

Supplementary Material

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

Lezhen Wang^{1†}, Ying Han^{3†}, Xiaotian Ma², Xuanlong Wang¹, Penghui Wei¹, Jie Guo⁴, Guang-fen Zhang⁵, Jianjun Li^{1*}

† These authors contributed equally to this work.

1 Department of Anesthesiology, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University, Qingdao, China.

2 Laboratory of Cerebrospinal Fluid Cytology and Neuroimmunology, Department of Central Laboratory, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University, Qingdao, China.

3 Department of Anesthesiology, The Second Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan, China.

4 Department of Anesthesiology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, China.

5 Department of Anesthesiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China.

* Corresponding author: Jianjun Li, M.D., Ph.D. E-mail: lj9573@163.com

Supplementary Table 1. Procedure-code rules used to identify cardiac surgical cohorts.

Cohort component	ICD-9-CM rule	ICD-10-PCS rule	Operational note
CABG	36.10–36.19	Pattern 021[0–3][0/4]	CABG identified during the index hospitalization.
Surgical valve procedures	35.10–35.14; 35.20–35.28	Open or percutaneous-endoscopic replacement, repair, or supplement procedures involving valve body sites F/G/H/J	Transcatheter or percutaneous procedures were separately flagged and excluded.
Thoracic aortic surgery	38.45	Open thoracic aortic procedures involving body sites W/X/Y	Thoracic aortic surgery took priority in the hierarchical surgical classification.
Transcatheter/percutaneous valve exclusion	Not applicable	Valve replacement, repair, or supplement with approach character 3; examples include 02RF3, 02RG3, and 02UG3	Full procedure-code review was used to flag concomitant transcatheter or percutaneous valve procedures.

CABG, coronary artery bypass grafting; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-PCS, International Classification of Diseases, Tenth Revision, Procedure Coding System. Code patterns are operational extraction rules rather than an exhaustive display of every expanded code.

Supplementary Table 2. Definitions of exposures, outcomes, and covariates.

Variable	Definition
First ICU-day RBC transfusion volume	Cumulative RBC transfusion volume recorded during the first 24 hours after ICU admission. Patients without a recorded RBC transfusion during this window were classified as receiving 0 mL.
Any first ICU-day RBC transfusion	RBC volume >0 mL during the first 24 h.
RBC volume categories	0, >0–350, >350–700, and >700 mL.
Subsequent ICU delirium	Any positive CAM-ICU assessment after the 24-h landmark and before ICU exit.
Valid CAM-ICU assessment	Assessment explicitly recorded as positive or negative; unavailable or unassessable records were not treated as negative assessments.
First-day minimum hemoglobin	Lowest hemoglobin concentration recorded during the first 24 hours after ICU admission.
First RBC administration time	Start time of the earliest RBC administration identified from 6 hours before to 24 hours after ICU admission among patients classified as transfused by the original first ICU-day exposure definition; used only as the timing anchor for the pre-transfusion hemoglobin analysis.
Pre-transfusion hemoglobin	Most recent hemoglobin concentration recorded strictly before the first RBC administration and within the preceding 6 hours. When multiple values were recorded at the selected time point, their mean was used in the primary analysis.
First lactate	First lactate concentration recorded during the first 24 hours after ICU admission.
Vasoactive/inotropic drug use	Any use of milrinone, dobutamine, dopamine, phenylephrine, vasopressin, norepinephrine, or epinephrine during the first 24 h.
APS III	Acute Physiology Score III derived from the first ICU day.
SOFA-2	Sequential Organ Failure Assessment 2 score derived from first-day data.
Benzodiazepine exposure	Any diazepam, lorazepam, or midazolam use during the first 24 h.
Invasive mechanical ventilation duration	Cumulative duration of invasive mechanical ventilation during the first 24 hours after ICU admission. Patients without recorded invasive mechanical ventilation during this window were assigned a duration of 0 hours.
Competing event	ICU exit without a previously observed positive post-landmark CAM-ICU assessment.

APS III, Acute Physiology Score III; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; RBC, red blood cell; SOFA-2, Sequential Organ Failure Assessment 2.

Supplementary Table 3. Missing data in variables used in the primary adjusted model.

Variable	Missing, n	Missing, %
Age	0	0.0
Sex	0	0.0
Body mass index	30	0.9
Hypertension	0	0.0
Diabetes mellitus	0	0.0
Congestive heart failure	0	0.0
Renal disease	0	0.0
Cerebrovascular disease	0	0.0
Atrial fibrillation	0	0.0
First-day minimum hemoglobin	6	0.2
First lactate	368	10.6
Vasoactive/inotropic drug use	0	0.0
APS III	0	0.0

A total of 390 patients were excluded from the complete-case primary regression, leaving 3,098 patients and 171 events. First lactate accounted for most missingness. Missing values were not imputed. APS III, Acute Physiology Score III.

Supplementary Table 4. Covariate balance before and after propensity score weighting.

Covariate	Before weighting	After stabilized IPTW	After truncated IPTW
Age	0.449	0.017	0.018
Male sex	0.475	0.021	0.031
Body mass index	0.288	0.015	0.029
Hypertension	0.113	0.030	0.039
Diabetes mellitus	0.024	0.002	0.007
Congestive heart failure	0.155	0.016	0.027
Renal disease	0.270	0.018	0.029
Cerebrovascular disease	0.122	0.007	0.014
Atrial fibrillation	0.199	0.013	0.001
Valve only	0.023	0.010	0.003
CABG + valve	0.290	0.002	0.010
Thoracic aortic surgery	0.116	0.037	0.042
Maximum absolute SMD	0.475	0.037	0.042

Values are absolute standardized mean differences. An absolute SMD less than 0.10 was considered acceptable. The IPTW analyses included 3,458 patients with complete data for all propensity score covariates. For stabilized IPTW, the effective sample size was 2,954 and the maximum weight was 6.37. After truncation at the 1st and 99th percentiles (limits, 0.38–2.64), the effective sample size was 3,039. CABG, coronary artery bypass grafting; IPTW, inverse probability of treatment weighting; SMD, standardized mean difference.

Supplementary Table 5. Additional model extension and hemoglobin-threshold interaction analyses.

Analysis	N	Events	Estimate	95% CI	P value
APS III + SOFA-2 model extension: any RBC vs no RBC	3098	171	OR 2.07	1.37–3.14	< 0.001
Interaction using hemoglobin threshold 7.5 g/dL	3098	171	OR 0.76	0.34–1.68	0.497
Interaction using hemoglobin threshold 8.0 g/dL	3098	171	OR 1.03	0.49–2.16	0.946
Interaction using hemoglobin threshold 9.0 g/dL	3098	171	OR 2.39	0.81–7.00	0.113

The APS III + SOFA-2 model was treated as a supplementary extension because both scores represent first-day illness severity. Interaction estimates are multiplicative interaction terms between RBC transfusion status and the corresponding first-day minimum-hemoglobin category. APS III, Acute Physiology Score III; CI, confidence interval; OR, odds ratio; RBC, red blood cell; SOFA-2, Sequential Organ Failure Assessment 2.

Supplementary Table 6. Post-landmark CAM-ICU observation opportunity according to first ICU-day RBC transfusion status.

Variable	No RBC (n=2,572)	RBC (n=916)	P value
Subsequent ICU delirium, n (%)	87 (3.4)	102 (11.1)	< 0.001
Post-landmark CAM-ICU assessments, count	3 (1–6)	5 (2–10)	< 0.001
Time to first post-landmark CAM-ICU assessment, h	8.8 (3.1–11.4)	9.6 (4.1–12.6)	< 0.001
CAM-ICU follow-up duration, d	0.97 (0.44–2.26)	1.87 (0.88–3.35)	< 0.001
CAM-ICU assessments per follow-up day	2.70 (2.06–4.50)	2.67 (2.11–4.14)	0.537
Total ICU length of stay, d	2.37 (1.95–3.81)	3.21 (2.21–5.03)	< 0.001
Post-landmark ICU length of stay, d	1.37 (0.95–2.81)	2.21 (1.21–4.03)	< 0.001

Values are median (interquartile range) unless otherwise stated. CAM-ICU follow-up duration was measured from the 24-h landmark to the last available post-landmark assessment. P values were calculated using the Wilcoxon rank-sum test or chi-square test, as appropriate. CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; RBC, red blood cell.

Supplementary Table 7. Fine–Gray competing-risk analyses for first ICU-day RBC transfusion and subsequent ICU delirium.

Model	N	Delirium events	Competing events	sHR	95% CI	P value
Unadjusted	3488	189	3299	3.46	2.60–4.60	< 0.001
Baseline-adjusted	3458	189	3269	2.37	1.75–3.21	< 0.001
Primary adjusted model	3098	171	2927	2.47	1.67–3.65	< 0.001
Extended sensitivity	3098	171	2927	1.74	1.15–2.63	0.009

The target event was subsequent ICU delirium after the 24-hour landmark. ICU exit without previously observed delirium was treated as the competing event. The baseline-adjusted model included age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, and atrial fibrillation. The primary adjusted model additionally included first-day minimum hemoglobin, first lactate, vasoactive or inotropic drug use, and APS III. The extended sensitivity model additionally included plasma and platelet transfusions, benzodiazepine exposure, and invasive mechanical ventilation duration. Fine–Gray models were fitted using the `crr` function in `cmprsk` version 2.2-12 in R version 4.4.3. APS III, Acute Physiology Score III; CI, confidence interval; ICU, intensive care unit; RBC, red blood cell; sHR, subdistribution hazard ratio.

Supplementary Table 8. Cumulative incidence estimates after the 24-hour landmark.

Group	Day	At risk	CIF: delirium	CIF: ICU exit without prior delirium
No RBC	1	1876	0.8%	26.8%
No RBC	2	1055	1.4%	57.8%
No RBC	3	584	1.6%	76.0%
No RBC	5	219	2.2%	89.4%
No RBC	7	107	2.6%	93.3%
No RBC	14	30	3.0%	95.8%
RBC	1	758	4.3%	13.3%
RBC	2	480	6.4%	41.4%
RBC	3	306	7.5%	59.3%
RBC	5	116	8.8%	78.6%
RBC	7	66	9.4%	83.5%
RBC	14	19	10.5%	87.6%

Cumulative incidence functions were estimated from the 24-hour landmark, treating ICU exit without previously observed delirium as a competing event. During complete follow-up, 87 delirium events and 2,485 competing events occurred in the no-RBC group, and 102 delirium events and 814 competing events occurred in the RBC group. CIF, cumulative incidence function; ICU, intensive care unit; RBC, red blood cell.

Supplementary Table 9. Multicollinearity diagnostics for the primary adjusted model.

Analysis population: 3,098 complete cases, including 171 subsequent ICU delirium events. Variance inflation factors and condition indices were calculated for the predictors included in the primary adjusted model.

Variable	VIF
First-day minimum hemoglobin	1.730
Renal disease	1.588
Hypertension	1.574
RBC transfusion status	1.437
Male sex	1.301
Surgery: valve only	1.299
Congestive heart failure	1.228
Diabetes mellitus	1.208
Age	1.202
Surgery: CABG plus valve	1.179
Surgery: thoracic aortic surgery	1.149
Body mass index	1.146
APS III	1.140
Atrial fibrillation	1.077
First lactate	1.058
Vasoactive/inotropic drug use	1.034
Cerebrovascular disease	1.021

All VIFs in the primary adjusted model were below 2. The maximum VIF was 1.730; the VIFs for first-day minimum hemoglobin and RBC transfusion status were 1.730 and 1.437, respectively. The maximum condition index was 2.557. In the extended sensitivity model, the maximum VIF was 1.739; the VIFs for first-day minimum hemoglobin and RBC transfusion status were 1.739 and 1.674, respectively. No substantial multicollinearity was identified in either model. APS III, Acute Physiology Score III; CABG, coronary artery bypass grafting; RBC, red blood cell; VIF, variance inflation factor.

Supplementary Table 10. Joint association of first-day minimum hemoglobin and RBC transfusion status with subsequent ICU delirium.

First-day minimum hemoglobin category	RBC transfusion status	Full cohort, n	Delirium, n (%)	Model cohort, n	Delirium, n (%)	Adjusted OR (95% CI)	P value
Hb ≥8.0	no RBC	2087	63 (3.0%)	1747	50 (2.9%)	Reference	
Hb ≥8.0	RBC	260	25 (9.6%)	246	23 (9.3%)	2.22 (1.28-3.83)	0.004
Hb <8.0	no RBC	480	23 (4.8%)	458	21 (4.6%)	1.07 (0.61-1.86)	0.824
Hb <8.0	RBC	655	77 (11.8%)	647	77 (11.9%)	2.42 (1.58-3.73)	< 0.001

The reference group was patients with first-day minimum hemoglobin ≥8 g/dL and no RBC transfusion within the first ICU day. Six patients with missing first-day minimum hemoglobin were excluded from the joint-category analysis. The adjusted model included age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, atrial fibrillation, first lactate, vasoactive/inotropic drug use, and APS III. Continuous first-day minimum hemoglobin was not included because hemoglobin category was part of the exposure definition. Interaction between hemoglobin <8 g/dL and RBC transfusion: OR 1.03 (95% CI 0.49-2.16), P = 0.946.

Supplementary Table 11. Additional sensitivity and propensity score–weighted analyses.

Sensitivity analysis	N	Events	OR	95% CI	P value	Diagnostics / notes
Restricted to ICU stay ≥ 48 h	2379	170	2.26	1.52-3.37	< 0.001	Multivariable
Excluding thoracic aortic surgery	2852	148	2.20	1.43-3.37	< 0.001	Multivariable
Excluding RBC transfusion >2100 mL (highest 5% among transfused patients)	3053	160	2.33	1.55-3.50	< 0.001	Multivariable
Stabilized inverse probability of treatment weighting	3458	189	2.24	1.64-3.05	< 0.001	ESS=2954; max SMD =0.037; max weight=6.37
IPTW truncated at the 1st/99th percentiles	3458	189	2.29	1.68-3.13	< 0.001	ESS=3039; max SMD =0.042; limits=0.38–2.64

ORs are for any RBC transfusion during the first 24 hours after ICU admission. Multivariable sensitivity analyses used the same covariates as the primary adjusted model. Propensity scores were estimated using pre-exposure covariates: age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, and atrial fibrillation. Stabilized IPTW estimates were obtained using weighted logistic regression with robust standard errors. In the truncated IPTW analysis, weights were limited at the 1st and 99th percentiles. IPTW indicates inverse probability of treatment weighting; ESS, effective sample size; SMD, standardized mean difference.

Supplementary Table 12. Patient and perioperative characteristics according to first ICU-day RBC transfusion status.

Variable	No RBC (n=2,572)	RBC (n=916)	Absolute SMD	Missing, n
Baseline characteristics				
Age, years	67.5 [60.1, 74.7]	72.9 [65.0, 79.6]	0.450	0
Male sex	1,935 (75.2%)	488 (53.3%)	0.471	0
Body mass index, kg/m ²	28.7 [25.3, 32.6]	26.9 [23.9, 30.5]	0.288	30
Surgical category				0
CABG only	1,481 (57.6%)	389 (42.5%)	0.306	
Valve only	617 (24.0%)	229 (25.0%)	0.024	
CABG + valve	294 (11.4%)	204 (22.3%)	0.293	
Thoracic aortic surgery	180 (7.0%)	94 (10.3%)	0.116	
Hypertension	1,412 (54.9%)	451 (49.2%)	0.114	0
Diabetes mellitus	954 (37.1%)	350 (38.2%)	0.023	0
Congestive heart failure	787 (30.6%)	348 (38.0%)	0.156	0
Renal disease	449 (17.5%)	263 (28.7%)	0.270	0
Cerebrovascular disease	261 (10.1%)	129 (14.1%)	0.121	0
Atrial fibrillation	783 (30.4%)	367 (40.1%)	0.202	0
Early postoperative characteristics				
APS III score	33 [26, 43]	38 [30, 50]	0.281	0
SOFA-2 score	7 [5, 9]	8 [7, 10]	0.468	0
First lactate, mmol/L	1.9 [1.4, 2.5]	2.2 [1.6, 3.0]	0.338	368
First-day minimum hemoglobin, g/dL	9.3 [8.3, 10.5]	7.3 [6.7, 8.1]	1.433	6
First-day minimum hemoglobin <8 g/dL	480 (18.7%)	655 (71.6%)	1.255	6
Vasoactive/inotropic drug use	2,244 (87.2%)	887 (96.8%)	0.360	0
Platelet transfusion	156 (6.1%)	312 (34.1%)	0.746	0
Plasma transfusion	47 (1.8%)	135 (14.7%)	0.482	0
Benzodiazepine exposure	264 (10.3%)	65 (7.1%)	0.113	0
Invasive mechanical ventilation	1,693 (65.8%)	800 (87.3%)	0.525	0
Invasive ventilation duration, h	4.9 [0.0, 9.1]	11.0 [5.7, 18.0]	0.783	0

Values are median [interquartile range] or n (%). Absolute standardized mean differences were calculated using available observations for each variable; for surgical categories, SMDs were calculated for each indicator variable. An absolute SMD less than 0.10 was considered indicative of good balance. Percentages were calculated using non-missing denominators. Early postoperative variables were measured during the first 24 hours after ICU admission and are presented descriptively. APS III, Acute Physiology Score III; CABG, coronary artery bypass grafting; ICU, intensive care unit; RBC, red blood cell; SMD, standardized mean difference; SOFA-2, Sequential Organ Failure Assessment 2.

Supplementary Table 13. Sequential adjustment models for first ICU-day RBC transfusion and subsequent ICU delirium.

Model	N	Events	OR	95% CI	P value
Unadjusted	3,488	189	3.58	2.66-4.82	<0.001
Baseline-adjusted	3,458	189	2.44	1.77-3.37	<0.001
Baseline-adjusted, restricted to primary complete-case cohort	3,098	171	2.45	1.73-3.47	<0.001
Primary adjusted model	3,098	171	2.56	1.72-3.82	<0.001
Extended sensitivity model	3,098	171	1.74	1.13-2.68	0.012

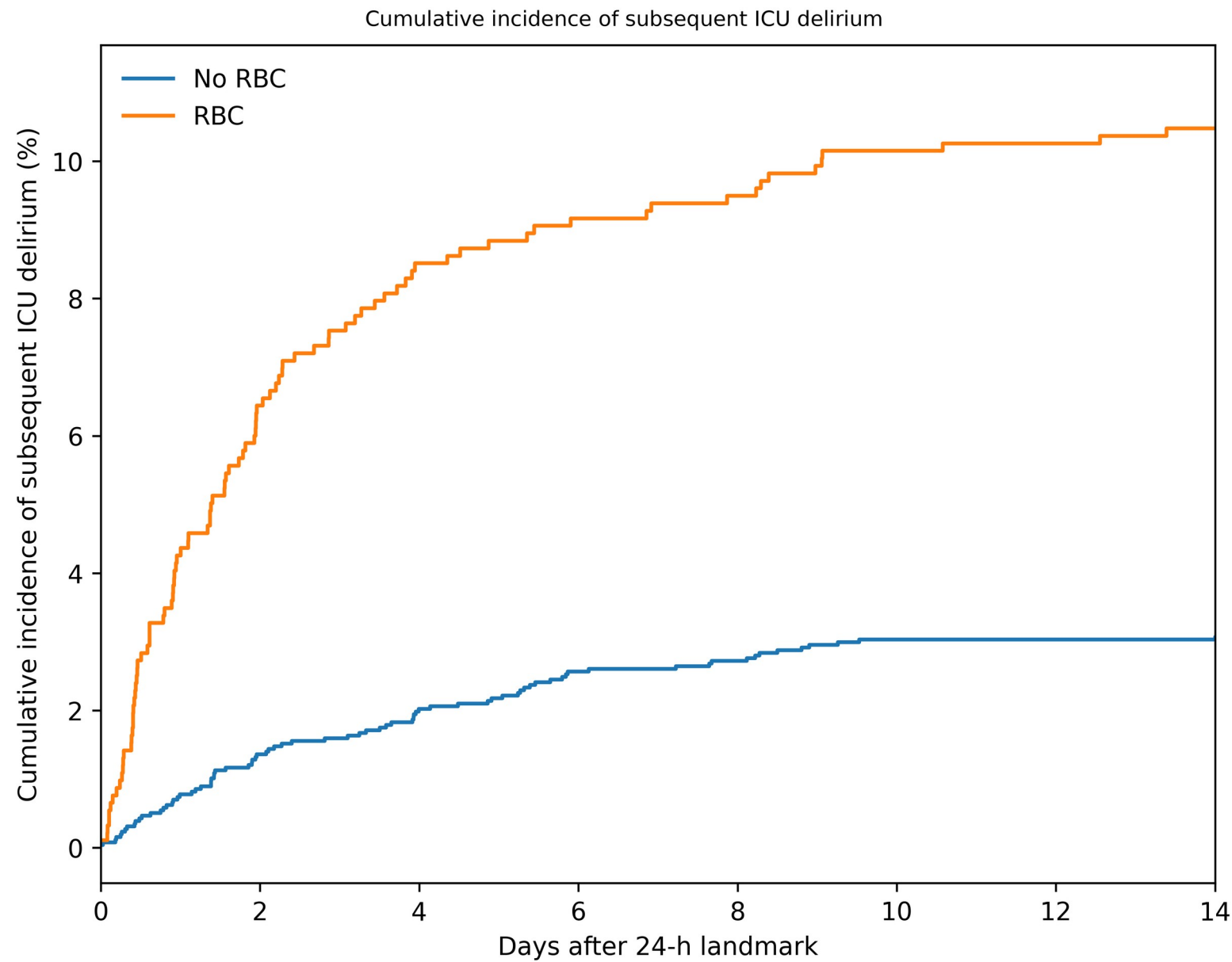
ORs are for any RBC transfusion during the first 24 hours after ICU admission. The baseline-adjusted model included age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, and atrial fibrillation. The baseline-adjusted model restricted to the primary complete-case cohort used the same covariates but was limited to the 3,098 patients included in the primary adjusted model. The primary adjusted model additionally included first-day minimum hemoglobin, first lactate, vasoactive or inotropic drug use, and APS III. The extended sensitivity model additionally included plasma and platelet transfusions, benzodiazepine exposure, and invasive mechanical ventilation duration. APS III, Acute Physiology Score III; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RBC, red blood cell.

Supplementary Table 14. Analyses using pre-transfusion hemoglobin among patients receiving first ICU-day RBC transfusion.

Analysis	N	Events	Term	Adjusted OR (95% CI)	P value
Pre-transfusion hemoglobin model	839	91	RBC volume, per 350 mL	1.24 (1.12-1.37)	<0.001
			Pre-transfusion hemoglobin, per 1 g/dL	0.94 (0.81-1.10)	0.448
Pre-transfusion hemoglobin model + first RBC timing	839	91	RBC volume, per 350 mL	1.26 (1.13-1.40)	<0.001
Pre-transfusion hemoglobin model + first RBC timing + APS III	839	91	RBC volume, per 350 mL	1.25 (1.12-1.39)	<0.001
Pre-transfusion hemoglobin model + APS III + first lactate + vasoactive/inotropic use	825	91	RBC volume, per 350 mL	1.23 (1.10-1.37)	<0.001
Model including invasive ventilation duration	825	91	RBC volume, per 350 mL	1.18 (1.06-1.31)	0.003
Duplicate-Hb sensitivity analysis	839	91	RBC volume, per 350 mL	1.24 (1.12-1.37)	<0.001
Excluding RBC volume >2,100 mL	797	82	RBC volume, per 350 mL	1.43 (1.19-1.71)	<0.001
Continuous pre-transfusion hemoglobin interaction	839	91	RBC volume × pre-transfusion hemoglobin	0.98 (0.93-1.03)	0.424
Pre-transfusion hemoglobin <8 g/dL interaction	839	91	RBC volume × hemoglobin <8 g/dL	1.09 (0.86-1.39)	0.469
RBC volume categories, reference >0-350 mL	839	91	>350-700 vs >0-350 mL	0.90 (0.42-1.90)	0.776
			>700 vs >0-350 mL	1.96 (1.01-3.80)	0.047

Among patients who received RBC transfusion during the first 24 hours, pre-transfusion hemoglobin was defined as the most recent hemoglobin measurement obtained strictly before the first RBC administration and within the preceding 6 hours. Of 916 transfused patients, 841 (91.8%) had an eligible pre-transfusion hemoglobin measurement; 839 patients with 91 subsequent delirium events had complete data for the baseline covariates included in the primary pre-transfusion hemoglobin model. When multiple hemoglobin values were recorded at the selected time point, their mean was used. The pre-transfusion hemoglobin model adjusted for age, sex, body mass index, surgical category, hypertension, diabetes mellitus, congestive heart failure, renal disease, cerebrovascular disease, atrial fibrillation, and pre-transfusion hemoglobin. Additional models further included the variables indicated in the analysis label. In the duplicate-Hb sensitivity analysis, the minimum rather than the mean was used when multiple hemoglobin measurements were recorded at the selected time point. Interaction estimates are multiplicative interaction terms. For the categorical RBC analysis, >0-350 mL was the reference category. Among 915 transfused patients with an available timestamp for the first-day hemoglobin nadir, the nadir occurred after initiation of the first RBC transfusion in 109 patients (11.9%). APS III, Acute Physiology Score III; CI, confidence interval; Hb, hemoglobin; ICU, intensive care unit; OR, odds ratio; RBC, red blood cell.

Supplementary Fig. 1. Unadjusted cumulative incidence of subsequent ICU delirium after the 24-h landmark according to first ICU-day RBC transfusion status.



Unadjusted cumulative incidence functions were estimated from the 24-hour landmark, treating ICU exit without previously observed delirium as a competing event. The target event was the first positive CAM-ICU assessment after the landmark. CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICU, intensive care unit; RBC, red blood cell.