

First ICU-day red blood cell transfusion burden and subsequent ICU delirium after cardiac surgery: a 24-h landmark study using MIMIC-IV

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Article

Keywords: Postoperative delirium, Red blood cell transfusion, Cardiac surgery, Intensive care unit, Anemia, Critical care

Posted Date: October 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11062424/v1>

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Additional Declarations: No competing interests reported.

Abstract

Postoperative delirium is common after cardiac surgery and is associated with adverse outcomes. Red blood cell (RBC) transfusion is frequently administered during the early postoperative period in the setting of anemia, bleeding, and physiological instability, but its association with delirium developing thereafter remains uncertain. We conducted a retrospective cohort study using MIMIC-IV and a 24-h landmark design. Among 3,488 patients without documented delirium during the first 24 h, 916 received RBC transfusion. Subsequent ICU delirium occurred in 11.1% of transfused and 3.4% of nontransfused patients. RBC transfusion was associated with higher odds of subsequent delirium after adjustment (aOR 2.56, 95% CI 1.72–3.82), with attenuation in the extended model (aOR 1.74, 95% CI 1.13–2.68). The largest estimate occurred with > 700 mL (aOR 3.75, 95% CI 2.36–5.94). Among transfused patients with pre-transfusion hemoglobin available, each 350-mL increase in RBC volume was associated with higher odds of subsequent delirium after adjustment for pre-transfusion hemoglobin and baseline covariates (n = 839; adjusted OR 1.24, 95% CI 1.12–1.37). Competing-risk analysis yielded a similar association (sHR 1.74, 95% CI 1.15–2.63). Early RBC transfusion was associated with subsequent ICU delirium, although residual confounding by indication remains possible.

Introduction

Postoperative delirium is a common complication after cardiac surgery and is associated with prolonged mechanical ventilation, longer intensive care unit (ICU) and hospital stays, and increased mortality [1]. Its reported incidence varies with the assessment tool and screening regimen; a recent meta-analysis of studies using validated methods estimated a pooled incidence of 23% [2]. Delirium after cardiac surgery has also been associated with early postoperative cognitive decline, less favorable cognitive trajectories over follow-up, subsequent dementia in older adults, and long-term mortality [3–6]. Its development is multifactorial and reflects the interaction between baseline vulnerability and surgical and postoperative factors [7]. An updated meta-analysis identified older age, atrial fibrillation, diabetes, combined cardiac procedures, and longer cardiopulmonary bypass time as risk factors [8].

The early postoperative period is also when red blood cell (RBC) transfusion is commonly administered after cardiac surgery to correct anemia, replace blood loss, and support oxygen delivery. Transfusion decisions are based not only on hemoglobin concentration but also on ongoing bleeding, ischemic risk, and the patient's overall condition [9]. Early RBC transfusion may therefore reflect a more complicated postoperative course. RBC transfusion may alter inflammatory and immune responses [10], and perioperative inflammation and neuroinflammation have been linked to postoperative delirium [11]. Thus, an association between early RBC transfusion and delirium may reflect the indication for transfusion, effects of the transfusion itself, or both.

Previous studies of transfusion and postoperative delirium after cardiac surgery have reported inconsistent findings. Large-volume perioperative RBC transfusion and postoperative blood product transfusion were associated with delirium in some studies, whereas another study found that only

platelet transfusion remained independently associated after adjustment [12–14]. A more recent cardiac surgery study found no association between RBC transfusion volume and delirium [15]. In a large general surgical cohort, intraoperative RBC transfusion was associated with postoperative delirium overall, but not in the cardiac surgery subgroup [16]. These studies differed in the blood products examined and in the timing and amount of transfusion. A systematic review also found that the temporal order of transfusion and delirium was unclear in most included studies [17]. Whether RBC transfusion during the first 24 h after ICU admission is associated with subsequent ICU delirium remains unclear.

We therefore conducted a retrospective cohort study using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database and a 24-h landmark design. RBC transfusion was assessed during the first 24 h after ICU admission, and subsequent delirium was assessed after this window among patients with no documented delirium during the first 24 h. We examined whether early postoperative RBC transfusion, considered as any transfusion and by cumulative volume, was associated with subsequent ICU delirium. We hypothesized that early RBC transfusion would be associated with a higher risk of subsequent ICU delirium.

Materials and Methods

Study design and data source

This retrospective cohort study used version 3.1 of the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, which contains deidentified electronic health record data from patients admitted to the intensive care units at Beth Israel Deaconess Medical Center [18, 19]. Database access was obtained after completion of the required human-subjects research training (CITI Program record ID: 76744882). The collection and sharing of MIMIC-IV data were approved by the institutional review board of Beth Israel Deaconess Medical Center, which granted a waiver of individual informed consent because the data were deidentified. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [20]. Clinical data were extracted from MIMIC-IV using structured query language.

Study population

Adults aged 18 years or older who underwent coronary artery bypass grafting (CABG), open valve surgery, or open thoracic aortic surgery were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS), procedure codes. Patients who underwent transcatheter or percutaneous valve procedures were excluded. For patients with multiple eligible postoperative ICU stays, only the first stay was included. Detailed procedure codes are provided in Supplementary Table S1.

Patients with an ICU stay shorter than 24 hours were excluded. The 24-hour landmark cohort included patients with at least 1 valid Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

assessment during the first 24 hours after ICU admission, no positive CAM-ICU assessment during this period, and at least 1 valid CAM-ICU assessment after the landmark. A valid assessment was defined as a CAM-ICU result recorded as positive or negative. This design separated exposure assessment during the first 24 hours from subsequent outcome ascertainment [21, 22]. The 24-hour landmark design is illustrated in Fig. 2.

The first 24 h after ICU admission constituted the exposure window, during which RBC transfusion burden and early clinical variables were assessed. Patients with a positive CAM-ICU assessment or no valid CAM-ICU assessment during this window were excluded. Subsequent ICU delirium was assessed after the 24-h landmark until ICU exit, and at least one valid post-landmark CAM-ICU assessment was required. Abbreviations: CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; RBC, red blood cell.

Exposure

The exposure was RBC transfusion administered during the first 24 hours after ICU admission. The primary analysis compared patients who received any RBC transfusion with those who received no RBC transfusion. Cumulative transfusion volume was examined in 4 categories: 0, greater than 0 to 350, greater than 350 to 700, and greater than 700 mL. Transfusion volume was also analyzed per 350-mL increase and as a continuous variable using restricted cubic splines.

Outcome

The primary outcome was subsequent ICU delirium, defined as any positive CAM-ICU assessment recorded after the 24-hour landmark and before ICU exit. The CAM-ICU has been validated for delirium assessment in critically ill patients, including patients receiving mechanical ventilation [23].

Covariates

Baseline covariates included age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, and atrial fibrillation. Early postoperative variables measured during the first 24 hours after ICU admission included first-day minimum hemoglobin concentration, the first lactate concentration, use of vasoactive or inotropic agents, Acute Physiology Score III (APS III) [24], and Sequential Organ Failure Assessment-2 (SOFA-2) score [25]. Plasma and platelet transfusions, benzodiazepine exposure, and cumulative duration of invasive mechanical ventilation during the first 24 hours were included in additional models. Detailed variable definitions are provided in Supplementary Table S2.

Statistical analysis

Continuous variables are presented as medians with IQRs and categorical variables as numbers and percentages. Continuous variables were compared using the Wilcoxon rank sum test. Categorical variables were compared using the Pearson χ^2 test or Fisher exact test, as appropriate. Missing data were not imputed. Analyses were based on complete cases for the variables included in each model. Missingness for individual variables is reported in Supplementary Table S3. All eligible patients were included, and no formal sample size calculation was performed.

Multivariable logistic regression was used to examine the association between RBC transfusion during the first 24 hours after ICU admission and subsequent ICU delirium. Results are reported as odds ratios (ORs) with 95% CIs. The primary adjusted model included age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, atrial fibrillation, first-day minimum hemoglobin concentration, first lactate concentration, vasoactive or inotropic drug use, and APS III. Multicollinearity was assessed using variance inflation factors. Condition indices and detailed diagnostics are reported in Supplementary Table S9. Because first-day minimum hemoglobin, lactate, vasoactive or inotropic drug use, and APS III were assessed during the same 24-hour period as RBC transfusion, the primary adjusted model was interpreted as an association model rather than as an estimate of the causal effect of transfusion.

Cumulative RBC transfusion volume was examined using the 4 categories defined above. Transfusion volume was also analyzed per 350-mL increase and with restricted cubic splines. Knots were placed at 0, 350, 700, and 2100 mL, with 0 mL as the reference. Likelihood ratio tests were used to assess the overall association and nonlinearity.

First-day minimum hemoglobin concentration and RBC transfusion were examined jointly in 4 groups defined by a hemoglobin concentration of less than 8 or at least 8 g/dL and receipt or nonreceipt of RBC transfusion. Continuous hemoglobin concentration was not included separately in this model. An interaction term between hemoglobin category and RBC transfusion status was used to assess effect modification. Additional analyses using first-day minimum hemoglobin thresholds of 7.5 and 9.0 g/dL and a model including both APS III and SOFA-2 are reported in Supplementary Table S5.

Among patients who received RBC transfusion during the first 24 hours, an additional analysis was performed using hemoglobin measured before the first transfusion. Pre-transfusion hemoglobin was defined as the most recent hemoglobin measurement obtained strictly before the first RBC administration and within the preceding 6 hours. When multiple hemoglobin values were recorded at the selected time point, their mean was used. Cumulative RBC volume was examined per 350-mL increase in relation to subsequent ICU delirium after adjustment for the baseline covariates listed above and pre-transfusion hemoglobin. An interaction term between continuous pre-transfusion hemoglobin and RBC volume was used to assess effect modification. Additional analyses using the minimum hemoglobin value when multiple measurements were recorded at the same time point, a pre-transfusion hemoglobin threshold of 8 g/dL, and further adjustment for transfusion timing and early postoperative variables were performed as sensitivity analyses.

In sensitivity analyses, SOFA-2 was substituted for APS III. Plasma and platelet transfusions, benzodiazepine exposure, and duration of invasive mechanical ventilation during the first 24 hours were added separately to the primary adjusted model and together in an extended sensitivity model. A model including baseline covariates only was also examined in the available baseline-complete cohort and after restriction to the primary complete-case cohort.

Propensity scores for RBC transfusion were estimated using logistic regression including age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, and atrial fibrillation [26]. Laboratory measurements, severity scores, treatments, and organ-support variables recorded during the first 24 hours were not included in the propensity score model. Stabilized inverse probability of treatment weights were used to estimate the average treatment effect. Weighted logistic regression with robust standard errors was used to estimate ORs and 95% CIs. Weights were also truncated at the 1st and 99th percentiles [27]. Covariate balance was assessed using absolute standardized mean differences, with values less than 0.10 considered acceptable. Weighting diagnostics are reported in Supplementary Table S4.

Additional analyses were performed after restricting the cohort to patients with an ICU stay of at least 48 hours, excluding patients who underwent thoracic aortic surgery, and excluding patients who received more than 2100 mL of RBCs.

To examine differences in delirium observation opportunity, the number of post-landmark CAM-ICU assessments, time from the landmark to the first assessment, duration of CAM-ICU follow-up, number of assessments per follow-up day, and post-landmark ICU length of stay were compared between the transfusion groups using the Wilcoxon rank sum test.

Because ICU exit precluded further assessment of ICU delirium, ICU exit without a previously observed positive post-landmark CAM-ICU assessment was treated as a competing event. Follow-up began at the 24-hour landmark. Delirium event time was defined as the time of the first positive post-landmark CAM-ICU assessment, and competing-event time was defined as the recorded ICU exit time. Fine-Gray subdistribution hazard models were used, with the same covariates as those in the corresponding logistic regression models [28].

All P values were 2-sided, and $P < 0.05$ was considered statistically significant. No adjustment was made for multiple comparisons; secondary and sensitivity analyses were considered exploratory. Analyses were performed using Python version 3.13.5 (Python Software Foundation), except for the competing-risk analyses, which were performed using R version 4.4.3 (R Foundation for Statistical Computing) with the `cmprsk` package, version 2.2–12.

Results

Study population and baseline characteristics

A total of 9825 adult patients who underwent cardiac surgery were identified. After excluding 13 patients with transcatheter or percutaneous valve procedure codes, 9812 patients remained. Of these, 470 had an ICU stay of less than 24 hours. We further excluded 208 patients with a positive CAM-ICU assessment during the first 24 hours, 2980 without a valid CAM-ICU assessment during this period, and 2666 without a valid CAM-ICU assessment after the 24-hour landmark. The final cohort included 3488 patients (Fig. 1).

Adult patients undergoing CABG, surgical valve surgery, or thoracic aortic surgery were identified using ICD-9-CM and ICD-10-PCS procedure codes. Transcatheter or percutaneous valve procedures and ICU stays shorter than 24 h were excluded. The landmark cohort required at least 1 valid CAM-ICU assessment during the first 24 h, no positive CAM-ICU assessment during this period, and at least 1 valid assessment after the landmark. Abbreviations: CABG, coronary artery bypass grafting; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care IV.

Subsequent ICU delirium occurred in 189 patients (5.4%). Patients who developed delirium were older, less often male, and more likely to have congestive heart failure, renal disease, cerebrovascular disease, or atrial fibrillation. They also had higher APS III and SOFA-2 scores, lower first-day minimum hemoglobin concentrations, and more frequent blood product transfusion during the first 24 hours (Table 1).

Table 1
Patient and Perioperative Characteristics According to Subsequent ICU Delirium Status

Variable	Overall (n = 3,488)	No subsequent ICU delirium (n = 3,299)	Subsequent ICU delirium (n = 189)	P value	Missing, n
Age, years	68.6 [61.1, 76.1]	68.3 [60.9, 75.9]	74.3 [68.5, 79.9]	< 0.001	0
Male sex	2423 (69.5%)	2313 (70.1%)	110 (58.2%)	< 0.001	0
Body mass index, kg/m ²	28.2 [24.8, 32.1]	28.3 [24.8, 32.1]	28.0 [24.4, 31.5]	0.174	30
Surgical category				< 0.001	0
CABG only	1870 (53.6%)	1793 (54.3%)	77 (40.7%)		0
Valve only	846 (24.3%)	802 (24.3%)	44 (23.3%)		0
CABG + Valve	498 (14.3%)	454 (13.8%)	44 (23.3%)		0
Thoracic aortic surgery	274 (7.9%)	250 (7.6%)	24 (12.7%)		0
Hypertension	1863 (53.4%)	1780 (54.0%)	83 (43.9%)	0.007	0
Diabetes mellitus	1304 (37.4%)	1229 (37.3%)	75 (39.7%)	0.502	0
Congestive heart failure	1135 (32.5%)	1045 (31.7%)	90 (47.6%)	< 0.001	0
Renal disease	712 (20.4%)	646 (19.6%)	66 (34.9%)	< 0.001	0
Cerebrovascular disease	390 (11.2%)	341 (10.3%)	49 (25.9%)	< 0.001	0
Atrial fibrillation	1150 (33.0%)	1054 (31.9%)	96 (50.8%)	< 0.001	0
APS III score	34.0 [27.0, 45.0]	34.0 [27.0, 44.0]	45.0 [33.0, 59.0]	< 0.001	0
SOFA-2 score	7.0 [6.0, 9.0]	7.0 [6.0, 9.0]	10.0 [9.0, 12.0]	< 0.001	0

Variable	Overall (n = 3,488)	No subsequent ICU delirium (n = 3,299)	Subsequent ICU delirium (n = 189)	P value	Missing, n
First lactate, mmol/L	2.0 [1.5, 2.7]	2.0 [1.5, 2.6]	2.2 [1.5, 2.9]	0.074	368
First-day minimum hemoglobin, g/dL	8.8 [7.6, 10.0]	8.8 [7.6, 10.0]	7.8 [6.9, 9.2]	< 0.001	6
First-day minimum hemoglobin < 8 g/dL	1135 (32.6%)	1035 (31.4%)	100 (53.2%)	< 0.001	6
Vasoactive/inotropic drug use	3131 (89.8%)	2965 (89.9%)	166 (87.8%)	0.367	0
Any RBC transfusion	916 (26.3%)	814 (24.7%)	102 (54.0%)	< 0.001	0
RBC transfusion volume, mL	0.0 [0.0, 280.0]	0.0 [0.0, 0.0]	286.0 [0.0, 981.0]	< 0.001	0
Platelet transfusion	468 (13.4%)	418 (12.7%)	50 (26.5%)	< 0.001	0
Plasma transfusion	182 (5.2%)	160 (4.8%)	22 (11.6%)	< 0.001	0
Benzodiazepine exposure	329 (9.4%)	302 (9.2%)	27 (14.3%)	0.019	0
Invasive mechanical ventilation	2493 (71.5%)	2343 (71.0%)	150 (79.4%)	0.013	0
Invasive ventilation duration, h	6.0 [0.0, 12.0]	6.0 [0.0, 11.3]	15.0 [4.0, 19.2]	< 0.001	0

Values are median [interquartile range] or n (%). P values were calculated using Mann-Whitney U tests, chi-square tests, or Fisher exact tests, as appropriate. Percentages were calculated using non-missing denominators. APS III, Acute Physiology Score III; CABG, coronary artery bypass grafting; ICU, intensive care unit; RBC, red blood cell; SOFA-2, Sequential Organ Failure Assessment 2.

First ICU-day RBC transfusion and subsequent ICU delirium

Among 3488 patients, 916 received RBC transfusion during the first 24 hours after ICU admission and 2572 did not. Subsequent ICU delirium occurred in 102 transfused patients and 87 nontransfused patients (11.1% vs 3.4%). Patient and perioperative characteristics according to first ICU-day RBC transfusion status are provided in Supplementary Table S12.

In the unadjusted analysis, RBC transfusion was associated with higher odds of subsequent ICU delirium (OR, 3.58; 95% CI, 2.66–4.82; $P < 0.001$). The primary complete-case analysis included 3098 patients, of whom 171 developed delirium. After adjustment for demographic characteristics, surgical category,

comorbidities, first-day minimum hemoglobin concentration, first lactate concentration, vasoactive or inotropic drug use, and APS III, the aOR was 2.56 (95% CI, 1.72–3.82; $P < 0.001$).

When SOFA-2 was substituted for APS III, the aOR was 2.06 (95% CI, 1.36–3.12; $P < 0.001$). After plasma and platelet transfusions were added to the model, the aOR was 2.26 (95% CI, 1.48–3.45; $P < 0.001$) (Table 2). The maximum variance inflation factor was 1.73 (Supplementary Table S9).

Table 2
Association between first ICU-day RBC transfusion and subsequent ICU delirium

Model	N	Events	OR	95% CI	P value
Unadjusted	3488	189	3.58	2.66–4.82	< 0.001
Primary adjusted model	3098	171	2.56	1.72–3.82	< 0.001
SOFA-2 model instead of APS III	3098	171	2.06	1.36–3.12	< 0.001
Primary adjusted model + plasma/platelet transfusion	3098	171	2.26	1.48–3.45	< 0.001
Primary adjusted model + benzodiazepine exposure	3098	171	2.56	1.72–3.82	< 0.001
Primary adjusted model + invasive ventilation duration	3098	171	1.83	1.21–2.76	0.004
Extended sensitivity model	3098	171	1.74	1.13–2.68	0.012

ORs are for any RBC transfusion within the first 24 h after ICU admission. The primary adjusted model included age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, atrial fibrillation, first-day minimum hemoglobin, first lactate, vasoactive/inotropic drug use, and APS III. The SOFA-2 model used first-day SOFA-2 instead of APS III. The extended sensitivity model additionally included plasma and platelet transfusions, benzodiazepine exposure, and invasive mechanical ventilation duration. CI, confidence interval.

RBC transfusion volume and first-day minimum hemoglobin concentration

The incidence of subsequent ICU delirium was 3.4% among patients who received no RBC transfusion, 7.4% among those who received greater than 0 to 350 mL, 7.6% among those who received greater than 350 to 700 mL, and 15.8% among those who received more than 700 mL.

Compared with no RBC transfusion, the aOR was 1.94 (95% CI, 1.02–3.70; $P = 0.045$) for greater than 0 to 350 mL, 1.80 (95% CI, 1.05–3.10; $P = 0.032$) for greater than 350 to 700 mL, and 3.75 (95% CI, 2.36–5.94; $P < 0.001$) for more than 700 mL (Table 3).

Table 3

Association between first ICU-day RBC transfusion volume categories and subsequent ICU delirium

RBC volume category	Patients, n	Delirium, n (%)	Primary adjusted OR (95% CI)	P value	SOFA-2 model OR (95% CI)	P value	Extended sensitivity OR (95% CI)	P value
0 mL	2572	87 (3.4%)	Reference		Reference		Reference	
> 0–350 mL	202	15 (7.4%)	1.94 (1.02–3.70)	0.045	1.72 (0.88–3.37)	0.112	1.69 (0.88–3.26)	0.114
> 350–700 mL	314	24 (7.6%)	1.80 (1.05–3.10)	0.032	1.45 (0.82–2.57)	0.196	1.35 (0.77–2.35)	0.294
> 700 mL	400	63 (15.8%)	3.75 (2.36–5.94)	< 0.001	2.81 (1.74–4.54)	< 0.001	2.30 (1.36–3.88)	0.002

Observed incidence was calculated in the full cohort (n = 3,488). Adjusted ORs were estimated in the complete-case cohort (n = 3,098; events = 171), using 0 mL as the reference. The extended sensitivity model additionally accounted for plasma and platelet transfusions, benzodiazepine exposure, and invasive mechanical ventilation duration. RBC volume categories of 0, greater than 0 to 350, greater than 350 to 700, and greater than 700 mL were prespecified based on the distribution of recorded transfusion volumes. The greater-than-700-mL category should not be interpreted as a validated clinical cutoff.

Table 3

(continued). Continuous effect of RBC transfusion volume

Model	Adjusted OR per 350 mL increase (95% CI)	P value
Primary adjusted model	1.27 (1.17–1.38)	< 0.001
SOFA-2 replacement model	1.19 (1.09–1.29)	< 0.001
Extended sensitivity model	1.18 (1.08–1.30)	< 0.001

Restricted cubic spline analysis showed an association between increasing RBC transfusion volume and subsequent ICU delirium (P < 0.001), without evidence of nonlinearity (P = 0.12) (Fig. 3). Results for each 350-mL increase are shown in Table 3.

Restricted cubic spline analysis was used to examine the association between cumulative RBC transfusion volume during the first 24 h after ICU admission and subsequent ICU delirium. The solid line represents adjusted odds ratios, and the shaded area represents 95% confidence intervals. The analysis included 3,098 complete cases with 171 delirium events and was adjusted for age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, atrial fibrillation, first-day minimum hemoglobin concentration, first lactate concentration,

vasoactive or inotropic drug use, and APS III. Knots were placed at 0, 350, 700, and 2,100 mL, with 0 mL used as the reference. The overall association was statistically significant ($P < 0.001$), with no statistically significant evidence of nonlinearity ($P = 0.12$). Abbreviations: APS III, Acute Physiology Score III; CI, confidence interval; ICU, intensive care unit; RBC, red blood cell.

Using patients with a first-day minimum hemoglobin concentration of at least 8 g/dL who did not receive RBC transfusion as the reference group, patients with first-day minimum hemoglobin of at least 8 g/dL who received transfusion had higher odds of subsequent delirium (aOR, 2.22; 95% CI, 1.28–3.83; $P = 0.004$). Among patients with first-day minimum hemoglobin less than 8 g/dL, the aOR was 1.07 (95% CI, 0.61–1.86; $P = 0.82$) without transfusion and 2.42 (95% CI, 1.58–3.73; $P < 0.001$) with transfusion. The interaction between first-day minimum hemoglobin category and RBC transfusion status was not statistically significant (P for interaction = 0.95) (Supplementary Table S10).

Pre-transfusion hemoglobin analysis

Among the 916 patients who received RBC transfusion during the first 24 hours, 841 (91.8%) had a hemoglobin measurement within 6 hours before the first transfusion. The median interval between the selected hemoglobin measurement and first RBC administration was 61 minutes. The adjusted analysis included 839 patients with 91 subsequent delirium events. After adjustment for baseline covariates and pre-transfusion hemoglobin, each 350-mL increase in cumulative RBC volume was associated with higher odds of subsequent ICU delirium (OR, 1.24; 95% CI, 1.12–1.37; $P < 0.001$). Pre-transfusion hemoglobin was not associated with subsequent delirium (OR per 1-g/dL increase, 0.94; 95% CI, 0.81–1.10; $P = 0.45$). There was no significant interaction between pre-transfusion hemoglobin and RBC volume (P for interaction = 0.42) (Supplementary Table S14).

Sensitivity and weighting analyses

The baseline-adjusted OR was 2.44 (95% CI, 1.77–3.37; $P < 0.001$) in 3,458 patients and 2.45 (95% CI, 1.73–3.47; $P < 0.001$) when restricted to the 3,098 patients included in the primary adjusted model (Supplementary Table S13).

The aOR was 2.56 (95% CI, 1.72–3.82; $P < 0.001$) after adjustment for benzodiazepine exposure and 1.83 (95% CI, 1.21–2.76; $P = 0.004$) after adjustment for the duration of invasive mechanical ventilation during the first 24 hours. When plasma and platelet transfusions, benzodiazepine exposure, and mechanical ventilation duration were included together, the aOR was 1.74 (95% CI, 1.13–2.68; $P = 0.012$).

In the stabilized inverse probability of treatment-weighted analysis, the weighted OR was 2.24 (95% CI, 1.64–3.05; $P < 0.001$). After weights were truncated at the 1st and 99th percentiles, the weighted OR was 2.29 (95% CI, 1.68–3.13; $P < 0.001$). The maximum absolute standardized mean difference after weighting was 0.037. Results of the analyses restricted to patients with an ICU stay of at least 48 hours, excluding thoracic aortic surgery, and excluding RBC transfusion volumes greater than 2100 mL are shown in Supplementary Table S11.

Delirium surveillance and competing-risk analysis

Patients who received RBC transfusion underwent more post-landmark CAM-ICU assessments than those who did not receive transfusion (median, 5 [IQR, 2–10] vs 3 [IQR, 1–6]; $P < 0.001$). The first post-landmark assessment occurred slightly later in the transfusion group (median, 9.60 [IQR, 4.05–12.58] vs 8.80 [IQR, 3.14–11.35] hours after the landmark; $P < 0.001$).

The duration of CAM-ICU follow-up was longer in the transfusion group (median, 1.87 [IQR, 0.88–3.35] vs 0.97 [IQR, 0.44–2.26] days; $P < 0.001$), as was post-landmark ICU length of stay (median, 2.21 [IQR, 1.21–4.03] vs 1.37 [IQR, 0.95–2.81] days; $P < 0.001$). The number of assessments per follow-up day was similar between groups (median, 2.67 [IQR, 2.11–4.14] vs 2.70 [IQR, 2.06–4.50]; $P = 0.54$) (Supplementary Table S6).

In the competing-risk analysis, ICU exit without previously observed delirium was treated as a competing event. RBC transfusion was associated with subsequent ICU delirium in the final adjusted model (subdistribution hazard ratio, 1.74; 95% CI, 1.15–2.63; $P = 0.009$) (Supplementary Table S7 and Supplementary Figure S1). Cumulative incidence estimates at prespecified time points are provided in Supplementary Table S8.

Discussion

In this 24-hour landmark cohort of adults admitted to the ICU after cardiac surgery, RBC transfusion during the first 24 hours was associated with subsequent ICU delirium among patients without documented delirium during that period. The estimate was attenuated after other blood products, benzodiazepine exposure, and duration of invasive mechanical ventilation were added to the model. The largest estimate was observed in patients who received more than 700 mL, although the spline analysis did not identify a clear volume threshold. The association did not differ according to whether first-day minimum hemoglobin concentration was below or at least 8 g/dL. Among transfused patients, greater cumulative RBC volume was also associated with subsequent delirium after adjustment for hemoglobin measured before the first transfusion, without evidence of interaction between pre-transfusion hemoglobin and RBC volume. The observed incidence of 5.4% applies only to delirium documented after the landmark in the selected cohort and should not be compared directly with overall postoperative delirium estimates, which vary with assessment tools and screening regimens [2].

The main contribution of this study was the separation of early postoperative RBC transfusion from subsequent delirium assessment. Previous studies examined different blood products and transfusion periods [12–16]. A systematic review found that the temporal order of transfusion and delirium was often unclear [17]. In a recent large surgical cohort, Xu et al. found an association between intraoperative RBC transfusion and postoperative delirium overall, but not in the cardiac surgery subgroup [16]. That study examined intraoperative transfusion and delirium within 7 postoperative days, whereas our analysis examined RBC transfusion during the first ICU day and delirium documented only after the 24-hour landmark. Our findings therefore address a narrower question: whether early postoperative RBC transfusion is associated with delirium recorded after the exposure window, rather than whether perioperative transfusion is associated with postoperative delirium in general.

The attenuation of the association after additional adjustment is clinically informative. RBC transfusion after cardiac surgery is generally administered in the setting of anemia, blood loss, ongoing bleeding, hemodynamic instability, or concern about inadequate oxygen delivery [9]. In the present analysis, adjustment for benzodiazepine exposure alone did not materially alter the RBC estimate, whereas the estimate was attenuated after adjustment for other blood products and invasive mechanical ventilation duration. This pattern suggests that the observed association may partly reflect the broader severity of postoperative illness and treatment burden accompanying transfusion. However, because these variables were measured during the same 24-hour window as RBC transfusion, they may represent treatment indications, cointerventions, or consequences of illness rather than conventional pre-exposure confounders. The additional analysis using hemoglobin measured before the first transfusion reduced one source of temporal ambiguity related to anemia severity, but did not address other determinants of transfusion. Transfusion-related inflammatory and immune effects are also biologically plausible [10, 11]. The available data could not determine whether the remaining association reflected unmeasured clinical severity, effects of transfusion, or both.

The volume and hemoglobin analyses further define the limits of interpretation. Patients receiving more than 700 mL had the largest adjusted estimate, but the association did not show a statistically significant nonlinear pattern. The 700-mL category should therefore not be considered a biological or clinical threshold. Higher transfusion volume may also reflect greater blood loss, surgical complexity, or postoperative instability. Similarly, the lack of interaction between RBC transfusion and first-day minimum hemoglobin category indicates that the association did not clearly differ between the 2 hemoglobin strata. It does not establish that transfusion at a particular hemoglobin concentration increases or decreases delirium risk. First-day minimum hemoglobin should be interpreted as a measure of early postoperative anemia rather than as the hemoglobin concentration that prompted transfusion, because the nadir could occur before or after transfusion. In the additional analysis among transfused patients, cumulative RBC volume remained associated with subsequent delirium after adjustment for hemoglobin measured within 6 hours before the first transfusion. There was also no evidence that this association differed according to pre-transfusion hemoglobin. These findings suggest that differences in hemoglobin immediately before transfusion did not fully account for the observed association between RBC volume and subsequent delirium. However, pre-transfusion hemoglobin alone cannot capture blood loss, ongoing bleeding, hemodynamic instability, surgical complexity, or other factors that influence transfusion decisions. Large randomized trials have compared restrictive and liberal transfusion thresholds after cardiac surgery, but neither was designed to establish a delirium-specific threshold; in TRICS III, delirium was a secondary outcome and did not differ significantly between strategies [29, 30]. The present volume categories and hemoglobin strata should therefore not be interpreted as defining a transfusion strategy for delirium prevention.

Differences in observation opportunity may also have contributed to the findings. Transfused patients remained in the ICU longer and underwent more CAM-ICU assessments, although the number of assessments per follow-up day was similar between groups. The association was also observed when ICU exit without previously documented delirium was treated as a competing event. These analyses

suggest that longer ICU observation alone was unlikely to account for the entire association. Nevertheless, CAM-ICU assessments were intermittent, and episodes occurring between assessments may not have been documented.

These findings should not be used to withhold an otherwise indicated transfusion. Decisions regarding RBC transfusion after cardiac surgery should continue to consider bleeding, anemia severity, hemodynamic status, ischemic risk, and oxygen-delivery requirements [9]. Receipt of RBC transfusion during the first ICU day may instead serve as a clinical cue to ensure consistent delirium assessment and delivery of established preventive care. ICU guidelines recommend regular assessment with a validated tool and support multicomponent nonpharmacologic interventions; more recent guidance also favors enhanced mobilization or rehabilitation [7, 31, 33]. Greater ABCDEF bundle performance was associated with lower next-day delirium in a large multicenter ICU quality-improvement cohort, and a recent small randomized trial in patients undergoing CABG suggested that preoperative cognitive training may reduce postoperative delirium [32, 34]. However, the present study did not test any preventive intervention or whether such care should be targeted according to transfusion status.

Limitations

This study has several limitations. First, residual confounding and confounding by indication remain likely. Although the models included measured comorbidities, illness severity, hemoglobin, lactate, vasoactive or inotropic support, other blood products, benzodiazepine exposure, and mechanical ventilation duration, information on blood loss, transfusion triggers, ongoing bleeding, cardiopulmonary bypass and aortic cross-clamp duration, and clinician decision-making was unavailable. The timing of hemoglobin relative to the first RBC transfusion was reconstructed in the pre-transfusion hemoglobin analysis, but other severity scores, treatments, and organ-support variables were measured during the same 24-hour period as RBC transfusion, and their temporal relation to transfusion could not always be determined. The pre-transfusion hemoglobin analysis was also limited to transfused patients with an available hemoglobin measurement within 6 hours before the first transfusion and could not account for other unmeasured determinants of transfusion.

Second, requiring valid CAM-ICU assessments both before and after the landmark may have introduced selection bias and limits the applicability of the findings to patients with shorter ICU stays or less frequent assessment. Third, CAM-ICU assessments were intermittent. The first positive assessment represented the time delirium was documented rather than necessarily the time it began, and short or fluctuating episodes may have been missed. Finally, the 24-hour landmark was not compared with alternative time points, and the outcome was limited to delirium documented after the landmark and before ICU exit. The findings therefore do not represent the overall incidence of postoperative delirium and require validation in other settings.

Among cardiac surgical ICU patients without documented delirium during the first 24 hours, RBC transfusion during this period was associated with subsequent ICU delirium. Greater RBC volume was also associated with subsequent delirium among transfused patients after accounting for pre-transfusion

hemoglobin, but residual confounding by indication remains likely. Prospective studies with detailed information on bleeding, transfusion indications, and the timing of transfusion and delirium are needed.

Declarations

Additional information

Competing interests

The authors declare no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82571352), China Postdoctoral Science Foundation (2024M761822), Qingdao Natural Science Foundation (25-1-1-231-zyyd-jch), and Qingdao Key Health Discipline Development Fund (QDZDZK-2025064).

Author Contribution

LW, PW, and JL supervised the project and reviewed and edited the manuscript. YH summarized the literature, prepared the initial manuscript, and prepared the figures. XW contributed to the literature review. XM reviewed the manuscript structure and revised the manuscript. JG and GFZ contributed to the methodology, clinical interpretation of the findings, and critical revision of the manuscript. PW and JL completed the final manuscript revision and figure preparation. All authors read and approved the final manuscript.

Data Availability

The data analyzed in this study are available from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1) database through PhysioNet (<https://doi.org/10.13026/kpb9-mt58>). Access is available to credentialed users who complete the required training and data-use agreement.

References

1. Lin, L. et al. Outcomes of postoperative delirium in patients undergoing cardiac surgery: a systematic review and meta-analysis. *Front. Cardiovasc. Med.* **9**, 884144 (2022).
2. Petersson, N. B. et al. Incidence and assessment of delirium following open cardiac surgery: a systematic review and meta-analysis. *Eur. J. Cardiovasc. Nurs.* **23**, 825–832 (2024).
3. Saczynski, J. S. et al. Cognitive trajectories after postoperative delirium. *N Engl. J. Med.* **367**, 30–39 (2012).

4. Brown, C. H. Cognitive decline after delirium in patients undergoing cardiac surgery. *Anesthesiology* **129**, 406–416 (2018). 4th et al.
5. Claesson Lingehall, H. et al. Preoperative cognitive performance and postoperative delirium are independently associated with future dementia in older people who have undergone cardiac surgery: a longitudinal cohort study. *Crit. Care Med.* **45**, 1295–1303 (2017).
6. Gottesman, R. F. et al. Delirium after coronary artery bypass graft surgery and late mortality. *Ann. Neurol.* **67**, 338–345 (2010).
7. Aldecoa, C. et al. Update of the European Society of Anaesthesiology and Intensive Care Medicine evidence-based and consensus-based guideline on postoperative delirium in adult patients. *Eur. J. Anaesthesiol.* **41**, 81–108 (2024).
8. Wang, Y. & Wang, B. Risk factors of delirium after cardiac surgery: a systematic review and meta-analysis. *J. Cardiothorac. Surg.* **19**, 675 (2024).
9. Tibi, P. et al. STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. *Ann. Thorac. Surg.* **112**, 981–1004 (2021).
10. Remy, K. E. et al. Mechanisms of red blood cell transfusion-related immunomodulation. *Transfusion* **58**, 804–815 (2018).
11. Taylor, J. et al. Postoperative delirium and changes in the blood-brain barrier, neuroinflammation, and cerebrospinal fluid lactate: a prospective cohort study. *Br. J. Anaesth.* **129**, 219–230 (2022).
12. Bucerius, J. et al. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. *J. Thorac. Cardiovasc. Surg.* **127**, 57–64 (2004).
13. Arenson, B. G., MacDonald, L. A., Grocott, H. P., Hiebert, B. M. & Arora, R. C. Effect of intensive care unit environment on in-hospital delirium after cardiac surgery. *J. Thorac. Cardiovasc. Surg.* **146**, 172–178 (2013).
14. Rudiger, A. et al. Intra-operative events during cardiac surgery are risk factors for the development of delirium in the ICU. *Crit. Care.* **20**, 264 (2016).
15. Sari, S. et al. The association of hemoglobin with postoperative delirium and atrial fibrillation after cardiac surgery: a retrospective sub-study. *Braz J. Anesthesiol.* **74**, 744424 (2024).
16. Xu, X. et al. Intraoperative allogeneic packed red blood cell transfusions and postoperative delirium: a retrospective cohort study in the USA. *eClinicalMedicine* **94**, 103885 (2026).
17. van der Zanden, V., Beishuizen, S. J., Swart, L. M., de Rooij, S. E. & van Munster, B. C. The effect of treatment of anemia with blood transfusion on delirium: a systematic review. *J. Am. Geriatr. Soc.* **65**, 728–737 (2017).
18. Johnson, A. E. W. et al. MIMIC-IV, a freely accessible electronic health record dataset. *Sci. Data.* **10**, 1 (2023).
19. Johnson, A. et al. MIMIC-IV (version 3.1). PhysioNet (2024). <https://doi.org/10.13026/kpb9-mt58>
20. von Elm, E. et al. The Strengthening the Reporting of Observational Studies in Epidemiology statement: guidelines for reporting observational studies. *Lancet* **370**, 1453–1457 (2007).

21. Jones, M. & Fowler, R. Immortal time bias in observational studies of time-to-event outcomes. *J. Crit. Care.* **36**, 195–199 (2016).
22. Putter, H. & van Houwelingen, H. C. Understanding landmarking and its relation with time-dependent Cox regression. *Stat. Biosci.* **9**, 489–503 (2017).
23. Ely, E. W. et al. Delirium in mechanically ventilated patients: validity and reliability of the Confusion Assessment Method for the Intensive Care Unit. *JAMA* **286**, 2703–2710 (2001).
24. Knaus, W. A. et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* **100**, 1619–1636 (1991).
25. Ranzani, O. T. et al. Development and validation of the Sequential Organ Failure Assessment (SOFA)-2 score. *JAMA* **334**, 2090–2103 (2025).
26. Austin, P. C. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar. Behav. Res.* **46**, 399–424 (2011).
27. Austin, P. C. & Stuart, E. A. Moving towards best practice when using inverse probability of treatment weighting using the propensity score to estimate causal treatment effects in observational studies. *Stat. Med.* **34**, 3661–3679 (2015).
28. Fine, J. P. & Gray, R. J. A proportional hazards model for the subdistribution of a competing risk. *J. Am. Stat. Assoc.* **94**, 496–509 (1999).
29. Murphy, G. J. et al. Liberal or restrictive transfusion after cardiac surgery. *N Engl. J. Med.* **372**, 997–1008 (2015).
30. Mazer, C. D. et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl. J. Med.* **377**, 2133–2144 (2017).
31. Devlin, J. W. et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit. Care Med.* **46**, e825–e873 (2018).
32. Pun, B. T. et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU Liberation Collaborative in over 15,000 adults. *Crit. Care Med.* **47**, 3–14 (2019).
33. Lewis, K. et al. A focused update to the clinical practice guidelines for the prevention and management of pain, anxiety, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit. Care Med.* **53**, e711–e727 (2025).
34. Jiang, Y. et al. Cognitive training for reduction of delirium in patients undergoing cardiac surgery: a randomized clinical trial. *JAMA Netw. Open.* **7**, e247361 (2024).

Figures

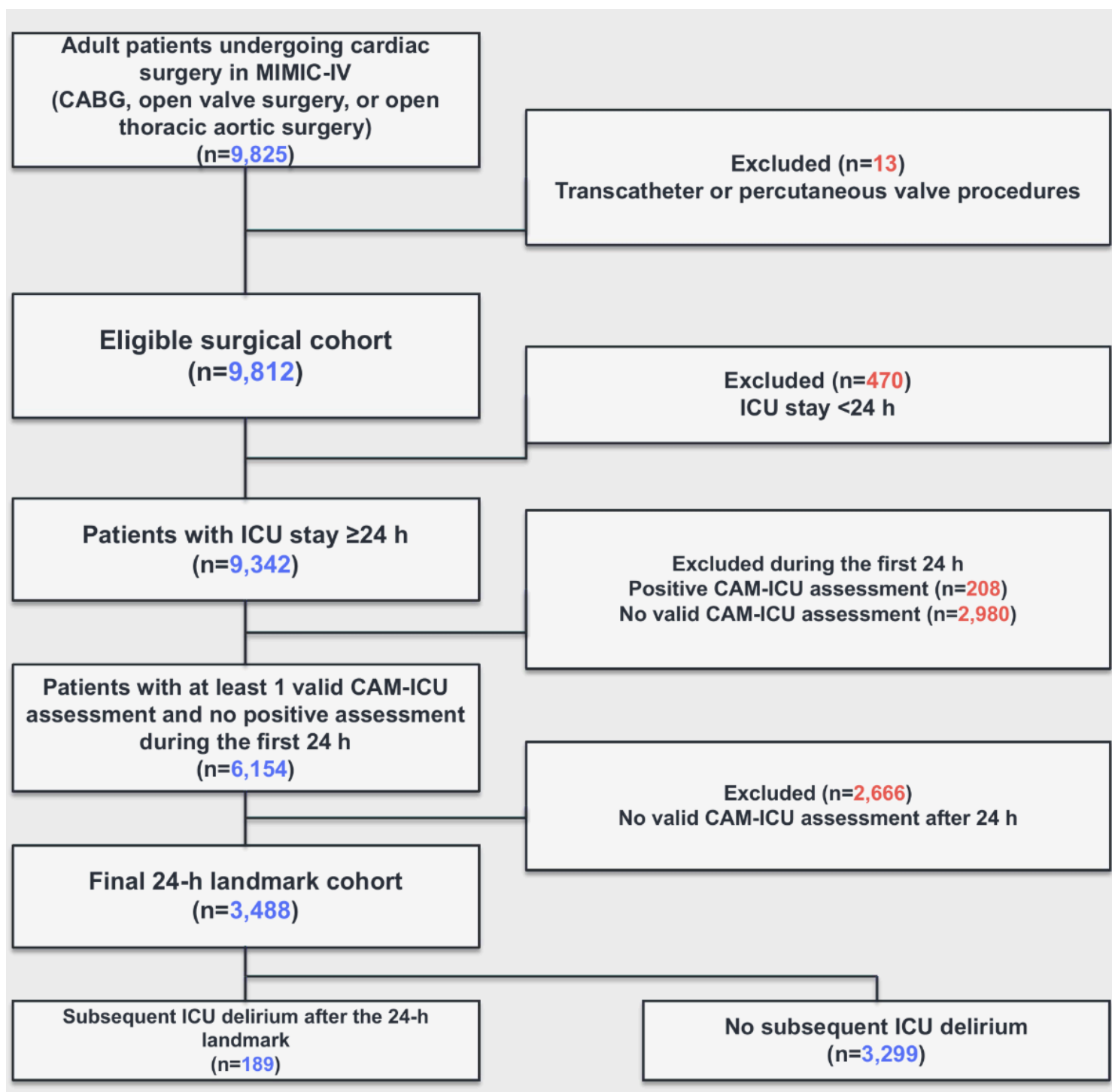


Figure 1

Flowchart of patient selection for the primary MIMIC-IV cohort.

Adult patients undergoing CABG, surgical valve surgery, or thoracic aortic surgery were identified using ICD-9-CM and ICD-10-PCS procedure codes. Transcatheter or percutaneous valve procedures and ICU stays shorter than 24 h were excluded. The landmark cohort required at least 1 valid CAM-ICU assessment during the first 24 h, no positive CAM-ICU assessment during this period, and at least 1 valid assessment after the landmark. Abbreviations: CABG, coronary artery bypass grafting; CAM-ICU,

Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care IV.

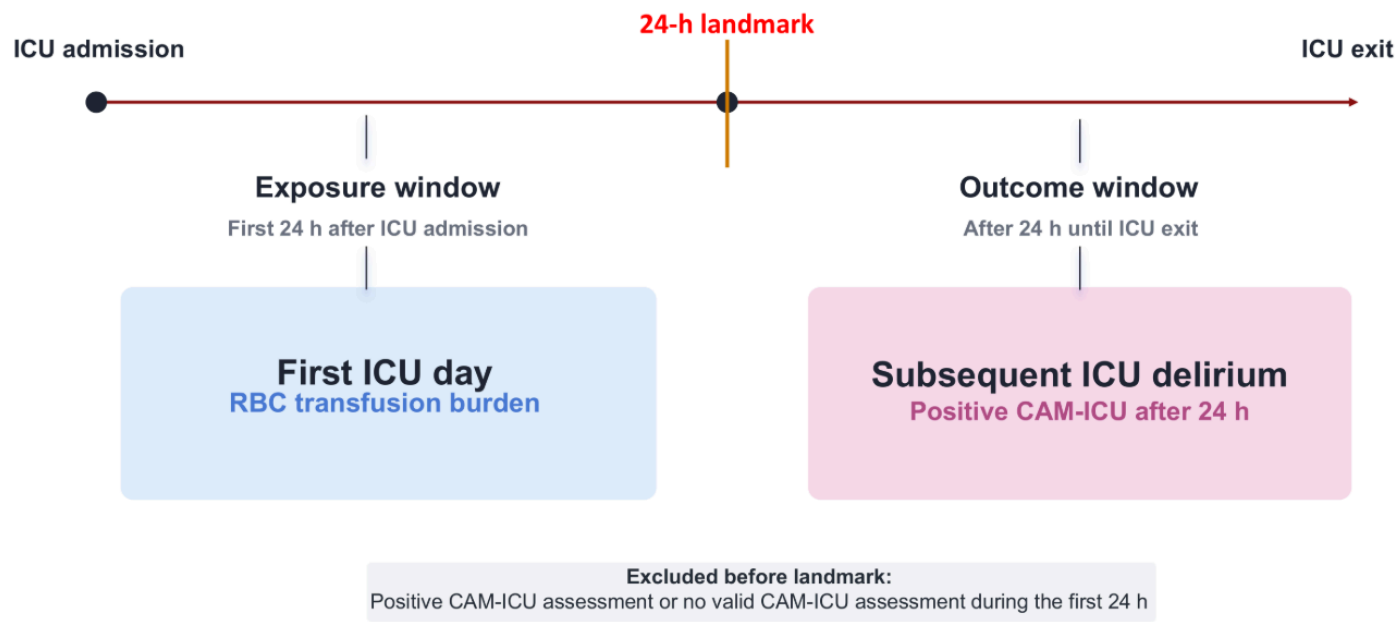


Figure 2

Schematic illustration of the 24-h landmark design.

The first 24 h after ICU admission constituted the exposure window, during which RBC transfusion burden and early clinical variables were assessed. Patients with a positive CAM-ICU assessment or no valid CAM-ICU assessment during this window were excluded. Subsequent ICU delirium was assessed after the 24-h landmark until ICU exit, and at least one valid post-landmark CAM-ICU assessment was required. Abbreviations: CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; RBC, red blood cell.

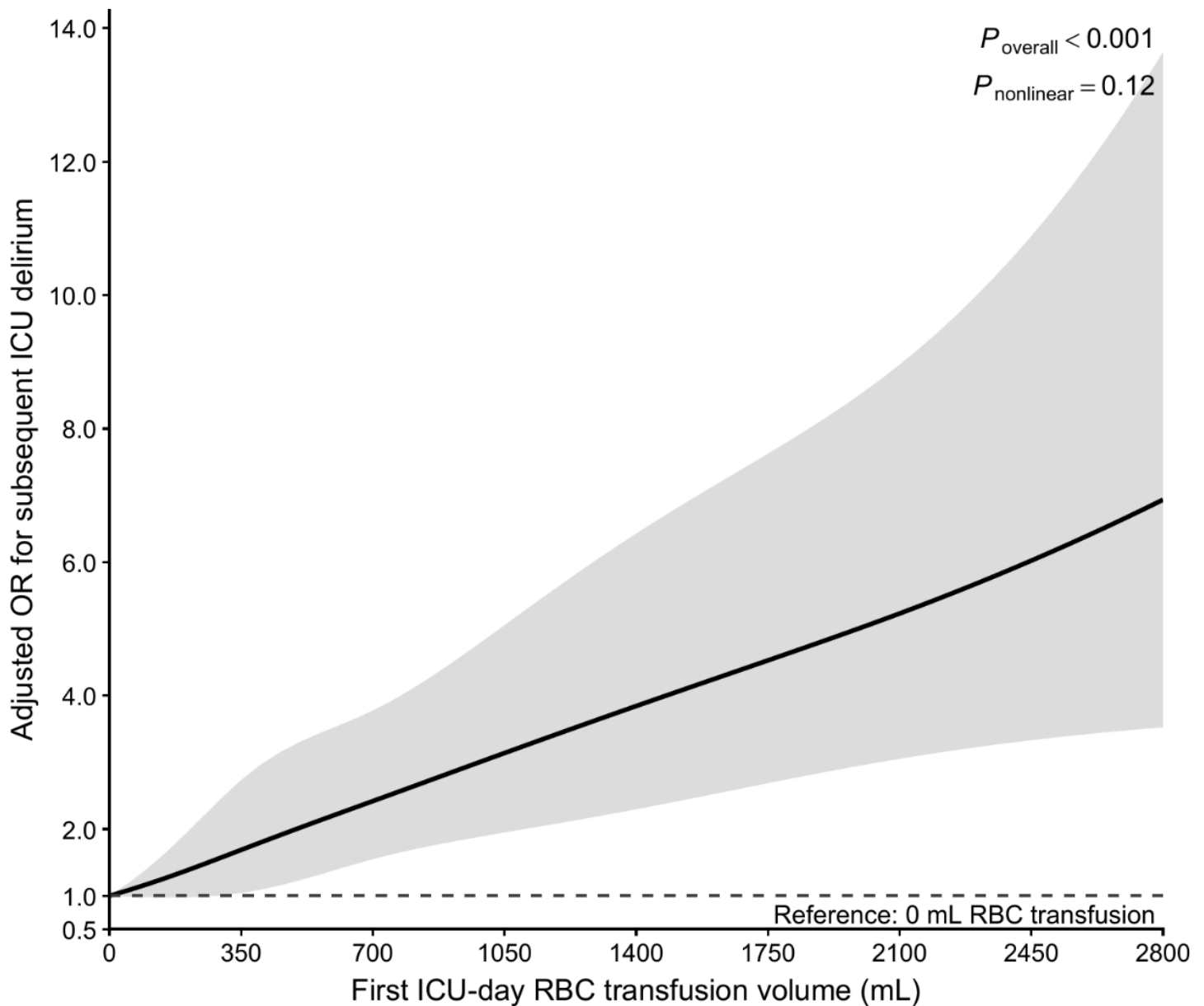


Figure 3

Dose-response association between first ICU-day RBC transfusion volume and subsequent ICU delirium.

Restricted cubic spline analysis was used to examine the association between cumulative RBC transfusion volume during the first 24 h after ICU admission and subsequent ICU delirium. The solid line represents adjusted odds ratios, and the shaded area represents 95% confidence intervals. The analysis included 3,098 complete cases with 171 delirium events and was adjusted for age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, atrial fibrillation, first-day minimum hemoglobin concentration, first lactate concentration, vasoactive or inotropic drug use, and APS III. Knots were placed at 0, 350, 700, and 2,100 mL, with 0 mL used as the reference. The overall association was statistically significant ($P < 0.001$), with no statistically

significant evidence of nonlinearity ($P = 0.12$). Abbreviations: APS III, Acute Physiology Score III; CI, confidence interval; ICU, intensive care unit; RBC, red blood cell.

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