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Red blood cell transfusion in acute brain injury subtypes: An observational cohort study

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ABSTRACT

Purpose: Optimal red blood cell (RBC) transfusion thresholds in acute brain injury (ABI) are poorly defined.
Materials and methods: We conducted a retrospective cohort study of adult patients with ABI and moderate anemia (Hb 7–10 g/dL) in a neurological intensive care unit (ICU) at an academic medical center between 2008 and 2015. Transfused and non-transfused patients were matched based on age, ABI subtype, pre-transfusion hemoglobin, and ICU length of stay (LOS) at the time of RBC transfusion. Multivariable regression analyses were performed to assess the relationship between RBC transfusion and hospital LOS, hospital mortality, ICU LOS, ICU mortality, and 24 h change in sequential organ failure assessment (SOFA) scores.
Results: 2638 patients met inclusion criteria, with 225 (8.5%) receiving RBC transfusion. Acute ischemic stroke was the most prevalent ABI diagnosis (43.3%) then intracranial hemorrhage (25.6%), subarachnoid hemorrhage (16.5%), and traumatic brain injury (TBI) (14.6%). In multivariable analyses, RBC transfusion was associated with longer hospital and ICU LOS, and higher SOFA scores. Each ABI subtype had similar results, except for TBI which showed no difference in hospital LOS. Mortality was not significantly different.
Conclusions: In moderately anemic patients with ABI, RBC transfusion was associated with longer hospital and ICU LOS. Prospective investigations are necessary to further assess these relationships.

1. Introduction

Anemia is associated with poor outcomes in patients with acute brain injury (ABI), including traumatic brain injury (TBI), acute ischemic stroke (AIS), nontraumatic intracranial hemorrhage (ICH), and non-traumatic subarachnoid hemorrhage (SAH) [1-13]. The principle concern for anemia is decreased cerebral oxygen delivery (DO_2) which may exacerbate brain injury and cellular hypoxia. In the healthy brain, cerebral vasodilation may maintain cerebral DO_2 during the early stages of anemia development [14]. However, such compensatory mechanisms are disrupted in brain injury, resulting in exacerbation of cellular hypoxia in the setting of decreased hemoglobin concentrations [15]. This has classically prompted intensivists to transfuse red blood cells more liberally in the patient with ABI compared to the general critical care population [16].

While there is evidence to suggest that red blood cell (RBC) transfusion can improve human brain metabolism and oxygenation [13,17], it is unclear if RBC-mediated increases in cerebral DO_2 confer protective benefit in the acutely injured brain. Indeed, numerous observational studies have demonstrated worse outcomes with RBC transfusion [6,10,11,18-23]. However, despite strong evidence in support of restrictive RBC transfusion strategies in other critically ill populations, there remains a paucity of high quality data in high-risk patients groups such as those with ABI, and the optimal hemoglobin level has yet to be elucidated.

The purpose of this study was to assess the relationships between RBC transfusion and patient-important outcomes in a larger and more diverse cohort of critically ill patients with ABI including TBI, AIS, ICH, and SAH. Specifically, we aimed to provide a thorough assessment of the role of RBC transfusion on outcomes in these four unique subgroups with more complete consideration of the severity of critical illness and comorbid disease than prior studies. Additionally, recognizing that the length of ICU stay at the time of RBC transfusion may influence clinical outcomes but is often overlooked in observational studies, we specifically designed this study to mitigate this potential confounding factor.

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We hypothesized that RBC transfusion would be associated with inferior or equivocal outcomes in all 4 brain injury subgroups when compared to non-transfused counterparts.

2. Materials and methods

This was a retrospective cohort study of patients who were admitted to the neurological intensive care unit of a single, teriary care, academic medical center. This study was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in the design and conduct of this study [24].

2.1. Study population

Consecutive adult (age ≥ 18) patients with an ICD-9 diagnosis of traumatic brain injury (TBI), acute ischemic stroke (AIS), nontraumatic intracranial hemorrhage (ICH), and non-traumatic subarachnoid hemorrhage (SAH) who were admitted to the neurological intensive care unit (ICU) of the study institution between January 2008 and December 2014 and had a hemoglobin value measured during their ICU stay were included. Relevant ICD-9 diagnosis codes are provided in Supplemental Table 1. Patient diagnoses were verified by manual review of electronic health records. Briefly, the neurological ICU is a 20-bed intensive care unit, that provides services to any patient with critical neurological illness and also serves as a progressive care unit for several neurosurgical services. Patients that denied access to their medical records for research purposes or those without a hemoglobin value measured during their ICU admission were excluded. For patients with multiple ICU admissions during the study period, only the first qualifying ICU admission was included in analysis.

2.2. Predictor and outcome variables

The primary predictor variable for this investigation was the presence or absence of RBC transfusion during the ICU encounter. Of note, for patients requiring multiple RBC transfusion episodes during the qualifying ICU encounter, only the first transfusion episode was utilized (e.g., no patient was included in the study more than once). Transfusions administered in non-ICU environments (e.g. emergency department, operating room) were not included in order to prevent the inclusion of RBC transfusion administered for non-related conditions or injuries. Of note, sensitivity analyses specifically excluding patients who received RBC transfusions prior to ICU admission were planned a priori. Additional patient-specific data utilized in outcome measurement included age, gender, body mass index, medical comorbidities and Charlson Comorbidity Index scores, Sequential Organ Failure Assessment (SOFA) scores, Glasgow Coma Scale (GCS) scores, and laboratory values including albumin, creatinine, hemoglobin, international normalized ratio (INR), and platelet count. The primary outcome for this investigation was hospital length of stay (LOS). Secondary outcomes included hospital mortality, ICU LOS and mortality, and change in SOFA score in the 24 h following RBC transfusion.

2.3. Data collection

Screening for eligible patients was performed with electronic health record databases known as the ICU and Perioperative Datamarts [25]. These institutional resources capture clinical and procedural data for all patients who are admitted to an acute care environment including procedural suites, operating rooms, intensive care units, and progressive care units at the study's participating institution. These data warehouses also contain information on patient demographics and baseline clinical characteristics, fluid and transfusion therapies, medications, laboratory values, outcomes, and lengths of stay. Additional baseline characteristics not included in the ICU and Perioperative datamarts were obtained from a second validated database, the Mayo Clinic Life Sciences System (MCLSS) [26]. Both databases have undergone extensive validation with superior accuracy when compared to manual data extraction techniques [27].

2.4. Statistical analysis

Baseline demographics, clinical characteristics, and procedure-related information are presented as frequency counts and percentages for categorical data and median and 25%–75% interquartile range (IQR) for continuous data elements. Baseline characteristics were compared between patients who were transfused versus not transfused using the chi-square test for categorical variables and the Wilcoxon rank test for continuous variables. Given expected differences between transfused and non-transfused patients, a matched design was used to assess the association between RBC transfusion and outcomes with planned multivariable adjustment for remaining between group imbalances. Matching variables included: age, ABI subtype, and pre-transfusion hemoglobin. Since transfusion could occur at any time during the ICU stay, cohort matching was performed as follows. For each transfused patient (exposed), a pool of potential controls was constructed which included all non-transfused patients who were admitted for the same diagnosis as the case and who were still in the ICU on the day that the case received a transfusion (index day). From this pool of potential controls, the greedy method was used to select the best match based on age and hemoglobin level.

Given the greatest degree of clinical equipoise occurs for patients with moderate anemia (i.e. hemoglobin ≥7 and < 10 g/dL) and a lack of potential non-transfused controls among those with more severe anemia, only patients with moderate anemia were included in the matched analyses. Standardized differences were calculated for baseline characteristics to assess the balance between transfused and non-transfused patients included in matched analyses. Hospital and ICU mortality were summarized as n (%) and analyzed using proportional hazards regression with a shared frailty model to account for the matched set design. For this analysis, the index day was used as time 0, and patients who survived were censored on the day of hospital (or ICU) discharge. Hospital and ICU length of stay were analyzed using linear regression with generalized estimating equations and robust variance to account for the matched set design. Lengths of stay were calculated from the index day (i.e. day of transfusion, as described previously), and only patients that survived to hospital (or ICU discharge) were included in the analysis.

Linear models of matched sets were adjusted for age and most recent SOFA score and Glasgow coma scale at the time the patient was selected into the study. Models for ICU and hospital length of stay were also adjusted for factors that remained with significant between group differences (utilizing a P-value threshold <0.1) in univariate analyses, including Charlson score, cirrhosis, chronic kidney disease, creatinine, pulmonary disease, peptic ulcer disease, cerebrovascular disease, and index day hemoglobin. SOFA scores 24 h following the index day were analyzed using multivariable linear regression with robust variance. Twenty-four hour SOFA scores for patients who were discharged or died on the index ICU day were imputed using last value carried forward. For mortality outcomes, the results were presented using the hazard ratio and corresponding 95% confidence interval, and, for length of stay and SOFA score, the results were presented using the point estimate and 95% confidence intervals for the difference between those transfused versus not transfused. To supplement the overall analysis, subgroup analyses were performed for each ABI subgroup. In all tests, a two-sided p-value <.05 was utilized for statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Total cohort

In the total cohort, 2638 patients met inclusion criteria over the 7 year study period with 225 (8.5%) recieving RBC transfusion during their ICU stay and a median (interquartile range) transfusion volume of 2 (1–2) units, where 1 unit has a volume of approximately 300 mL. Among transfused patients, the median pre-transfusion hemoglobin was 8.0 (7.4–9.1) g/dL with a median post-transfusion hemoglobin of 9.4 (8.6–10.3) g/dL. Basic demographic and clinical characteristics for the unmatched transfused and non-transfused patients are provided in Table 1. Briefly, patients receiving RBC transfusion were sicker with higher rates of congestive heart failure, leukemia, and lymphoma, suffered more significant neurological insults as evidenced by lower admission and nadir GCS scores, and were more severely anemic. AIS was the most prevalent ABI diagnosis (43.3%) followed by nontraumatic ICH (25.6%), non-traumatic SAH (16.5%), and TBI (14.6%). Overall, 12% of patients died in the hospital [40/225 (17.8%) transfused and 276/2413 (11.4%) non-transfused], with 48% of deaths occuring in the ICU [22/225 (9.8%) transfused and 130/2413 (5.4%) non-transfused]. Baseline demographic and clinical characteristics for patients according to ABI subtype are provided in Supplemental Table 2.

Table 1
Baseline demographic and clinical characteristics of transfused and non-transfused patients with acute brain injury.

Characteristic	Nontransfused (n = 2413)	Transfused (n = 225)	P
Admission characteristics			
Age	68 (55, 79)	62 (49, 72)	<0.001
Sex			0.265
Male	1252 (51.9%)	108 (48.0%)	
Female	1161 (48.1%)	117 (52.0%)	
Diagnosis			<0.001
Acute ischemic stroke	1075 (44.6%)	67 (29.8%)	
Non-traumatic intracranial hemorrhage	624 (25.9%)	51 (22.7%)	
Non-traumatic subarachnoid hemorrhage	396 (16.4%)	39 (17.3%)	
Traumatic brain injury	318 (13.2%)	68 (30.2%)	
Admission GCS score, $n = 2361/223$	14 (12, 15)	10 (7, 14)	<0.001
Admission SOFA score	2 (1, 5)	6 (4, 8)	<0.001
Pre-ICU laboratory values			
aPTT, $n = 1199/159$	28 (25, 32)	29 (25, 33)	0.099
Creatinine, $n = 1568/183$	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	0.481
Albumin, $n = 237/40$	3.6 (3.1, 4.1)	3.4 (2.9, 3.7)	0.055
Hemoglobin, $n = 1485/178$	13.3 (12.0, 14.6)	11.4 (9.2, 13.4)	<0.001
INR, $n = 1397/171$	1.0 (1.0, 1.2)	1.1 (1.0, 1.3)	0.001
Platelets, $n = 1521/180$	222 (176, 275)	215 (148, 282)	0.126
Charlson comorbidity index	3 (2, 5)	3 (1, 5)	0.002
Preexisting conditions			
AIDS	13 (0.5%)	1 (0.4%)	0.852
Connective tissue disease	74 (3.1%)	8 (3.6%)	0.686
Congestive heart failure	196 (8.1%)	29 (12.9%)	0.014
Cancer	630 (26.1%)	53 (23.6%)	0.403
Cirrhosis	39 (1.6%)	5 (2.2%)	0.497
Diabetes mellitus type 2	592 (24.5%)	55 (24.4%)	0.976
Chronic kidney disease	244 (10.1%)	31 (13.8%)	0.085
Cerebrovascular disease	424 (17.6%)	33 (14.7%)	0.271
Hemiplegia	18 (0.7%)	0 (0.0%)	0.194
Leukemia	18 (0.7%)	8 (3.6%)	<0.001
Lymphoma	40 (1.7%)	8 (3.6%)	0.042
Myocardial infarction	240 (9.9%)	18 (8.0%)	0.347
Peptic ulcer disease	102 (4.2%)	8 (3.6%)	0.630
Peripheral vascular disease	87 (3.6%)	12 (5.3%)	0.192
Pulmonary disease	31 (1.3%)	1 (0.4%)	0.271
Dementia	62 (2.6%)	4 (1.8%)	0.467

Abbreviations: GCS, glasgow coma scale; SOFA, sequential organ failure assessment; ICU, intensive care unit; aPTT, activated partial thromboplastin time; INR, international normalized ratio; AIDS, acquired immunodeficiency syndrome.
Continuous variables are summarized as median (Q1, Q3) and compared using rank-sum tests. Categorical variables are summarized as n (%) and compared using Chi-square tests. Where missing data exists the number of observations with non-missing data in each group are presented.

3.2. Matched cohort

Of the 225 transfused patients, 169 (75.1%) had a pre-transfusion hemoglobin in the range of 7.0 to 9.9 g/dL. There was no difference in the number of days from hospital to ICU admission between groups (p=0.687; Supplemental Table 3). In the transfused group, 136 (85%) of patients were admitted to the ICU on day 1 or 2 of hospitalization compared to 140 (88%) in the non-transfused group. The median (min, max) ICU day of the transfusion was 2 (1, 19). 160 patients were matched 1:1 with patients not-receiving RBC transfusion (Table 2). Results from multivariable analyses of the matched sets are presented in Table 3. RBC transfusion was found to be associated with longer ICU LOS (estimated difference 3.44 days, 95% CI 2.36 to 4.53, $p < 0.001$), longer hospital LOS (estimated difference 4.86 days, 95% CI 2.40 to 7.33, $p < 0.001$), and higher SOFA scores 24 h after the index date (estimated difference 0.47, 95% CI 0.03 to 0.92, $p = 0.037$). No significant difference was found for ICU mortality (HR 0.87, 95% CI 0.37 to 2.03, $p = 0.742$) or hospital mortality (HR 0.80, 95% CI 0.44 to 1.46, $p = 0.467$).

3.3. Subgroup analysis by ABI subtype

Results of matched analyses performed separately for each ABI subtype are presented in Table 4. Briefly, transfusion was associated with increased ICU LOS for all acute brain injury subtypes. Unique from other brain injury subtypes, hospital mortality was significantly higher for subjects with ICH not receiving RBC transfusion (43.2% compared to 21.6% in transfused subjects; $p = 0.003$).

4. Discussion

In a matched cohort of moderately anemic patients with ABI requiring neurocritical care, RBC transfusion was associated with longer hospital and ICU LOS and higher SOFA scores 24 h after the index date compared to nontransfused patients. Additionally, a higher hospital and ICU LOS was found in each ABI subtype, with the exception of TBI in which no significant differences in hospital LOS were observed with RBC transfusion. Despite the associations between RBC transfusion and increased ICU and hospital durations, there were no differences in mortality based upon the presence or absence of transfusion. This was observed in each ABI subgroup, except for ICH in which RBC transfusion was associated with improved mortality. Moreover, higher SOFA scores 24 h after the index date were found in transfused compared to non-transfused patients with AIS and SAH, but this relationship was not significant in those with ICH and TBI. On the whole, RBC transfusion was not associated with improved clinical outcomes in those with ABI.

RBC transfusion in ABI remains vigorously debated, and a critical laboratory or hemodynamic threshold(s) for RBC transfusion remains unclear. Experimental evidence suggests that further exacerbation of brain injury occurs when hemoglobin falls below 10 g/dL, [28-31] and cerebral DO2 appears to be maximized at a hematocrit of 31% after global brain ischemia [32]. In SAH specifically, hemoglobin concentrations below 9 g/dL have been associated with brain hypoxia and cellular dysfunction with the use of cerebral microdialysis catheters [13]. Given these findings and the fact that anemia has been associated with poor outcomes across subtypes of acute brain injury, [2-4,6-9,11,] correction of anemia with the ultimate goal of cerebral DO2 enhancement would seem like a particulary suitable indication for RBC transfusion. Indeed, RBC transfusion can augment cerebral DO2 in anemic patients with acute brain injury, though it is unclear if this translates to improved clinical outcomes [33,34]. Moreover, the relationship between RBC

Table 2
Baseline demographic and clinical characteristics of transfused and non-transfused patients with acute brain injury – Matched sets.

Characteristic	Nontransfused (n = 160)	Transfused (n = 160)	P
Admission characteristics			
Age	65 (53, 75)	63 (50, 76)	0.236
Sex			0.433
Male	80 (50.0%)	73 (45.6%)	
Female	80 (50.0%)	87 (54.4%)	
Diagnosis			1.000
Acute ischemic stroke	48 (30.0%)	48 (30.0%)	
Non-traumatic intracranial hemorrhage	37 (23.1%)	37 (23.1%)	
Non-traumatic subarachnoid hemorrhage	23 (14.4%)	23 (14.4%)	
Traumatic brain injury	52 (32.5%)	52 (32.5%)	
Admission GCS score	12 (8, 15)	10 (7, 14)	0.119
Admission SOFA score	5 (3, 9)	5 (4, 8)	0.677
Characteristics at index ICU day			
Hemoglobin (g/dL)	8.3 (7.9, 8.7)	8.0 (7.6, 8.6)	0.001
GCS	11 (7, 14)	11 (8, 14)	0.806
SOFA score	4 (2, 7)	5 (4, 7)	0.005
Pre-ICU laboratory values			
aPTT, $n = 108/115$	30 (26, 36)	29 (25, 33)	0.204
Creatinine, $n = 125/132$	1.0 (0.7, 1.5)	0.9 (0.7, 1.1)	0.004
Albumin, $n = 39/23$	3.2 (2.4, 3.5)	3.4 (2.8, 3.7)	0.457
Hemoglobin, $n = 120/129$	9.9 (8.8, 12.7)	11.3 (9.2, 13.3)	0.010
INR, $n = 116/121$	1.2 (1.0, 1.5)	1.1 (1.0, 1.4)	0.105
Platelets, $n = 121/130$	242 (136, 304)	218 (159, 282)	0.626
Charlson comorbidity index	4 (2, 6)	3 (1, 5)	0.016
Preexisting conditions			
AIDS	2 (1.3%)	1 (0.6%)	0.562
Connective tissue disease	5 (3.1%)	6 (3.8%)	0.759
Congestive heart failure	17 (10.6%)	23 (14.4%)	0.310
Cancer	50 (31.3%)	42 (26.3%)	0.323
Cirrhosis	15 (9.4%)	4 (2.5%)	0.009
Diabetes mellitus type 2	51 (31.9%)	41 (25.6%)	0.217
Chronic kidney disease	40 (25.0%)	22 (13.8%)	0.011
Cerebrovascular disease	35 (21.9%)	22 (13.8%)	0.058
Hemiplegia	0 (0.0%)	0 (0.0%)	
Leukemia	3 (1.9%)	4 (2.5%)	0.702
Lymphoma	6 (3.8%)	4 (2.5%)	0.520
Myocardial infarction	28 (17.5%)	18 (11.3%)	0.111
Peptic ulcer disease	14 (8.8%)	6 (3.8%)	0.065
Peripheral vascular disease	8 (5.0%)	10 (6.3%)	0.627
Pulmonary disease	4 (2.5%)	0 (0.0%)	0.044
Dementia	5 (3.1%)	2 (1.3%)	0.252

Abbreviations: GCS, glasgow coma scale; SOFA, sequential organ failure assessment; ICU, intensive care unit; aPTT, activated partial thromboplastin time; INR, international normalized ratio; AIDS, acquired immunodeficiency syndrome.
Continuous variables are summarized as median (Q1, Q3) and compared using rank-sum tests. Categorical variables are summarized as n (%) and compared using Chi-square tests. Where missing data exists the number of observations with non-missing data in each group are presented.

transfusion and cerebral DO2 is not readily-predictable as RBC transfusion does not reliably result in improved tissue oxygenation or cellular metabolism [15]. In fact, paradoxical reductions in brain tissue oxygen tension (PbtO2) have been measured in approximately one-third of transfusion episodes [35].

As the decision to transfuse RBCs is most controversial for patients with moderate anemia (defined as hemoglobin concentrations between 7 and 10 g/dL), we examined relationships between RBC transfusion and outcomes for patients with ABI falling within this hemoglobin range. Our findings expand on the existing literature regarding RBC transfusion in patients with moderate anemia. Additionally, we conducted subgroup analyses based on each ABI subtype, finding that transfusion was associated with a longer lengths of stay for the majority of ABI subtypes.

In those with AIS and SAH, RBC transfusion was associated with a longer hospital and ICU LOS but no difference in mortality. This is consistent with another retrospective study in which RBC transfusion for patients with AIS was associated with increased ICU LOS [10]. In patients with SAH, our findings corroborate the findings of a previous investigation of patients with SAH that found no relationship between RBC transfusion and mortality or long-term modified rankin score but did observe longer LOS with RBC transfusion [36]. However, our results differ from a previous retrospective study that observed higher mortality following RBC transfusion in those with SAH; LOS was not reported [22]. Certainly, the observed between-study differences in mortality may be related to low statistical power for this outcome in the current investigation, as described in the limitations section.

In those with TBI, RBC transfusion was associated with an increased ICU LOS but we did not observe an association between transfusion and other outcomes. Our results are similar to a subgroup analysis of the the TRICC trial, in which there were no observed differences in mortality or hospital LOS based upon liberal or restrictive transfusion approaches [37]. However, a previous observational study of 139 patients with TBI and moderate anemia did observe longer hospital LOS with RBC transfusion, as well as worse long-term functional outcomes as measured by Glasgow Outcome Scale-Extended score [6]. ICU LOS was not reported.

Finally, in this investigation, RBC transfusion was associated with longer hospital and ICU LOS in those with ICH. Paradoxically, however, patients receiving transfusion had lower hospital mortality. Our findings are similar to a previous retrospective cohort study that found improved mortality when patients with ICH received RBC transfusion [38]. Of note, this previous study contained only few patients with moderate anemia as most patients were mildly anemic (i.e. hemoglobin >10 g/dL). Furthermore, LOS outcomes were not reported. It must be noted that our results should be considered hypothesis generating, though it is possible that patients with ICH may behave differently from other ABI subgroups with regards to anemia tolerance and experience differential responses to transfusion therapies. Further study in this population is clearly warranted.

Table 3
Multivariable analyses comparing matched-sets of transfused to nontransfused patients.

Outcome	Nontransfused	Transfused	Estimate (95% CI)	P
ICU length of stay (d)	1 (0, 4)	4 (2, 9)	3.44 (2.36 to 4.53)	<0.001
ICU mortality	14 (8.8%)	12 (7.5%)	0.87 (0.37 to 2.03)	0.742
Hospital length of stay (d)	7 (3, 12)	12 (6, 18)	4.86 (2.40 to 7.33)	<0.001
Hospital mortality	28 (17.5%)	24 (15.0%)	0.80 (0.44 to 1.46)	0.467
SOFA score	3 (1, 5)	4 (2, 6)	0.47 (0.03 to 0.92)	0.037

Abbreviations: 95% CI, 95% confidence interval; ICU, intensive care unit; d, days; SOFA, sequential organ failure assessment.
Hospital LOS, ICU LOS, and SOFA score are summarized as median (Q1, Q3) and compared with linear regression using generalized estimating equations with robust variance to account for the matched set design. Hospital and ICU mortality are summarized as n (%) and compared using shared frailty model to account for the matched set design. All analyses are adjusted for age and most recent SOFA score and Glasgow coma scale at the time the patient was selected into the study. Models for ICU and hospital length of stay also include Charlson score, cirrhosis, CKD, creatinine, pulmonary disease, peptic ulcer disease, cerebrovascular disease, and index day hemoglobin. Results are presented as Estimates with 95% confidence intervals for the estimated effect in those transfused versus not transfused.

Table 4
Multivariable analyses comparing matched-sets of transfused and nontransfused patients for each acute brain injury subtype.

Outcome	Nontransfused	Transfused	Estimate (95% CI)	P
Acute ischemic stroke				
ICU length of stay (d)	1 (0, 3)	3 (2, 8)	4.20 (2.59 to 5.82)	<0.001
Hospital length of stay (d)	7 (3, 11)	12 (5, 18)	6.66 (2.26 to 11.05)	0.003
Hospital mortality	8 (16.7%)	5 (10.4%)	0.47 (0.15 to 1.45)	0.189
SOFA score	3 (1, 4)	4 (2, 6)	0.76 (0.02 to 1.50)	0.043
Non-traumatic intracranial hemorrhage				
ICU length of stay (d)	1 (0, 3)	5 (2, 10)	4.47 (1.66 to 7.28)	0.002
Hospital length of stay (d)	4 (2, 12)	12 (8, 18)	6.72 (0.13 to 13.31)	0.046
Hospital mortality	16 (43.2%)	8 (21.6%)	0.24 (0.09 to 0.62)	0.003
SOFA score	4 (2, 8)	4 (2, 7)	−0.05 (−1.41 to 1.31)	0.943
Non-traumatic subarachnoid hemorrhage				
ICU length of stay (d)	4 (2, 7)	7 (4, 14)	4.12 (0.52 to 7.72)	0.025
Hospital length of stay (d)	9 (6, 14)	18 (10, 21)	9.05 (4.24 to 13.86)	<0.001
Hospital mortality	2 (8.7%)	3 (13.0%)	1.32 (0.22 to 7.99)	0.763
SOFA score	1 (1, 4)	4 (2, 6)	1.30 (0.31 to 2.28)	0.010
Traumatic brain injury				
ICU length of stay (d)	1 (1, 3)	3 (2, 8)	2.36 (1.11 to 3.62)	<0.001
Hospital length of stay (d)	7 (4, 12)	8 (5, 14)	1.33 (−2.18 to 4.83)	0.459
Hospital mortality	2 (3.8%)	8 (15.4%)	3.53 (0.75 to 16.66)	0.111
SOFA score	2 (1, 5)	4 (3, 6)	0.75 (−0.01 to 1.51)	0.054

Abbreviations: 95% CI, 95% confidence interval; ICU, intensive care unit; d, days; SOFA, sequential organ failure assessment.
Hospital LOS, ICU LOS, and SOFA score are summarized as median (Q1, Q3) and compared with linear regression using generalized estimating equations with robust variance to account for the matched set design. Hospital mortality is summarized as n (%) and compared using shared frailty model to account for the matched set design. Linear models were adjusted for age and most recent SOFA score and Glasgow coma scale at the time the patient was selected into the study. Models for ICU and hospital length of stay also include Charlson score, cirrhosis, CKD, pulmonary disease, peptic ulcer disease, cerebrovascular disease, and index day hemoglobin. Due to the small sample within each diagnosis group, analyses for hospital mortality were unadjusted. Results are presented as Estimates with 95% confidence intervals for the estimated effect in those transfused versus not transfused.

4.1. Study limitations

There are several limitations to this study. First, this is a retrospective evaluation of critically ill patients. While careful statistical adjustments were utilized to address differences in illness severity, the potential for residual confounding remains, with those receiving RBC transfusion potentially representing a sicker patient cohort. Of note, we attempted to ameliorate this possibility through matched analyses, including matching based upon length of stay, age, ABI subtype, and pre-transfusion hemoglobin, as well as with multivariable adjustment. However, it is quite possible that patients who received RBC transfusion displayed features of inadequate tissue oxygen delivery (e.g. altered mentation, changes in blood pressure and heart rate) when compared to patients not receiving RBCs. These features are difficult to capture in a retrospective review, and therefore they may not have been represented in our statistical analyses. Second, details regarding brain injury subtypes, including mechanisms and severity of specific insults, were not universally available for patients and hence were not included. It is possible that the effects of RBC transfusion on outcomes may be dependent on these specific characteristics (e.g. stroke or hemorrhage size, mechanism of TBI, evolution of clinical symptoms). Additionally, it is possible that some patients received RBC transfusion in response to active bleeding rather than for the enhancement of cerebral DO_2 in an otherwise compensated physiologic state. In an attempt to adjust for this, in a *post-hoc* analysis we identified all patients that received RBCs in the 24 h before the qualifying ICU transfusion, assuming that these patients may have experienced acute blood loss. To this end, only 6 patients were identified, and their exclusion did not modify the study results. As an additional limitation, functional outcomes were not available for analysis. Finally, the total number of transfused patients was limited, and thus, the study was likely underpowered to detect differences in mortality leading to wide confidence intervals. Subgroup analyses of the matched cohort by ABI subtype also were similarly underpowered for measured outcomes. At the level of subgroup analysis in the matched cohort, few mortalities occurred in the ICU, thus, ICU mortality was not reported. Larger prospective studies will be necessary to further clarify the impact of RBC transfusion on survival.

5. Conclusions

This study specifically sought to assess the relationship between RBC transfusion and patient-important outcomes in a large cohort of patients requiring neurological intensive care with diverse mechanisms of ABI. To that end, RBC transfusion was associated with increased ICU and hospital LOS, findings which were consistent accross each subgroup of ABI, except for the TBI subgroup that did not have longer hospital LOS. These findings support a growing body of evidence that RBC transfusion is not associated with improved outcomes in those with ABI and moderate anemia, despite the known deleterious effects of anemia and theoretical benefits of RBC transfusion on cerebral DO_2. While a randomized clinical trial directly assessing the impact of RBC transfusion on patient-important outcomes is warranted in this unique population, this study suggests that a restrictive transfusion strategy may be appropriate for patients with acute brain injury and moderate levels of anemia.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.11.006.

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