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# Association between the plasma-to-red blood cell ratio and survival in geriatric and non-geriatric trauma patients undergoing massive transfusion: a retrospective cohort study

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## Abstract

**Background:** The benefits of a high plasma-to-red blood cell (RBC) ratio on the survival of injured patients who receive massive transfusions remain unclear, especially in older patients. We aimed to investigate the interaction of age with the plasma-to-RBC ratio and clinical outcomes of trauma patients.

**Methods:** In this retrospective study conducted from 2013 to 2016, trauma patients who received massive transfusions were included. Using a generalized additive model (GAM), we assessed how the plasma-to-RBC ratio and age affected the in-hospital mortality rates. The association of the plasma-to-RBC ratio [low (< 0.5), medium (0.5–1.0), and high ( $\geq 1.0$ )] with in-hospital mortality and the incidence of adverse events were assessed for the overall cohort and for patients stratified into non-geriatric (16–64 years) and geriatric ( $\geq 65$  years) groups using logistic regression analyses.

**Results:** In total, 13,894 patients were included. The GAM plot of the plasma-to-RBC ratio for in-hospital mortality demonstrated a downward convex unimodal curve for the entire cohort. The low-transfusion ratio group was associated with increased odds of in-hospital mortality in the non-geriatric cohort [odds ratio 1.38, 95% confidence interval (CI) 1.22–1.56]; no association was observed in the geriatric group (odds ratio 0.84, 95% CI 0.62–1.12). An increase in the transfusion ratio was associated with a higher incidence of adverse events in the non-geriatric and geriatric groups.

**Conclusion:** The association of the non-geriatric age category and plasma-to-RBC ratio for in-hospital mortality was clearly demonstrated. However, the relationship between the plasma-to-RBC ratio with mortality among geriatric patients remains inconclusive.

**Keywords:** Damage control resuscitation, Geriatric trauma, Massive transfusion, Trauma registry

## Background

Massive transfusion (MT) plays a critical role in the resuscitation of trauma patients presenting in hemorrhagic shock [1, 2]. Studies have demonstrated that an increased transfusion ratio of plasma-to-red blood cells (RBCs) may prevent the development of trauma-induced

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coagulopathy and may also have the potential to improve the survival rate of severely injured patients [3–5]. However, other studies have failed to show any benefit of the high plasma-to-RBC transfusion ratio approach [6–8]. A recent randomized controlled trial also failed to show a clinically important difference in overall mortality between patients who received transfusion with a 1:1 blood product ratio of plasma and RBCs and those who received transfusion with a 1:2 ratio [9].

The scope of MT practices is mainly derived from studies in younger adults, and there is even less evidence showing the impact of early plasma transfusion practices on the elderly [10]. Elderly patients have generally reduced physiological reserve and an increased prevalence of comorbidities [11]. Higher transfusion ratios imply a larger total volume transfused, increasing the risk of complications, such as intravascular volume overload, transfusion-related lung injury, and infections [12–14]. A previous study using data from a Japanese administrative database, which included a large number of older adults, reported that a higher plasma-to-RBC ratio was associated with increased incidence of adverse events after MT in a ratio-dependent manner [15]. Although several investigators have documented increased mortality with increased age among trauma patients who received massive transfusions, the interaction between age and the effect of transfusion ratio has not been evaluated [16, 17].

This study aimed to assess the age-related heterogeneity in the association between plasma-to-RBC transfusion ratio and clinical outcomes in severely injured patients who required massive transfusion.

## Methods

### Study design and setting

This retrospective cohort study utilized the data from the American College of Surgeons Trauma Quality Improvement Program (TQIP) database. The TQIP database is a subset of the National Trauma Databank and contains trauma-related variables reported by trauma centers in the USA. The observation period was 4 years, from January 2013 to December 2016. At the end of 2016, more than 700 Level 1 and Level 2 trauma centers had participated in the TQIP. The study and its protocols were approved by the institutional review committee of Riverside University Health System—Comparative Effectiveness and Clinical Outcomes Research Center. The requirement for informed consent for each patient was waived based on the use of anonymized patient and hospital data.

### Patient selection

Severely injured patients who received massive transfusions were included in the analyses. To meet the TQIP

inclusion criteria, patients were aged >16 years, with an Abbreviated Injury Scale (AIS) score >2 in at least one body region. Patients were excluded if their age, outcome, or length of hospital stay were unknown. We also excluded patients who arrived at the emergency department with no signs of life or died within the first 30 min of arrival [15, 18]. Patients who were transferred from another hospital or had isolated traumatic brain injury (AIS of the head >2; AIS of other body parts, ≤2) were also excluded, since we aimed to assess the appropriate transfusion ratio in patients requiring massive transfusion due to hemorrhage.

### Data collection

The following variables were included in the study analyses: age, sex, comorbidities, mechanism of injury, Injury Severity Score (ISS), each body region's AIS score, vital signs (systolic blood pressure, heart rate, and respiratory rate), Glasgow Coma Scale score upon arrival at the emergency department, hospital characteristics (trauma center level and teaching status), amount of blood transfusion within 4 h and 24 h (RBC, platelets, and plasma), hemostatic procedures, ICU length of stay and hospital length of stay, in-hospital complications, and in-hospital and 24-h mortality.

### Definitions and outcomes

A severely injured patient was defined as a patient with ISS ≥ 16. Massive transfusion was defined as transfusion of ≥ 5 units of RBC within 4 h of hospital admission or ≥ 10 units within 24 h of hospital admission, in accordance with previous studies [15, 17, 19–21]. Non-geriatric patients were defined as those aged between 16 and 64 years, and geriatric patients were defined as those aged ≥ 65 years. The study outcomes were in-hospital mortality rate, 24-h mortality rate, and incidence of pre-determined adverse events. The adverse events related to blood transfusion were defined as cardiac, respiratory, and renal failure, as well as thrombotic events and sepsis, which developed after hospital arrival.

### Statistical analysis

After selecting the study cohort, we performed robust linear regression analyses to statistically detect and remove outliers of plasma and RBC transfusion variables, considering the issue of registration errors in the values [22]. Missing values were then imputed using patient characteristics (age, sex), severity upon arrival to the emergency department (Revised Trauma Score [RTS], ISS, and AIS score of each body region), and comorbidities on arrival (cardiac, pulmonary, liver, or renal diseases, and diabetes) using the random forest method for each study cohort with the missForest

package (version 1.4) of R software (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria) [23].

The associations between plasma-to-RBC transfusion ratios and outcomes were assessed as follows. First, we investigated the associations of the plasma-to-RBC ratio with in-hospital mortality, 24-h mortality, and incidence of adverse events in the entire study cohort using a non-linear generalized additive model (GAM), using the *mgcv* package (version 1.8-38) of R software, which was used to account for the possible non-linear relationship between the plasma-to-RBC ratio and outcomes based on the results of our previous study and preliminary analysis [15, 18]. The model was fitted using the residual maximum likelihood method, and adjusted for sex, ISS, RTS, injured body region, total prehospital time (time from injury to arrival at the hospital), trauma center level, and hospital type (university, community, and non-teaching). These variables were selected after considering a clinical perspective and previous reports [15, 18]. Second, we assessed the interaction of different age categories (i.e., non-geriatric patients or geriatric patients) with the association between the plasma-to-RBC ratio and in-hospital mortality of severely injured patients using a GAM. Third, the patients were classified into two age categories: non-geriatric and geriatric groups. Associations between the plasma-to-RBC ratio and outcomes (in-hospital mortality rate, 24-h mortality rate, and incidence of adverse events) were evaluated using a GAM adjusting for the aforementioned variables, which were used to visualize relationships between the plasma-to-RBC ratio and the outcomes in two different age groups. Fourth, the patients with different plasma-to-RBC ratios at 24 h were categorized into three groups: low ( $< 0.5$ ), medium ( $0.5\text{--}1.0$ ), and high ( $\geq 1.0$ ). These three categories were chosen based on a clinical perspective and previous reports [18, 24]. Using a logistic regression model, the association between the plasma-to-RBC ratio categories and the outcomes was numerically compared between two consecutive categories (i.e., low vs. medium, medium vs. high, and low vs. high), adjusted for age, sex, comorbidities, injury mechanisms, total prehospital time, ISS, RTS and AIS in each body region (head, neck, thorax, abdomen, upper extremities, and pelvis/lower extremities), trauma center levels, and hospital type. We also performed Cox proportional hazard regression analyses after adjusting for age, sex, ISS, RTS, injured body region, and hospital types to further evaluate the risk of mortality at 28 days among the low, medium, and high subgroups in the non-geriatric and geriatric groups. Plasma-to-RBC ratios at 4 h and 24 h were treated as time-dependent covariates, and mortality after 28 days was treated as survival in this model [25]. The *survival* (version 3.2-13) and *survminer*

(version 0.4.9) packages in R were used for the Cox proportional hazard regression analyses.

We performed sensitivity analyses using logistic regression models considering the possible effect of biases in observational studies on blood transfusion in trauma. First, we excluded all patients who died within the first 24 h to consider the impact of patients who died before plasma could be administered (survivor bias). Second, we included patients with similar plasma-to-RBC ratio categories between 4 and 24 h. For this analysis, we ensured that the transfusion strategy was consistent until 24 h by excluding patients whose transfusion ratio categories were different in the first 4 h vs. 24 h to reduce the risk of survivor and plasma delay bias [26]. Third, we carried out the same analysis for the cohort without severe traumatic brain injury (AIS of the head  $< 3$ ), considering the different pathophysiology in patients with traumatic brain injuries [15].

Chi-square or Fisher's exact test was used for categorical variables, and the Mann-Whitney *U* test was used for continuous variables. Values are presented as median (25–75% interquartile range) and frequency (percentage). Estimated data are presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). All statistical analyses were performed using R software. The level of significance was defined as a *p* value  $< 0.05$ .

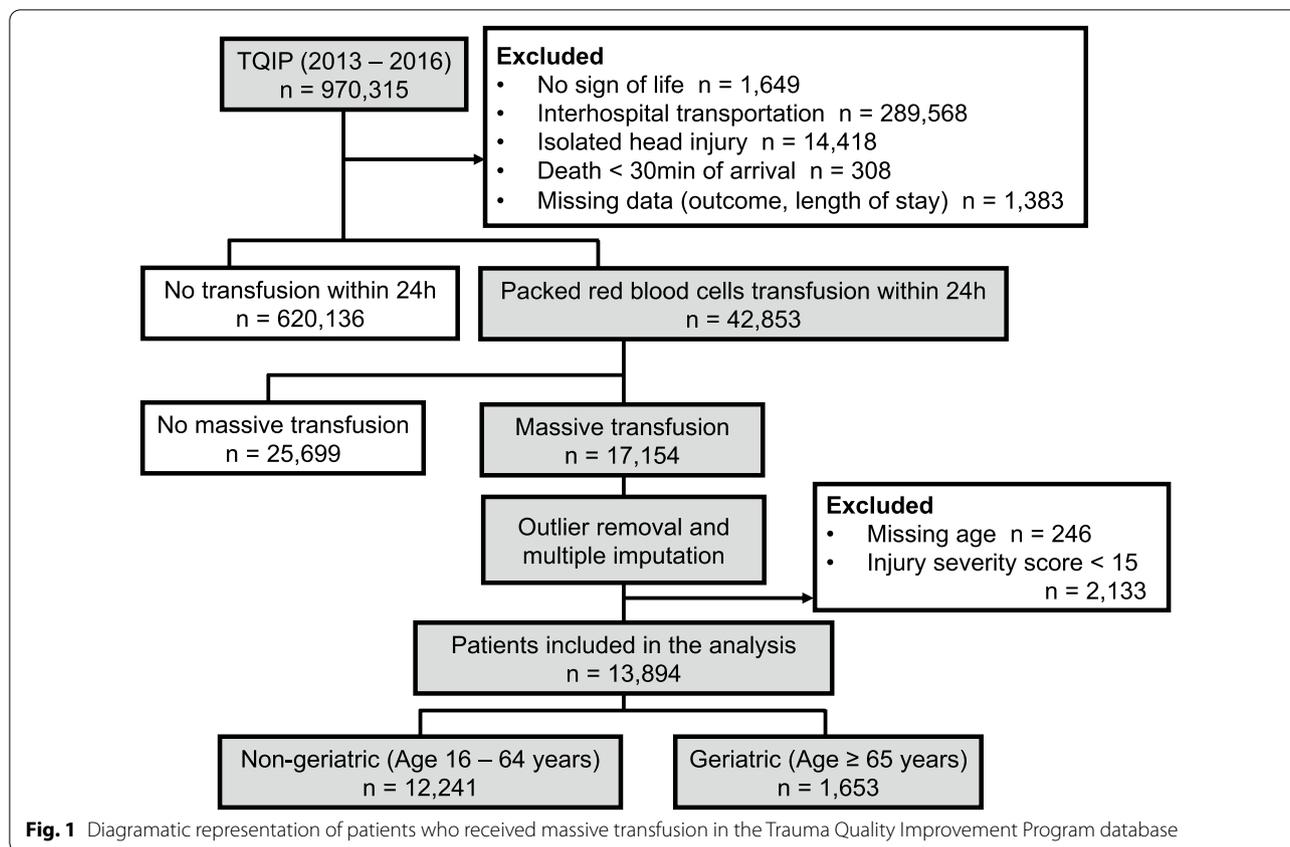
## Results

### Patients' characteristics

In total, 970,315 trauma patients were identified in the TQIP database between 2013 and 2016, of which 17,154 received  $\geq 5$  units of RBC within 4 h or  $\geq 10$  units of RBC within 24 h of hospital arrival. We excluded 3305 (19.2%) patients due to unknown age, outcome, or outliers of blood transfusion data. A total of 13,894 trauma patients received massive transfusions and met the inclusion criteria of the study, including 12,241 (88.1%) non-geriatric and 1653 (11.9%) geriatric patients (Fig. 1). Patients' and hospital characteristics are summarized in Table 1. Geriatric patients were more likely to exhibit blunt mechanisms of injury and have more comorbidities. No significant differences in ISS and trauma center level between the study groups were observed. The in-hospital mortality rate was 30.5% for the entire study cohort, and it was significantly higher for geriatric patients than for non-geriatric patients (47.3% vs. 28.3%). The incidence of adverse events was similar among the two groups (22.8% vs. 21.9%) (Table 2).

### Association between the plasma-to-RBC ratio and the outcomes

Using a non-linear GAM to analyze the entire cohort, the plot for assessing the in-hospital and 24-h mortality rates



**Fig. 1** Diagrammatic representation of patients who received massive transfusion in the Trauma Quality Improvement Program database

after adjusting for multiple covariables demonstrated a downward convex unimodal curve (Fig. 2A, B). A trend toward a higher incidence of adverse events was observed for higher plasma-to-RBC ratios (Fig. 2C). We then confirmed that the interaction between the age category and plasma-to-RBC ratio at 24 h was statistically significant ( $p$  for interaction  $< 0.001$ ), suggesting the existence of an interaction between age categorization and the plasma-to-RBC ratio with mortality.

After patients were subdivided into two age categories, the GAM plots of the plasma-to-RBC ratio for both in-hospital and 24-h mortality rates demonstrated a downward convex unimodal curve in the non-geriatric group (Fig. 2D, E). However, the plot showed no specific threshold in the risk of in-hospital mortality among the geriatric group (Fig. 2G). A trend toward increased incidence of adverse events was observed for higher plasma-to-RBC ratios in both non-geriatric and geriatric groups (Fig. 2F, I).

Considering generalizability and the results of the GAM plots, we divided the plasma-to-RBC ratios into the following three categories: low ( $< 0.5$ ), medium ( $0.5-1.0$ ), and high ( $\geq 1.0$ ). In the categorized multivariate regression analysis, the low ratio group was associated

with higher in-hospital and 24-h mortality rates than the medium ratio group among the non-geriatric patients (Table 3 and Additional file 1: Table S1). However, there was no association between the transfusion ratio and mortality rate in the geriatric group (Table 3). As per the GAM plots, an increase in the plasma-to-RBC ratio was significantly associated with increased incidence of adverse events in both the non-geriatric and geriatric groups and between the low and medium ratio groups (Table 3).

A multivariate Cox proportional hazard regression analysis revealed that the low plasma-to-RBC transfusion ratio was associated with a higher risk of 28-day mortality (hazard ratio 1.13, 95% CI 1.05–1.22,  $p < 0.001$ ) compared to the medium ratio after controlling for multiple confounders in the non-geriatric patients. A similar association was lacking for the medium ratio group of geriatric patients (Fig. 3 and Table 4).

The sensitivity analyses showed that the association of a low plasma-to-RBC ratio with in-hospital mortality rate remained significantly higher in the subsets of 10,359 patients, whose plasma-to-RBC ratio category was the same at 4 h and 24 h, as well as for the 8252 patients without severe traumatic brain injury in the

**Table 1** Description of patients and hospital characteristics

Description	Non-geriatric age group (n = 12,241)	Geriatric age group (n = 1653)	p-value
Patients' characteristics			
Age, median (IQR)	33 (24–48)	72 (68–79)	< 0.001
Sex (male) n (%)	9647 (78.8)	1056 (65.5)	< 0.001
Mechanism of injury			< 0.001
Blunt injury, n (%)	9407 (76.8)	1422 (86.0)	
Penetrating injury, n (%)	2834 (23.2)	231 (14.0)	
Total prehospital time, median (IQR)	37 (24–63)	45 (31–69)	< 0.001
Comorbidities			
Heart failure, n (%)	45 (0.4)	59 (3.6)	< 0.001
Renal failure, n (%)	61 (0.5)	12 (0.7)	0.071
Cerebrovascular disease, n (%)	52 (0.4)	31 (1.9)	< 0.001
Diabetes, n (%)	546 (4.5)	264 (16.0)	< 0.001
Respiratory disease, n (%)	320 (2.6)	115 (7.0)	< 0.001
Liver cirrhosis, n (%)	181 (1.5)	35 (2.1)	0.062
Dementia, n (%)	7 (0.1)	41 (2.5)	< 0.001
SBP in the ED, median (IQR)	74 (60–90)	70 (57–83)	< 0.001
RTS, median (IQR)	6.1 (3.4–7.6)	6.8 (3.8–7.6)	< 0.001
AIS injured region			
Head ≥ 3, n (%)	3,989 (32.6)	634 (38.4)	< 0.001
Face ≥ 3, n (%)	371 (3.0)	39 (2.4)	0.151
Neck ≥ 3, n (%)	543 (4.4)	39 (2.4)	0.008
Thorax ≥ 3, n (%)	8481 (69.3)	1192 (76.2)	< 0.001
Abdomen ≥ 3, n (%)	7110 (58.1)	758 (47.2)	< 0.001
Spine ≥ 3, n (%)	1321 (10.8)	239 (13.5)	0.001
Upper extremity ≥ 3, n (%)	1067 (8.7)	86 (6.0)	< 0.001
Pelvis/lower extremity ≥ 3, n (%)	5383 (44.0)	792 (51.5)	< 0.001
Surface ≥ 3, n (%)	2 (0.001)	1 (0.001)	1.000
ISS, median (IQR)	29 (22–41)	29 (22–41)	0.677
Hospital characteristics			
Trauma center level			0.087
Level 1, n (%)	9108 (74.4)	1186 (71.7)	
Level 2, n (%)	3133 (25.6)	467 (28.3)	
Teaching status			0.004
University, n (%)	7602 (62.1)	957 (57.9)	
Community, n (%)	3752 (30.7)	565 (34.2)	
Non-teaching, n (%)	887 (7.2)	131 (7.9)	

IQR interquartile range; SBP systolic blood pressure; ED emergency department; RTS Revised Trauma Score; AIS Abbreviated Injury Scale; ISS Injury Severity Score

non-geriatric group (Additional file 2: Table 2). After excluding patients who died within the first 24 h, the association between the plasma-to-RBC ratios and in-hospital mortality rate was diminished in the non-geriatric group (OR vs. medium group, 0.98; 95% CI 0.56–1.51) (Additional file 2: Table S2). In accordance with the entire cohort, significant correlations between transfusion ratios and in-hospital mortality were absent in all sub-populations of the geriatric group (Additional file 2: Table S2).

## Discussion

In this study, we evaluated the association between plasma-to-RBC ratios and outcomes in severely injured geriatric and non-geriatric patients using a nationwide trauma database. We observed that patients who received massive transfusion with a low plasma-to-RBC ratio had significantly greater odds of mortality than patients who received plasma transfusion with a ratio in the range of 0.5–1.0 among non-geriatric severely injured patients. However, an apparent trend in mortality according to the

**Table 2** Blood transfusion, hemorrhage control requirements, and outcomes

Variable	Non-geriatric age group (n = 12,241)	Geriatric age group (n = 1653)	p-value
Blood transfusion, units			
Within 4 h			
RBC, median (IQR)	9 (6–14)	8 (6–13)	<0.001
Plasma, median (IQR)	6 (3–9)	4 (3–9)	<0.001
Platelets, median (IQR)	1 (0–2)	1 (0–2)	0.024
Within 24 h			
RBC, median (IQR)	11 (7–16)	10 (7–16)	0.188
Plasma, median (IQR)	7 (4–12)	6 (4–11)	0.001
Platelets, median (IQR)	2 (1–3)	2 (1–3)	0.074
Hemorrhage control			
Angioembolization, n (%)	1713 (13.9)	337 (20.4)	<0.001
Surgery, n (%)	9743 (79.6)	1128 (68.2)	<0.001
Outcome			
In-hospital mortality, n (%)	3464 (28.3)	782 (47.3)	<0.001
24-h mortality, n (%)	2231 (18.2)	430 (26.0)	<0.001
Hospital LOS, median (IQR)	14 (3–27)	9 (1–22)	<0.001
ICU admission, n (%)	10,641 (86.9)	1444 (87.3)	0.668
ICU LOS, median (IQR)	8 (2–12)	7 (2–16)	0.157
Ventilator days, median (IQR)	4 (2–12)	4 (1–12)	0.443
Any adverse events, n (%)	2685 (21.9)	377 (22.8)	0.440
Cardiac failure, n (%)	43 (0.4)	44 (2.7)	<0.001
Respiratory failure, n (%)	698 (5.7)	82 (5.0)	0.241
Renal failure, n (%)	856 (7.0)	136 (8.2)	0.075
Thrombosis, n (%)	1337 (11.0)	134 (12.2)	0.102
Sepsis, n (%)	370 (3.0)	37 (3.0)	1.000
Others, n (%)	1052 (8.6)	149 (9.0)	0.412

RBC red blood cell; IQR interquartile range; LOS length of stay; ICU intensive care unit

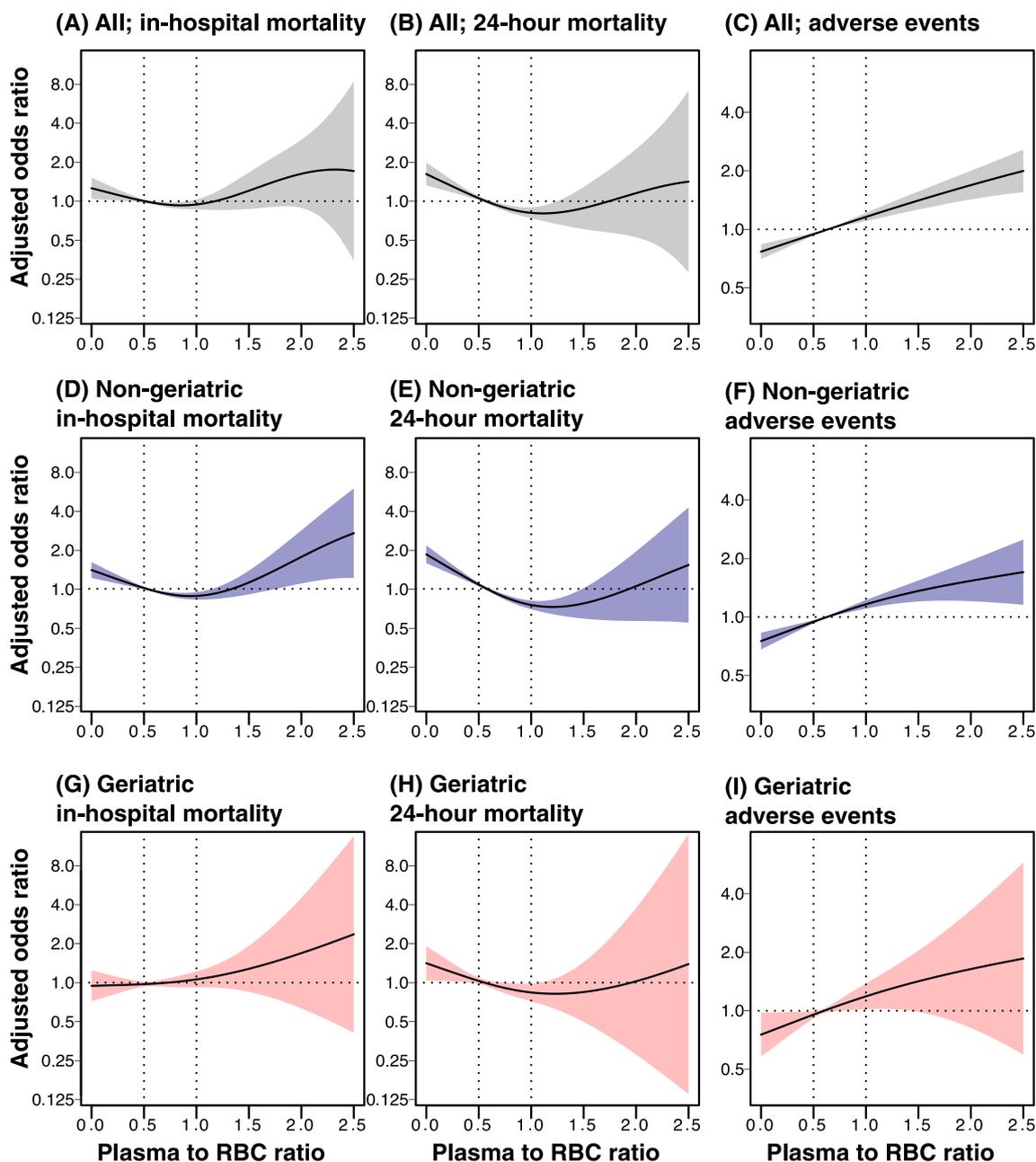
plasma-to-RBC ratio was absent in the geriatric group. Furthermore, an increased incidence of adverse events was observed in the geriatric and non-geriatric trauma patients who received massive transfusions with higher plasma-to-RBC ratios.

Transfusions with balanced plasma-to-RBC ratios as close to 1:1 have been reported to be associated with a reduction in the risk of death from hemorrhage [4, 27, 28]; however, several early observational studies on blood product ratios might have been affected by survival or selection biases. A meta-analysis conducted by a committee of the Eastern Association for the Surgery of Trauma could not provide high-grade evidence supporting the survival benefit of a higher plasma-to-RBC transfusion strategy [2]. The PROPPR trial, the only large randomized controlled trial comparing outcomes between patients who received transfusion in either 1:1:1 or 1:1:2 ratio of plasma, platelets, and RBC, was unable to demonstrate a statistically significant difference between the 24-h and 30-day mortality rates [9]. Therefore, the

conclusive optimal plasma-to-RBC transfusion ratio remains undetermined.

Based on the results of this study, we postulated that the results of previous studies might have been affected by the heterogeneity of the analyzed participants in terms of injury mechanisms and surgical interventions, as well as patient characteristics [2, 29, 30]. Hence, we focused on the differences in the association of transfusion ratios and mortality rate according to age, since advanced age is an independent risk factor for mortality after massive transfusion [17, 31, 32]. Although Cannon et al. reported that the impact of plasma-to-RBC ratio on the mortality of severely injured patients was affected by age, their study targeted a pediatric population [29]. To the best of our knowledge, this is the first study to examine the association of age (whether geriatric or not) with transfusion product ratios and mortality.

Plasma transfusions can cause several adverse events, including, but not limited to, transfusion-associated circulatory overload, transfusion-related acute lung injury,



**Fig. 2** Generalized additive model evaluating the association between plasma-to-red blood cell ratios and outcomes. Association of plasma-to-red blood cell ratios and study outcomes in the entire cohort (A–C) and in the non-geriatric group (D–F) and geriatric group (G–I). Mortality and adverse events were analyzed using the non-linear logistic generalized additive model adjusted for sex, injury mechanisms, Revised Trauma Score, Injury Severity Score, and Abbreviated Injury Scale Score in each body region (head, neck, thorax, abdomen, upper extremities, and pelvis/lower extremities), total prehospital time, trauma center level, and hospital type (university, community, and non-teaching). Adverse events included cardiac, respiratory, and renal failure, as well as thrombotic events and sepsis. The shaded region represents the 95% confidence intervals for the estimated points

allergic reactions, and transfusion-transmitted viral infections, suggesting that excessive administration of plasma might potentially increase the risk of adverse outcomes [12–14]. A previous large-scale retrospective

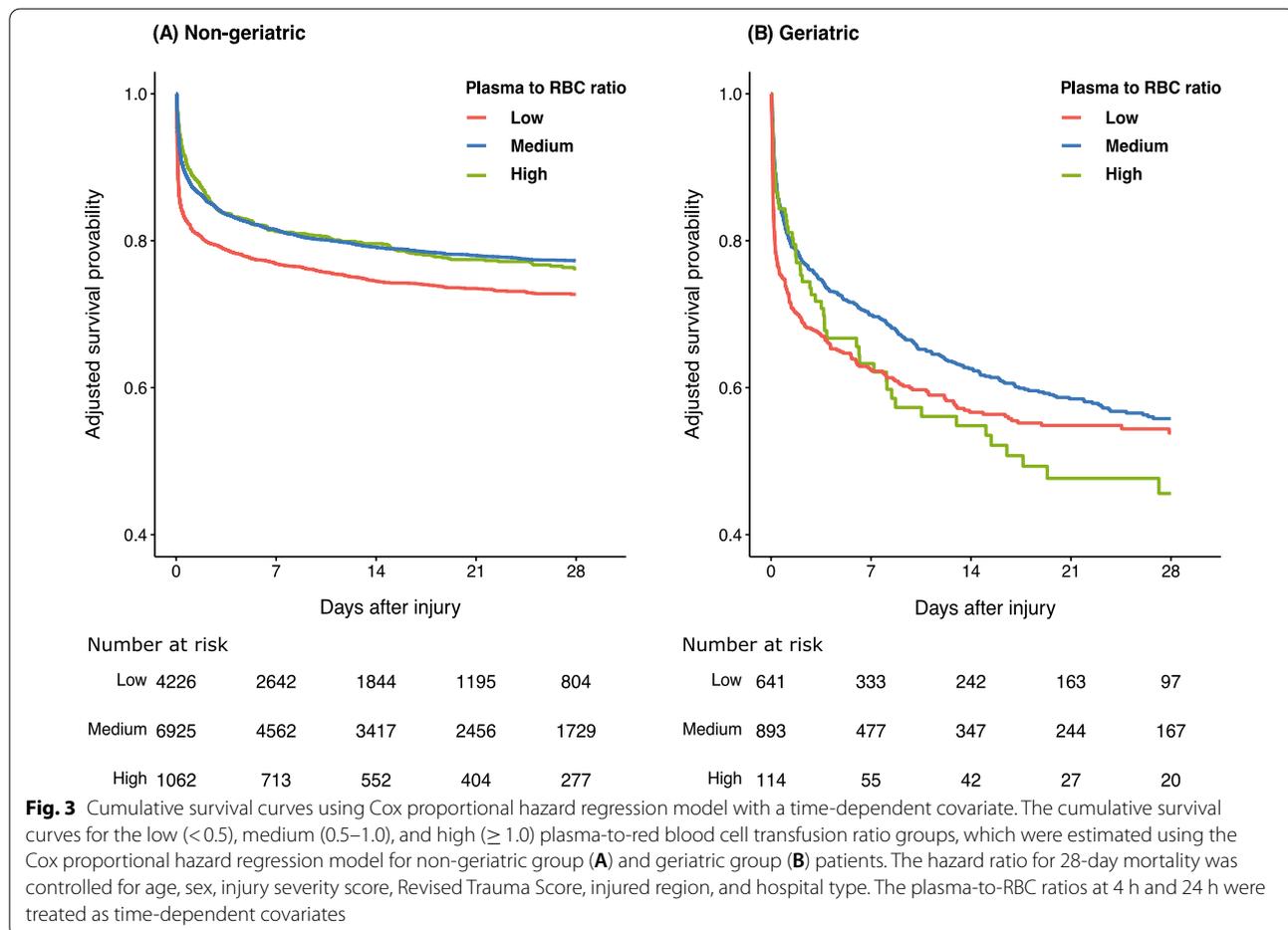
study analyzing a Japanese administrative database failed to show significant differences in in-hospital mortality and transfusion strategies among low (<0.75), medium (0.75–1.25), and high ( $\geq 1.25$ ) plasma-to-RBC ratios, and

**Table 3** Logistic regression analysis evaluating outcomes according to plasma-to-RBC ratio categories

Plasma-to-RBC ratio category	Non-geriatric group			Geriatric group		
	n	Age: 16–64 years OR (95% CI)	p	n	Age: ≥ 65 years OR (95% CI)	p
In-hospital mortality						
Low	4239	1.38 (1.22–1.56)	<0.001	642	0.84 (0.62–1.12)	0.233
Medium	6938	1.00 [Reference]		897	1.00 [Reference]	
High	1064	1.21 (0.98–1.49)	0.149	114	1.34 (0.80–2.27)	0.276
24-h mortality						
Low	4239	1.75 (1.50–2.00)	<0.001	642	1.11 (0.79–1.55)	0.522
Medium	6938	1.00 [Reference]		897	1.00 [Reference]	
High	1064	0.92 (0.71–1.18)	0.57	114	0.85 (0.42–1.63)	0.657
Adverse events						
Low	4239	0.70 (0.62–0.80)	<0.001	642	0.6 (0.43–0.84)	0.002
Medium	6938	1.00 [Reference]		897	1.00 [Reference]	
High	1064	1.16 (0.96–1.39)	0.111	114	0.79 (0.43–1.40)	0.438

Patients were stratified according to plasma-to-RBC ratio as follows: low <0.5, medium 0.5–1.0, and high ≥ 1.0. The model was adjusted for age, sex, comorbidities, injury mechanisms, total prehospital time, Revised Trauma Score, Injury Severity Score, and Abbreviated Injury Scale score, in each body region (head, neck, thorax, abdomen, upper extremities, and pelvis/lower extremities), trauma center levels, and hospital types (university, community, and non-teaching). Adverse events; cardiac failure, respiratory failure, acute renal failure, thrombotic events, and sepsis

RBC red blood cell



**Table 4** Cox proportional hazard regression analysis of transfusion ratio categories with 28-day mortality

Plasma-to-RBC ratio category	Non-geriatric group			Geriatric group		
	n	Age: 16–64 years HR (95% CI)	p	n	Age: ≥ 65 years HR (95% CI)	p
Low	4,226	1.13 (1.05–1.22)	< 0.001	641	0.94 (0.92–1.21)	0.396
Medium	6,925	1.00 [Reference]		893	1.00 [Reference]	
High	1,062	1.07 (0.93–1.20)	0.383	114	0.92 (0.72–1.18)	0.53

Patients were stratified according to the plasma-to-RBC ratio as follows: low < 0.5, medium 0.5–1.0, and high ≥ 1.0. Cox proportional hazard regression analysis controlling for age, sex, Injury Severity Scale, Revised Trauma Score, injured body region, and hospital types to evaluate the risk of mortality at 28 days between low, medium, and high groups in non-geriatric and geriatric groups. Plasma-to-RBC ratios at 4 and 24 h were treated as time-dependent covariates, and mortality for > 28 days was treated as survival in this model

RBC red blood cell

the high plasma-to-RBC ratio strategy was associated with an increase in adverse events [15]. However, there was no association between the plasma-to-RBC ratio and transfusion-related complications in the PROPPR trial [9]. These observed differences may be partially explained by the participants’ age in the cohort: median age was 61 years and 34 years in the Japanese study and PROPPR trial, respectively. Although a considerable number of studies have also reported a higher incidence of adverse events after massive transfusion in older patients, the association between the plasma-to-RBC ratio and adverse events has not been investigated in that subgroup of older patients [10, 31, 33, 34]. In this study, an association between the plasma-to-RBC transfusion ratio and mortality was not observed in the geriatric trauma population. Alternative transfusion strategies for injured geriatric patients, such as developing prediction scores for massive transfusion requirements or point-of-care-based coagulation tests, may be required to improve their outcomes and minimize the risk of transfusion-related complications [35, 36].

Geriatric trauma has become increasingly common as the population ages, particularly in several developed countries [37]. A body of evidence has documented significantly worse outcomes in older patients compared to their younger counterparts [32, 37, 38]. However, geriatric-specific data on blood transfusion ratios during trauma-related resuscitation are scarce. Although recent studies have reported that early aggressive transfusion of plasma is associated with better outcomes than delayed transfusion, others have also raised concerns regarding the safety of increased plasma transfusion, citing the increased risk of complications [39]. In our study, there was no significant association among the different plasma transfusion ratios with mortality of geriatric patients, whereas a low plasma-to-RBC transfusion ratio was associated with a higher risk of 28-day mortality in the non-geriatric patients. One possible explanation is that

the effect size of plasma-to-RBC ratio is lower among elderly patients than younger patients due to the reduced physiological reserve and high prevalence of pre-existing comorbidities [11, 40]. Although some other researchers have advocated a restrictive blood transfusion protocol for geriatric trauma patients, the benefit and adverse events of this strategy must be further evaluated in future studies [41, 42]. Another possible reason is the “Do Not Attempt Resuscitation” (DNAR) order. In general, DNAR orders are more often in geriatric patients [43, 44]. This trend might also have reduced the effect size of plasma-to-RBC ratio in this study.

One of the strengths of this study was that we confirmed the association between the transfusion ratio and mortality using a time-dependent Cox regression model. Survival bias could be reduced by treating the plasma-to-RBC ratio as a time-dependent covariate. We also confirmed consistent results in the sub-analysis on a cohort with a similar transfusion ratio at 4-h and 24-h time points and on a cohort without severe head injury.

The limitations of this study should be acknowledged. First, since this was a retrospective analysis, the presence of survival bias cannot be excluded. Fresh frozen plasma takes longer to administer than RBC, and some patients with devastating conditions might have died before receiving adequate plasma volume. We excluded patients who died within 30 min of arrival at the emergency department, thus aiming to reduce some of the potential survival bias. Second, the TQIP database does not contain detailed information about medications administered to trauma patients. Geriatric patients are more likely to take anticoagulants or antiplatelet agents, which can be a confounding factor for plasma transfusion and outcomes. Third, we compared the outcomes between heterogeneous groups of geriatric and non-geriatric trauma patients. The number of non-geriatric patients age ≥ 65 years was relatively small, as with any trauma database, and this could lead to a type II error.

Fourth, a controversy exists regarding the definition of massive transfusions. Massive transfusion is commonly defined as administration of  $\geq 10$  units of RBC within the first 24 h, as used in this study [19]. However, several researchers have raised concerns regarding this traditional definition [45–47]. Alternatively, others have defined massive transfusion as a transfusion of  $\geq 3$ –4 units of RBC during the initial phase of resuscitation, which is mainly within the first hour [45, 47, 48]. The TQIP database includes the amount of blood products administered within 4 h of admission, but not in the first hour. Therefore, we used a substitute criterion ( $\geq 5$  units of RBC in 4 h), which has been used in previous studies [20, 21]. DNR orders are important variables that affect the outcomes and transfusion strategies in trauma patients [43, 44]. A lack of this information can also be considered a limitation of the study. Finally, since we used a national data set from a single country, external validation may be needed.

## Conclusions

In conclusion, age interacted with the association between the plasma-to-RBC ratio and in-hospital mortality in severely injured patients who underwent massive transfusions. Massive transfusion with a low plasma-to-RBC ratio ( $< 0.5$ ) was not beneficial, especially in non-geriatric adult trauma patients. The association between the plasma-to-RBC ratio and mortality among geriatric patients remains inconclusive.

## Abbreviations

AIS: Abbreviated Injury Scale; CI: Confidence intervals; GAM: Generalized additive model; ISS: Injury Severity Score; OR: Odds ratios; PROPPR: Pragmatic, Randomized Optimal Platelet and Plasma Ratios; RBC: Red blood cell; TQIP: Trauma Quality Improvement Program.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s40560-022-00595-7>.

**Additional file 1: Table S1.** Results of logistic regression analysis for outcomes according to plasma-to-red blood cell ratio categories.

**Additional file 2: Table S2.** Logistic regression model for in-hospital mortality among sub-populations, excluding the following patients from the entire cohort.

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## Authors' contributions

MK and AE carried out data collection. MK, AE, and AS performed data analysis. MK, TS, YO, and RC conceived the study, and MK, AE, AS, TS, YO, and RC participated in its design and coordination. MK, AE, AS, and RC drafted the manuscript. All authors read and approved the final manuscript.

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## Availability of data and materials

All data used in this study are available from the American College of Surgeons Trauma Quality Improvement Program.

## Declarations

### Ethics approval and consent to participate

The study and its protocols were approved by the institutional review committee of Riverside University Health System—Comparative Effectiveness and Clinical Outcomes Research Center. The requirement for informed consent for each patient was waived based on the use of anonymized patient and hospital data.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that there are no competing financial interests.

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