total of 5162 patients (368 patients (7.1%) with AC) were included in the final analysis (figure 1). The summary of the included studies and their main results are shown in table 1, the baseline characteristics of their populations are shown in table 2 and the cancer type distribution is shown in table 3.

Risk of bias in the included studies

The included studies were collectively at moderate risk of bias according to the 'Newcastle-Ottawa Scale' assessment tool. Importantly, the studies of Watanabe *et al*[16] and Mangner *et al*[17] did not give explicit statements regarding the adequacy of follow-up in their cohorts or did not adjust for specific confounders. The summary of

Table 1 Summary of the included studies

Study ID	Design	Population	Valve of TAVR (self vs balloon expandable)	Follow-up	Main findings
Watanabe *et al*[16]	Japanese, multicentre registry (OCEAN-TAVI)	From October 2013 to August 2015, 749 patients with severe AS (47 with active cancer) underwent TAVR in 8 centres.	Balloon expandable	1 year	Similar postprocedural outcomes at the 30-day follow-up. No significant differences in the all-cause mortality at the 30-day and 1-year follow-ups.
Mangner *et al*[17]	Single-centre, prospective cohort study	From February 2006 to September 2014, 1821 patients with severe AS (99 with active cancer) underwent TAVR after a multidisciplinary heart team discussion.	Any	1 year	Similar postprocedural and all-cause mortality outcomes at the 30-day follow-up, but the all-cause mortality was significantly higher in patients with active cancer at the 1-year follow-up.
Landes *et al*[18]	Worldwide registry (TOP-AS)	From 2016 to January 2019, 2744 patients (222 with active cancer) underwent TAVR in 18 centres.	Any	Still ongoing	Similar postprocedural and all-cause mortality outcomes at the 30-day follow-up, but the all-cause mortality was significantly higher in patients with active cancer at the 1-year follow-up.

AS, aortic stenosis; OCEAN-TAVI, Optimized Transcatheter Valvular Intervention; TAVR, transcatheter aortic valve replacement; TOP-AS, TAVR in Oncology Patients with Severe Aortic Stenosis.

the quality assessment domains from the included studies is shown in table 4.

All-cause mortality

This outcome was reported in the three included studies. There were no statistically significant differences in the all-cause mortality at the 30-day follow-up when comparing patients with AC to those patients without AC (RR 0.92, 95% CI 0.53 to 1.59, p=0.76 (figure 2A)); the pooled studies were homogeneous (p=0.70; I^2=0%). However, patients with AC showed a significantly higher all-cause mortality at the 1-year follow-up than those without AC (RR 1.71, 95% CI 1.26 to 2.33, p=0.0006 (figure 2B)); the pooled studies were homogeneous (p=0.94; I^2=0%). After subgrouping the entire population with AC into those with limited and advanced cancer stages (with the advanced stage defined[4] as cancers with a stage greater than T2, and/or N1, and/or M1 as well as any malignancy considered refractory, relapsing or recurrent), the following findings were observed:

- Compared with patients without cancer, those with limited cancer stages showed similar rates of all-cause mortality both at the 30-day (figure 3A) and 1-year (figure 3B) follow-ups.
- Compared with patients without cancer, those with advanced cancer stages had similar rates of all-cause mortality at the 30-day follow-up (figure 3C) but suffered a significantly higher rate of all-cause mortality at the 1-year follow-up (figure 3D).
- Patients with advanced cancer experienced similar all-cause mortality rates at the 30-day follow-up compared with those with limited cancer (RR 2.30, 95% CI 0.75 to 7.03, p=0.14), with no heterogeneity between studies (p=0.71; I^2=0%). The all-cause mortality rate at the 1-year follow-up was significantly higher in patients with advanced cancer than in those with limited cancer (RR 2.33, 95% CI 1.31 to 4.12, p=0.004), with no heterogeneity across the studies (p=0.93; I^2=0%).

Safety outcome

Bleeding (any)

This outcome was reported in the three included studies. There were no statistically significant differences in patient bleeding at the 30-day follow-up between patients with AC and those without AC (RR 1.31, 95% CI 0.75 to 2.30, p=0.34 (figure 4A)); the pooled studies were heterogeneous (p=0.0003; I^2=88%). Sensitivity analysis after exclusion of the Landes *et al*'s[18] study rendered heterogeneity non-significant (p=0.07; I^2=68%) and did not affect the overall pooled estimate nor the statistical significance of the results (RR 1.0, 95% CI 0.63 to 1.58, p=0.99).

Stroke (any)

This outcome was reported in the three included studies. Patients with AC suffered similar rates of strokes at the 30-day follow-up compared with those patients without

Table 2 Baseline characteristics of participants in the included studies

Study ID		Watanabe et al[16]	Mangner et al[17]	Landes et al[18]
Demographics				
Age (years) Mean (SD) or median (range)	With cancer	83 (80–87)*	81 (77–84)	78.8±7.5*
	Without cancer	85 (82–88)	81 (77–84)	81.3±7.1
Male sex n (%)	With cancer	21 (45)	59 (59.6)*	138 (62)*
	Without cancer	232 (33)	628 (42.7)	1135 (45)
BMI (kg/m^2) Mean (SD) or median (range)	With cancer	23.6 (21.0–26.2)*	26.6 (23.9–29.5)	26.6±4.8*
	Without cancer	21.7 (19.2–24.1)	27.4 (24.4–31.2)	28±5.0
Diabetes mellitus n (%)	With cancer	14 (30)	38 (38.4)	62 (28)
	Without cancer	175 (25)	640 (43.6)	908 (36)
Hypertension n (%)	With cancer	35 (75)	92 (93.9)	169 (76)*
	Without cancer	531 (75.6)	1365 (93.6)	2320 (92)
Comorbidities				
Previous MI n (%)	With cancer	5 (11)	17 (17.3)	29 (13)
	Without cancer	59 (8)	175 (12.0)	226 (9)
PAD n (%)	With cancer	11 (23)	8 (8.2)	35 (16)
	Without cancer	108 (15)	171 (11.7)	252 (14)
Cerebrovascular disease n (%)	With cancer	5 (11)	11 (11.2)	24 (11)
	Without cancer	101 (14)	143 (9.8)	452 (18)
COPD n (%)	With cancer	15 (32)*	13 (13.1)	37 (17)
	Without cancer	138 (20)	248 (16.9)	428 (17)
Preprocedural parameters				
STS score (%) Mean (SD) or median (range)	With cancer	5.4 (3.4–7.5)*	6.0 (3.8–10.9)	4.9±3.4*
	Without cancer	7.0 (4.6–9.4)	6.7 (4.1–10.6)	6.2±4.4
Aortic valve area (cm^2) Mean (SD) or median (range)	With cancer	0.65 (0.56–0.74)	0.7 (0.5–0.8)	0.72±0.22*
	Without cancer	0.62 (0.50–0.74)	0.7 (0.5–0.8)	0.65±0.20
Mean pressure gradient (mm Hg) Mean (SD) or median (range)	With cancer	50.4 (38.8–62.1)	44 (35–58)	49±20
	Without cancer	48.0 (36.2–59.9)	42 (33–52)	48±16
LVEF (%) Mean (SD) or median (range)	With cancer	65.9 (54.0–66.4)	57 (45–64)	56±14
	Without cancer	65.0 (59.9–70.5)	58 (45–65)	56±8

*P<0.05 for patients with cancer compared with patients without cancer in each study.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; STS, Society of Thoracic Surgeons.

Table 3 Cancer types in patients with active cancer (n=368)

Gastrointestinal	83 (22.6%)
Prostate	68 (18.4%)
Haematological	63 (17.1%)
Female breast	53 (14.4%)
Lung	41 (11.1%)
Urinary tract	28 (7.6%)
Thyroid	8 (2.2%)
Others	24 (6.5%)

AC (RR 0.77, 95% CI 0.36 to 1.63, p=0.50 (figure 4B)); the pooled studies were homogeneous (p=0.70; I^2=0%).

Need for a pacemaker

This outcome was reported in the three included studies. Patients with cancer required a postprocedural pacemaker significantly more than those without cancer (RR 1.29, 95% CI 1.06 to 1.58, p=0.01 (figure 4C)), with minimal heterogeneity between studies (p=0.33; I^2=10%).

Acute kidney injury

This outcome was reported in the three included studies. There were no statistically significant differences in the incidence of AKI at the 30-day follow-up when comparing

Table 4 Risk of bias assessment

Study ID	Selection	Comparability	Outcome	NOS score
Watanabe *et al*[16]	****	–	**	6
Mangner *et al*[17]	***	–	**	5
Landes *et al*[18]	****	*	***	8

Asterisks denote the quality of each domain (from lowest to highest) as follows: Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.
NOS, Newcastle-Ottawa Scale.

those with AC to patients without AC (RR 0.98, 95% CI 0.69 to 1.39, p=0.90 (figure 4D)), with a low level of heterogeneity between studies (p=0.21; I^2=37%).

Efficacy outcome

Device success

This outcome was reported in the three included studies. Both groups enjoyed similar rates of device success (RR 1.02, 95% CI 0.99 to 1.05, p=0.16 (figure 5A)), with a low level of heterogeneity between studies (p=0.22; I^2=34%).

Residual mean gradient

This outcome was reported in the three included studies. There were no statistically significant differences between those with AC and those without AC regarding postprocedural residual transvalvular mean gradient (MD 0.54 mm Hg, 95% CI −0.99 to 2.08, p=0.49; figure 5B), but there was a marked heterogeneity between the studies (p<0.0001; I^2=91%). Sensitivity analysis after the exclusion of the Landes *et al*'s[18] study markedly lessened the heterogeneity, rendering it non-significant (p=0.28; I^2=16%), and did not affect the overall pooled estimate nor the statistical significance of the results (MD −0.7 mm Hg, 95% CI −0.47 to 0.34, p=0.75).

DISCUSSION

Through the current meta-analysis, we aimed to add a piece of knowledge to help clinicians make better decisions for this subset of complex patients who have severe AS and concomitant AC. Our main findings were as follows: first, apart from a significantly higher need for a postprocedural pacemaker in patients with cancer, TAVR was associated with similar all-cause mortality, safety and efficacy outcomes at the 30-day follow-up in patients with and without AC. Second, at the 1-year follow-up, the all-cause mortality rate was significantly higher in patients with cancer than in patients without cancer. Third, the pooled estimate for all-cause mortality was independent of cancer stage (whether advanced or limited) at the 30-day follow-up but not at the 1-year follow-up; in addition, at the 1-year follow-up, only patients with limited

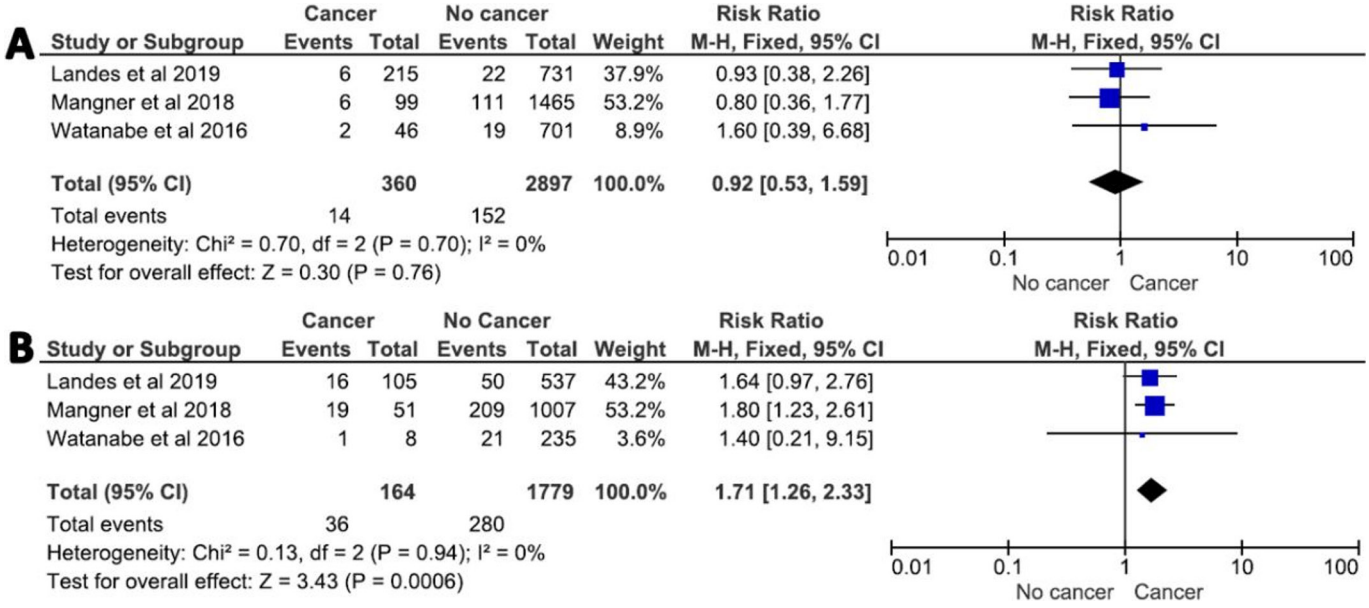

Figure 2 All-cause mortality (patients with and without cancer). Forest plots with individual and summary estimates of the RRs with 95% CIs for the all-cause mortality at the 30-day (A) and 1-year (B) follow-ups (data of Landes *et al*[18] are from propensity-matched cohorts). A fixed effect model was applied to estimate the RR with its 95% CI. Square and diamond sizes are proportional to the study weight. Interstudy heterogeneity, which was separately reported for each outcome, was tested using Cochran's Q test and expressed using I^2 values (see text for details). RR, risk ratio.

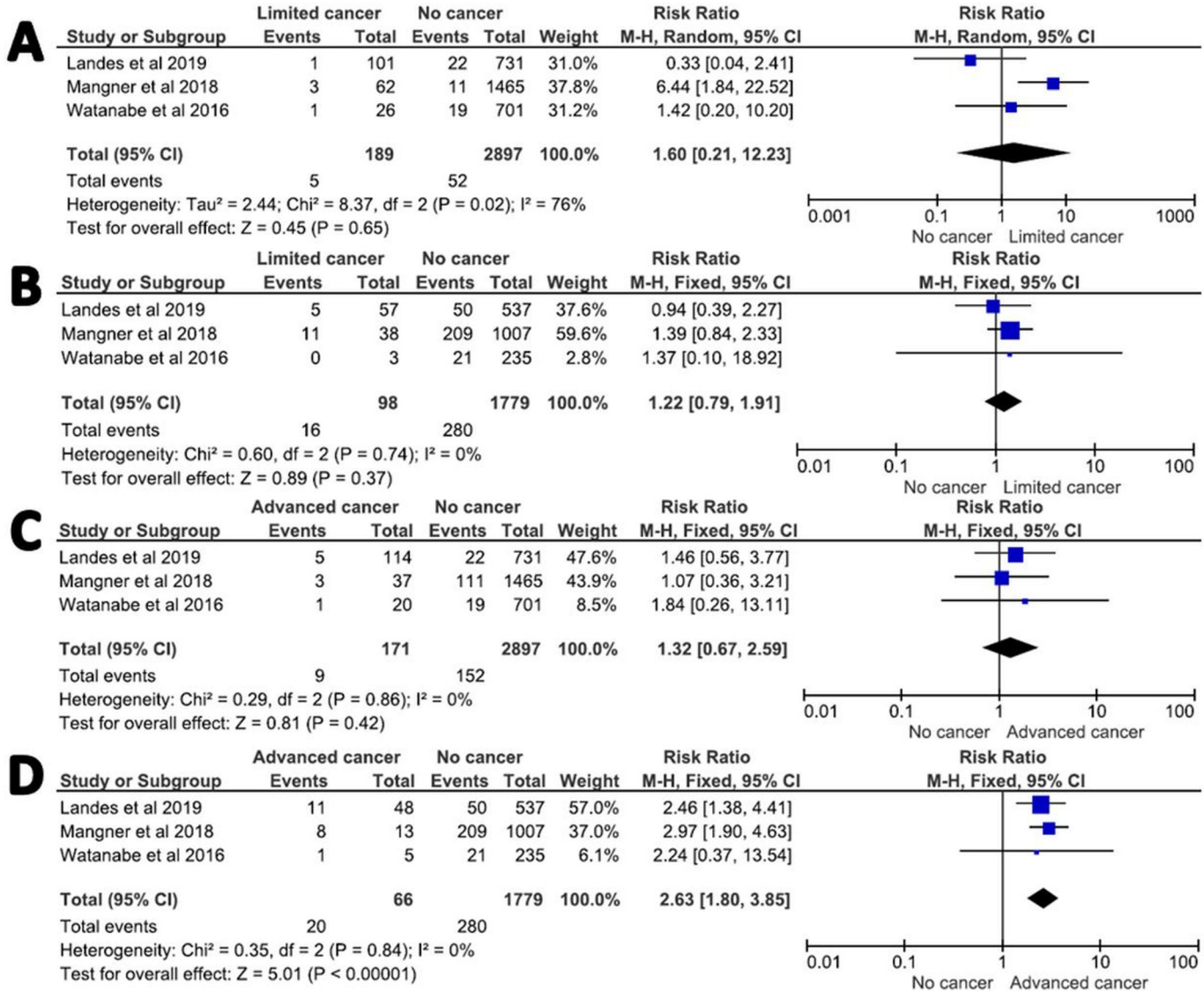

Figure 3 All-cause mortality (limited and advanced cancers). Forest plots with individual and summary estimates of the RRs with 95% CIs for the all-cause mortality of patients with limited cancer compared with patients without cancer at the 30-day (A) and 1-year (B) follow-ups, together with the all-cause mortality of patients with advanced cancer compared with patients without cancer at the 30-day (C) and 1-year (D) follow-ups (data of Landes *et al*[18] are from propensity-matched cohorts). A fixed effect model was applied (random effects model was used for panel A due to significant heterogeneity) to estimate the RR with its 95% CI. Square and diamond sizes are proportional to the study weight. Interstudy heterogeneity, which was separately reported for each outcome, was tested using Cochran's Q test and expressed using I² values (see text for details). RR, risk ratio.

cancer stages experienced similar rates of all-cause mortality compared with those without cancer.

Current guidelines do not recommend TAVR in patients whose life expectancy is less than 1 year.[1] Here, our finding of a higher all-cause mortality at the 1-year follow-up in patients with cancer undergoing TAVR is noteworthy but needs to be interpreted with caution, considering the observational nature of the included studies (with the inherent bias introduced by confounders) and the heterogeneity of the examined population (many cancer types with variable therapies, prognoses, and so on). Moreover, predicting the life expectancy in patients with cancer is usually difficult,[26] and cancer itself is not reflected in the conventional preoperative risk scores as the Society of Thoracic Surgeons score. This becomes true if we know that at the 1-year follow-up, mortalities in patients with cancer were mainly non-cardiovascular (cancer related in 50% of patients in the study of Watanabe *et al*,[16] 66% in Mangner *et al*[17] and 50% in Landes *et al*[18]). Unfortunately, estimates for cardiovascular and non-cardiovascular mortalities were not reported within the included studies in a uniform manner that allows the inclusion of these data into a meta-analysis. In the above context, we interestingly showed that only patients with limited (but not advanced) cancer stages had rates of all-cause mortality at the 1-year follow-up similar to those without cancer (figure 3B). Therefore, we suggest to involve a specialised oncologist who usually considers

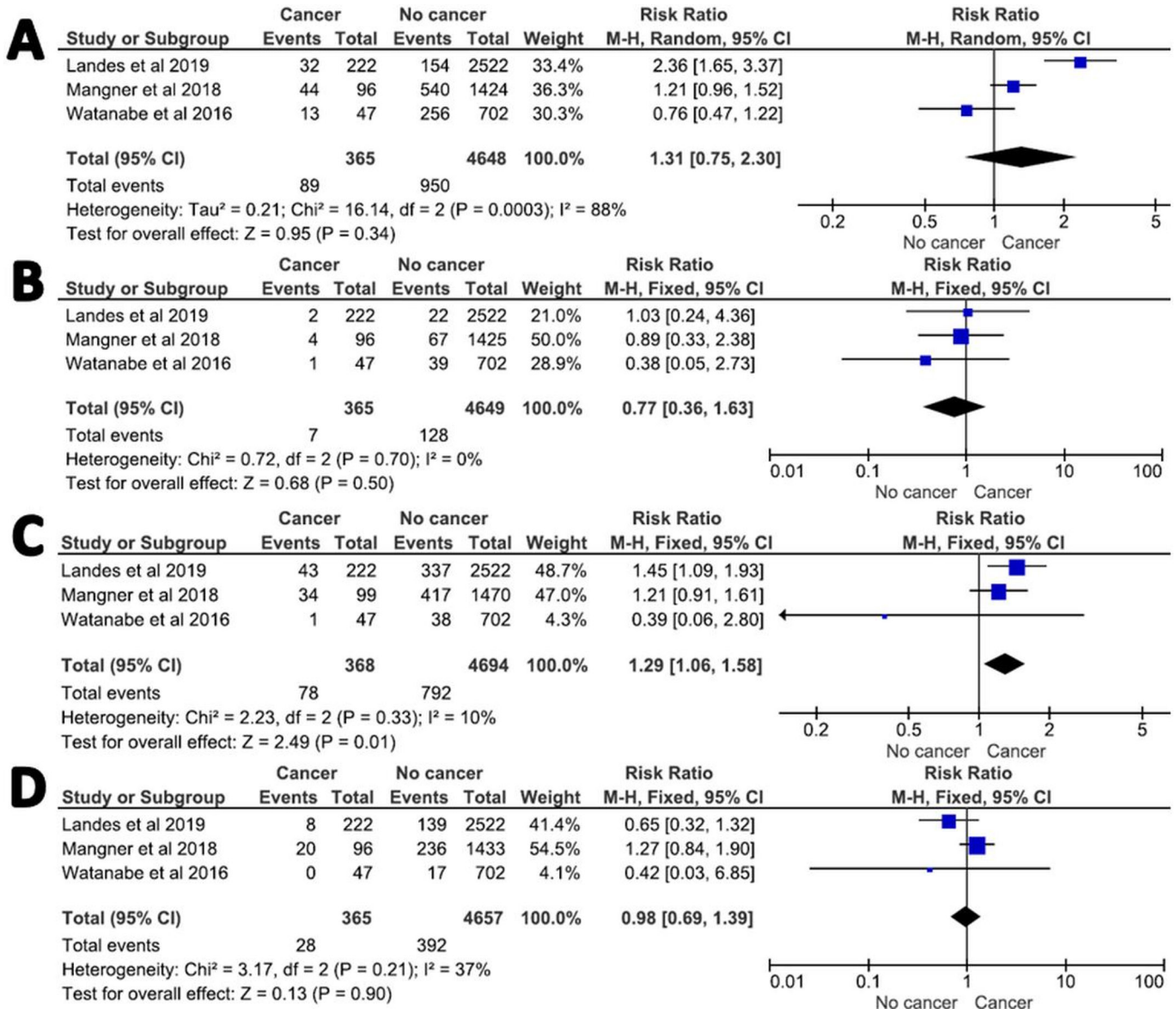

Figure 4 Safety outcome (patients with and without cancer). Forest plots with individual and summary estimates of the RRs with 95% CIs for bleeding (any) (A), stroke (any) (B), need for a pacemaker (C) and acute kidney injury (D). A fixed effect model was applied (random effects model was used for panel A due to significant heterogeneity) to estimate the RR with its 95% CI. Square and diamond sizes are proportional to the study weight. Interstudy heterogeneity, which was separately reported for each outcome, was tested using Cochran's Q test and expressed using I^2 values (see text for details). RR, risk ratio.

cancer stage in the decision-making process and to apply additional preoperative scores, for example, frailty assessment by using the 'Katz index',[27] as these might refine the risk assessment process among these patients.

The significantly higher need for a postprocedural pacemaker in patients with cancer in the current study might be explained by the well-known arrhythmogenic impact of various antineoplastic therapies (eg, methotrexate, 5-fluorouracil and cisplatin),[28] putting patients with cancer at a higher risk for such a complication (by making their cardiac conductive tissue more vulnerable to any mechanical injury imposed by the TAVR procedure).

The marked heterogeneity between studies observed for the bleeding outcome in the present meta-analysis could be resolved to some extent if we excluded the study by Landes *et al*[18] from the final analysis; however, this did not affect the overall pooled estimate nor the statistical significance of the result. The authors in the Landes *et al*'s[18] paper hypothesised that the significantly higher rates of bleeding among patients with cancer in their study could be an accidental finding, given that the number of bleeding events was small (32 out of 222) and that this difference was no longer present after propensity score matching, especially since the rates of vascular complications were similar between groups in their study.

Significant between-studies heterogeneity regarding residual mean gradient outcome could be resolved if we excluded the study by Landes *et al*[18] from the final analysis. Again, this did not affect the overall pooled estimate nor the statistical significance of the result. Explanation

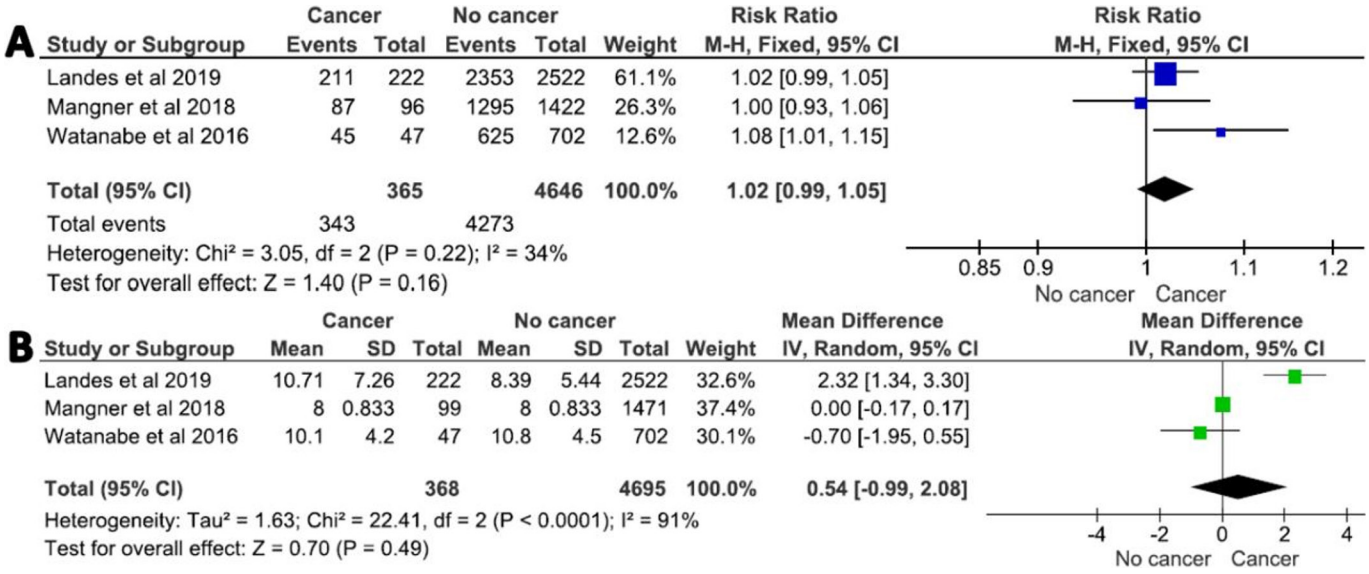

Figure 5 Efficacy outcome (patients with and without cancer). Forest plots with individual and summary estimates of the RRs with 95% CIs for the device success (A) and MD with 95% CIs for the residual mean gradient (B). A fixed effect model was applied to estimate the RR with its 95% CI (random effects model was used for panel B due to significant heterogeneity). Square and diamond sizes are proportional to the study weight. Interstudy heterogeneity, which was separately reported for each outcome, was tested using Cochran's Q test and expressed using I² values (see text for details). MD, mean difference; RR, risk ratio.

for the significant differences in residual mean gradient (favouring patients without cancer) in the Landes *et al*'s[18] paper remains elusive. We suggest that the global multicentric nature of the Landes *et al*'s work (with many different operators having different practising patterns) could have led to this finding. Moreover, the authors in the study by Landes *et al*[18] stated that differences in postprocedural echocardiographic parameters, although being 'statistically significant', were too small in magnitude to be 'clinically significant'.

Notably, we did not include symptoms and QoL outcomes in this meta-analysis for three main reasons. First (and most importantly), symptoms of AS in patients with cancer may be multifactorial and not merely caused by the stenotic valve due to considerable overlap with paraneoplastic symptoms. Second, all included studies did not use formally validated questionnaires for the QoL assessment, leaving only subjective symptoms for analysis. Third, these data were not reported within the included studies in a uniform and consistent manner that allows for them to be included into a meta-analysis.

The present study has some strength points. To the best of our knowledge, this is the first systematic review and meta-analysis in the literature addressing this clinical question. It reaffirms the findings of individual studies with a higher degree of evidence and statistical power, giving clinicians a chance to make better informed decisions. Moreover, our pooled estimates (with the little heterogeneity observed across studies) came from different ethnic groups (Japan in Watanabe *et al*,[16] Germany in Mangner *et al*[17] and a worldwide set of patients 'including Americans' in Landes *et al*[18]). This fact, in and of itself, makes sense and implies that any findings from this meta-analysis might be extrapolatable to a broad spectrum of patients.

Few limitations to this study exist. First, all studies included in the present meta-analysis are observational and, hence, are not without confounders and risk of bias. Therefore, despite being the best attainable estimate to date, any conclusions drawn are hypothesis generating and should be cautiously interpreted. Of course, randomised trials comparing TAVR to optimal medical treatment in patients with cancer and severe AS are essential to definitively solve this clinical conundrum; however, these types of studies are lacking, as shown by our systematic review, and it remains doubtful whether such trials will exist in light of some potentially prohibitive ethical issues.[29] Second, our study population represents a widely heterogeneous small number of patients with cancer (different types, therapies, prognoses, and so on). Accordingly, it was very difficult to stratify them according to each cancer type. This would require access to a large patient-level database, which is not currently available. Nonetheless, we tried to provide some estimates about the prognosis by stratifying patients with cancer into those with limited and advanced cancer stages. Third, although including studies using different TAVR devices (balloon expandable and self-expandable) might be suggested as a limitation, randomised trial data showed that both devices are equal in terms of the cardiovascular mortality and combined safety endpoint at the 30-day follow-up.[30] Finally, we understand that data on long-term valve dysfunction during follow-up are important, but unfortunately, they were not presented in the included studies.

CONCLUSION

In patients with AS and concomitant AC, apart from a significantly higher need for a postprocedural pacemaker, TAVR is associated with similar all-cause mortality, safety and efficacy outcomes at the 30-day follow-up. However, the all-cause mortality at the 1-year follow-up appears to be dependent on the cancer stage. Treatment decisions should remain largely individualised among this subset of complex patients, considering that AC is not represented in preoperative risk scores and that cancer stage might matter, as we showed. This study highlights the urge to better identify the subgroup of patients with cancer and AS for whom TAVR is likely to be futile.

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