Red blood cell transfusion and mortality after transcatheter aortic valve implantation via transapical approach: A propensity-matched comparison from the TRITAVI registry

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ABSTRACT

Objective: Bleeding is frequent during transcatheter aortic valve implantation (TAVI), especially when performed through a transapical approach (TA), and is associated with a worse prognosis. The present study aims to test the implication of red blood cell (RBC) transfusion and the optimal transfusion strategy in this context.

Methods: Among 11,265 participants in the multicenter TRITAVI (Transfusion Requirements in Transcatheter Aortic Valve Implantation) registry, 548 patients (4.9%) who received TA-TAVI at 19 European centers were included. One-to-one propensity score matching was performed to reduce treatment selection bias and potential confounding among transfused versus non-transfused patients. The primary endpoint of the study was the 30-day occurrence of all-cause mortality.

Results: 209 patients (38 %) received RBC transfusions. The primary endpoint occurred in 47 (8.6 %) patients. Propensity score matching identified 188 pairs of patients with and without RBC transfusion. In the propensity score-matched analysis, RBC transfusion was associated with increased 30-day mortality (HR 3.35, 95 % CI 1.51 – 7.39; p = 0.002). At multivariable cox regression analysis, RBC transfusion was an independent predictor of 30-day mortality (HR 3.07, 95 % CI 1.01–9.41, p = 0.048), as well as baseline ejection fraction (HR 0.96, 95 % CI 0.92–0.99, p = 0.043), and acute kidney injury (HR 3.95, 95 % CI 1.11–14.05, p = 0.034).

Conclusions: RBC transfusion is an independent predictor of short-term mortality in patients undergoing TA-TAVI, regardless of major bleeding.

Clinical trial registration: https://www.clinicaltrials.gov Unique identifier: NCT03740425.

1. Introduction

Transcatheter aortic valve implantation (TAVI) for severe aortic stenosis has demonstrated significant clinical benefit in large randomized trials as compared to medical management in patients with prohibitive operative risk [1] and at least equivalent results compared with surgical aortic valve replacement (SAVR) in patients at high [2], intermediate [3], and even low risk [4–7].

With the advancement of device technology and procedural techniques, most TAVI procedures have been performed through the transfemoral (TF) approach in recent years [8–12]. However, alternative approaches such as transapical (TA), *trans*-subclavian, direct aortic, and others still play an important role in patients with poor vascular access [13–16]. TA-TAVI could offer a favorable alternative to SAVR in selected high-risk profile patients when TF-TAVI appears unfeasible [17], allowing a minimally invasive off-pump aortic valve implantation and avoiding general anesthesia, aortic clamping, and sternotomy [18]. TA approach is the only antegrade approach and provides easy wiring with excellent control. However, it has some potential drawbacks including apical bleeding risk, postoperative pain, and higher periprocedural and in-hospital mortality when compared to TF-TAVI [19–23].

Periprocedural bleeding is frequent after TAVI [24] and is associated with higher mortality [25] and risk of AKI [26]. Therefore red blood cell (RBC) transfusion is often administrated, and more frequently in those undergoing TA as compared to TF-TAVI [27]. There is no consensus on the relative benefit and the optimal transfusion strategy, and indication in the TAVI setting remains a matter of debate due to the marked inconsistency of the available evidence [28–33].

Previously, among patients undergoing heart surgery, the Transfusion Requirements in Cardiac Surgery (TRICS) III trial documented that a "restrictive" RBC transfusion strategy (i.e. when hemoglobin (Hb) < 7.5 g/dl) was noninferior to a "liberal" approach (i.e. when Hb was < 9.5 g/dl) for the composite occurrence of death, myocardial infarction (MI), stroke, or new-onset renal failure requiring dialysis [34].

In the specific setting of TF-TAVI, explored in The Transfusion Requirements in Transcatheter Aortic Valve Implantation (TRITAVI) registry, we already highlighted the negative prognostic role of RBC transfusion, demonstrating increased mortality and risk of acute kidney injury (AKI) early after the procedure in transfused patients, and its independent predictive role on short-term mortality [35–39]. Thus, we explored whether RBC transfusion would be a predictor of adverse outcomes also among patients receiving TA-TAVI, who have a marked frailty profile.

2. Methods

2.1. Study population

The TRITAVI is an investigator-initiated registry designed to collect data on patients with severe aortic stenosis undergoing TAVI that enrolled 11,265 consecutive patients with symptomatic severe AS who underwent TAVI at 19 European sites (11 in Italy, 1 in Spain, 1 in Poland, 5 in Finland, 1 in England) from January 2012 to December 2020. Among them, 587 received TA-TAVI, and for the present analysis, we excluded those with unavailable follow-up (n = 5) or no data about blood count (n = 22) and/or transfusion requirement (n = 12), accounting for 548 patients (4.9 %) in the final study population.

The pre-procedural screening was performed through clinical assessment (patient demographics, symptoms, comorbidities, laboratory examinations, and risk evaluation), echocardiography, and multidetector angio-computed tomography.

Local multidisciplinary heart teams evaluated all cases and confirmed eligibility for TA-TAVI, which was performed as per the Centers' common experience and with the best contemporary standards. All patients provided written informed consent for the procedure and subsequent data collection per local practice for retrospective data.

Patients' data were entered on a common excel data sheet, and advancement of data collection and analysis were shared among all study participant centers periodically during the study progress.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent for the procedure and subsequent data collection per local practice for retrospective data.

2.2. Laboratory measurements, bleeding, and blood transfusions

Preprocedural hemoglobin (Hb) was considered as the baseline preprocedural Hb, and the lowest Hb level during hospitalization after TA-TAVI was the nadir Hb. The difference between them was defined as Hb drop.

There was no predefined Hb threshold to initiate RBC transfusion, and the decision to transfuse was at the discretion of the interventional or clinical cardiologist, cardiac surgeon, and/or anesthesiologist on a case-by-case basis. Blood transfusion was defined as any RBC product given after the TAVI. According to the Valve Academic Research Consortium (VARC-3) [40], bleeding events were classified as type 1: overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, or requiring 1 unit of whole blood/RBC; type 2: overt bleeding that

requires a transfusion of 2–4 units of whole blood/RBC or associated with a hemoglobin drop of > 3 g/dL; type 3: overt bleeding in a critical organ (intracranial, intraspinal, intraocular, pericardial associated with hemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome, or overt bleeding causing hypovolemic shock or severe hypotension or requiring vasopressors or surgery, reoperation, surgical exploration, or post-thoracotomy chest tube output ≥ 2 L within 24-hours, or overt bleeding requiring a transfusion of ≥ 5 units of whole blood/red blood cells, or overt bleeding associated with a hemoglobin drop ≥ 5 g/dL; type 4: overt bleeding leading to death.

In the present analysis, type 2 to 4 bleeding were computed together as "major" bleeding.

Since we aimed to evaluate the impact of RBC transfusions on clinical outcomes independently of the occurrence of bleeding, we excluded RBC transfusion alone from the bleeding definitions.

2.3. Clinical follow-up and endpoints

In-hospital outcomes were collected, and all patients discharged alive were followed up with a 30-day clinic visit.

The primary endpoint of the study was all-cause mortality at 30 days. Co-primary endpoints were 30-day nonfatal myocardial infarction (MI), cerebrovascular accident (CVA), stage 2 to 4 acute kidney injury (AKI) defined according to VARC- 3 criteria [40], and major cardiovascular events (MACE) defined as the composite of death, MI and CVA.

Echocardiographic outcomes were evaluated before discharge; par-avalvular aortic regurgitation severity was assessed according to VARC-3 criteria [40]; for the present study, only paravalvular aortic regurgitation grades more than mild were analyzed.

2.4. Statistical analysis

Categorical variables were summarized as frequencies and percentages. Continuous variables were reported as either mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution, as assessed by the Shapiro-Wilk's test.

Propensity score matching was used to reduce treatment selection bias and potential confounding factors. The propensity score was estimated for each patient using a logistic regression model including several baseline covariates of interest: age, sex, body mass index (BMI), heart failure class III-IV according to New York Heart Association (NYHA), peripheral arterial disease (PAD), coronary artery disease (CAD), previous MI, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG), previous CVA, chronic obstructive pulmonary disease (COPD), baseline creatinine, baseline Hb, atrial fibrillation (AF), left ventricle ejection fraction (LVEF).

Baseline patient characteristics that were either unequally distributed among the transfusion groups or that correlated with the primary endpoint were included in the propensity score model. We stratified patients according to RBC transfusions and performed one-to-one matching using nearest-neighbor matching without replacement (caliper width < 0.2, standard deviations of the logit of the propensity score) of patients with and without RBC transfusions. The method of standardized mean differences (SMD) was used to assess the balance of covariates distribution between groups before and after matching. An SMD ≤ 0.1 indicated an irrelevant difference between the means of the two groups.

Within the matched cohort, Cox's proportional-hazard model was used to estimate transfusion versus no transfusion hazard ratio (HR) and the corresponding 95 % confidence intervals (CI) on the matched pairs. Kaplan Meier plots graphically depicted event rates for each treatment group.

To explore the effect of transfusion within different nadir hemoglobin levels (≤9.5 and > 9.5 g/dL), and within different degrees of hemoglobin drop (<3 and ≥ 3 g/dL), we performed different matching within each stratum. Moreover, all the steps and analyses illustrated above were repeated in a cohort of "uncomplicated" patients, composed of patients who did not experience major vascular complications nor major bleeding after TAVI.

A multivariate logistic regression model was applied to determine the patient's characteristics predictive of RBC transfusion. The results of the model were expressed as adjusted odds ratio (OR) and relative 95 % CI. Variables included were selected among those with a p-value < 0.10 at univariate regression analysis. Two models were built, the first including only clinical variables, the second one including also major periprocedural bleeding and vascular complications.

All statistical analyses were performed using R Statistical Software (version 3.1.2.; R Foundation for Statistical Computing, Vienna, Austria). Propensity score and matching procedures were conducted using the Match-It package in R. All p-values were two-tailed and a p-value < 0.05 was considered indicative of a statistically significant association.

3. Results

3.1. Baseline patient characteristics

The study cohort consisted of 548 patients, 240 (43.8 %) were female, mean age was 79.8 years (SD 6.8); 209 subjects (38 %) received RBC transfusions, with 4.2 ± 0.9 units. In 166 cases (79 %) ≥ 2 units of RBC were administered. Baseline characteristics of the study population are shown in Table 1, as stratified for transfusion requirement. As compared with the control group, patients who received RBC transfusion were significantly older, more frequently male, and with a history of previous CABG and lower Hb levels.

A 1:1 propensity score-matched analysis identified 188 matched pairs of patients with versus without RBC transfusion. There were no significant differences in any baseline characteristics between the matched groups of patients (Table 1, Figs. 1 and 2).

3.2. Independent predictors for the need of transfusion after TAVI

After TAVI, RBC transfusion was more frequently administered to patients having a lower nadir Hb value: in 27 /30 patients (90 %) with a nadir Hb < 7.5 mg/dl, in 133 / 250 cases (53 %) with a nadir Hb between 7.5 and 9.5 mg/dl and in 48 / 268 subjects (18 %) with a nadir Hb > 9.5 mg/dl (p < 0.001).

Among the explored variables age, female sex, PAD, and lower baseline Hb level were independently associated with RBC transfusion at multivariable logistic regression analysis. However, after correcting also for major bleeding, only baseline Hb correlated with transfusion after TAVI (Table 2).

3.3. Primary and secondary outcomes

At 30 days, all-cause death occurred in 47 (8.6 %) patients; nonfatal MI occurred in 6 (1.1 %), CVA in 5 (0.9 %), MACE in 50 (9.1 %) and stage 2–4 AKI in 51 (9.3 %) patients.

Patients who received RBC transfusion had higher 30-day mortality than the control group (HR 2.43, 95 % CI 1.35–4.35, p = 0.003) (Fig. 3).. After propensity score matching, mortality was still higher among those who received RBC transfusion (HR 3.35, 95 % CI 1.51–7.39, p = 0.002) (Table 3).

Among the secondary endpoints, in the matched cohort, patients who received RBC transfusion had a higher risk of MACE (HR 2.70, 95 % CI 1.56—4.65, p < 0.001) and of AKI type 2–4 (Odds Ratio [OR] 2.69, 95 % CI 1.30–5.61, p = 0.008) (Table 3).

After stratification according to Hb drop after TAVI, the 30-day mortality was still higher in transfused versus non-transfused patients, both in the 88 pairs of patients with a Hb drop > 3 g/dL (HR 2.88, 95 % CI 1.04–7.99, p = 0.040) and in the 63 pairs with a Hb drop ≤ 3 g/dL

Table 1
Baseline characteristics before and after propensity score matching (PSM).

	Before PSM				After PSM			
	No RBC transfusion (n = 339)	RBC transfusion (n = 209)	P	SMD	No RBC transfusion (n = 188)	RBC transfusion (n = 188)	P	SMD
Age (mean ± SD)	79.00 ± 6.96	80.97 ± 6.43	**0.001**	0.293	80.28 ± 6.23	80.65 ± 6.52	0.57	0.059
Female, n (%)	209 (61.7)	99 (47.4)	**0.001**	0.290	88 (46.8)	92 (48.9)	0.76	0.043
BMI, kg/m^2 (mean ± SD)	26.14 ± 4.05)	25.94 (4.67)	0.58	0.048	25.82 ± 3.80	25.86 ± 4.73	0.93	0.009
Diabetes, n (%)	124 (36.6)	63 (30.1)	0.15	0.137	62 (33.0)	61 (32.4)	1.00	0.011
NYHA class III-IV, n (%)	273 (80.5)	174 (83.3)	0.49	0.071	151 (80.3)	154 (81.9)	0.79	0.041
CAD, n (%)	167 (49.3)	107 (51.2)	0.73	0.039	93 (49.5)	96 (51.1)	0.84	0.032
Previous MI, n (%)	86 (25.4)	54 (25.8)	0.98	0.011	45 (23.9)	45 (23.9)	1.00	0.001
Previous PCI, n (%)	116 (34.2)	70 (33.5)	0.94	0.015	57 (30.3)	65 (34.6)	0.44	0.091
Previous CABG, n (%)	102 (30.1)	46 (22.0)	**0.04**	0.185	47 (25.0)	44 (23.4)	0.81	0.037
Previous CVA, n (%)	46 (13.6)	35 (16.7)	0.37	0.089	35 (18.6)	28 (14.9)	0.41	0.100
PAD, n (%)	150 (44.2)	110 (52.6)	0.07	0.168	96 (51.1)	95 (50.5)	1.00	0.011
COPD, n (%)	96 (28.3)	52 (24.9)	0.44	0.078	51 (27.1)	51 (27.1)	1.00	0.001
AF, n (%)	114 (33.6)	64 (30.6)	0.53	0.064	65 (34.6)	62 (33.0)	0.83	0.034
Baseline Creatinine (mean ± SD)	1.31 ± 1.00	1.35 ± 0.91	0.60	0.047	1.33 ± 1.09	1.29 ± 0.59	0.66	0.045
Baseline Dialysis, n (%)	6 (1.8)	5 (2.4)	0.85	0.044	3 (1.6)	3 (1.6)	1.00	0.001
Baseline Hb (mean ± SD)	12.48 ± 1.65	11.64 (1.72)	**<0.001**	0.497	11.94 ± 1.59	11.84 ± 1.67	0.54	0.064
Baseline LVEF (mean ± SD)	54.16 ± 10.82	54.05 ± 11.42	0.91	0.010	54.06 ± 10.38	54.12 ± 11.39	0.96	0.005

Values are expressed as mean ± standard deviation or n (%). AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVA = cerebro vascular accident; Hb = hemoglobin; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SMD = standardized mean difference.
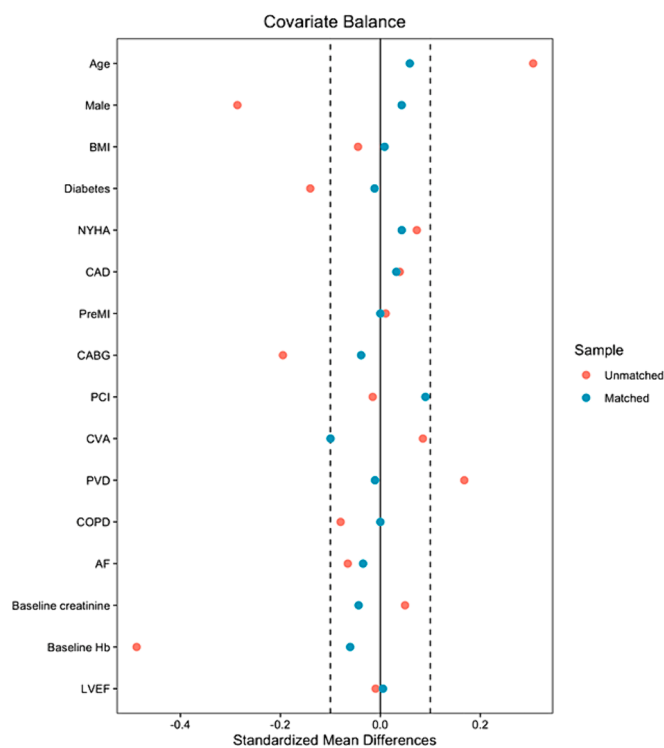
Fig. 1. Love plot showing changes in standardized mean difference before (red) and after (blue) matching. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(HR 3.97, 95 % CI 1.11–14.25, p = 0.030) (Fig. 4).

Furthermore, the 30-day mortality was not significantly different among the 110 pairs of RBC transfused and non-transfused patients with a nadir Hb value ≤ 9.5 g/dL (HR 1.65, 95 % CI 0.68—3.97, p = 0.270). In the 42 pairs with a nadir Hb > 9.5 mg/dl, mortality was only numerically, but not significantly, higher in transfused patients than in controls (HR 2.80, 95 %CI 0.74–10.56, p = 0.200) (Fig. 5).

To evaluate the impact of RBC transfusions irrespective of peri-procedural complications, we excluded patients who experienced

periprocedural major bleeding events and further analyzed 86 matched pairs of "uncomplicated" patients. In this analysis, RBC transfusion was associated with a trend towards higher 30-day mortality (HR 1.84, 95 % CI 0.73–4.60, p = 0.220; Fig. 6).

At multivariable cox regression analysis, RBC transfusion was confirmed as an independent predictor of 30-day mortality (HR 3.07, 95 % CI 1.01–9.41, p = 0.048), as well as baseline EF (HR 0.96, 95 % CI 0.92–0.99, p = 0.043), and AKI (HR 3.95, 95 % CI 1.11–14.05, p = 0.034) (Table 4).

4. Discussion

To the best of our knowledge, this is the first study assessing the impact of RBC transfusion on short-term adverse outcomes in a large series of patients with severe aortic stenosis undergoing TA-TAVI.

Our main finding is that RBC transfusion is frequent after TA-TAVI and is independently associated with early mortality, as well as with MACE and AKI, regardless of Hb drop and major bleeding. Accordingly, the present study confirms and extends previous findings [34–36]: RBC transfusion is associated with increased mortality after TAVI, likely according to different scenarios: (1) as an index of an adverse condition, when it is administered for ongoing overt bleeding without having time to obtain a true nadir hemoglobin value; (2) as a marker of risk in patients with several comorbidities frequently also affected by chronic anemia; (3) as a mediator of risk, when given for a "cosmetic" approach, aiming to normalize subnormal Hb values, in the absence of a detectable threat [34–36].

Although RBC may be lifesaving in several circumstances [41], it is frequently empirically administered, often in the absence of overt major bleeding [42], and only based on Hb concentrations or drop or in the presence of hypovolemia [43], being considered not harmful or ameliorating oxygen transportation [44–46]. Transfusion Requirements in Cardiac Surgery (TRICS) III trial showed that, among patients undergoing cardiac surgery, a "restrictive" transfusion strategy − with Hb < 7.5 g/dl − was non-inferior in terms of composite occurrence of death, MI, stroke, or new-onset dialysis to a "liberal" approach – with transfusion adopted in case of Hb < 9.5 g/dl [34]. Similarly, here we report that RBC transfusion correlates with increased early mortality, and the finding seems irrespective of periprocedural major bleeding [35,36].

To exclude that the noted relationship with mortality may be a surrogate marker for periprocedural events, we attempted to separate
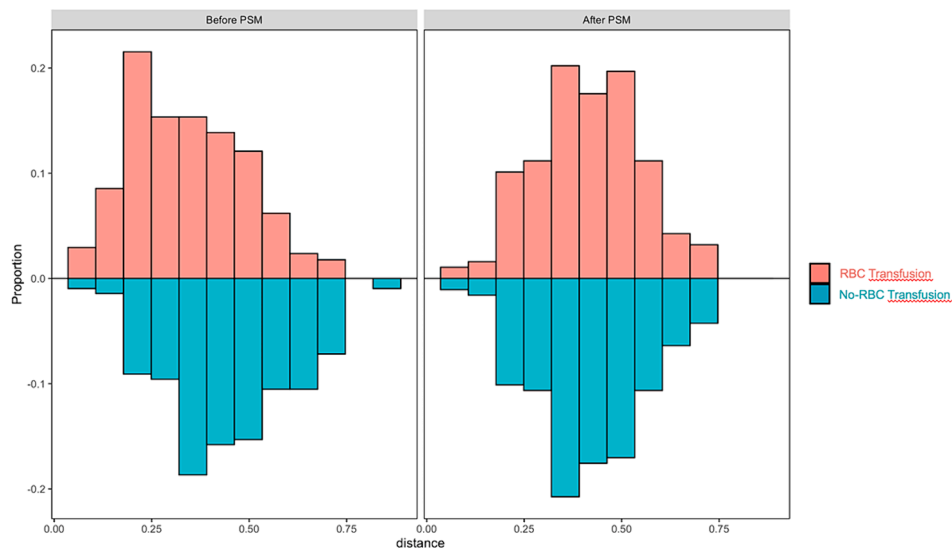
Fig. 2. Mirrored histogram showing the propensity score distribution and overlapping in unmatched and matched samples in the transfusion (red) and in the no transfusion (green) groups. PSM = propensity score matching. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
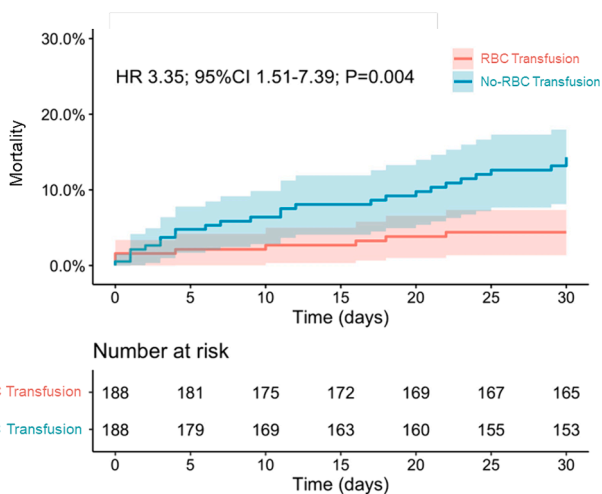Multivariable logistic regression for RBC transfusion.

Variable	Model 1		Model 2	
	OR_{adj} (95 %CI)	p-value	OR_{adj} (95 %CI)	p-value
Major bleeding	–	–	18.54 (10.90–31.53)	<0.001
Baseline Hb (g/dl)	0.75 (0.67–0.84)	<0.001	0.58 (0.50–0.68)	<0.001
Age	1.04 (1.01–1.07)	0.016	1.01 (0.99–1.01)	0.302
PAD	1.54 (1.06–2.24)	0.024	1.12 (0.72–1.76)	0.566
Female sex	1.41 (1.00–2.08)	0.050	1.12 (0.70–1.79)	0.638

CI = confidence interval; ORadj = adjusted odds ratio; other abbreviations as in previous tables.

Fig. 3. Kaplan-Meyer estimates of 30-day mortality according to RBC transfusion after TA-TAVI in the propensity score-matched cohort.

Table 3
Primary and secondary endpoints in the non-matched and matched cohorts.

	No RBC transfusion	RBC transfusion	HR (95 % CI)	p-value
Non-matched cohort	**n = 339**	**n = 209**		
Death, n (%)	19 (5.6)	28 (13.4)	2.43 (1.35–4.35)	**0.003**
Non-fatal CVA, n (%)	1 (0.3)	5 (2.4)	8.28 (0.96–71.45)	0.057
Non-fatal MI, n (%)	4 (1.2)	1 (0.5)	0.40 (0.05–3.62)	0.417
MACE, n (%)	36 (10.6)	52 (24.8)	2.78 (1.75–4.45)	**<0.001**
AKI type 2–4	19 (5.6)	32 (15.3)	3.04 (1.67–5.53)*	**<0.001**
Matched cohort	**n = 188**	**n = 188**		
Death, n (%)	8 (4.3)	26 (13.8)	3.35 (1.51 – 7.39)	**0.002**
Non-fatal CVA, n (%)	0 (0.0)	5 (2.7)	NA	NA
Non-fatal MI, n (%)	1 (0.5)	1 (0.5)	1.02 (0.06 – 16.37)	0.99
MACE, n (%)	18 (9.6)	46 (24.5)	2.70 (1.56 – 4.65)	**<0.001**
AKI type 2–4	11	27	2.69 (1.30–5.61)*	**0.008**

* Odds Ratio.

Values are expressed as n (%). AKI = acute kidney injury; HR = hazard ratio; MACE = major cardiovascular events. Other abbreviations as in previous tables.

the prognostic impact of RBC transfusion from major bleeding, and by stratifying the cohort by Hb drop and nadir. Even if conventional statistical significance was not reached with the smaller sample size of this subgroup analysis, RBC transfusion consistently predicted a trend toward an increased risk of early mortality in the population of "uncomplicated" patients.

Clinicians have been adopting restrictive transfusion strategies after surgical or transfemoral aortic valve implantation principally driven by wide evidence as previously shown. We hope that the present results support a conservative transfusion strategy to be translated even in the TA approach. Clearly, further prospective randomized studies are required to confirm and validate our findings.
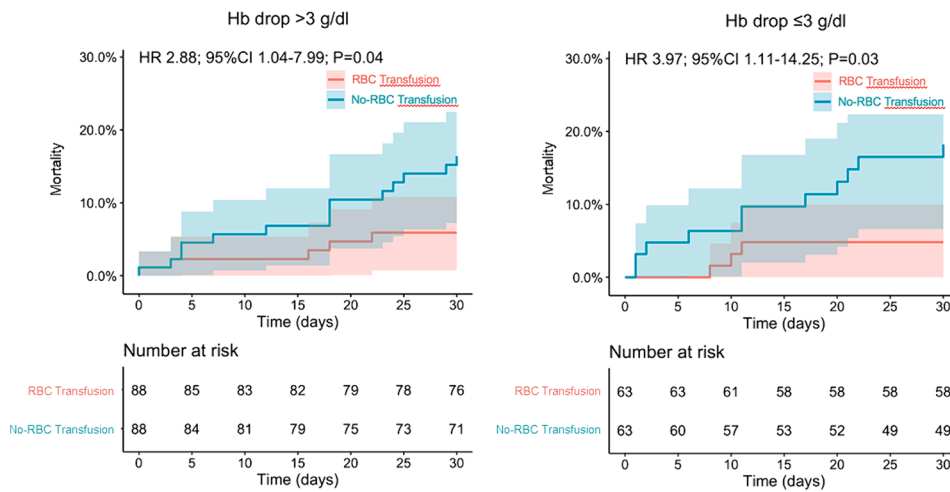
Fig. 4. Kaplan-Meyer estimates of 30-day mortality according to red blood cell blood transfusion after transapical transcatheter aortic valve implantation. On the left panel, the propensity score-matched cohort was stratified for hemoglobin (Hb) drop value > 3 g/dL. On the right panel, the propensity score-matched cohort was stratified for hemoglobin (Hb) drop value ≤ 3 g/dL. HR indicates hazard ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
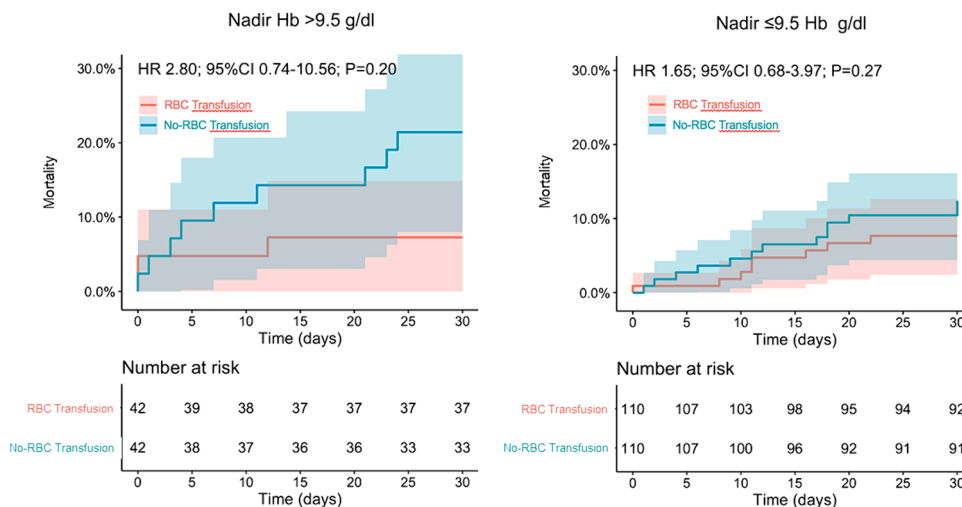
Fig. 5. Kaplan-Meyer estimates of 30-d mortality according to red blood cell transfusion in the propensity score-matched cohort as stratified for nadir hemoglobin (Hb) value > 9.5 g/dL (left) or ≤ 9.5 g/dL (right). HR indicates hazard ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.1. Study limitations

Our study has several limitations. The TRITAVI is an observational study without independent adjudication of events or an independent core laboratory imaging analysis, and due to the registry nature data may include not negligible risks of bias, a significant number of missing values, and potential erroneous assumptions. Also, several important information, such as bleeding sites, were not collected. Although propensity score matching adjustments have resulted in two comparing groups with homogeneous baseline characteristics, unmeasured confounders might remain and might have affected the results due to the non-randomized nature of the study. Due to the retrospective nature of the study, the decision to perform an RBC transfusion was at the discretion of the clinicians of each participating center. The decision to perform percutaneous coronary intervention at the time of TAVI was left at the discretion of the performing physician, and this might have also affected the outcome [47]. Analysis of the antithrombotic treatment was not part of the present evaluation, but might affect bleeding and the decision to administer RBC transfusion. Our findings derive from collected data from different centers in the period 2012–2020, adopting various implant techniques, sheath sizes, and types of valves, which may not be representative of current "state-of-the-art" practice. Lastly, patient selection has also evolved in the last decade currently including a more favorable risk profile necessarily reflecting in reduced adverse outcome rate.

5. Conclusions

Conventional use of RBC transfusion is an independent predictor of early mortality after TA-TAVI, irrespective of major bleeding. Uncertainties remain on the optimal strategy for RBC transfusion in this setting. The findings of the present study support a restrictive use of RBC transfusion that should be strictly limited to life-saving situations. Thus, physicians should refrain from the use of RBC transfusion as a fluid repletion mean or to cosmetically correct a lower-than-expected hemoglobin value until appropriately powered randomized clinical trials definitely proof and validate the value of RBC transfusion after TAVI.
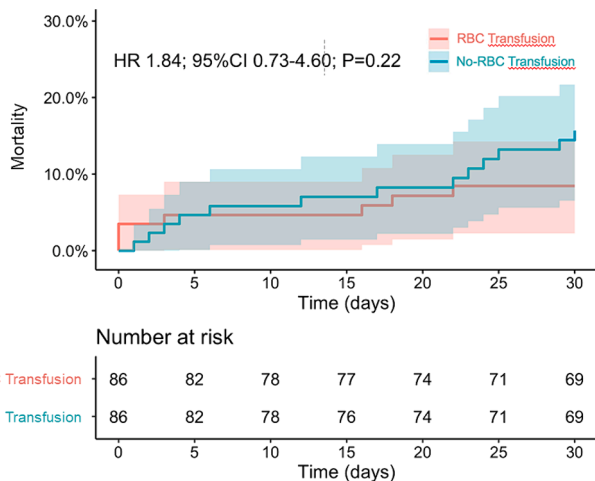
Fig. 6. Kaplan-Meyer estimates of 30-day mortality for the subgroup of uncomplicated patients, who did not experience major bleeding, according to RBC transfusion. HR indicates hazard ratio.

Table 4
Univariate and Multivariate (Proportional Hazard Cox Regression) analysis for 30-day mortality.

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95 %CI)	p-value	HR(95 %CI)	p-value
Major bleeding	1.81 (1.01–3.24)	0.045	2.19 (0.67–7.13)	0.191
Baseline LVEF	0.96 (0.93–0.99)	0.050	0.96 (0.92–0.99)	**0.043**
PVL	2.19 (1.29–3.71)	<0.001	1.59 (0.73–3.51)	0.247
RBC transfusion	2.43 (1.35–4.35)	0.016	3.07 (1.01–9.41)	**0.048**
PAD	1.78 (0.97–3.30)	0.064	1.73 (0.57–5.27)	0.330
STS score	1.10 (1.05–1.15)	<0.001	1.06 (0.99–1.13)	0.074
AKI type 2–4	4.94 (2.67–9.13)	<0.001	3.95 (1.11–14.05)	**0.034**

PVL = paravalvular leak; STS = Society of Thoracic Surgeons. Other abbreviations as in previous tables. Abbreviations as in previous tables.

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CRediT authorship contribution statement

Francesco Radico: Resources, Investigation. **Fausto Biancari:** Conceptualization. **Fabrizio D'Ascenzo:** Conceptualization. **Francesco Saia:** Resources, Investigation. **Giampaolo Luzi:** Data curation. **Francesco Bedogni:** Resources, Investigation. **Ignacio J. Amat-Santos:** Funding acquisition. **Vincenzo De Marzo:** Software, Methodology, Formal analysis. **Arnaldo Dimagli:** Validation. **Timo Mäkikallio:** Methodology, Investigation. **Eugenio Stabile:** Writing – original draft, Visualization, Validation. **Sara Blasco-Turrión:** Validation, Software, Project administration. **Luca Testa:** Methodology, Funding acquisition. **Marco Barbanti:** Supervision, Methodology, Funding acquisition. **Corrado Tamburino:** Data curation, Conceptualization. **Italo Porto:** Methodology. **Franco Fabiocchi:** Software, Resources, Methodology. **Federico Conrotto:** Supervision, Project administration. **Francesco Pelliccia:** Resources, Investigation. **Giuliano Costa:** Resources, Funding acquisition, Data curation. **Giulio G. Stefanini:** Investigation, Data curation. **Andrea Macchione:** Data curation, Conceptualization. **Michele La Torre:** Visualization, Software, Methodology. **Francesco Bendandi:** Resources, Investigation. **Tatu Juvonen:** Resources,

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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