

Association of blood transfusion with acute kidney injury after transcatheter aortic valve replacement: A meta-analysis

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Author contributions: Thongprayoon C and Cheungpasitporn W contributed equally to this work; Thongprayoon C and Cheungpasitporn W contributed to performing the search, analysis and interpretation of data, analysis of data and final approval of the version to be published; Gillaspie EA contributed to critical revising of the intellectual content and final approval of the version to be published; Greason KL contributed to critical revising of the intellectual content and final approval of the version to be published; Kashani KB contributed to concept and design, critical revising of the intellectual content and final approval of the version to be published.

Conflict-of-interest statement: All authors report no conflicts-of-interest.

Data sharing statement: No additional data are available.

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Manuscript source: Invited manuscript

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Received: March 19, 2016
Peer-review started: March 22, 2016
First decision: April 20, 2016
Revised: April 23, 2016
Accepted: June 27, 2016
Article in press: June 29, 2016
Published online: September 6, 2016

Abstract

AIM

To assess red blood cell (RBC) transfusion effects on acute kidney injury (AKI) after transcatheter aortic valve replacement (TAVR).

METHODS

A literature search was performed using MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and clinicaltrials.gov from the inception of the databases through December 2015. Studies that reported relative risk, odds ratio or hazard ratio comparing the risks of AKI following TAVR in patients who received periprocedural RBC transfusion were included. Pooled risk ratio (RR) and 95%CI were calculated using a random-effect, generic inverse variance method.

RESULTS

Sixteen cohort studies with 4690 patients were included in the analyses to assess the risk of AKI after TAVR in patients who received a periprocedural RBC transfusion. The pooled RR of AKI after TAVR in patients who received a periprocedural RBC transfusion was 1.95 (95%CI: 1.56-2.43) when compared with the patients who did not receive a RBC transfusion. The meta-analysis was

then limited to only studies with adjusted analysis for confounders assessing the risk of AKI after TAVR; the pooled RR of AKI in patients who received periprocedural RBC transfusion was 1.85 (95%CI: 1.29-2.67).

CONCLUSION

Our meta-analysis demonstrates an association between periprocedural RBC transfusion and a higher risk of AKI after TAVR. Future studies are required to assess the risks of severe AKI after TAVR requiring renal replacement therapy and mortality in the patients who received periprocedural RBC transfusion.

Key words: Acute kidney injury; Transcatheter aortic valve replacement; Meta-analysis; Mortality; Blood transfusion

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Core tip: We performed this meta-analysis to assess the impact of periprocedural red blood cell (RBC) transfusion on the risk of acute kidney injury (AKI) after transcatheter aortic valve replacement (TAVR). We verified a significant association between peri-procedural RBC transfusion and AKI after a TAVR with an overall 1.95-fold increased risk of AKI compared to those who did not receive transfusion. This study highlights the importance of vigilance when considering transfusions and should impact the clinical management of the high-risk group of patients undergoing TAVR.

Thongprayoon C, Cheungpasitporn W, Gillaspie EA, Greason KL, Kashani KB. Association of blood transfusion with acute kidney injury after transcatheter aortic valve replacement: A meta-analysis. *World J Nephrol* 2016; 5(5): 482-488 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v5/i5/482.htm> DOI: <http://dx.doi.org/10.5527/wjn.v5.i5.482>

INTRODUCTION

Patients with severe symptomatic aortic stenosis have destitute prognosis with medical treatment alone^[1]. Transcatheter aortic valve replacement (TAVR), also known as transcatheter aortic valve implantation, is an exciting new approach to the treatment of high-risk or inoperable patients with severe aortic stenosis^[2-6]. Despite advances in TAVR procedures, acute kidney injury (AKI) is one of the most frequent complications of TAVR, ranging in the literature from 15% to 57%^[3,7-9]. Notably, the subset of patients, who develop AKI after TAVR, also have a high mortality rate of 9%-44% at 30 d and 32%-56% at 1 year^[7,8].

Perioperative anemia has been shown to be independently associated with AKI after cardiac surgery^[10,11]. Anemia can result in decreased renal oxygen delivery, increased oxidative stress and impaired hemostasis^[10]. Thus, perioperative red blood cell (RBC) transfusion is used to improve oxygen delivery. However, stored RBC

transfusion can also promote a pro-inflammatory state, impair tissue oxygen delivery, and induce tissue oxidative stress^[12,13]. The association of AKI with RBC transfusion after TAVR is conflicting. While a few studies have demonstrated a higher incidence of AKI among patients who received periprocedural RBC transfusion^[14-23], the others have shown no such association^[24-29]. Thus, we conducted this meta-analysis to assess the impact of periprocedural RBC transfusion on the risk of AKI after TAVR.

MATERIALS AND METHODS

Search strategy

Two investigators (Thongprayoon C and Cheungpasitporn W) independently searched published studies and conference abstracts indexed in MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and clinicaltrials.gov from the inception of the databases through December 2015. The search strategy used is described in the supplementary material. A manual search for additional relevant studies using the references from these retrieved articles was also performed. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for a systematic review and meta-analysis^[30].

Inclusion criteria

We included studies that: (1) enrolled adult (≥ 18 years old) patients; (2) provided information about periprocedural RBC transfusion and comparator patients who did not receive RBC transfusion; (3) included AKI after TAVR as an outcome; (4) were randomized clinical trials or observational studies (case-control, cross-sectional or cohort studies) published as original studies or conference abstracts; and (5) provided data to calculate odds ratios (ORs), relative risks, hazard ratios (HRs) or standardized incidence ratios with 95% CIs. No language limits were applied.

Study eligibility was independently determined by the two investigators noted previously. Differing decisions were resolved by mutual consensus. The quality of each study was evaluated using the Newcastle-Ottawa quality assessment scale^[31].

Data extraction

A standardized data collection form was used to extract the following information: Last name of the first author, article title, study design, year of study, country of origin, year of publication, sample size, AKI definition, blood transfusion, confounder adjustment, and the adjusted effect estimate with 95%CI.

Statistical analysis

Review Manager software (Version 5.3, Copenhagen, Denmark) from the Cochrane Collaboration was used for data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian

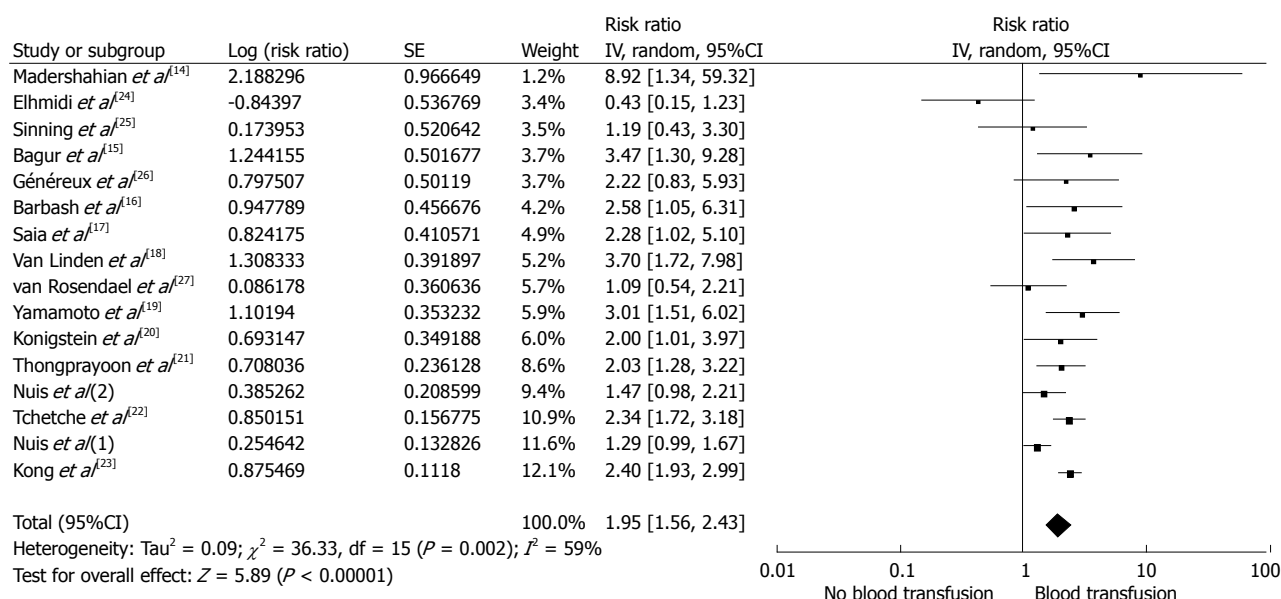


Figure 1 Forest plot of comparing the risk of acute kidney injury after transcatheter aortic valve replacement in patients who received red blood cell transfusion and those who did not. Square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95%CI for the outcome of interest.

and Laird^[32]. Given the high likelihood of between-study variances, a random-effect model was used. Statistical heterogeneity was assessed using Cochran's Q test. This statistic was complemented with the I^2 statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. An I^2 of 0%-25% represents insignificant heterogeneity, 26%-50% low heterogeneity, 51%-75% moderate heterogeneity and > 75% high heterogeneity^[33]. The presence of publication bias was assessed by funnel plots of the logarithm of ORs vs their standard errors^[34].

RESULTS

Our search strategy yielded 1327 articles. Of these, 1169 articles were excluded based on their relevance and the eligibility criteria, following the review of their title and abstract. The remaining 158 articles underwent full-length review and an additional 142 were excluded for failing to meet the criteria: 114 articles did not report the outcome of interest; and 28 articles were not observational studies or randomized clinical trials. Sixteen cohort studies were included in the meta-analysis to assess the risk of AKI after TAVR in patients who received periprocedural RBC transfusion (Table 1). Of the 16 cohort studies, eight studies performed adjusted analysis for known risk factors for AKI^[14,15,19,20,23,24,28,29]. Supplementary Item 2 outlines our search methodology and selection process.

Study quality

All observational studies were considered moderate to high quality, with a median Newcastle-Ottawa quality assessment scale of 6.5 (range: 6-8) as shown in Table 1.

AKI definition

All included studies identified the AKI occurrence, based on the change in serum creatinine (SCr) or GFR after TAVR. One of the included studies also used urine output criteria for the AKI diagnosis^[25]. Twelve^[16,17,19-23,25-29] of the 16 included studies used standard AKI definitions (modified Risk, Injury, Failure, Loss of kidney function^[35]; Acute Kidney Injury Network^[36]; or Kidney Disease Improving Global Outcomes criteria^[37]), as shown in Table 1.

AKI risk

The pooled risk ratio (RR) of AKI following TAVR in patients who received a RBC transfusion was 1.95 (95%CI: 1.56-2.43; $I^2 = 59\%$). Figure 1 shows the forest plot of the included studies. When meta-analysis was limited to the studies using standard AKI definitions, the pooled RRs were 1.89 (95%CI: 1.55-2.31; $I^2 = 50\%$). To minimize the effects of confounders, we performed a sensitivity analysis and excluded studies that did not include an adjusted analysis for known risk factors for AKI. The pooled RR of AKI after TAVR remained significant in patients who received periprocedural RBC transfusions (RR = 1.85; 95%CI: 1.29-2.67; $I^2 = 75\%$), shown in Figure 2.

Nuis *et al*^[28] assessed the dose response relationship of a RBC transfusion and AKI, and demonstrated an increased risk of AKI with a higher number of RBC transfusions with ORs of 1.47 (95%CI: 0.98-2.22), 3.05 (95%CI: 1.24-7.53), 4.81 (95%CI: 1.45-15.95) for 1-2 units, 3-4 units, and ≥ 5 units of RBC transfusion, respectively. Reporting of severe AKI requiring renal replacement therapy (RRT) was limited. Van Linden *et al*^[18] reported a higher risk of AKI requiring RRT with an OR of 8.8 (95%CI: 1.7-45.6; Table 1).

Table 1 Main characteristics of the studies included in this meta-analysis

Ref.	Country ¹	Year	n	Transfusion definition	AKI definition (changes in baseline)	RR for AKI	Confounder adjustment	S, C, O ²
Sinning <i>et al</i> ^[25]	Germany	2010	77	RBC in 2 d post-procedure	Increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ or U output < 0.5 mL/kg per hour for > 6 h in 48 h post procedure	1.19 (0.43-3.31)	None	3, 0, 3
Bagur <i>et al</i> ^[15]	Canada	2010	213	Peri-procedural blood	Decrease in eGFR of $> 25\%$ at 48 h post procedure or hemodialysis needed during index hospitalization	3.47 (1.30-9.29)	HTN, COPD	3, 1, 3
Van Linden <i>et al</i> ^[18]	Germany	2011	261	Blood > 4 u in 7 d post-operative	Decrease in eGFR of $> 25\%$ or increase in SCr of 50% in 7 d post procedure	AKI 3.7 (1.7-7.9) RRT 8.8 (1.7-45.6)	None	3, 0, 3
Nuis <i>et al</i> ^[29]	Netherlands	2011	118	Peri-procedural RBC	Increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ in 72 h post procedure	1.29 (1.01-1.70)	Previous MI, leukocyte count, logistic EuroScore	3, 1, 3
Elhmidi <i>et al</i> ^[24]	Germany	2011	234	Post-operative blood	Decrease in eGFR of $> 25\%$ or increase in SCr of 50% in 7 d post procedure	0.43 (0.15-1.23)	Baseline creatinine, STS score, DM	3, 2, 3
Madershahian <i>et al</i> ^[14]	Germany	2012	50	RBC	Increase in SCr of ≥ 0.5 mg/dL or $\geq 25\%$ from baseline within 48 h post procedure	8.92 (1.34-59.26)	COPD and contrast amount	3, 1, 3
Kong <i>et al</i> ^[23]	Australia	2012	52	Peri-procedural RBC	SCr criteria of RIFLE classification in 48 h post procedure	2.4 (2.0-3.1)	TA, history of HTN	3, 1, 3
Tchetche <i>et al</i> ^[22]	France, Netherlands, Italy	2012	743	RBC	Increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ in 72 h post procedure	2.34 (1.72-3.18)	None	3, 0, 3
Barbash <i>et al</i> ^[16]	United States	2012	165	Post procedure blood	Increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ in 72 h post procedure	2.58 (1.05-6.29)	None	3, 0, 3
Nuis <i>et al</i> ^[28]	Netherlands, Canada, Germany, Belgium, Columbia	2012	995	RBC in 24 h post procedure	Increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ in 72 h post procedure	1-2 u, 1.47 (0.98-2.22); 3-4 u, 3.05 (1.24-7.53); ≥ 5 u, 4.81 (1.45-15.95)	PVD, CHF, maximal leukocyte count, logistic EuroScore	3, 2, 3
Saia <i>et al</i> ^[17]	Italy	2013	102	Peri-procedural RBC	Increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ in 72 h post procedure	2.28 (1.02-5.10)	None	3, 0, 3
Konigstein <i>et al</i> ^[20]	Israel	2013	251	Blood	Increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ in 72 h post procedure	2.00 (1.01-3.97)	Gender, HTN, DM, dyslipidemia, PVD, CHF, stroke, COPD, PHTN, VC, CKD, valve type and size	3, 2, 3
Yamamoto <i>et al</i> ^[19]	France	2013	415	RBC	Increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ in 72 h post procedure	3.01 (1.54-6.15)	Contrast amount and LVEF	3, 1, 3
Généreux <i>et al</i> ^[26]	United States	2013	218	Blood	VARC-modified RIFLE stage 2 or 3 until discharge	2.22 (0.83-5.92)	None	3, 0, 3
Thongprayoon <i>et al</i> ^[21]	United States	2015	386	Intra-operative RBC	Increase in SCr of ≥ 0.3 mg/dL in 48 h or $\geq 50\%$ in 7 d post procedure	2.03 (1.28-3.23)	None	3, 0, 3
van Rosendaal <i>et al</i> ^[27]	Netherlands	2015	210	Peri-procedural RBC	Increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$ in 7 d post procedure	1.09 (0.54-2.22)	None	3, 0, 3

¹Countries are listed by their three letter country code; ²Quality Assessment Newcastle-Ottawa scale: S: Selection; C: Comparability; O: Outcome. AKI: Acute kidney injury; CHF: Congestive heart failure; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; HTN: Hypertension; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; PHTN: Pulmonary hypertension; PVD: Peripheral vascular disease; RIFLE: Risk, injury, failure, loss of kidney function, and end-stage kidney disease; SCr: Serum creatinine; STS: Society of thoracic surgeons; TA: Transapical approach; VARC: Valve academic research consortium; VC: Vascular complication; RBC: Red blood cell.

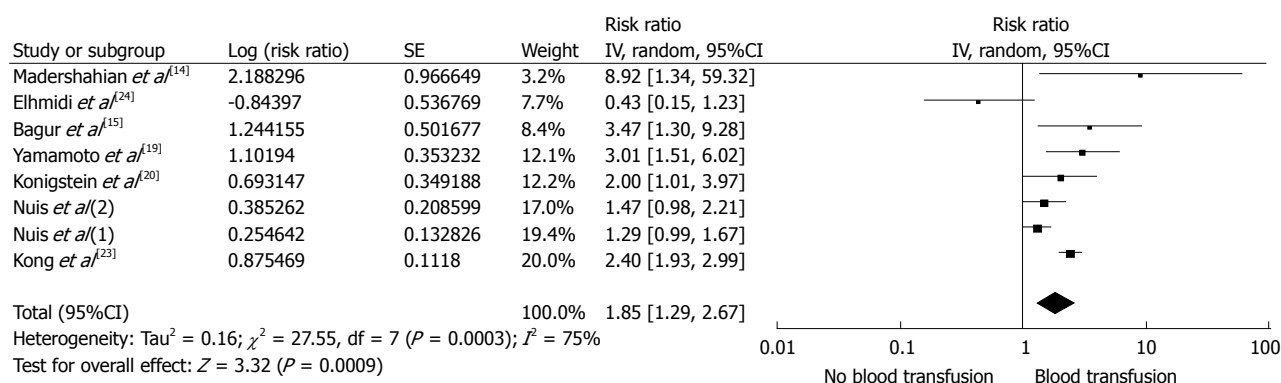


Figure 2 Forest plot of the adjusted analysis comparing the risk of acute kidney injury after transcatheter aortic valve replacement in patients who received red blood cell transfusion and those who did not. The square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

Evaluation for publication bias

Funnel plots to evaluate publication bias for the risk of AKI after TAVR in patients who received a RBC transfusion are summarized in Supplementary Figures 1 and 2. The graphs demonstrate no obvious asymmetry and, thus, suggest an insignificant publication bias.

DISCUSSION

In this meta-analysis, we verified a significant association between peri-procedural RBC transfusion and AKI after a TAVR with an overall 1.95-fold increased risk of AKI compared to those who did not receive transfusion. This association remained significant when adjusting for potential confounders.

The mechanism for the higher incidence of AKI after TAVR in patients with a periprocedural RBC transfusion is not well-elucidated. Analysis has shown that preserved RBCs used in transfusions undergo progressive structural and functional changes during storage, such as reduced deformability and increased tendency to aggregate. These changes result in the deterioration of RBC function and viability, and the resultant accumulation of free iron and pro-inflammatory agents^[38] leads to AKI^[8,39-41]. Studies have also shown an association between RBC transfusions and increased leukocyte count in patients who developed AKI after TAVR^[28,29].

Nuis *et al*^[28] reported that the number of RBC transfusions was an independent predictor of AKI following TAVR. In their study, a higher number of RBC transfusions were found to be associated with a higher AKI incidence. Interestingly, the investigators did not find significant associations between AKI and the clinical indications for transfusion (*i.e.*, baseline anemia, bleeding complications, or blood loss).

The risks of transfusion-associated AKI is not limited to TAVR; patients undergoing coronary artery bypass grafting or surgical aortic valve replacements who require transfusions also have a higher frequency of AKI^[41-43].

Although the included studies in our meta-an-

alysis were all of moderate to high quality, there are some limitations of this study that bear mentioning. First, there were statistical heterogeneities among the enrolled studies. The potential sources of these heterogeneities include the variations in the diagnostic methodology of AKI after TAVR and the differences in confounder adjustment methods. Second, the data on severe AKI requiring RRT after TAVR is lacking. Further studies are certainly warranted to further delineate the impact of transfusions after TAVR with specific regard to the severity of AKI. Third, the data on valve size and approaches for TAVR procedure were limited. These factors might have affected the risk of AKI following TAVR. Lastly, this is a meta-analysis of observational studies with the inherent limitation that a causal relationship cannot be inferred.

The threshold for transfusions is constantly changing. The deleterious effects of transfusions are well documented, and many institutions have worked hard to create protocols to diminish unnecessary transfusions. Our meta-analysis demonstrates an association between periprocedural RBC transfusion and a higher risk of AKI following TAVR. In many cases, patients undergoing TAVR have considerable debility and comorbid conditions. This study highlights the importance of vigilance when considering transfusions and should impact the clinical management of the high-risk group of patients undergoing TAVR.

COMMENTS

Background

Transcatheter aortic valve replacement (TAVR) is an exciting new approach to the treatment of high-risk or inoperable patients with severe aortic stenosis. Despite advances in TAVR procedures, acute kidney injury (AKI) is one of the most frequent complications of TAVR, associated with significant morbidity and mortality following the procedures.

Research frontiers

The association of AKI with red blood cell (RBC) transfusion after TAVR is conflicting in the findings of numerous literature. It is thus necessary to assess the impact of periprocedural RBC transfusion on the risk of AKI after TAVR.

Innovations and breakthroughs

In this study, the authors verified a significant association between peri-procedural RBC transfusion and AKI after a TAVR with an overall 1.95-fold increased risk of AKI compared to those who did not receive transfusion.

Applications

The data in this study highlights the importance of vigilance when considering transfusions and should impact the clinical management of the high-risk group of patients undergoing TAVR.

Terminology

PRISMA: Preferred reporting items for systematic reviews and meta-analyses, etc.

Peer-review

This is a reasonable first meta-analysis of association of blood transfusion with AKI after transcatheter aortic valve replacement. The results have potential clinical applications.

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