

Review  
Article

# Impact of Chronic Kidney Disease on the Prognosis of Transcatheter Aortic Valve Replacement in Patients with Aortic Stenosis: A Meta-Analysis of 133624 Patients

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**Purpose:** The impact of chronic kidney disease (CKD) on the prognosis of transcatheter aortic valve replacement (TAVR) remains unclear. The purpose of this meta-analysis was to assess the impact of CKD and different stages of CKD on prognosis in patients undergoing TAVR.

**Methods:** As of June 2020, we performed a comprehensive literature search on relevant studies using PubMed, Embase, Cochrane Library, and Web of Science. Subsequently, we pooled the risk ratio (RR) of individual studies via random effects to analyze heterogeneity, quality assessment, and publication bias.

**Results:** A total of 20 studies, involving 133624 patients, were eligible for analysis. Patients with CKD had higher all-cause mortality at 30 days (RR: 1.39, 95% confidence interval [CI]: 1.31–1.47,  $P < 0.001$ ), 1 year (RR: 1.36, 95% CI: 1.24–1.49,  $P < 0.001$ ), and 2 years (RR: 1.2, 95% CI: 1.05–1.38,  $P = 0.009$ ) of follow-up. Moreover, they also had higher acute kidney injury (AKI) (RR: 1.38, 95% CI: 1.16–1.63,  $P < 0.001$ ) and bleeding (RR: 1.33, 95% CI: 1.18–1.50,  $P < 0.001$ ) at 30 days. CKD3 alone also increased all-cause mortality at follow-ups. Risk of all-cause mortality increased with severity of CKD for stages 3, 4, and 5 at follow-up.

**Conclusion:** Patients with CKD are at an increased risk of all-cause mortality, AKI, and bleeding events after TAVR. Moreover, the mortality risk rises with increasing severity of CKD.

**Keywords:** chronic kidney disease, transcatheter aortic valve replacement, meta-analysis, prognosis

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## Introduction

With a rise in the global aging population, aortic stenosis (AS) has become one of the most common valvular diseases.<sup>1)</sup> Apart from affecting patient's quality of life, severe AS can bring about death, in a relatively short period, if not treated with valve replacement.<sup>2)</sup> In the last decade, transcatheter aortic valve replacement (TAVR) has gained popularity as an alternative to surgical aortic valve replacement (SAVR) for patients, who are either inoperable or are at high risk to intermediate risk for surgery.<sup>3,4)</sup>

Chronic kidney disease (CKD) often coexists with AS, likely due to similar risk factors and pathophysiology.<sup>5)</sup> Recently, CKD was reported in approximately 75% of patients with severe AS.<sup>6)</sup> Mechanistically, it was demonstrated that CKD accelerates dystrophy calcification in the aortic valve, which contributes to severe AS 10 to 20 years earlier than in the general population.<sup>7)</sup> It is well known that CKD is detrimental to the course of valvular heart disease and prognosis of cardiovascular intervention.<sup>8,9)</sup> Moreover, the presence of CKD is also shown to increase both short- and long-term mortality in SAVR patients, with short-term mortality reaching as high as 21%.<sup>10)</sup>

The prognostic effects of CKD on TAVR, however, remain unclear. Moreover, little is known about the difference of prognosis among different CKD stages. High-quality meta-analysis is increasingly recognized as one of the key tools in the assessment of clinical effectiveness.<sup>11,12)</sup> At present, there is no meta-analysis on the outcome of preoperative CKD on long-term prognosis of TAVR. Therefore, our meta-analysis aimed to investigate the outcome of CKD, and different stages of CKD, on the short-, medium-, and long-term prognosis of TAVR patients.

## Methods

The selected publications were systematically reviewed,<sup>13)</sup> according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines, and the complete research protocol was registered in the Prospero database (CRD42020200317).<sup>14,15)</sup> In addition, the methodology quality was assessed using the Assessment of Multiple Systematic Reviews tool.<sup>16,17)</sup>

### Search strategy

We conducted an extensive and systematic computerized literature review, using the PubMed, Cochrane Library, EMBASE, and Web of Science databases, and searched from the inception of indicated databases till June 2020 using general terminology such as “TAVI,” “TAVR,” “transcatheter aortic valve implantation,” “transcatheter aortic valve replacement,” “chronic kidney disease,” “chronic kidney failure,” and “CKD.” To further ensure no relevant publications were overlooked, we also manually searched the list of references for publications that might meet our requirements.

### Study selection

Two researchers independently conducted literature searches, qualification assessment, and data extraction. In case of disagreement, it was settled through mutual discussion or negotiation with a third party. The inclusion criteria for the meta-analysis were as follows: (1) report of clinical outcome of AS and CKD patients after TAVR and (2) participants without CKD served as controls. Alternately, the exclusion criteria included the following: (1) repeated publication or overlapping of patients; (2) unclear report or unable to calculate relevant results based on published data; (3) conference, reviews, case reports, and editorials; and (4) non-English language studies.

### Study end points

The main outcome of our study was all-cause mortality after TAVR at the short-term (30 days), medium-term (1 year), and long-term (2 years) follow-ups. Secondary outcomes included stroke, bleeding, permanent pacemaker implantation (PPI), acute kidney injury (AKI), and major vascular complications at the short-term (30 days) follow-up. All outcomes after TAVR were defined according to the standard described by VARC.

### Data extraction

We used standardized data sheets to extract data of patients and studies, including study type, first author, region, year, the number of patients, CKD definition, follow-up time, age, gender, left ventricular ejection fraction, past history, logistic European system for cardiac operative risk evaluation (EuroSCORE), Society of Thoracic Surgeons (STS) score, access site, and valve type.

### Quality assessment

The risk of bias in the cohort study was assessed using the Newcastle Ottawa Scale.<sup>18)</sup> The quality score consisted of three main parts: the selection of study group, comparability of study group, and determination of the result of interest. A study with a score >7 (out of 9) was considered to have a low bias risk; moderate risk was 5–7 and high risk was <5.

### Definition of CKD

CKD was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m<sup>2</sup>, whereas CKD3 was eGFR ≥30–59 mL/min/1.72 m<sup>2</sup>, CKD4 was eGFR ≥15–29 mL/min/1.72 m<sup>2</sup>, CKD5 was eGFR <15 mL/min/1.72 m<sup>2</sup>,

and lastly, no CKD was normal kidney function to CKD2: eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup>.

### Statistical analysis

The frequency of categorical variables and the standardized means with standard deviations of continuous variables were used for descriptive analysis. The risk ratio (RR) and 95% confidence interval (CI) of the results were performed using a meta-analysis for random effects models. The evaluation of the heterogeneity of different studies used the Cochrane Q-statistic to calculate the I<sup>2</sup> values, where <25%, 25%–50%, and >50%, respectively, indicated low, medium, and high heterogeneity. Sensitivity analysis further explored significant heterogeneity. Publication bias was assessed by funnel plot asymmetric analysis and Egger's regression test. P values were bilateral, and P < 0.05 was set as statistical significance threshold. Stata15.0 (StataCorp, College Station, TX, USA) statistical analysis software was used for data analysis.

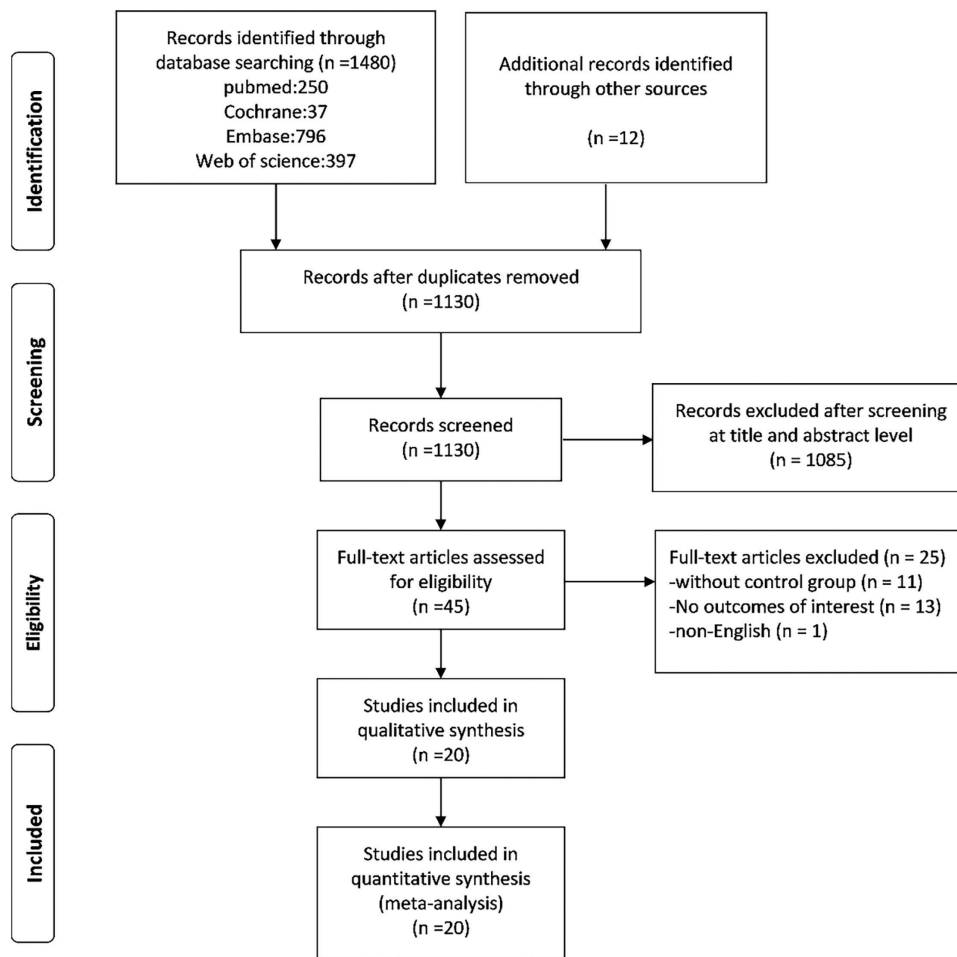
## Results

### Study selection

As illustrated in **Fig. 1**, 1480 publications were identified in the preliminary search. In addition, 12 suitable publications were obtained from the list of references. After eliminating study duplicates, 1130 retrieved articles were screened by title and abstract. In all, 45 articles were read in full to determine their inclusion in the analysis. A total of 25 more publications were eliminated due to 11 lacking a control group, 13 not producing an outcome of interest, and 1 not being written in the English language. Finally, 20 articles, with a total of 133624 patients, fulfilled the inclusion criteria and were selected for analysis.<sup>19–38)</sup>

### Study characteristics and quality assessment

A majority of the selected publications (10) were retrospective in nature and were published between the years 2012 and 2020. **Table 1** summarizes the contents



**Fig. 1** Flow chart of the publication selection process, based on the PRISMA statement. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

**Table 1 Study characteristics**

Study	Year	Country	Study design	CKD group
D'Ascenzo et al. <sup>20)</sup>	2013	Italy	Prospective, multicenter	eGFR $\geq 60$ mL/min/1.73 m <sup>2</sup> , 30–59 mL/min/1.73 m <sup>2</sup> , 15–29 mL/min/1.73 m <sup>2</sup>
Wessely et al. <sup>19)</sup>	2012	Germany	Retrospective, single center	Pre-procedural eGFR $\leq 60$ mL/min, equivalent to CKD stage $\geq 3$
Dumonteil et al. <sup>21)</sup>	2013	France	Retrospective, multicenter	Normal eGFR ( $\geq 90$ mL/min), mild (60–89 mL/min), moderate (30–59 mL/min), and severe ( $< 30$ mL/min) CKD and those on chronic hemodialysis
Yamamoto et al. <sup>24)</sup>	2013	France	Prospective, multicenter	eGFR $\geq 60$ mL/min/1.73 m <sup>2</sup> (CKD stage 1 + 2), 30–59 mL/min/1.73 m <sup>2</sup> (CKD stage 3), 15–29 mL/min/1.73 m <sup>2</sup> (CKD stage 4)
Goebel et al. <sup>22)</sup>	2013	Germany	Prospective, single center	Normal kidney function, CKD stage 3 and worse
Nguyen et al. <sup>23)</sup>	2013	USA	Retrospective, single center	Mild or normal (GFR $> 60$ ), moderate (30 $<$ GFR $\leq 60$ ), severe or dialysis (GFR $\leq 30$ or preoperative dialysis)
Allende et al. <sup>25)</sup>	2014	Canada	Retrospective, multicenter	CKD stages 1–2 (eGFR $\geq 60$ mL/min/1.73 m <sup>2</sup> ), stage 3 (30–59 mL/min/1.73 m <sup>2</sup> ), stage 4 (15–29 mL/min/1.73 m <sup>2</sup> ) and stage 5 ( $< 15$ mL/min/1.73 m <sup>2</sup> )
Rahman et al. <sup>27)</sup>	2015	UK	Retrospective, single center	CKD group (eGFR $< 60$ mL/min/1.73 m <sup>2</sup> ) and no-CKD group (eGFR $> 60$ mL/min/1.73 m <sup>2</sup> )
Ferro et al. <sup>26)</sup>	2015	UK	Prospective, multicenter	eGFR: $\geq 60$ (CKD stages 1–2), 45–59 (CKD stage 3a), 30–44 (CKD stage 3b), 15–29 (CKD stage 4), $< 15$ mL/min/1.73 m <sup>2</sup> or on dialysis (CKD stage 5)
Thourani et al. <sup>29)</sup>	2016	USA	Retrospective, multicenter	None/mild RD (GFR $> 60$ mL/min), moderate RD (GFR 30–60 mL/min), severe RD (GFR $\leq 30$ mL/min)
Codner et al. <sup>28)</sup>	2016	Europe	Prospective, multicenter	eGFR $> 60$ mL/min/1.73 m <sup>2</sup> (group I), 31–60 mL/min/1.73 m <sup>2</sup> (group II), $\leq 30$ mL/min/1.73 m <sup>2</sup> (group III), dialysis (group IV)
Lüders et al. <sup>32)</sup>	2017	Germany	Retrospective, multicenter	Structural abnormalities or genetic traits that point to kidney disease (CKD stage 1), normal or mild reduced renal function (CKD stage 2), moderate renal insufficiency (CKD stage 3), severe renal insufficiency (CKD stage 4), end-stage renal failure (CKD stage 5).
Gupta et al. <sup>30)</sup>	2017	USA	Retrospective, multicenter	Patients with CKD were identified using ICD-9-CM codes 35.05 and 35.06
Hansen et al. <sup>31)</sup>	2017	USA	Retrospective, multicenter	CKD stage 1: eGFR $> 90$ mL/min/m <sup>2</sup> , stage 2: GFR 60–89 mL/min/m <sup>2</sup> , stage 3: eGFR of 30–59 mL/min/m <sup>2</sup> , stage 4: GFR of 15–29 mL/min/m <sup>2</sup> , stage 5: eGFR $< 15$ mL/min/m <sup>2</sup>
Franzone et al. <sup>33)</sup>	2018	Switzerland.	Prospective, multicenter	None or mild renal dysfunction: eGFR $\geq 60$ mL/min/1.73 m <sup>2</sup> , moderate renal dysfunction: eGFR 30–59 mL/min/1.73 m <sup>2</sup> , severe renal dysfunction eGFR $\leq 30$ mL/min/1.73 m <sup>2</sup>
Pineda et al. <sup>34)</sup>	2019	USA	Prospective, multicenter	None/mild (eGFR $> 60$ mL/min/1.73 m <sup>2</sup> ), moderate/severe (eGFR $\leq 60$ mL/min/1.73 m <sup>2</sup> )
Yap et al. <sup>38)</sup>	2020	Singapore	Prospective, single center	CKD 1 (eGFR $\geq 90$ mL/min/1.73 m <sup>2</sup> ), CKD 2 (eGFR 69–89 mL/min/1.73 m <sup>2</sup> ), CKD 3 (eGFR $\geq 30$ –59 mL/min/1.73 m <sup>2</sup> ), CKD 4 (eGFR $\geq 15$ –29 mL/min/1.73 m <sup>2</sup> ), CKD 5 or ESRF (eGFR $< 15$ mL/min/1.73 m <sup>2</sup> )
Li et al. <sup>37)</sup>	2021	USA	Retrospective, single center	eGFR $> 60$ , eGFR = 30–60, eGFR $< 30$
Bandyopadhyay et al. <sup>35)</sup>	2020	International	Prospective, multicenter	No CKD: eGFR $\geq 60$ mL/min/1.73 m <sup>2</sup> , mild CKD: eGFR 45–59 mL/min/1.73 m <sup>2</sup> , moderate/severe CKD: eGFR $< 45$ mL/min/1.73 m <sup>2</sup>
Gracia et al. <sup>36)</sup>	2020	USA	Prospective, single center	CrCl $\geq 60$ mL/min, CrCl 30–60 mL/min, CrCl $< 30$ mL/min

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; ICD-9-CM: international classification of diseases, ninth revision, clinical modification; ESRF: end stage renal failure; CrCl: creatinine clearance

of these publications, including the study design, year of publication, country of research, and CKD definition. Based on the Newcastle Ottawa observational study bias risk scale (**Table 2**), the total score of 20 observational studies was >5, indicating that the bias risk was low.

### Patient characteristics

The baseline characteristics of patients, included in this study, are summarized in **Table 2**. A total of 133624 patients with AS received TAVR. The average age was 81.8 years (75.584.5 years), and among them, 49.9% (0–57.6%) were men. In 7 studies (among 12 reports), the average logistic EuroSCORE was >20%. In all 9 reported studies, the average STS score was >5%. Of the 133624 patients, 30.9% had diabetes mellitus (ranging from 22% to 43.6%), 84.2% had hypertension (ranging from 62.9% to 96.3%), 48.9% had peripheral vascular disease (ranging from 6.8% to 45.4%), and 25.8% had chronic obstructive pulmonary disease (ranging from 10.2% to 55.9%). Generally, the most common vascular access is the transfemoral approach. In the selected publications, only balloon-expandable valves were used in one study, only self-expandable valves were used in one study, and multiple valve types were used in the remaining studies.

### All-cause mortality

At the 30-day follow-up, all-cause mortality was markedly increased in all stage CKD patients, as compared to no CKD (**Fig. 2**). The relevant statistics are as follows: CKD (RR: 1.39, 95% CI: 1.31–1.47,  $P < 0.001$ ,  $I^2 = 6.7%$ ), CKD3 (RR: 1.29, 95% CI: 1.22–1.37,  $P < 0.001$ ,  $I^2 = 0%$ ), CKD4 (RR: 2.1, 95% CI: 1.91–2.31,  $P < 0.001$ ,  $I^2 = 0%$ ), and CKD5 (RR: 2.25, 95% CI: 2.0–2.51,  $P < 0.001$ ,  $I^2 = 0%$ ) (**Fig. 3**).

At the 1-year follow-up, all-cause mortality was again markedly increased in patients with varying stages of CKD versus no CKD (**Fig. 2**). The relevant statistics are as follows: CKD (RR: 1.36, 95% CI: 1.24–1.49,  $P < 0.001$ ,  $I^2 = 43.8%$ ), CKD3 (RR: 1.24, 95% CI: 1.19–1.28,  $P < 0.001$ ,  $I^2 = 0.8%$ ), CKD4 (RR: 1.89, 95% CI: 1.62–2.19,  $P < 0.001$ ,  $I^2 = 58.6%$ ), and CKD5 (RR: 2.24, 95% CI: 1.75–2.87,  $P < 0.001$ ,  $I^2 = 58.6%$ ) (**Fig. 4**). Of note, although sensitivity analyses were conducted one by one to exclude studies, the results remained unchanged.

At the 2-year follow-up, all-cause mortality was still increased in patients with varying stages of CKD, as compared to no CKD (**Fig. 2**). The relevant statistics are as follows: CKD (RR: 1.2, 95% CI: 1.05–1.38,  $P = 0.009$ ,

$I^2 = 36%$ ), CKD3 (RR: 1.11, 95% CI: 1.01–1.21,  $P = 0.024$ ,  $I^2 = 26.4%$ ), CKD4 (RR: 1.68, 95% CI: 1.26–2.24,  $P < 0.001$ ,  $I^2 = 85.4%$ ), and CKD5 (RR: 1.9, 95% CI: 1.56–2.31,  $P < 0.001$ ,  $I^2 = 0%$ ) (**Fig. 5**). Subsequent sensitivity analyses failed to alter the results.

### Secondary outcomes

#### Bleeding

Based on our results, CKD patients of all stages are more prone to bleeding than patients without CKD (**Table 3**). The relevant statistics are as follows: CKD (RR: 1.33, 95% CI: 1.18–1.50,  $P < 0.001$ ,  $I^2 = 47.4%$ ), CKD3 (RR: 1.26, 95% CI: 1.02–1.55,  $P = 0.034$ ,  $I^2 = 55.3%$ ), CKD4 (RR: 1.56, 95% CI: 1.07–2.26,  $P = 0.021$ ,  $I^2 = 57.4%$ ), and CKD5 (RR: 1.58, 95% CI: 1.05–2.38,  $P = 0.029$ ,  $I^2 = 68.8%$ ). Upon excluding each study one by one, the sensitivity analysis results still remained the same.

#### AKI

CKD patients of all stages were at a higher risk for AKI, relative to patients without CKD (**Table 3**). The relevant statistics are as follows: CKD (RR: 1.38, 95% CI: 1.16–1.63,  $P < 0.001$ ,  $I^2 = 13.1%$ ), CKD3 (RR: 1.28, 95% CI: 1.11–1.48,  $P = 0.001$ ,  $I^2 = 0%$ ), CKD4 (RR: 2.12, 95% CI: 1.73–2.59,  $P < 0.001$ ,  $I^2 = 0%$ ), and CKD5 (RR: 1.9, 95% CI: 1.37–2.62,  $P < 0.001$ ,  $I^2 = 0%$ ).

#### Stroke

According to the pooled results of short-term stroke, CKD4 patients who received TAVR were significantly more vulnerable to stroke than non-CKD patients who received TAVR (RR: 2.41, 95% CI: 1.6–3.63,  $P < 0.001$ ,  $I^2 = 0%$ ) (**Table 3**). However, there was no discernible difference between other stages of CKD patients and non-CKD patients who received TAVR. The relevant statistics are as follows: CKD (RR: 1.21, 95% CI: 0.86–1.70,  $P = 0.268$ ,  $I^2 = 50.5%$ ), CKD3 (RR: 1.26, 95% CI: 0.95–1.67,  $P = 0.112$ ,  $I^2 = 0%$ ), and CKD5 (RR: 0.98, 95% CI: 0.56–1.71,  $P = 0.953$ ,  $I^2 = 19.3%$ ). Of note, one by one exclusion of studies did not alter the sensitivity analysis results.

#### Major vascular complications

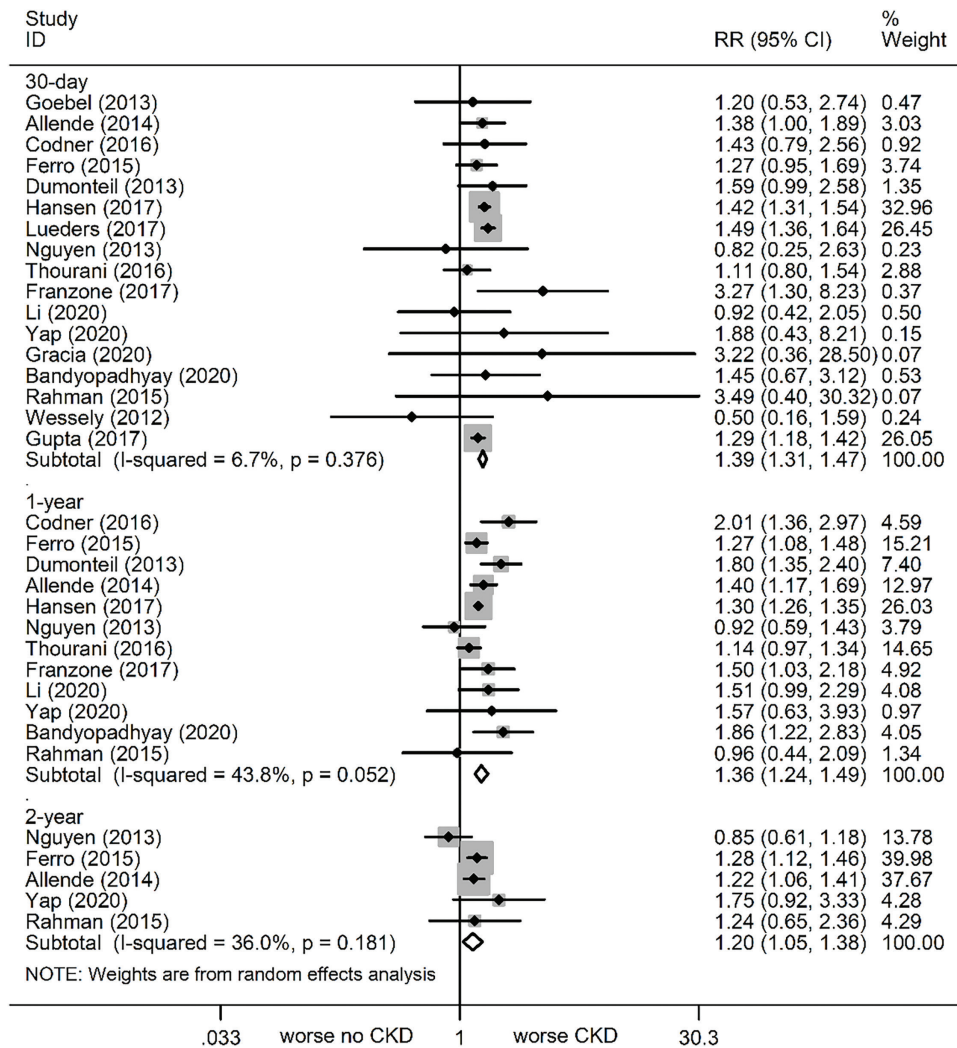
There were no discernible differences in the major vascular complications between CKD of all stages and no CKD (**Table 3**). The relevant statistics are as follows: CKD (RR: 1.05, 95% CI: 0.97–1.13,  $P = 0.203$ ,  $I^2 = 0%$ ),

Table 2 Baseline features of patients

Study	Total	Male	Age(Y)	DM	HTN	PVD	COPD	LVEF	Transfemoral	STS score	Logistic EuroSCORE	NOS
D'Ascenzo et al. <sup>20)</sup>	364	42.3	82.4	31.2	86.6	23.6	NR	52.4	84.2	6.6	23.2	7
Wessely et al. <sup>19)</sup>	183	44.8	81.1	30.0	84.2	12.2	23.9	58.7	NR	NR	23.5	8
Dumonteil et al. <sup>21)</sup>	942	53.8	81.0	28.5	69.5	25.3	34.5	NR	84.1	NR	20.9	7
Yamamoto et al. <sup>24)</sup>	642	48.1	83.6	22.6	70.6	28.5	29.1	51.0	67.1	6.8	19.9	7
Goebel et al. <sup>22)</sup>	270	44.4	81.6	27.6	96.3	41.6	22.1	NR	NR	14.0	33.5	6
Nguyen et al. <sup>23)</sup>	321	55.8	82.3	43.6	95.0	34.6	48.9	49.2	NR	NR	NR	8
Allende et al. <sup>25)</sup>	2075	49.9	80.1	30.1	78.8	20.1	29.8	54.7	73.7	6.5	29.9	8
Rahman et al. <sup>27)</sup>	118	57.6	81.3	22.0	NR	6.8	24.6	NR	77.1	NR	20.9	8
Ferro et al. <sup>26)</sup>	3696	53.5	82.3	22.4	NR	NR	27.0	NR	70.1	NR	18.9	8
Thourani et al. <sup>29)</sup>	2531	52.4	84.5	36.4	91.7	42.3	55.9	52.4	57.7	11.5	NR	9
Codner et al. <sup>28)</sup>	1204	44.5	81.6	31.7	91.8	NR	25.8	51.9	90.7	7.0	NR	7
Lüders et al. <sup>32)</sup>	28716	43.9	81.0	33.5	62.9	12.0	15.2	NR	69.7	NR	19.9	7
Gupta et al. <sup>30)</sup>	41025	52.3	81.1	34.6	79.5	29.7	33.2	NR	NR	NR	NR	7
Hansen et al. <sup>31)</sup>	44778	51.3	82.0	36.7	89.4	30.5	NR	57.0	71.9	NR	NR	7
Franzone et al. <sup>33)</sup>	927	46.9	82.6	26.0	84.0	11.3	13.3	53.9	NR	6.12	19.6	8
Pineda et al. <sup>34)</sup>	3733	54.1	83.2	37.3	92.8	45.4	54.3	53.9	80.5	8.9	22.1	7
Yap et al. <sup>38)</sup>	216	49.1	75.5	39.8	81.9	16.2	10.2	NR	77.8	6.5	16.1	7
Li et al. <sup>37)</sup>	733	49.9	82.0	30.5	85.9	36.4	NR	NR	67.8	NR	NR	8
Bandyopadhyay et al. <sup>35)</sup>	852	0	82.2	26.1	81.2	10.1	18.3	56.1	90.6	7.9	NR	7
Gracia et al. <sup>36)</sup>	298	51.7	79.9	38.9	NR	8.1	20.8	NR	99.7	NR	NR	7

Values are mean or % (n/N)

DM: diabetes mellitus; HTN: hypertension; LVEF: left ventricular ejection fraction; PVD: peripheral vascular disease; EuroSCORE: European system for cardiac operative risk evaluation; STS: society of thoracic surgeons; COPD: chronic obstructive pulmonary disease; NR: not reported; NOS: Newcastle-Ottawa scale



**Fig. 2** Forest plots comparing all-cause mortality risk between CKD and non-CKD patients. CKD: chronic kidney disease; RR: risk ratio; CI: confidence interval

CKD3 (RR: 1.11, 95% CI: 0.93–1.33, P = 0.240, I<sup>2</sup> = 0%), CKD4 (RR: 1.26, 95% CI: 0.88–1.81, P = 0.211, I<sup>2</sup> = 0%), and CKD5 (RR: 1.01, 95% CI: 0.57–1.79, P = 0.983, I<sup>2</sup> = 19.3%).

**PPI**

There were no discernible differences in the PPI risk between CKD of all stages and no CKD (Table 3). The relevant statistics are as follows: CKD (RR: 1.09, 95% CI: 0.96–1.25, P = 0.192, I<sup>2</sup> = 38.8%), CKD3 (RR: 1.08, 95% CI: 0.94–1.26, P = 0.279, I<sup>2</sup> = 0%), CKD4 (RR: 0.77, 95% CI: 0.54–1.11, P = 0.161, I<sup>2</sup> = 0%), and CKD5 (RR: 1.3, 95% CI: 0.69–2.46, P = 0.412, I<sup>2</sup> = 71.3%).

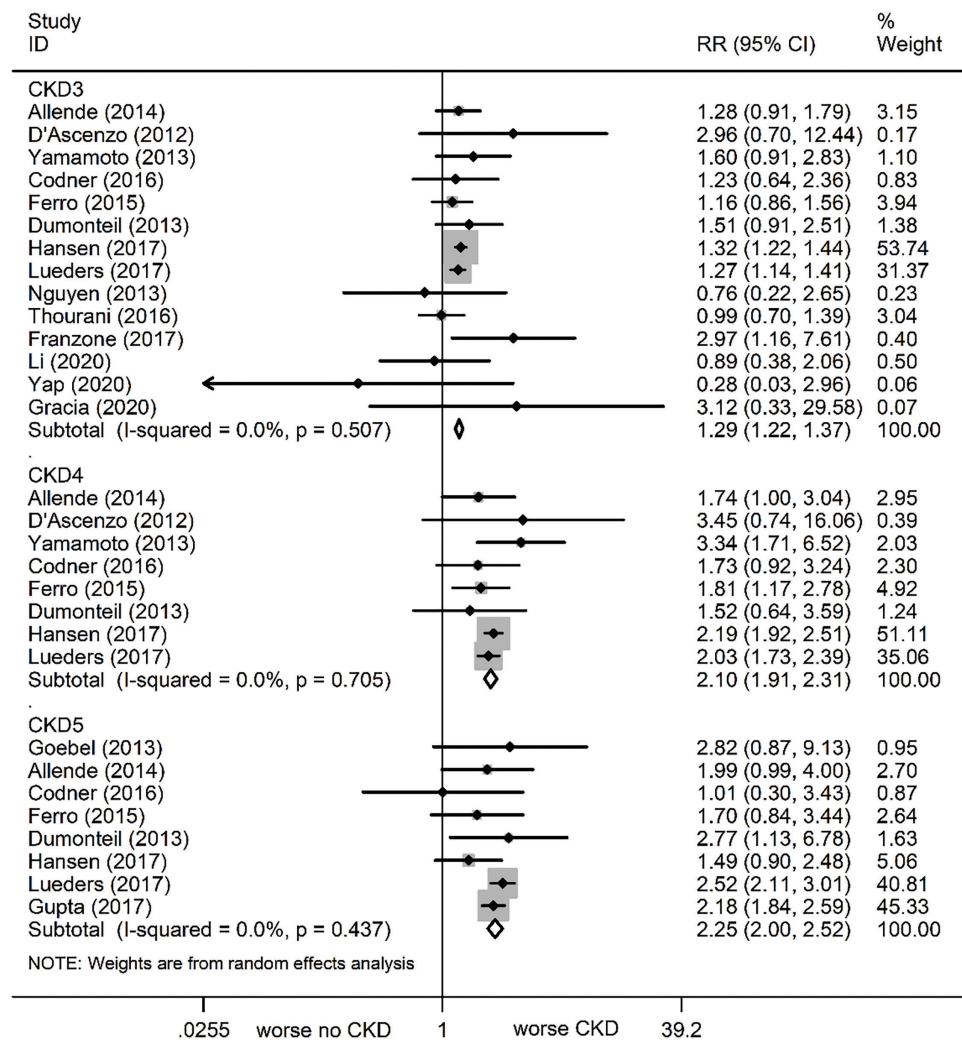
**Publication bias**

Funnel plots determined main outcome publication bias, and the results revealed good symmetry. The

P-values obtained by the Egger’s regression test were 0.76 (30 days), 0.34 (1 year), and 0.83 (2 years), indicating the lack of publication bias.

**Discussion**

The current report, involving 20 studies on 133624 patients with 58315 events of CKD, is the first pooled analysis of the effect of CKD on long-term clinical outcome after TAVR. The main outcomes of this study were as follows. (1) Preoperative CKD increased all-cause mortality in patients with TAVR, according to the short-, medium- and long-term follow-ups. (2) Preoperative CKD elevated procedural complications, including AKI and bleeding, but no differences were observed in the major vascular complications, stroke, and PPI. (3) The all-cause mortality after TAVR was higher in patients



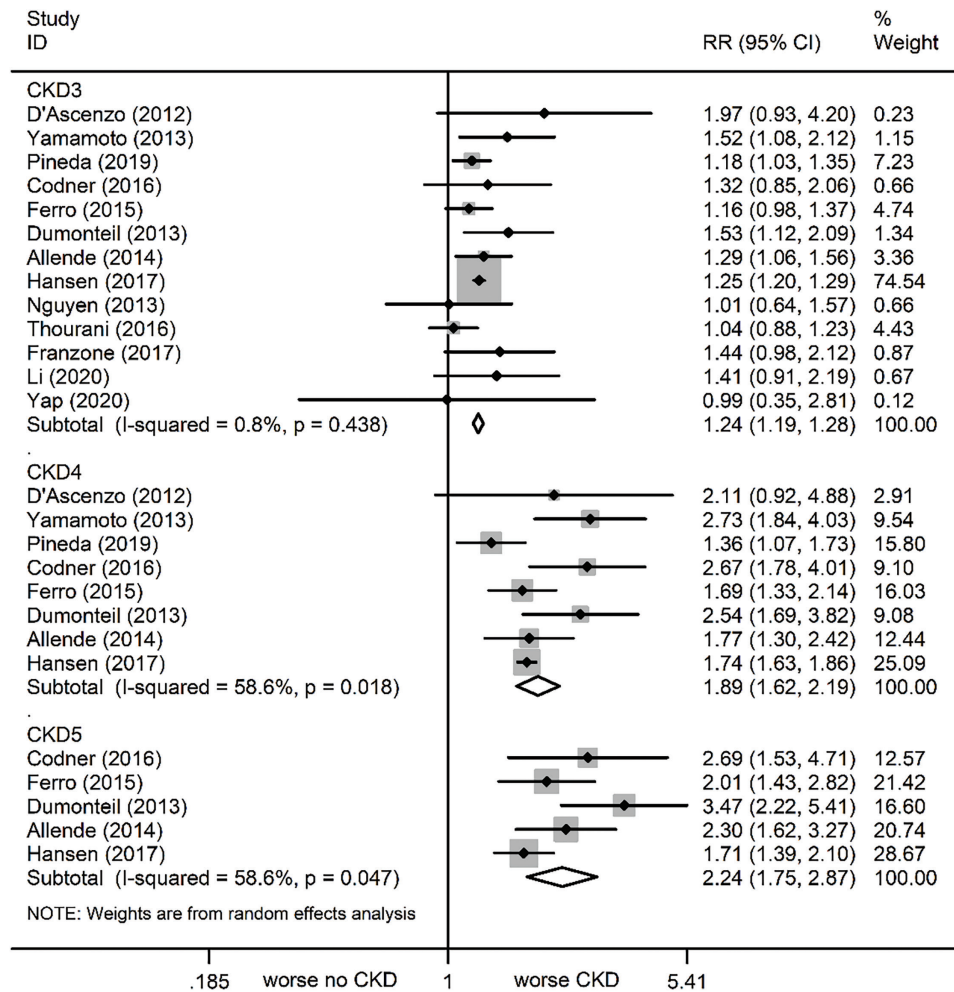
**Fig. 3** Forest plots comparing 30-day all-cause mortality risk in varying severity CKD patients. CKD: chronic kidney disease; RR: risk ratio; CI: confidence interval

with moderate CKD (CKD3) than in patients without CKD. (4) Lastly, the risk of all-cause mortality and bleeding increased with the severity of CKD.

With an increase in TAVR recommendations, it is essential to identify prognosis-related risk factors, among which is CKD. The relationship between CKD and prognosis after TAVR is controversial. Gupta et al.,<sup>30)</sup> for instance, conducted a national study of 41000 patients, who received TAVR between 2012 and 2014, in the United States. According to their report, CKD or end stage renal failure (ESRF) patients were more susceptible to in-hospital deaths than patients without CKD (3.8% vs. 4.5% vs. 8.3%,  $P < 0.001$ ). In another study, involving 42189 patients receiving TAVR from 2011 to 2014,<sup>39)</sup> 62.1% ( $n = 26229$ ) did not have CKD or ESRD, 33.7% ( $n = 14252$ ) were diagnosed with CKD, and 4% ( $n = 1708$ ) had ESRD. Using the non-CKD/ESRD

patients as reference, the in-hospital mortality of CKD patients (4.5% vs. 3.7%, odds ratio [OR] = 1.34, 95% CI: 1.20–1.31) and ESRD patients (8.2% vs. 3.7%, OR = 2.51, 95% CI: 2.02–3.12) were reported to be significantly elevated (both  $P < 0.001$ ). However, not all studies point to CKD as a critical independent predictor of mortality in TAVR recipients. Goebel et al.,<sup>22)</sup> for instance, demonstrated that CKD3 or higher patients did not exhibit an increase in the 30-day mortality rate after TAVR (7.0% vs. 7.1%,  $P = 0.97$ ). Moreover, there have been conflicting results on the impact of CKD3 on clinical prognosis. While some studies reported that CKD3 is not a predictor of mortality after TAVR,<sup>28,40)</sup> remaining studies suggested otherwise.<sup>41,42)</sup> Bohbot et al.,<sup>43)</sup> for example, published the largest study on severe AS patients with CKD. Upon adjusting for the established outcome predictors, patients with moderate or severe





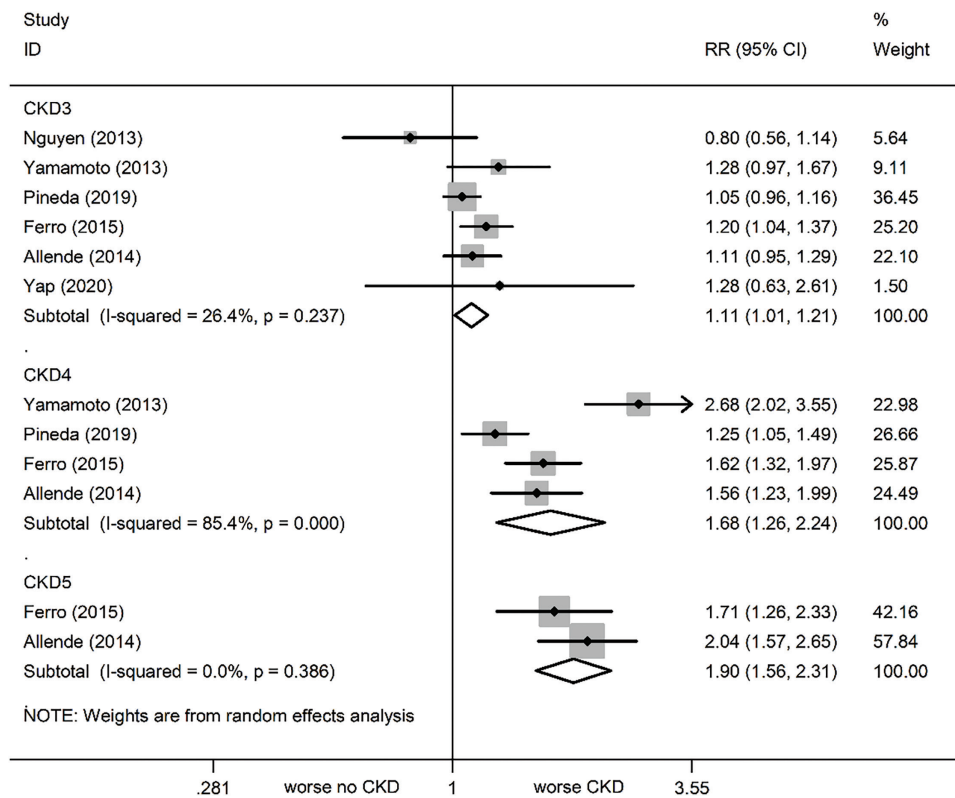
**Fig. 4** Forest plots comparing 1-year all-cause mortality risk in varying severity CKD patients. CKD: chronic kidney disease; RR: risk ratio; CI: confidence interval

CKD were shown to have higher all-cause mortality compared to those without CKD.

With our extensive review of all published data, we compiled substantial evidence that CKD, particularly CKD3, is associated with an enhanced all-cause mortality rate during follow-ups after TAVR. The most likely reasons for this may be as follows: First, the patients, receiving TAVR, have a higher incidence of coronary heart disease, systolic and diastolic heart failure, and conduction disturbance. Underlying CKD can exacerbate these cardiovascular abnormalities, thereby increasing the risk of death.<sup>25)</sup> Moreover, due to the advanced age of CKD patients, the logistic EuroSCORE and STS score were significantly higher, thus negatively impacting the survival of patients after TAVR.<sup>35,36)</sup> Conversely, Codner et al. published a report that failed to show an association between CKD3 and 1-year mortality rate (OR: 1.66; 95% CI: 0.95–2.9).<sup>28)</sup> However, Gargiulo et al.<sup>41)</sup> demonstrated

an increased risk of 1-year all-cause mortality (OR: 1.34, 95% CI: 1.11–1.64) in CDK patients after TAVR. The discrepancy in results from different trials may be due to inadequate sample size and incomparable demographics of patients.

With regard to TAVR surgical complications, Gupta et al.<sup>30)</sup> demonstrated an increased risk of major bleeding in CKD patients versus non-CVD patients (16.8% vs. 13.1%). Similarly, in our study, the incidence of post-TAVR bleeding in CKD patients was remarkably higher than in patients without CKD. The coagulation dysfunction in CKD has multifactorial mechanisms that include loss of normal platelet function, due to excess uremic toxins and metabolites; interaction of platelet–vascular wall affected by anemia; vascular structural changes caused by arteriosclerosis; impaired endothelial integrity; and insufficient anticoagulant excretion.<sup>44)</sup>



**Fig. 5** Forest plots comparing 2-year all-cause mortality risk in varying severity CKD patients. CKD: chronic kidney disease; RR: risk ratio; CI: confidence interval

**Table 3 Secondary outcomes**

Outcomes	Studies	Patients	RE RR	95% CI	P-value	I <sup>2</sup>
<b>AKI</b>						
CKD	5	4267	1.38	1.16–1.63	P < 0.001	13.1
CKD3	5	3738	1.28	1.11–1.48	P = 0.001	0
CKD4	4	2018	2.12	1.73–2.59	P < 0.001	0
CKD5	2	1487	1.9	1.37–2.62	P < 0.001	0
<b>Bleeding</b>						
CKD	10	53358	1.33	1.18–1.50	P < 0.001	47.4
CKD3	9	10484	1.26	1.02–1.55	P = 0.034	55.3
CKD4	4	3444	1.56	1.07–2.26	P = 0.021	57.4
CKD5	4	30252	1.58	1.05–2.38	P = 0.029	68.8
<b>Major vascular complications</b>						
CKD	7	47759	1.05	0.97–1.13	P = 0.203	0
CKD3	6	5978	1.11	0.93–1.33	P = 0.240	0
CKD4	4	2018	1.26	0.88–1.81	P = 0.211	0
CKD5	3	28763	1.01	0.57–1.79	P = 0.983	37.3
<b>Stroke</b>						
CKD	9	49616	1.21	0.86–1.70	P = 0.268	50.5
CKD3	9	8267	1.26	0.95–1.67	P = 0.112	0
CKD4	5	3723	2.41	1.60–3.63	P < 0.001	0
CKD5	5	30408	0.98	0.56–1.71	P = 0.953	19.3
<b>PPI</b>						
CKD	8	48027	1.09	0.96–1.25	P = 0.192	38.8
CKD3	5	5686	1.08	0.94–1.26	P = 0.279	0
CKD4	3	1872	0.77	0.54–1.11	P = 0.161	0
CKD5	4	28917	1.3	0.69–2.46	P = 0.412	71.3

CI: confidence interval; RR: risk ratio; CKD: chronic kidney disease; AKI: acute kidney injury; PPI: permanent pacemaker implantation

In the latest report by Bandyopadhyay et al.,<sup>35)</sup> AKI risk did not alter significantly between CKD patients and non-CKD patients after TAVR. Interestingly, in another study, CKD patients were reported to have a markedly elevated rate of AKI after TAVR, specifically, 34% AKI in CKD patients versus 10.6% in patients without CKD.<sup>30)</sup> Consistent with the later study, we also observed a significantly elevated AKI risk in CKD versus non-CKD patients. Among the contributing factors of AKI are the type and volume of contrast media used, hypotension caused by rapid ventricular pacing and balloon aortic valvuloplasty, microembolic events after catheter advancement, prosthesis implantation and valve expansion, and potential hemodynamic disorders associated with paravalvular regurgitation or arrhythmias.<sup>33)</sup> In multiple studies, AKI has been proposed to be an independent risk factor for increased mortality.<sup>25)</sup> Therefore, patients with severe CKD require appropriate procedural planning to reduce AKI and subsequent mortality risk.

## Limitations

This meta-analysis had certain limitations. (1) There may have been some bias in the inclusion of research and registration data. (2) Some mortality data, extracted from the Kaplan–Meier curve, may have provided a less than accurate result. (3) We used a summary of events published in each study, rather than individual data. Therefore, confounding and selection bias cannot be ruled out. (4) Most of the studies reported only up to 1-year mortality, and few studies assessed long-term outcomes of CKD. (5) The research language was limited to English, which may lead to potential language bias.

## Conclusion

In patients with AS, CKD increased the 30-day, 1-year, and 2-year all-cause mortality after TAVR. In addition, poor prognosis risk rises with increasing severity of CKD. Hence, our results contribute to the stratification of CKD-related risks in patients receiving TAVR. It is urgent and necessary to fully examine the specific prevention and management measures that would optimize the prognostic outcomes of AS and CKD patients undergoing TAVR.

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## Disclosure Statement

All authors have no conflicts of interest relevant to the topic in discussion.

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