Do not forget the platelets: The independent impact of red blood cell to platelet ratio on mortality in massively transfused trauma patients

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Ander Dorken Gallastegi, Leon Naar, Apostolos Gaitanidis, Anthony Gebran, Charlie J. Nederpelt, Jonathan J. Parks, John O. Hwabejire, Jason Fawley, April E. Mendoza, Noelle N. Saillant, Peter J. Fagenholz, George C. Velmahos, Haytham M.A. Kaafarani have nothing to disclose.

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Ander Dorken Gallastegi, MD, Leon Naar, MD, Apostolos Gaitanidis, MD, Anthony Gebran, MD, Charlie J. Nederpelt, MD, Jonathan J. Parks, MD, John O. Hwabejire, MD, MPH, Jason Fawley, MD, April E. Mendoza, MD, MPH, Noelle N. Saillant, MD, Peter J. Fagenholz, MD, George C. Velmahos, MD, PhD, *and* **Haytham M.A. Kaafarani, MD, MPH**, *Boston, Massachusetts*

BACKGROUND: Balanced blood component administration during massive transfusion is standard of care. Most literature focuses on the impact of red blood cell (RBC)/fresh frozen plasma (FFP) ratio, while the value of balanced RBC:platelet (PLT) administration is less established. The aim of this study was to evaluate and quantify the independent impact of RBC:PLT on 24-hour mortality in trauma patients receiving massive transfusion.

METHODS: Using the 2013 to 2018 American College of Surgeons Trauma Quality Improvement Program database, adult patients who received massive transfusion (≥10 U of RBC/24 hours) and ≥1 U of RBC, FFP, and PLT within 4 hours of arrival were retrospectively included. To mitigate survival bias, only patients with consistent RBC:PLT and RBC:FFP ratios between 4 and 24 hours were analyzed. Balanced FFP or PLT transfusions were defined as having RBC:PLT and RBC:FFP of ≤2, respectively. Multivariable logistic regression was used to compare the independent relationship between RBC:FFP, RBC:PLT, balanced transfusion, and 24-hour mortality.

RESULTS: A total of 9,215 massive transfusion patients were included. The number of patients who received transfusion with RBC:PLT >2 (1,942 [21.1%]) was significantly higher than those with RBC:FFP >2 (1,160 [12.6%]) ($p < 0.001$). Compared with an RBC:PLT ratio of 1:1, a gradual and consistent risk increase was observed for 24-hour mortality as the RBC:PLT ratio increased ($p < 0.001$). Patients with both FFP and PLT balanced transfusion had the lowest adjusted risk for 24-hour mortality. Mortality increased as resuscitation became more unbalanced, with higher odds of death for unbalanced PLT (odds ratio, 2.48 [2.18–2.83]) than unbalanced FFP (odds ratio, 1.66 [1.37–1.98]), while patients who received both FFP and PLT unbalanced transfusion had the highest risk of 24-hour mortality (odds ratio, 3.41 [2.74–4.24]).

CONCLUSION: Trauma patients receiving massive transfusion significantly more often have unbalanced PLT rather than unbalanced FFP transfusion. The impact of unbalanced PLT transfusion on 24-hour mortality is independent and potentially more pronounced than unbalanced FFP transfusion, warranting serious system-level efforts for improvement. (*J Trauma Acute Care Surg.* 2022;93: 21–29.

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level IV.
KEY WORDS: Trauma; transfusion; blood; platelets; plasma.

Exsanguination, especially from noncompressible truncal hemorrhage, is the leading cause of trauma-related preventable deaths.[1–5] Damage-control surgery and resuscitation in severely injured patients requiring massive transfusion aim to proactively mitigate the lethal triad of trauma (hypothermia, acidosis, and coagulopathy), a reliable predictor of imminent death, by abbreviating the initial surgical procedure, delaying definitive repair, permissive hypotension, minimizing crystalloids, and balanced blood transfusion.[6–9] Both military and civilian patient data suggest that early and balanced administration of plasma and platelets (PLTs) is associated with higher survival.[10,11] As a result, massive transfusion protocols were designed and widely adopted across the world to provide balanced administration of red blood cells (RBCs), plasma, and PLTs early in the resuscitation of trauma patients.[12–15]

Modern blood banks store blood products as isolated components rather than whole blood, primarily for logistical considerations.[16] Platelet and fresh frozen plasma (FFP) are two critical blood components that represent distinct yet closely interconnected functions of the hemostatic system.[17] Following the initial reports from the military suggesting an association between the RBC-to-FFP (RBC:FFP) ratio and survival, several studies have attempted to study the optimal ratio for resuscitation in trauma patients requiring massive transfusion. The majority continued to focus on the relationship between balanced RBC:FFP transfusion and survival.[10,18–29] The randomized controlled Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial evaluated the impact of balanced FFP and PLT administration simultaneously, comparing early resuscitation with a PLT:FFP:RBC ratio of 1:1:1 versus 1:1:2.[30] It found no statistically significant difference in 24-hour or 30-day all-cause mortality between the two arms, although patients in the 1:1:1 arm had lower mortality from exsanguination.[30] With most studies being focused on RBC:FFP and only a few exploring the relationship between RBC-to-PLT ratio (RBC:PLT) and survival following traumatic injury, the independent impact of an unbalanced RBC:PLT ratio on survival remains largely unknown.[31–34]

Using a large national database, we sought to (1) study the prevalence of unbalanced PLT transfusion in trauma centers across the United States and (2) quantify the independent

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From the Division of Trauma, Emergency Surgery, and Surgical Critical Care (A.D.G., L.N., A. Gaitanidis, A. Gebran, J.J.P., J.O.H., J.F., A.E.M., N.N.S., P.J.F., G.C.V., H.M.A.K.), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; and Leiden University Medical Center, Leiden, Netherlands (C.J.N.).
This study was presented at the 35th Eastern Association for the Surgery of Trauma (EAST) Annual Scientific Assembly, January 11–15, 2022, in Austin, Texas.
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Address for reprints: Haytham M.A. Kaafarani, MD, MPH, Trauma, Emergency Surgery, and Surgical Critical Care, Massachusetts General Hospital, Harvard Medical School, Suite 810, 165 Cambridge St, Boston, MA 02114; email: hkaafarani@mgh.harvard.edu.

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association between the RBC:PLT ratio and survival among massively transfused trauma patients.

PATIENTS AND METHODS

Data Source

The American College of Surgeons Trauma Quality Improvement Program (ACS-TQIP) database, years 2013 to 2018, was used as the data source. Data linkage between data sets was not performed.

Patient Population

Adult patients (≥18 years) who received massive transfusion (≥10 U of RBC within 24 hours) and at least 1 U of RBC, PLT, and FFP within 4 hours of presentation were included. Patients who had no signs of life upon arrival to the emergency department, who died in the emergency department, and who were transferred were excluded.

Mitigating Survival Bias

To mitigate the impact of survival bias, only patients who had a consistent RBC:PLT and RBC:FFP ratio at 4 hours and 24 hours from arrival were included. A consistent ratio was defined as a ≤1-U difference in RBC:PLT and RBC:FFP ratios at the 4- and 24-hour time points. This method of mitigating survival bias aims to exclude patients who received "compensatory transfusions" after the first 4 hours as a virtue of surviving longer, and it has been described previously.[18]

Definitions

The ACS-TQIP database includes data on blood product transfusions at 4 and 24 hours from arrival. Blood product transfusion volume is reported as milliliters or as units. When transfusion volume is reported in units, a conversion factor is provided to define the volume of 1 U of blood product at the corresponding institution. To achieve consistent and comparable values of transfusion volume, transfusion data for all analyzed blood products were converted to milliliters using the provided conversion factor, and ultimately 1 U of blood product was defined as the following: RBC, 300 mL; FFP, 250 mL; and PLT, 50 mL. RBC:PLT and RBC:FFP ratios were calculated using transfusion volumes received within 24 hours of presentation. RBC:PLT and RBC:FFP ratios were rounded to the nearest integer. All ratios smaller than 1:1 were grouped as "1:1," and ratios larger than 6:1 were grouped as "≥6:1."

For the pragmatic purpose of this study, RBC:PLT and RBC:FFP ratios of 2 or below were considered balanced component administration for both PLT and FFP, respectively. To corroborate the interaction between and the independent impact of

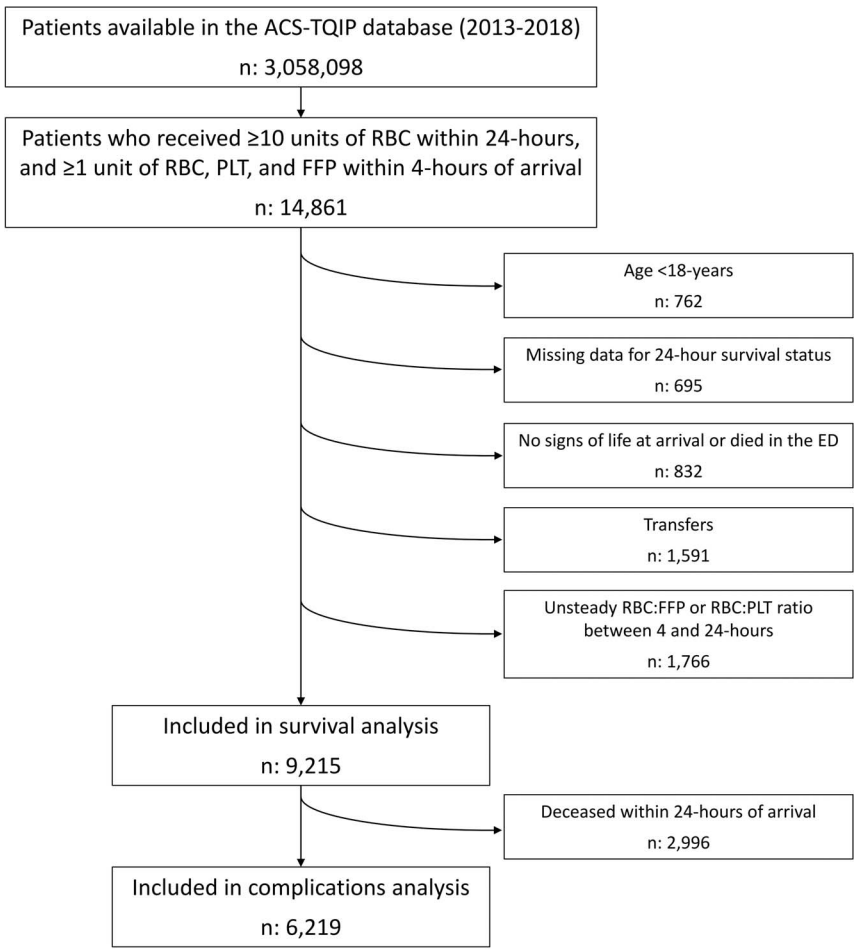

Figure 1. No signs of life at arrival or died in the ED.

TABLE 1. Patient Characteristics of the Study Cohort

	All Patients	RBC:PLT ≤2	RBC:PLT >2	*p*
No. patients	9,215	7,273	1,942	
Age, median (IQR), y	37 (26–54)	37 (26–54)	35 (25–52)	<0.001
Sex, n (%)				0.025
Male	7,319 (79.5%)	5,742 (79.0%)	1,577 (81.3%)	
Female	1,892 (20.5%)	1,529 (21.0%)	363 (18.7%)	
BMI, median (IQR)	27.18 (23.85–31.70)	27.27 (23.87–31.88)	26.88 (23.84–31.25)	0.17
Race, n (%)				<0.001
White	4,940 (56.0%)	3,973 (57.2%)	967 (51.7%)	
Black or African American	2,628 (29.8%)	1,986 (28.6%)	642 (34.3%)	
Asian	225 (2.6%)	185 (2.7%)	40 (2.1%)	
Other race	1,022 (11.6%)	801 (11.5%)	221 (11.8%)	
Ethnicity, n (%)				0.22
Not Hispanic or Latino	7,289 (84.2%)	5,772 (84.4%)	1,517 (83.3%)	
Hispanic or Latino	1,369 (15.8%)	1,064 (15.6%)	305 (16.7%)	
Insurance, n (%)				<0.001
Private	3,102 (34.6%)	2,504 (35.4%)	598 (31.7%)	
Governmental	2,764 (30.8%)	2,255 (31.9%)	509 (26.9%)	
Other	3,096 (34.5%)	2,314 (32.7%)	782 (41.4%)	
Trauma center level, n (%)				0.13
1	4,822 (59.9%)	3,788 (59.6%)	1,034 (61.0%)	
2	1,703 (21.2%)	1,374 (21.6%)	329 (19.4%)	
3	1,523 (18.9%)	1,190 (18.7%)	333 (19.6%)	
Hospital teaching status, n (%)				<0.001
University	5,414 (58.9%)	4,178 (57.6%)	1,236 (63.7%)	
Community	3,022 (32.9%)	2,482 (34.2%)	540 (27.8%)	
Nonteaching	756 (8.2%)	592 (8.2%)	164 (8.5%)	
Systolic blood pressure, median (IQR), mm Hg	100 (80–128)	100 (80–128)	100 (79–127)	0.46
Heart rate, median (IQR), min^{-1}	115 (93–134)	115 (93–133)	115 (93–134)	0.38
Shock index, median (IQR)	1.10 (0.83–1.47)	1.10 (0.83–1.47)	1.11 (0.83–1.49)	0.43
Glasgow Coma Scale, median (IQR)	10 (3–15)	10 (3–15)	10 (3–15)	0.29
Mechanism of injury, n (%)				<0.001
Blunt	4,635 (50.3%)	3,730 (51.3%)	905 (46.6%)	
Penetrating	3,536 (38.4%)	2,682 (36.9%)	854 (44.0%)	
Mixed blunt and penetrating	1,016 (11.0%)	836 (11.5%)	180 (9.3%)	
Other	24 (0.3%)	21 (0.3%)	3 (0.2%)	
Injury Severity Score, median (IQR)	30 (22–41)	30 (22–41)	29 (21–41)	0.041
Regional injury severity				
AIS head, median (IQR)	0 (0–3)	0 (0–3)	0 (0–3)	<0.001
AIS face, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	<0.001
AIS thorax, median (IQR)	3 (0–4)	3 (0–4)	3 (0–4)	0.099
AIS abdomen, median (IQR)	3 (1–4)	3 (2–4)	3 (1–4)	0.91
AIS extremity, median (IQR)	2 (0–3)	2 (0–3)	2 (0–3)	<0.001
AIS external, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.19
Comorbidities, n (%)				
Heart failure	75 (0.8%)	58 (0.8%)	17 (0.9%)	0.73
Hypertension	1,006 (10.9%)	841 (11.6%)	165 (8.5%)	<0.001
Chronic kidney disease	37 (0.4%)	30 (0.4%)	7 (0.4%)	0.75
Cirrhosis	224 (2.4%)	181 (2.5%)	43 (2.2%)	0.49
COPD	199 (2.2%)	175 (2.4%)	24 (1.2%)	0.002
Bleeding disorder	166 (1.8%)	147 (2.0%)	19 (1.0%)	0.002
Diabetes	431 (4.7%)	360 (4.9%)	71 (3.7%)	0.016
RBC volume, median (IQR), U	17.50 (12.83–26.67)	17.33 (12.5–26)	17.5 (13.5–28)	<0.001
PLT volume, median (IQR), U	12 (8–21)	15 (10–25)	5 (4–8)	<0.001
FFP volume, median (IQR), U	12.6 (8.10–20)	13 (8.528–20.52)	11 (7–18)	<0.001

Continued next page

TABLE 1. *(Continued)*

	All Patients	RBC:PLT ≤2	RBC:PLT >2	*p*
Hemorrhage control intervention within 4 h of arrival, n (%)	7,234 (78.6%)	5,642 (77.7%)	1,592 (82.1%)	<0.001
Laparotomy	5,017 (54.4%)	3,956 (54.4%)	1,061 (54.6%)	0.85
Thoracotomy	1,401 (15.2%)	1,033 (14.2%)	368 (18.9%)	<0.001
Peripheral vascular	736 (8.0%)	590 (8.1%)	146 (7.5%)	0.39
Angioembolization	809 (8.8%)	690 (9.5%)	119 (6.1%)	<0.001

AIS, Abbreviated Injury Scale; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

unbalanced PLT and unbalanced FFP administration, patients were grouped into four discrete component ratio categories: "balanced transfusion" defined as RBC:PLT ≤2 and RBC:FFP ≤2, "unbalanced FFP" defined as RBC:PLT ≤2 and RBC:FFP >2, "unbalanced PLT" defined as RBC:PLT >2 and RBC:FFP ≤2, and "unbalanced transfusion" defined as RBC:PLT >2 and RBC:FFP >2. To evaluate outcomes associated with stricter adherence to balanced blood component administration, a sensitivity analysis was performed for 24-hour mortality, defining "balanced transfusion" as RBC:PLT ≤1 and RBC:FFP ≤1, "unbalanced FFP" as RBC:PLT ≤1 and RBC:FFP >1, "unbalanced PLT" as RBC:PLT >1 and RBC:FFP ≤1, and "unbalanced transfusion" as RBC:PLT >1 and RBC:FFP >1.

The primary outcome was 24-hour mortality, defined as death due to any cause within 24 hours of arrival. Secondary outcomes were in-hospital mortality and in-hospital complications. In-hospital complications included venous thromboembolism, surgical site infection, central line–associated bloodstream infection, ventilator-associated pneumonia, sepsis, acute respiratory distress syndrome (ARDS), acute kidney injury, cerebrovascular accident, extremity compartment syndrome, pressure ulcer, unplanned intubation, and unplanned admission to the intensive care unit. Venous thromboembolism was defined as experiencing deep vein thrombosis and/or pulmonary embolism. Surgical site infection was defined as experiencing superficial incisional infection, deep surgical site infection, or organ space infection. In-hospital complications were evaluated only for patients who survived longer than 24 hours.

Statistical Analysis

Descriptive statistics were computed and compared across different RBC:PLT ratios. The χ^2 Test was used to compare categorical variables, and the Kruskal-Wallis test for continuous variables. The percentage of patients who received blood transfusion with RBC:PLT >2 versus RBC:FFP >2 were compared with the McNemar's test, pairing RBC:PLT and RBC:FFP ratios per patient. The association between RBC:PLT and primary and secondary outcomes was evaluated with univariable and multivariable logistic regression adjusting for RBC:FFP in addition to other clinically relevant variables described below. Twenty-four-hour and in-hospital mortality were compared between the four component ratio categories (balanced transfusion, unbalanced FFP, unbalanced PLT, and unbalanced transfusion) with univariable and multivariable logistic regression. All multivariable models were adjusted for the following variables selected a priori: 24-hour RBC transfusion volume, age, sex, race, ethnicity, insurance status, vital signs at the time of presentation (systolic blood pressure, heart rate, oxygen saturation), Glasgow Coma Scale at the time of presentation, Injury Severity Score, Abbreviated Injury Scale scores per body region

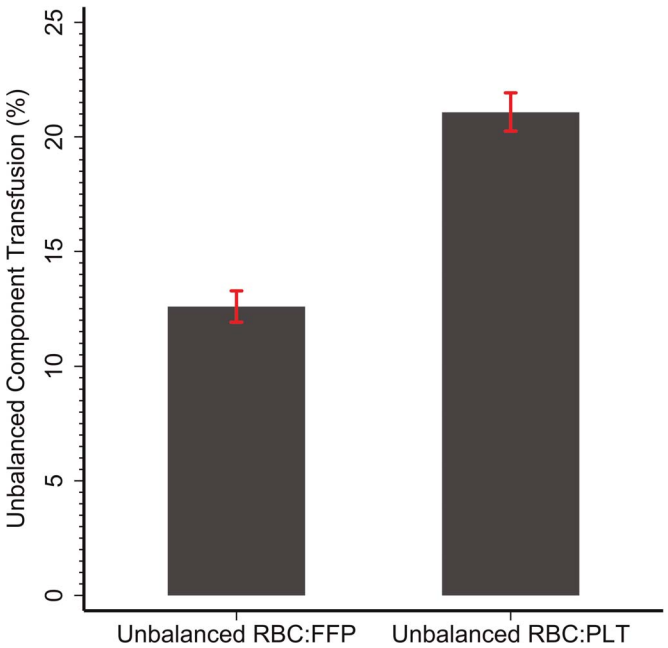

Figure 2. Unbalanced RBC:FFP (>2) versus unbalanced RBC:PLT (>2) rates in the study cohort.

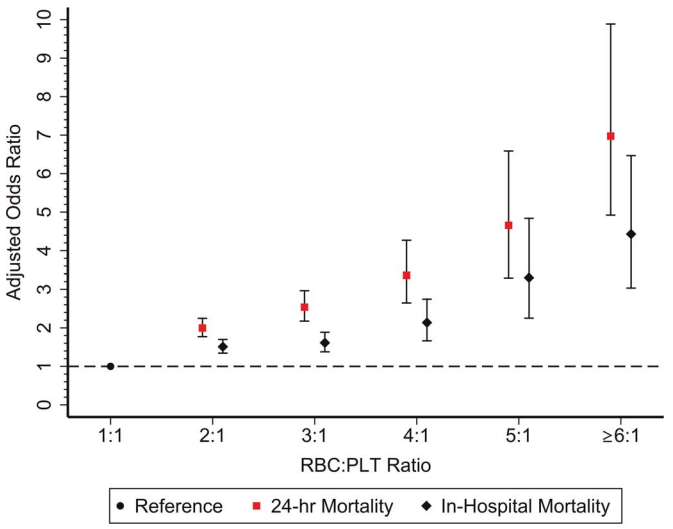

Figure 3. Risk-aORs of RBC:PLT, for 24-hour and in-hospital mortality.

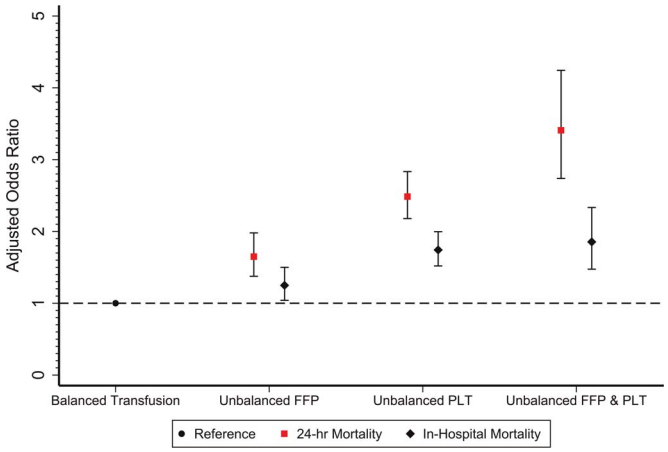

Figure 4. Risk-aORs by deviation from balanced transfusion.

(head, thorax, abdomen, and extremity), mechanism of injury (blunt, penetrating, mixed, and other), American College of Surgeons trauma center level, and hospital teaching status. Secondary outcome analysis for in-hospital complications was adjusted for multiple comparisons using the Benjamini-Hochberg method. Results were reported as univariable odds ratios and multivariable risk-adjusted odds ratios (aORs). Receiver operating characteristic curves and calibration plots were constructed for each multivariable model. Multicollinearity among covariates was assessed with the variance inflation factor.

Patients who had missing data for inclusion and exclusion criteria, transfusion volume, or survival status were excluded. The remaining missing data points for variables included in multivariable models were imputed via multiple imputation by chained equations, computing 10 imputations for each missing data point. Descriptive statistics were reported using original (unimputed) data.

Categorical variables were reported as number of patients (percentage), and continuous variables were reported as median (interquartile range [IQR]). The level of statistical significance was set at a two-sided p value of <0.05. All analyses were performed using STATA version 17 (StataCorp 2021, College Station, TX).

Ethical Oversight and Reporting

This study was submitted to and exempted from approval by the Mass General Brigham Institutional Review Board. The Strengthening the Reporting of Observational Studies in Epidemiology statement and Reporting of Studies Conducted Using Observational Routinely Collected Health Data statement were followed in the reporting of results (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/C398).[35,36] Investigators had full access to the analyzed data set. Codes used for the isolation of the study population, definition of variables, and analyses are available upon request.

RESULTS

A total of approximately 3 million patients were available in the ACS-TQIP database years 2013 to 2018. Following the application of inclusion and exclusion criteria, 9,215 patients were included in survival analyses (Fig. 1). Among these, only 6,219 patients survived beyond 24 hours and were included in analyses evaluating in-hospital complications. Descriptive statistics for demographic variables, comorbidities, injury severity, and hospital-level variables are provided in Table 1. In summary, the median age was 37 years (IQR, 26–54 years), 1,892 (20.5%) were female, the median injury severity score was 30 (IQR, 22–41), and the most frequent mechanism of injury was isolated blunt trauma (4,635 [50.3%]). At least one hemorrhage control intervention was performed in 7,234 patients (78.6%), the most common being exploratory laparotomy (5,017 [54.4%]). The overall 24-hour and in-hospital mortality rates of the cohort were 32.5% (2,996) and 48.1% (4,432), respectively.

TABLE 2. Association Between the RBC:PLT Ratio and In-hospital Complications

	Univariable		Multivariable	
Complication, No. Patients (Incidence)	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Venous thromboembolism, n = 718 (11.5%)	1.01 (0.93–1.09)	0.86	1.00 (0.92–1.08)	0.96
Surgical site infection, n = 584 (9.4%)	1.05 (0.96–1.14)	0.50	1.02 (0.93–1.11)	0.99
CLABSI, n = 71 (1.1%)	0.82 (0.62–1.09)	0.37	0.85 (0.64–1.13)	0.86
Extremity compartment syndrome, n = 149 (2.4%)	0.97 (0.82–1.15)	0.93	0.91 (0.76–1.08)	0.74
Unplanned intubation, n = 325 (5.2%)	1.05 (0.95–1.18)	0.56	1.10 (0.99–1.24)	0.38
Acute kidney injury, n = 866 (13.9%)	0.84 (0.77–0.91)	<0.001	0.86 (0.79–0.94)	0.013
Acute myocardial infarction, n = 53 (0.9%)	0.97 (0.74–1.29)	0.92	1.14 (0.85–1.53)	0.70
ARDS, n = 429 (6.9%)	0.99 (0.89–1.09)	0.95	1.02 (0.92–1.13)	0.90
Sepsis, n = 402 (6.5%)	0.92 (0.83–1.03)	0.36	0.94 (0.84–1.05)	0.64
Cerebrovascular accident, n = 158 (2.5%)	0.93 (0.78–1.10)	0.58	0.99 (0.83–1.18)	1.00
Pressure ulcer, n = 385 (6.2%)	0.91 (0.81–1.02)	0.59	0.96 (0.85–1.08)	0.73
Unplanned ICU admission, n = 339 (5.5%)	1.09 (0.98–1.21)	0.43	1.10 (0.99–1.23)	0.55
Ventilator-associated pneumonia, n = 599 (9.6%)	0.94 (0.86–1.02)	0.33	0.99 (0.90–1.08)	0.92

In-hospital complications were evaluated only for patients who survived past 24 hours (n = 6,219).
p Values were adjusted for multiple comparisons with the Benjamini-Hochberg correction.
Odds ratios represent the increase in complication risk per 1-U increase in the RBC:PLT ratio.
CI, confidence interval; CLABSI, central line–associated bloodstream infection; ICU, intensive care unit; OR, odds ratio.

Prevalence of RBC:PLT Ratio Greater Than 2

Significantly more patients had an RBC:PLT ratio greater than 2 (1,942 [21.1%]) than an RBC:FFP ratio greater than 2 (1,160 [12.6%]) ($p < 0.001$, Fig. 2).

RBC:PLT Versus Mortality

In multivariable analysis, higher RBC:PLT ratios were associated with a statistically significant increase in the risk of 24-hour and in-hospital mortality (Fig. 3; Supplemental Digital Content, Supplementary Tables 1S and 2S, http://links.lww.com/TA/C399). Compared with an RBC:PLT ratio of 1:1, a gradual and consistent increase in the risk of 24-hour and in-hospital mortality was observed as the RBC:PLT ratio increased, ultimately reaching an aOR of 6.97 (4.92–9.89) for 24-hour mortality and 4.43 (3.03–6.47) for in-hospital mortality in patients who received transfusion with an RBC:PLT ratio of 6:1 or greater (Fig. 3; Supplemental Digital Content, Supplementary Tables 1S and 2S, http://links.lww.com/TA/C399).

Balanced Versus Unbalanced Transfusion

Among the four blood component ratio categories, balanced transfusion (RBC:PLT ≤2 and RBC:FFP ≤2) was associated with the lowest 24-hour mortality rate (1,808 [27.5%], Fig. 4). Compared with balanced transfusion, unbalanced FFP (aOR, 1.65 [1.37–1.98]; $p < 0.001$), and unbalanced PLT (aOR, 2.48 [2.18–2.83]; $p < 0.001$) were associated with significantly higher risk of 24-hour mortality following risk adjustment for relevant confounders (Fig. 4; Supplemental Digital Content, Supplementary Table 3S, http://links.lww.com/TA/C399). Patients who received unbalanced transfusion (RBC:PLT >2 and RBC:FFP >2) had the highest adjusted risk of 24-hour mortality among the four blood component ratio categories (aOR, 3.41 [2.74–4.24]; $p < 0.001$; Fig. 4; Supplemental Digital Content, Supplementary Table 3S, http://links.lww.com/TA/C399). A similar pattern of increased risk was observed between the four categories for in-hospital mortality (Fig. 4; Supplemental Digital Content, Supplementary Table 4S, http://links.lww.com/TA/C399).

Unbalanced PLT Versus Unbalanced FFP

Unbalanced PLT transfusion was associated with a significantly higher adjusted risk of 24-hour mortality (aOR, 1.51 [1.22–1.85]; $p < 0.001$) compared with unbalanced FFP.

RBC:PLT Versus Complications

Among 6,219 patients who survived longer than 24 hours, the most frequently observed in-hospital complications were acute kidney injury (866 [13.9%]), venous thromboembolism (718 [11.5%]), and ventilator-associated pneumonia (599 [9.6%]). Increasing RBC:PLT ratios (i.e., lower relative PLT transfusions) were associated with a lower risk of acute kidney injury in univariable and multivariable analyses ($p < 0.001$, Table 2). The RBC:PLT ratio was not significantly associated with any of the remaining in-hospital complications.

Sensitivity Analysis

Sensitivity analysis with a stricter definition of balanced transfusion as RBC:PLT ≤1 and RBC:FFP ≤1 yielded parallel results to the main analysis (Supplemental Digital Content, Supplementary Table 5S, http://links.lww.com/TA/C399).

Missing Data and Multivariable Model Diagnostics

Variables with >10% missing data were trauma center level (missing, 1,167 [12.7%]), respiratory rate (missing, 1,157 [12.6%]), and oxygen saturation (missing, 1,378 [14.9%]). All missing data points were imputed using multiple imputation by chained equations (Supplemental Digital Content, Supplementary Table 6S, http://links.lww.com/TA/C399). Postestimation diagnostics (receiver operating characteristic curve, calibration plot, variance inflation factor) for multivariable model performance were provided in the Supplemental Digital Content (Supplementary Tables 1S to 5S, http://links.lww.com/TA/C399; Supplementary Fig. 1S, http://links.lww.com/TA/C400; Supplementary Fig. 2S, http://links.lww.com/TA/C401; Supplementary Fig. 3S, http://links.lww.com/TA/C402; Supplementary Fig. 4S, http://links.lww.com/TA/C403; Supplementary Fig. 5S, http://links.lww.com/TA/C404; Supplementary Fig. 6S, http://links.lww.com/TA/C405; Supplementary Fig. 7S, http://links.lww.com/TA/C406; Supplementary Fig. 8S, http://links.lww.com/TA/C407; Supplementary Fig. 9S, http://links.lww.com/TA/C408; and Supplementary Fig. 10S, http://links.lww.com/TA/C409).

DISCUSSION

In this large nationwide analysis of trauma patients receiving massive transfusion, we found that unbalanced PLT transfusion occurs more frequently than unbalanced FFP and that RBC:PLT is independently associated with both 24-hour and in-hospital mortality. In fact, the risk-adjusted odds of mortality increased gradually and consistently as the RBC:PLT ratio incrementally deviated from 1:1, and the relationship was stronger than that for RBC:FFP, with patients who have unbalanced PLT transfusion being at a higher risk of mortality compared with those with unbalanced FFP transfusion.

Trauma-induced coagulopathy is a well-described phenomenon that results from widespread tissue injury and the metabolic derangements associated with hemorrhagic shock.[17] Acidosis, hypothermia, and hypocalcemia are known to contribute to trauma-induced coagulopathy by impairing the function of both PLTs and coagulation factors, leading to the "lethal triad" of trauma.[37] While PLTs and plasma are stored in blood banks as separate blood products, the intricate interplay between PLTs and coagulation factors is being increasingly recognized.[38–41] Particularly, most cell-based models of coagulation place PLTs in a central role enhancing coagulation factor function and orchestrating the hemostatic response.[42] Specifically, the propagation phase of coagulation, which plays a crucial role in clot development by allowing an exponential increase in thrombin formation, occurs primarily on PLT surfaces.[38,39] In trauma patients, for example, both quantitative and qualitative PLT defects have been described.[43] While it remains unclear whether the impaired PLT function can be addressed with transfusion therapy alone, balanced PLT administration promises to mitigate coagulopathy. In our data, we observed a gradual increase in the risk-adjusted odds of 24-hour mortality, as the composition of transfused blood products deviated upwards from RBC:PLT of 1:1. In addition, patients who received balanced FFP but unbalanced PLT transfusions had considerably increased risk of mortality, higher than that for patients with unbalanced FFP but balanced PLT transfusion patterns. This finding is aligned with our current understanding of PLTs as the facilitator of coagulation

cascade propagation and suggests that PLT transfusions could help potentiate the hemostatic benefit of coagulation proteins provided with plasma.

This finding is supported by the prior landmark randomized controlled PROPPR trial that evaluated the benefit of balanced blood component administration in trauma resuscitation.[30] With a pragmatic design, PROPPR randomized 680 trauma patients to receive transfusions with a PLT:FFP:RBC ratio of 1:1:1 versus 1:1:2.[30] While the trial fell short of demonstrating the 10% predefined difference between the two groups for 24-hour mortality, patients in the 1:1:1 cohort had significantly lower mortality from exsanguination within 24 hours and were significantly more likely to achieve anatomical hemostasis.[30] The PROPPR study was not designed to analyze the independent impact of PLT versus FFP transfusions, as the study protocol aimed to provide equal RBC:FFP and RBC:PLT ratios per patient, regardless of randomization group.[30,44] However, in a post hoc analysis of the PROPPR trial including patients who received only the first cooler of blood products, patients who received PLT transfusion had significantly higher 24-hour and 30-day survival, shorter ventilator-free days, and a higher rate of achieving anatomical hemostasis compared with those who did not receive any PLTs, following statistical adjustment for differences in FFP transfusion.[31]

A few additional observational studies evaluated the relationship between RBC:PLT ratio and survival in trauma patients.[31–34,45] Most of these studies were conducted at single Level 1 trauma centers and divided patients into two or three categories based on the RBC:PLT ratio (e.g., low, medium, high). Our analysis included a significant number of patients who were managed at Level 2 (1,703 [21.2%]) and Level 3 (1,523 [18.9%]) trauma centers across the United States and adjusted all multivariable models for trauma center level as a potential confounder. Our results indicate that the RBC:PLT ratio is significantly associated with mortality, not only as a dichotomous variable but in a continuous way, with gradual increase in risk-adjusted mortality for incremental deviations from RBC:PLT = 1:1.

Because trauma-induced coagulopathy shifts from a hypocoagulant to a hypercoagulant phenotype following the hyperacute phase of injury, many researchers and clinicians have concerns that increased administration of PLT could lead to a higher risk of thromboembolic complications.[17] This is especially relevant because PLTs play a crucial role in the immune response to injury and infections, with their role in hyperinflammatory complications of trauma such as ARDS being an area of active research.[46–49] Similar to the PROPPR trial, which found no statistically significant difference in the incidence of in-hospital complications between patients who received PLT:FFP:RBC = 1:1:1 versus 1:1:2, our study found no significant association between the RBC:PLT ratio and the incidence of venous thromboembolism, ARDS, or infectious complications (sepsis, ventilator-associated pneumonia, central line–associated bloodstream infection, or surgical site infection).[30] The only in-hospital complication that was significantly associated with RBC:PLT was acute kidney injury, which had a higher incidence in patients who had lower RBC:PLT ratios (i.e., received higher amounts of PLT relative to RBC). This finding may be influenced by the higher number of patients who survived through hospitalization at lower RBC:PLT ratios, although the potential impact of PLT transfusions on acute kidney injury cannot be dismissed.

Our study has a few limitations. First, we cannot completely exclude residual survival bias. We attempted to mitigate it by only including patients who had consistent RBC:FFP and RBC:PLT transfusion ratios at 4 and 24 hours. Second, it was not possible to discern the collection method of PLTs (i.e., apheresis vs. pooled from whole blood) from the ACS-TQIP database. Third, the age of administered blood products was not available in the analyzed dataset.[50] Fourth, we did not account for the administration of prehospital blood products, whole blood, other hemostatic blood derivatives (e.g., fibrinogen concentrate, cryoprecipitate, prothrombin complex concentrate), or antifibrinolytic agents. Finally, our study only included patients who received massive transfusion (10 U of RBC within 24 hours) at trauma centers participating in ACS-TQIP. Generalizability to alternative definitions of massive transfusion and to submassive transfusion may be limited.

CONCLUSION

In this large nationwide analysis, we found that trauma patients receiving massive transfusion significantly more often have unbalanced PLT rather than unbalanced FFP transfusion. The impact of unbalanced PLT transfusion on 24-hour mortality is independent and potentially more pronounced than unbalanced FFP transfusion, warranting serious system-level efforts for improvement.

AUTHORSHIP

A.D.G., L.N., A. Gaitanidis, A. Gebran, C.J.N., J.J.P., J.O.H., J.F., A.E.M., N.S.N., P.J.F., G.C.V., and H.M.A.K. performed the study design. A.D.G., L.N., A. Gaitanidis, A. Gebran, C.J.N., and H.M.A.K. performed the data analysis. A.D.G., L.N., A. Gaitanidis, A. Gebran, C.J.N., J.J.P., J.O.H., J.F., A.E.M., N.S.N., P.J.F., G.C.V., and H.M.A.K. performed the interpretation. A.D.G. and H.M.A.K. performed the writing. A.D.G., L.N., A. Gaitanidis, A. Gebran, C.J.N., J.J.P., J.O.H., J.F., A.E.M., N.S.N., P.J.F., G.C.V., and H.M.A.K. performed the critical revision.

DISCLOSURE

The authors declare no conflicts of interest.

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