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Association between red blood cell transfusion and adverse clinical outcomes is Independent of cardiac history: a multicenter observational InPUT study analysis

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Abstract

Purpose Red-blood-cell (RBC) transfusion is one of the most frequent interventions in critical care patients. While patients with acute cardiac conditions are more likely to receive transfusions at higher haemoglobin thresholds than other critically ill patients, data on RBC transfusion practice for critically ill patients with pre-existing cardiac conditions are scarce.

Methods Using the International Point-Prevalence Study of Intensive-Care Unit Transfusion Practices cohort, weighted logistic regression investigated the association between the RBC units transfused and the primary composite outcome of 28-day mortality, new-onset acute kidney injury or ventilatory weaning failure. Interactions with cardiac history (acute coronary syndrome and/or heart failure) were tested.

Results Cardiac history was present in 746 of 3643 patients (20%) and 894 of 3643 (25%) received at least one RBC unit. Transfusion rates were similar in patients with and without cardiac history (25% *vs.* 24%; p = 0.51). Among transfused patients, median nadir haemoglobin during ICU stay was slightly higher in those with cardiac history (7.6 g/dL *vs.* 7.4 g/dL respectively; p = 0.007), whereas stated haemoglobin transfusion threshold did not statistically

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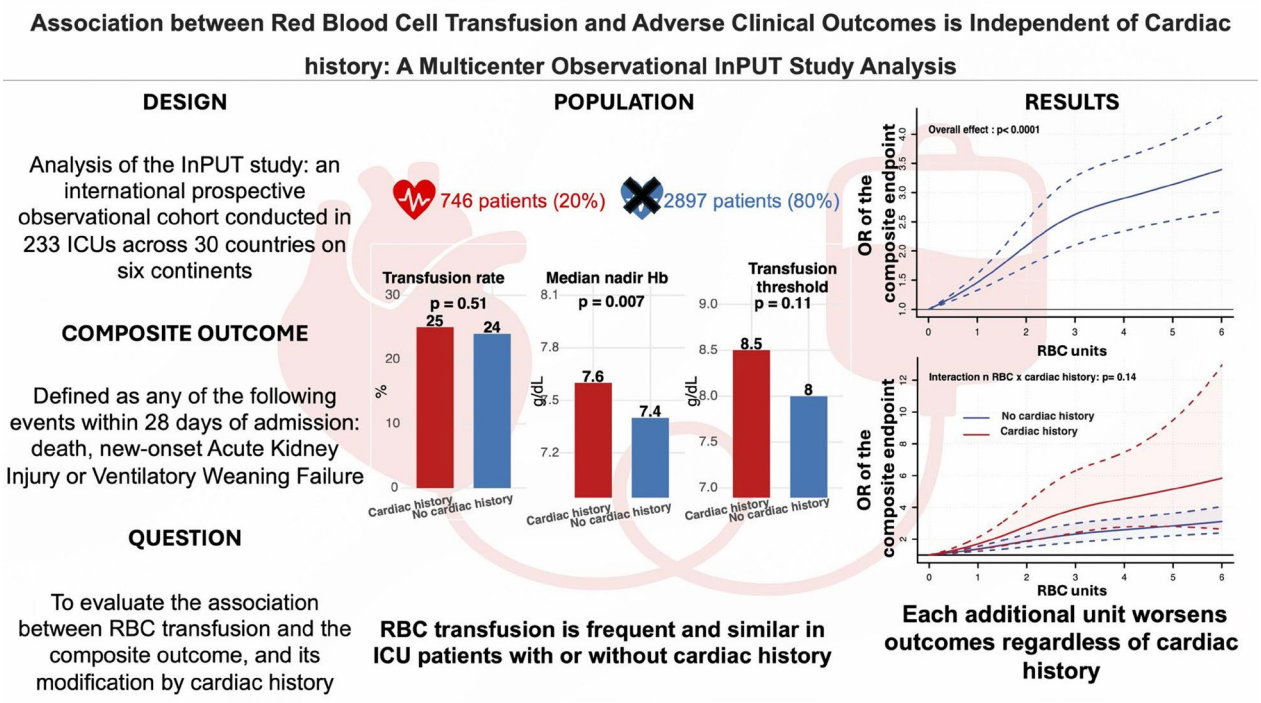
differ (8.5 g/dL *vs.* 8.0 g/dL; p = 0.11). Each additional RBC unit increased the odds of the composite outcome in the whole cohort (2.18, 95% CI 1.85–2.56, p < 0.0001), without interaction with cardiac history (p = 0.44).

Conclusions RBC transfusion was commonly and similarly prescribed in critically ill patients with or without cardiac history. Each additional unit was associated with a worse outcome with no evidence of differential effect due to cardiac history.

Trial registration NL9049 (Dutch Trial Register), registered on 16 November 2020.

Keywords Red blood cell transfusion, Intensive care units, Critical care, Heart failure

Graphical Abstract



Introduction

Red blood cell (RBC) transfusion remains one of the most common bedside interventions in intensive care with 25 to 50% of patients receiving at least one unit during their stay [1–3]. Although RBC transfusion is life-saving in patients with haemorrhagic shock or trauma, conditions representing only 10 to 20% of intensive care unit (ICU) admissions, it is most often prescribed to treat anaemia [1, 2]. The latter affects up to 60% of patients at ICU admission and up to 90% during their stay [4]. Large randomised trials and current guidelines support a restrictive transfusion strategy as safe for almost all critically ill patients. However, adherence in clinical practice remains disappointingly low, particularly among patients with cardiac history [5–10]. While, there is no universally accepted definition of what constitutes a cardiac history, the World Health Organization considers acute coronary syndrome (ACS) and heart failure (HF) among the leading causes of chronic cardiovascular disease [11]. Thus, up to 40% of critically ill patients have a cardiac history at ICU admission. In this population, anaemia is highly prevalent and represents an independent, actionable risk factor for both hospitalisation and mortality [2, 12]. Whereas current guidelines recommend a higher transfusion threshold in acute cardiac conditions, the latest meta-analysis on this topic found no clear difference in myocardial infarction or death at 30 days, leaving the optimal approach for pre-existing cardiac history poorly documented [8–10].

In this analysis of the The International Point Prevalence Study of Intensive Care Unit Transfusion Practices (InPUT), we investigated transfusion practice in critically ill patients focusing on their cardiac history and assessed whether the latter interfered in the association between RBC transfusion with 28-day composite outcome of death or acute kidney injury (AKI) or ventilatory weaning failure (VWF) [1].

Methods

Study design and oversight

This analysis is based on the InPUT-study, an international, multicentre, prospective observational cohort study of transfusion practices in ICUs [1]. In brief, the study was conducted across 233 centres in 30 countries spanning six continents from March 2019 to October 2022. All adult patients admitted to the ICU during a predefined study week were included. For each unit of RBC transfusion, the clinical indication was recorded. Patients were followed for up to 28 days during their stay in the ICU.

Definitions

The composite outcome was defined as any of the following events within 28 days of admission: death, organ dysfunction manifested as new-onset AKI or VWF. Acute kidney injury was characterized by an increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 mmol/l), within 48 h or an increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or urine volume < 0.5 ml/kg/h for 6 h. Ventilatory weaning failure was considered present in the event of failure to pass a spontaneous-breathing trial or the need for reintubation within 48 h following extubation.

A cardiac history referred to a documented history of ACS history or HF history prior to ICU admission. In subgroup analyses comparing patients with an ACS history with those who had HF history, patients who had both conditions were classified in the HF group.

Acute coronary syndrome encompassed a spectrum of clinical presentations consistent with acute myocardial ischemia including unstable angina, non–ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction. Heart failure definition included an ejection fraction < 40% and HF must have been recorded prior to this current hospital-admission as a chronic condition (existing > 6 months) or patient must be using drugs prescribed with the indication HF.

Nadir haemoglobin level was the lowest haemoglobin level recorded during the whole ICU stay. Haemoglobin threshold indicated the threshold used to determine the indication for each RBC transfusion.

Outcomes

The primary outcome of this study was to assess the association between RBC transfusion and the primary composite endpoint in the whole InPUT cohort and whether cardiac history modified this association.

Data collection

In the InPUT study, the following data were collected from the time of ICU admission until day 28, or until death or discharge, whichever occurred first: demographic information, past medical history including HF and ACS, ICU admission diagnosis, daily laboratory results including nadir haemoglobin levels on the whole ICU stay, and organ support therapies such as renal replacement therapy or mechanical ventilation. New-onset adverse events were recorded, including ACS, AKI, sepsis, acute respiratory distress syndrome, gastro-intestinal bleeding, VWF, liver failure, cerebrovascular event, bone marrow failure, retinal haemorrhage.

Particular attention was given to transfusion events, with documentation of the declared haemoglobin threshold, the number of RBC units transfused, and the time from ICU admission to the first RBC unit transfused. For each RBC transfusion event, the reasons behind the decision to transfuse were recorded and categorized as either clinical criteria or pathophysiological triggers.

Statistical analyses

Description

Analytical data are presented as the median with first and third quartiles for continuous variables whereas categorical variables as numbers and percentages. Comparisons of baseline characteristics according to groups were conducted by using Wilcoxon or Kruskal–Wallis tests for continuous variables and the Fisher exact test or X^2 test for categorical variables.

First, comparisons were made between patients with a cardiac history and those without; and second, between patients with a HF history (with or without an ACS history) and those with an ACS history alone.

The reasons and triggers for transfusion were analysed according to cardiac history using the non-imputed dataset. Since individual patients could receive multiple RBC units for different indications, a generalised linear mixed-effects model with a binomial distribution and a random effect for patients was used to assess the association with the cardiac history. P-values corresponding to the fixed effect (cardiac history) were reported.

Management of missing data

A missing data map was initially generated to visualise both the proportion and the distribution of missing values across the dataset. To address missingness, a non-parametric imputation method using the Random Forest algorithm was applied. The imputation was performed using the missForest package, with a maximum of 10 iterations and 100 trees per forest. To assess the quality of the imputation, we compared the distributional consistency of each continuous variable before and after imputation. Specifically, density plots of the observed (non-imputed) data were overlaid with those of the imputed data. A good overlap between the distributions

indicates that the imputation was correct. The imputed data set was used in all following analyses.

Weighted analyses

All analyses presented are weighted. To control for confounding, a stabilised inverse probability of treatment weighting (IPTW) approach was used based on a logistic regression propensity score model. The model included the following variables: continent of origin, age, sex, Do Not Resuscitate order, Do Not Intubate order, referral status, referring facility, patient type (medical/surgical), reason for admission, presence of ACS, HF, chronic kidney disease, malignant haematological diseases, solid tumours, presence of shock, APACHE IV score, haemoglobin and platelet count at admission, prothrombin time at admission, use of mechanical ventilation, and renal replacement therapy. Propensity scores were derived from this model, and stabilised IPTW were calculated accordingly. To limit the influence of extreme weights, values above five were truncated. The final weights were normalized to preserve sample size. The distribution of stabilised IPTW by transfusion status was plotted. Covariate balance before and after weighting was assessed using mean standardised differences with a threshold limit of 0.15.

Primary outcome analyses

Associations between the number of RBC units transfused or the status of transfusion (yes/no) and the primary composite outcome, as well as its individual components, were assessed using weighted logistic regression models. Stabilised IPTW, previously calculated, were applied to account for baseline confounding. The number of RBC units transfused was modelled as a continuous variable using restricted cubic splines, with knots defined according to Harrell's recommendations [13]. The reference value was set to zero unit transfused. Wald tests were used to assess both the overall association and departure from linearity. In addition, interaction effects between the number of RBC units transfused and cardiac history were evaluated. Results were visualised as odds ratios with 95% confidence intervals across the range of RBC transfused units. E-Value was also computed to quantifies how strong an unmeasured confounder would need to be, with respect to both treatment and primary outcome, to reduce the observed association to null.

Secondary outcomes

Weighted logistic regression models using stabilised IPTW on the imputed dataset assessed the interactions of transfusion status with cardiac history (ACS alone *vs.* HF with or without ACS *vs.* neither ACS nor HF) on the composite outcome and its individual components. In addition, subgroup analyses were performed in patients transfused for non-bleeding reasons only and in those in whom no physiological trigger influenced the decision to transfuse.

A two-tailed p value of less than 0.05 was considered significant. Statistical analyses were performed using R 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Population characteristics

The entire cohort of 3,643 patients was included in this post hoc analysis. Baseline characteristics are detailed in Table 1. In summary, 746 patients (20%) had a documented cardiac history, including 381 with an ACS history and 427 with a HF history. Compared to patients without cardiac history, those with a cardiac history were older (70 [61–77] *vs.* 62 [49–71] years, $p < 0.0001$) and less frequently female gender (31% *vs.* 40%, $p < 0.0001$). Reasons for ICU admission differed significantly between patients with and without a cardiac history ($p < 0.0001$): out-of-hospital or in-hospital cardiac arrest (7% vs 3%) and shock (15% vs 11%) were more frequent in those with a cardiac history, whereas acute brain injury (3% vs 7%), trauma (1% vs 6%), and metabolic disturbances (4% vs 8%) were less frequent.

Events during the ICU stay are summarized in Table S1 in Supplement 1. Patients with cardiac history were more frequently managed with invasive mechanical ventilation (51% *vs.* 43%, $p = 0.0001$) and renal replacement therapy (5% *vs.* 3%, $p = 0.004$) and had a higher median Sequential Organ Failure Assessment score during their ICU stay (4 [2–7] *vs.* 3 [2–6], $p < 0.0001$). Additionally, during their ICU stay they experienced a higher incidence of organ dysfunction, including ACS, AKI, sepsis, or VWF.

RBC transfusion

Admission laboratory values were comparable between groups. The overall transfusion rate was similar in patients with and without cardiac history with one of four patients receiving RBC transfusion in both groups ($p = 0.51$, Table 2). Among RBC transfused patients, the number of RBC units administered was also similar: 2 [1–4] in patients without cardiac history and 2 [1–3] in those with cardiac history ($p = 0.98$, Table 3). Moreover, RBC transfused patients with a cardiac history had slightly higher nadir haemoglobin levels during their ICU stay than those without such a history (7.6 [6.9–8.5] *vs.* 7.4 [6.7–8.1] g/dL; $p = 0.007$), whereas their haemoglobin transfusion thresholds (8.5 [8.0–9.0] *vs.* 8.0 [7.0–9.0] g/dL; $p = 0.11$) and the interval from ICU admission to the first RBC unit (2 [1–4] *vs.* 2 [1–3] days; $p = 0.30$) were comparable (Table 3). Among patients with a nadir Hb threshold < 8 g/dL, only 205 patients (6%) in the overall

Table 1 Characteristic of the population at inclusion according to cardiac history status

Variables	n (2897)	No cardiac history	n (746)	Cardiac history	p-value
Age, y	2897	62 (49—71)	746	70 (61—77)	< 0.0001
Female Gender	2897	1148 (40%)	746	228 (31%)	< 0.0001
Medical history (multiple options possible)					
Acute coronary syndrome	2897	0 (0%)	746	381 (51%)	< 0.0001
Heart failure	2897	0 (0%)	746	427 (57%)	< 0.0001
Chronic kidney failure	2897	197 (7%)	746	132 (18%)	< 0.0001
Chronic obstructive pulmonary disease	2897	301 (10%)	746	111 (15%)	0.0006
Liver failure	2897	93 (3%)	746	17 (2%)	0.18
Benign haematologic disease	2897	27 (1%)	746	8 (1%)	0.73
Haematologic malignancy	2897	79 (3%)	746	16 (2%)	0.37
Organ transplant	2897	43 (1%)	746	11 (1%)	0.98
Bone marrow transplant	2897	9 (0%)	746	0 (0%)	0.27
None	2897	1387 (48%)	746	0 (0%)	< 0.0001
Code Status					
Do not resuscitate	2873	128 (4%)	734	47 (6%)	0.028
Do not intubate	2879	99 (3%)	737	37 (5%)	0.044
Do not transfuse	2729	12 (0%)	699	1 (0%)	0.43
APACHE IV score	2446	46 (28—69)	572	50 (27—76)	0.041
Emergency admission	2897	1895 (65%)	746	477 (64%)	0.45
Referred from	2895		746		0.027
Emergency department		897 (31%)		248 (33%)	
General Ward		507 (18%)		116 (16%)	
Operation theater/OR		1218 (42%)		295 (40%)	
Other (*i.e.*, home, other ICU)		30 (1%)		17 (2%)	
Other hospital		243 (8%)		70 (9%)	
Referring specialty	2897		746		< 0.0001
Cardiology		110 (4%)		185 (25%)	
Cardiothoracic surgery		366 (13%)		172 (23%)	
Gastrointestinal surgery		271 (9%)		44 (6%)	
Gynaecology		77 (3%)		3 (0%)	
Internal medicine		569 (20%)		123 (16%)	
Neurology		127 (4%)		22 (3%)	
Neurosurgery		272 (9%)		19 (3%)	
Orthopaedic surgery		87 (3%)		21 (3%)	
Other (*i.e.*, emergency, ENT)		84 (3%)		5 (1%)	
Pulmonology		344 (12%)		57 (8%)	
Surgery		365 (13%)		75 (10%)	
Trauma surgery		141 (5%)		10 (1%)	
Urology		84 (3%)		10 (1%)	
Surgery < 24 h before ICU admission	2891	1295 (45%)	745	307 (41%)	0.079
Reason for ICU admission	2891		744		< 0.0001
Acute brain injury		204 (7%)		25 (3%)	
In- or out-of-hospital cardiac arrest		81 (3%)		52 (7%)	
Metabolic disturbances		238 (8%)		30 (4%)	
Postoperative monitoring		1046 (36%)		259 (35%)	
Other		228 (8%)		80 (11%)	
Respiratory failure		608 (21%)		183 (25%)	
Shock		322 (11%)		110 (15%)	
Trauma		164 (6%)		5 (1%)	
Outcomes					
28-day mortality	2691	472 (18%)	708	146 (21%)	0.059

Table 1 (continued)

Variables	n (2897)	No cardiac history	n (746)	Cardiac history	p-value
Acute kidney injury or ventilatory weaning failure	2897	547 (19%)	746	214 (29%)	< 0.0001
Composite endpoint	2714	815 (30%)	719	289 (40%)	< 0.0001

APACHE, Acute Physiology and Chronic Health Evaluation; ENT, ear, nose, and throat; ICU, intensive care unit; OR, operating room; RBC, red blood cell. Presented as No. (%) for frequency data, median (shown first–third quartile borders) for continuous variables. The APACHE IV score is used to reflect the patient's severity of illness, expressed by a 0–286 range, in which higher severity of illness is reflected by a higher score

Table 2 Transfusion characteristics during intensive care unit stay according to cardiac history

Variables[a]	n (2897)	No cardiac history	n (746)	Cardiac history	p-value
Transfusion					
Received RBC	2897	704 (24%)	746	190 (25%)	0.51
Number of days of transfusion	660	1 (1—2)	186	1 (1—2)	0.43
No. of RBC units transfused per transfused day[b]	659	1 (1—2)	186	1 (1—2)	0.33
Number of RBC unit transfused	704	2 (1—4)	190	2 (1—3)	1.00
ESA administered	2897	20 (1%)	746	14 (2%)	0.003
Iron administered	2897	29 (1%)	746	6 (1%)	0.62
Admission laboratory values					
Hb level, g/dL	2308	12 (10—14)	609	12 (10—14)	0.55
Anemia					
Female	894	519 (58%)	195	112 (57%)	0.87
Male	1414	825 (58%)	414	241 (58%)	0.96
Laboratory values during ICU stay					
Nadir Hb, g/dL	2849	10 (8—12)	739	10 (8—12)	0.34
Anemia during ICU stay[c]	2849	2389 (84%)	739	614 (83%)	0.61

ESA, Erythropoiesis–stimulating agents; Hb, hemoglobin; ICU, intensive care unit; RBC, red blood cell

[a]Presented as No. (%) for frequency data, continuous variables presented as median (shown first–third quartile borders)

[b]Calculated as the sum of RBC transfused divided by the days a transfusion was administered per patient

[c]Anemia defined as <12 g/dL for females and <13 g/dL for males, according to the definition by the World Health Organization

Table 3 Transfusion characteristics in RBC-transfused patients with and without cardiac history

Variables	n	No cardiac history	n	Cardiac history	p-value
Number of RBC units transfused	703	2.0 (1.0—4.0)	190	2.0 (1.0—3.0)	0.98
Nadir Hb during ICU stay, g/dL	701	7.4 (6.7—8.1)	190	7.6 (6.9—8.5)	0.007
Hemoglobin threshold, g/dL	508	8.0 (7.0—9.0)	137	8.5 (8.0—9.0)	0.11
Time to the first RBC transfusion, days	659	2.0 (1.0—3.0)	186	2.0 (1.0—4.0)	0.30

Hb, hemoglobin; ICU, intensive care unit; RBC, red blood cell

Continuous variables presented as median (shown first–third quartile borders)

cohort did not receive an RBC transfusion: 163 (6%) with a cardiac history and 42 (6%) without (Table S2 in Supplement 1). Reasons and triggers for RBC transfusion were similar between patients with and without cardiac history (Table S3 in Supplement 1).

Except for a higher nadir Hb threshold higher in patients with an ACS history alone, no significant difference in RBC transfusion practices was observed between patients with an ACS history and those with HF history (Table S4 in Supplement 1).

Missing data are shown in Figure S1 in Supplement 1. The distribution of stabilized IPTW between the RBC transfused and non-transfused groups, along with the mean standardized differences before and after weighting, are displayed in Figures S2 and S3 in Supplement 1, respectively.

Primary outcome

Figure 1 shows unweighted and weighted association between RBC transfusion and the composite outcome or its components In the overall cohort, each additional RBC unit was associated with higher odds of the composite outcome (OR 2.18, 95% CI 1.85–2.56; $p < 0.0001$) but no interaction by cardiac history status was observed ($p = 0.44$). Using the E-value (which quantifies how strong an unmeasured confounder would need to be to nullify the association), the minimum strength of association that an unmeasured confounder would need to have with both RBC transfusion and the composite outcome in the overall cohort to explain away the observed association was 2.32 for the point estimate and 2.06 for the lower bound of the 95% CI, conditional on measured covariates. Figure 2, panel A illustrates the incremental association between the number of transfused RBC units and the composite outcome in all studied patients. Figure 2 further shows similar association in patients with and without cardiac history, whether for the primary composite endpoint (panel B), for the 28-day risk of death (panel C) and for the risk of new-onset AKI or VWF (panel D).

Secondary outcomes

Figure 3 depicts the association between RBC transfusion and both the composite outcome and its individual

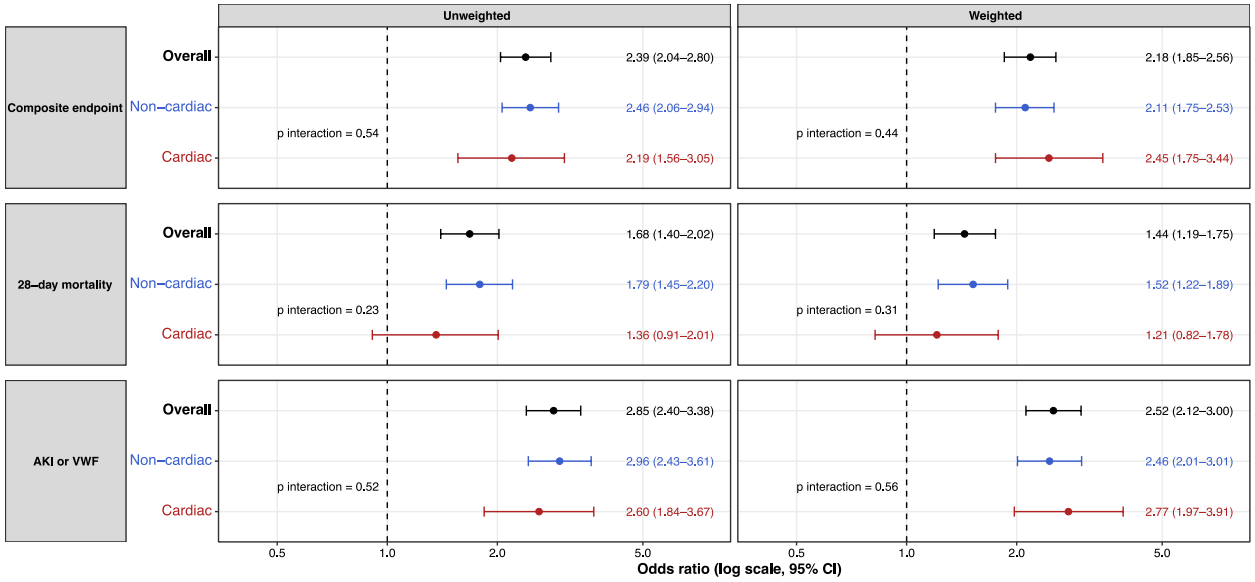


Fig. 1 Forest plot illustrating the association between the number of transfused RBC units and the odds of the primary composite outcome or its components, shown in the overall InPUT cohort and after stratification by cardiac history**.** Results are presented for the unweighted multivariable logistic-regression model and the corresponding model weighted with IPTW. Black circles are point estimates (OR per additional RBC unit); horizontal bars indicate 95% confidence intervals; the dashed vertical line indicates OR = 1. pint values report the interaction term testing whether the RBC transfusion effect differs between patients with and without a cardiac history

components, stratified by cardiac history; no ACS/HF history, ACS history alone, and HF history (with or without ACS). The odds of new-onset AKI or VWF rose in patients with a HF history (OR 3.91, 95% CI 2.51–6.16) and in patients with no ACS or HF histories (OR 2.46, 95% CI 2.00–3.01) but not in those with isolated ACS history (OR 1.55, 95% CI 0.83–2.83; interaction p = 0.047). In two subgroup analyses (patients without active bleeding as the indication for RBC transfusion and those in whom no physiological trigger influenced the decision to transfuse), results were consistent with those in the overall cohort for the primary outcome: transfusion was associated with harm in each subgroup, with no evidence of interaction with cardiac history (Table S5 in Supplement 1).

Discussion

In this analysis, RBC transfusion was commonly and similarly prescribed in patients with and without cardiac history. An incremental increase in RBC transfusion was associated, within the first 28-day, with worse organ dysfunction and death in the entire InPUT cohort. However, this detrimental association was similar among ICU patients regardless the cardiac history. Within the cardiac history subgroup, the effect appeared stronger in patients with a history of HF than in those with prior ACS.

RBC transfusion practice

RBC transfusion practices were comparable between patients with and without a cardiac history, in terms of the proportion transfused, the total units administered, and the interval from ICU admission to the first transfusion. However, the transfusion threshold in patients with a cardiac history was 8.5 g/dL, with only 25% of these patients transfused at a threshold below 8 g/dL, globally above the most recent European and North American guidelines, which recommend a threshold of 7 g/dL and 7–8 g/dL, respectively, for the general ICU population [8, 10]. Although patients with a cardiac history were more clinically severe at ICU admission, the overall reasons and triggers for RBC transfusion were similar in both groups. Given that some evidence suggests that the harmful effects of RBC transfusion can manifest in critically ill patients from the very first unit transfused, further efforts are crucial to improve adherence to the guidelines [14]. Finally, data on transfusion thresholds in critically ill patients with cardiac comorbidities remain scarce, and the two most recent guidelines do not specifically address this population. Ding et al. analysed a large cohort of 258,826 ICU episodes to assess how haemoglobin levels and cardiac history influence the association between RBC transfusion and hospital mortality. They suggested that in patients with a cardiac history but no acute cardiac event, transfusion was associated with reduced mortality only when the haemoglobin level was below 8.7 g/dL [12].

Transfusion outcome in cardiac patients

RBC transfusion was found more harmful in patients with a HF history with more new-onset AKI or VWF.

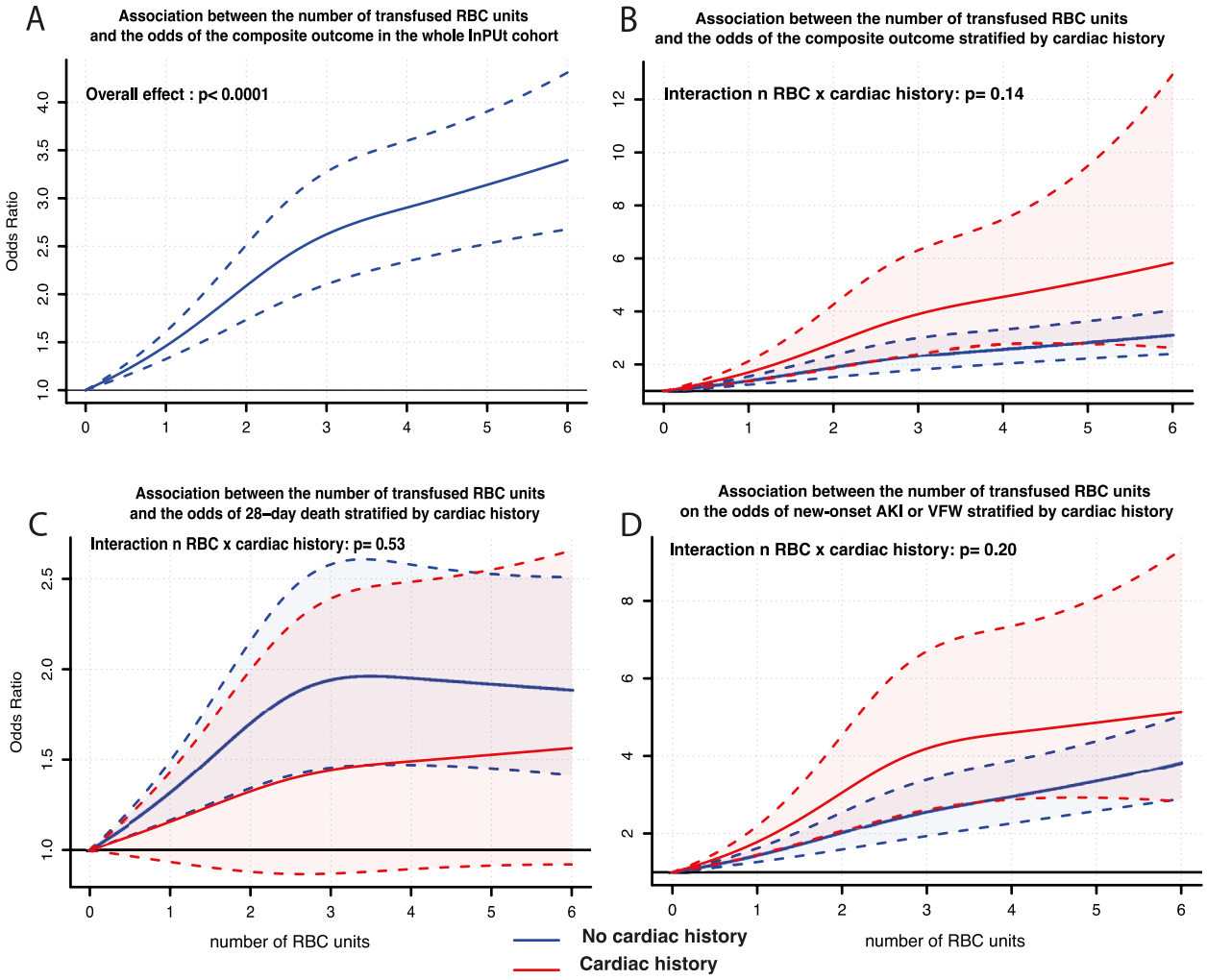


Fig. 2 Associations between the number of transfused RBC units and the primary composite outcome and its components, stratified by cardiac history (**A**) OR for the composite outcome (28-day mortality, new-onset AKI or VWF) by number of transfused RBC units in the whole study population. (**B**) OR for the composite outcome by number of transfused RBC units, stratified by cardiac history. (**C**) OR for 28-day mortality by number of transfused RBC units, stratified by cardiac history. (**D**) OR for new-onset organ dysfunction (new-onset AKI or VWF) by number of transfused RBC units, stratified by cardiac history. In all panels, the x-axis shows the number of transfused RBC units and the y-axis the corresponding OR. ORs and 95% confidence intervals were derived using weighted imputed logistic-regression models; shaded bands indicate the 95% confidence intervals, and the horizontal dashed line indicates OR = 1

In a previous large European cohort of 1,551 unselected ICU patients, our team found that in-ICU transfusion was associated with increased mortality, possibly due to transfusion-related kidney injury [14]. Moreover, a post hoc analysis of the REALITY trial investigated outcomes stratified by HF history. The analysis showed that a liberal transfusion strategy was associated with higher 30-day all-cause mortality in patients with pre-existing HF. This difference was primarily driven by deaths related to HF, in line with our findings [15]. By contrast, in the same post hoc analysis of the MINT trial, restrictive transfusion resulted in numerically (but not significantly) higher rates of death or myocardial infarction and death in patients with than in those without pre-existing HF [16]. Risk–benefit assessment of RBC transfusion in critically ill patients is delicate, particularly in those with a cardiac history.

Individual vs. collective benefits

Our results on the primary outcome, derived from observational data, should not be used to advocate for any particular transfusion strategy. The neutral result of our primary outcome suggests at first glance that a cardiac history should not influence transfusion decision-making in critically ill patients. However, the subgroup analyses also support a more nuanced and personalised transfusion strategy in critically ill patients with cardiac histories, where decisions should be guided by a comprehensive assessment of factors such as cause of admission, most often unrelated to cardiac origin, underlying diseases, oxygen supply–demand balance or haemodynamic

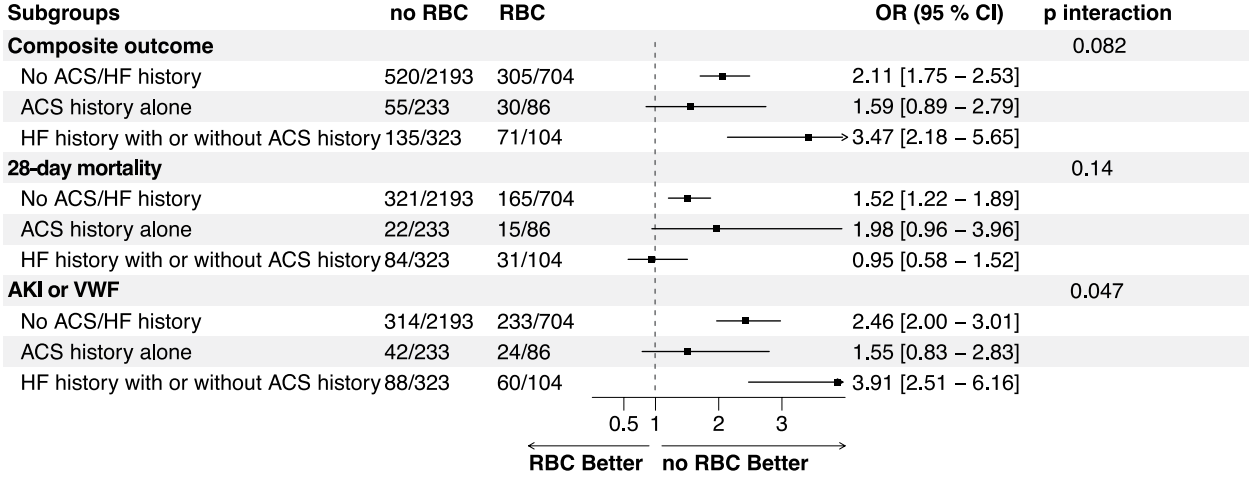


Fig. 3 Forest plot illustrating the association between RBC transfusion and outcomes across baseline cardiac history strata. Patients were grouped as having (1) no history of ACS or HF, (2) ACS history alone, or (3) HF history (with or without prior ACS). The plot displays odds ratios and 95% CI for the composite outcome, the 28-day mortality alone and AKI or VWF**.** Analyses were performed using weighted imputed logistic-regression models. The vertical dashed line indicates OR = 1

status. Although the indication for RBC transfusion should be limited to situations where the likelihood of benefit is highest, it is essential to emphasise that the best strategy remains prevention and the use of alternative treatments to increase haemoglobin level. In this cohort, the rate of iron and erythropoietin supplementations is particularly low. However, results from recent clinical trials of iron supplementation have been conflicting in HF patients with iron deficiency, although the intervention appears safe [17, 18]. Erythropoiesis-stimulating agents (ESAs) also remain a matter of debate, as their use has not been shown to reduce the need for RBC transfusion in critically ill patients [19]. However, meta-analyses of randomized controlled trials suggest that ESAs may decrease mortality in heterogeneous populations of critically ill adults [20]. French guidelines support their use in critically ill, anaemic patients (Hb 10.0–12.0 g/dL), in the absence of contraindications, to reduce RBC transfusion requirements and potentially decrease mortality [21]. In ambulatory patients with HF and anaemia, ESAs increase the risk of thromboembolic events and do not improve clinical outcomes [22]. Finally, the appropriateness of a 7 g/dL hemoglobin threshold warrants re-evaluation. Recent analyses of large ICU databases show no improvement in organ dysfunction with RBC transfusion versus no transfusion at this threshold, suggesting that individualized targets beyond a fixed 7 g/dL cut-off merit further evaluation [23].

Limitations

As for any observational study, causality cannot be ascertained. Despite the use of weighting methods based on the propensity score, we cannot exclude the unmeasured confounding that may have influenced the assessment of RBC transfusion association with outcome. However, we found, using an E-value sensitivity analysis, that our adjustment is probably robust as only a confounder exhibiting ≥ 2.3-fold associations with both transfusion and the primary composite outcome could fully account for the observed effect. The inclusion of patients with specific conditions (e.g., acute brain injury, post-cardiac surgery, cardiology admissions), for whom transfusion practices are better defined, may have introduced heterogeneity and limited the interpretability of our findings despite statistical adjustment. Despite the large overall cohort size, the number of patients actually exposed to RBC transfusion, particularly among those with a cardiac history, was limited, with most patients receiving only one unit and many never reaching hemoglobin levels at which transfusion is typically considered. As a result, the effective sample size for assessing the association of interest was substantially reduced, likely limiting statistical power and increasing the risk of both type I and type II errors, particularly in the context of residual confounding. This power issue is particularly relevant for subgroup analyses; for instance, in the ACS-only subgroup, only 86 patients received an RBC transfusion. ACS and HF were only recorded on the medical history and not stratified according to their specific characteristics or severity. Similarly, to better understand our results more data on the haemodynamic status and cardiac function would have been necessary. Specifically, data on ejection fraction, cardiac index and biomarkers such as brain natriuretic peptides are lacking. While focusing on RBC transfusion, we did not specifically assess the impact of other blood products on outcomes. Notably, plasma transfusion practices differed between patients with and without a cardiac history in our study. Finally, we only

included the continent of origin in the propensity score calculation and we cannot rule out that residual heterogeneity and clustering effects remain.

In conclusion, RBC transfusion is a common practice in critically ill patients often outside the recommended thresholds and is associated with increased 28-day mortality or organ dysfunction, most notably new-onset AKI or VWF. However, a cardiac history per se does not confer additional transfusion-related risk, except in patients with prior HF, highlighting the need for individualized transfusion strategies in this vulnerable subgroup.

Abbreviations

ACS	Acute coronary syndrome
AKI	Acute kidney injury
CI	Confidence interval
ESA	Erythropoiesis-stimulating agents
HF	Heart failure
Hb	Hemoglobin
ICU	Intensive care unit
InPUT	International point prevalence study of intensive care unit transfusion practices
IPTW	Inverse probability of treatment weighting
OR	Odds ratio
R	R statistical computing environment
RBC	Red blood cell
RCT	Randomized controlled trial
VWF	Ventilatory weaning failure

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05745-5.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

Group Information

The InPUT Study Group members appear in Supplement Material file 2.

Responsibility for the integrity of the analysis

The statisticians did not have direct access to the raw data. The statisticians developed the analysis script using mock-up data and sent it to the designated statistician, Dr Schenk, in the Netherlands, who executed the script on the full dataset. Accordingly, Dr Schenk, who holds the raw data, assumes full responsibility for the integrity of the data and the accuracy of the analysis.

Author contributions

Conceptualization: AK and AM Formal analysis: AK and KD Writing—original draft preparation: AK, AM, GB, BL, NG, JB Writing—review and editing: All authors Administrative, technical, or material support: JS.

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Data availability

No. Additional information: Explanation for why data not available: sub-studies or secondary analyses can be requested by following the procedure as stated. Reasonable data request will be taken in consideration. Additional, related documents can be requested separately.

Declarations

Ethics approval and consent to participate

Approval from the institutional review board of the Amsterdam University Medical Center, followed by approval from relevant national and local ethical committees. Informed consent was obtained according to national regulations, either orally or in writing from the patient or legal representative; in some countries, consent was waived due to the noninvasive, observational design.

Consent for publication

Not applicable.

Competing interests

Dr Cecconi reported receiving personal fees from Edwards Lifesciences, GE Healthcare, and Directed Systems outside the submitted work. Dr Feldheiser reported receiving personal fees from Baxter and Medtronic outside the submitted work. Dr Scheeren reported serving as senior medical director for Edwards Lifesciences (Garching, Germany). Dr McQuilten reported receiving grants from the Australian National Blood Authority and the National Health and Medical Research Council during the conduct of the study. Dr Flint reported receiving grants from the Australian National Blood Authority and Blood Synergy (Monash University) during the conduct of the study. Dr Piagnerelli reported receiving grants from the Centre Fédéral d'Expertise Belge – KCE grant for the COVID-19 study outside the submitted work. Dr Gurjar reported receiving royalties for edited books (Manual of ICU Procedures and Textbook of Ventilation, Fluids, Electrolytes and Blood Gases) from the publisher Jaypee Brothers Medical Publishers (Pvt) Ltd, New Delhi. Dr Pfortmueller reported receiving grants from Orion Pharma, Abbott Nutrition International, B. Braun Medical AG, CSEM AG, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, Nestlé, Pierre Fabre Pharma AG, Pfizer, Bard Medica SA, Abbott AG, Anandic Medical Systems, PanGas AG Healthcare, Bracco, Hamilton Medical AG, Fresenius Kabi, Getinge Group Maquet AG, Dräger AG, Teleflex Medical GmbH, GlaxoSmithKline, Merck Sharp and Dohme AG, Eli Lilly and Co, Baxter, Boehringer Ingelheim, Aseptuva, Astellas, AstraZeneca, CSL Behring, Novartis, Covidien, and Nycomed outside the submitted work; the funds were paid into departmental funds and no personal financial gain applied. Dr Nielsen reported receiving personal fees from Adrenomed outside the submitted work. Dr Vlaar reported receiving personal fees from a VIDI grant (ZonMW: 0915017). Remaining authors declared no conflict. Dr Mebazaa reported grants from Roche, 4teen4, Sphyngotec, Abbott Diagnostics, Windtree; consulting fees from Roche, Adrenomed, Corteria, Fire-1, and Johnson & Johnson; is co-inventor of a patent (owned by S-Form Pharma) on combined therapies to treat dyspnoea in heart failure; participated on a Data Safety Monitoring Board or Advisory Board for SECRET-HF, sponsored by the French Government, for S-Form, SunWaves, and Implicity; received honorarium for lectures from Merck, Novartis, Roche, and Bayer; and received equipment from Sphyngotec. Dr Kimmoun participated on a Data Safety Monitoring Board or Advisory Board for the LEVOSAH trial and PROCARD trial; and received financial support for attending meetings, travel, or both for the Critical Care Clinical Trialists Workshop 2024 and 2025. Dr Baudry reported reports personal fees from Abbott, AstraZeneca, Boehringer Ingelheim and Novartis, outside the submitted work. Dr Girerd reported honoraria from AstraZeneca, Bayer, Boehringer, Cardiostory, Lilly, Echosens, NP medical, Novartis, Novo Nordisk, Roche diagnostics. Dr Levy reported receiving personal fees from Abiomed, Gettinge, Baxter, Novartis, Sanofi, Amomed, and Orion, outside the submitted work.

Additional Information

This cohort was registered at the NetherlandsTrial Registry No.NL9049 (Date of registration: November 16, 2020, https://trialsearch.who.int/Trial2.aspx?TrialID=NL-OMON28052).

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