Received: 1 February 2022 | Revised: 24 May 2022 | Accepted: 24 May 2022

DOI: 10.1111/trf.16978

ORIGINAL RESEARCH

TRANSFUSION

Over-transfusion with blood for suspected hemorrhagic shock is not associated with worse clinical outcomes

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Abstract

Background: We evaluated patient outcomes after early, small volume red blood cell (RBC) transfusion in the setting of presumed hemorrhagic shock. We hypothesized that transfusion with even small amounts of blood would be associated with more complications.

Study design and methods: Retrospective review of trauma patients admitted to a Level 1 trauma center between 2016–2021. Patients predicted to require massive transfusion who survived ≥72 h were categorized according to units of RBCs transfused in the first 24 h. A Cox regression model stratified by dichotomized ISS and adjusted for SBP <90 mm Hg and pulse >120 bpm on arrival was used to estimate hazard ratios (HRs) for outcomes of interest.

Results: A total of 3121 (24%) received RBC transfusion within the first 24 h. Massive transfusion protocol (MTP) was activated in 38% (1188/3121): 17% received no RBCs, 27.4% 1–3 units, 32.4% 4–9 units, and 22.7% ≥10 units. Mean ISS increased with each category of RBC transfusion. There was no difference in the risk of acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), infection, cardiac arrest, venous thromboembolism or stroke for patients receiving 1–3 units compared to the non-transfused group or 4–9 units group ($p > 0.05$). Compared to those receiving ≥10 units, the 1–3 units group had a significantly lower risk of AKI, ARDS, and cardiac arrest.

Discussion: Early empiric RBC transfusion for presumed hemorrhagic shock may subject patients to potential over-transfusion and end-organ damage. Among patients meeting clinical triggers for MTP, 1–3 units of allogeneic RBCs is not associated with worse outcomes.

KEYWORDS
blood transfusion, hemorrhage, hemorrhagic shock, hemostasis, RBC transfusion

Abbreviations: ABC, assessment of blood consumption; AIS, abbreviated injury scale; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CLABSI, central line-associated bloodstream infection; DVT, deep venous thrombosis; ED, emergency department; FAST, focused assessment with sonography for trauma; HR, hazard ratios; ICU, intensive care unit; INR, international normalized ratio; IRB, institutional review board; ISS, injury severity score; MTP, massive transfusion protocol; NTDS, national trauma data standard; PE, pulmonary embolism; PROMMTT, prospective, observational multicenter, major trauma transfusion; PROPPR, pragmatic, randomized optimal platelet and plasma Ratios; RBC, red blood cells; SBP, systolic blood pressure; TACO, transfusion-associated circulatory overload; TRALI, transfusion-associated acute lung injury; VAP, ventilator associated pneumonia; VTE, venous thromboembolic events.

1 | INTRODUCTION

Up to 40% of trauma deaths occurring after hospital admission involve massive hemorrhage from truncal injury.[1] Early identification and management of massive hemorrhage with blood products in a balanced ratio improves survival after severe injury.[1] Meyer et al showed that every minute of delay increased the odds of mortality by 5%.[2] Conversely, unnecessary exposure to blood products has been associated with a higher risk of complications.[3]

Red blood cell (RBC) transfusions are an independent risk factor for mortality, perioperative infections, multiorgan failure, and intensive care unit (ICU) admission.[3] Allogeneic blood transfusion can induce tolerance in the host immune system, resulting in higher rates of postoperative and nosocomial infections, longer hospital stays, and increased use of hospital resources.[4] The volume of transfused blood may be directly related to the negative clinical effects. Shorr et al showed a dose-dependent increase in ventilator-associated pneumonia in transfused medical and surgical patients.[5] This effect is not limited to RBCs, as Peju and colleagues found a statistically significant association between platelet and plasma transfusions and the risk of ICU-acquired infections among critically ill patients with septic shock.[6]

Despite the evidence supporting early and aggressive transfusion of trauma patients with hemorrhagic shock, it remains unclear how this strategy impacts those patients with only limited transfusion requirements. We sought to evaluate patient outcomes after early, small volume RBC transfusion in the setting of presumed hemorrhagic shock. We hypothesized that transfusion with even small volumes of blood would be associated with a higher incidence of complications.

2 | MATERIALS AND METHODS

This was a retrospective review of trauma patients admitted to our Level 1 trauma center between January 2016 and March 2022. This study was exempt from Institutional Review Board (IRB) approval given the study design and de-identified data. Data on RBC units transfused and massive transfusion protocol (MTP) activation were collected from the blood bank records and trauma registry. Patients predicted to require massive transfusion who survived ≥72 h from the time of arrival were categorized according to units of RBCs transfused in the first 24 h: 0, 1–3, 4–9, ≥10 units. The number of patients receiving ≥10 units of RBCs was small compared to the other groups, so these were combined into one category. Patients that received whole blood were excluded as they received fewer units of RBCs and had better outcomes, and therefore would have resulted in a selection bias.

2.1 | Definitions and protocols

Small volume RBC transfusion was defined as receiving up to 3 units of blood. Patients that were predicted to require massive transfusion on arrival, but stabilized after 0–3 units of packed red blood cells were considered "over-transfused." Prediction of the need for massive transfusion was based on our trauma center's protocol for MTP activation. Patients that appear to be in hemorrhagic shock on arrival to our trauma bay receive an Emergency Department (ED) "Quick Pack" consisting of 1 unit of RBC and 1 unit of plasma to start the resuscitation process. Next, we assess for MTP triggers which include at least one of the following criteria: 1. Assessment of Blood Consumption (ABC) score of ≥2 (consisting of Penetrating mechanism, ED Systolic Blood Pressure (SBP) ≤90 mm Hg, ED heart rate ≥120 bpm, Positive Focused Assessment with Sonography for Trauma (FAST) exam; 2. Two or more of the following: International normalized ratio (INR) >1.5, Base deficit < −6, hemoglobin <11 g/dl, platelets <200 K/μl, Shock index >1 (heart rate/SBP); 3. Persistent hemodynamic instability; 4. Attending physician assessment.

2.2 | Statistical analysis

Patient demographic, injury, and clinical characteristics were compared among the blood transfusion groups using a Fisher's exact test or Kruskal-Wallis test for categorical and continuous variables, respectively. Cox proportional hazard models were used to estimate hazard ratios and associated 95% confidence intervals for the association between RBC transfusion category and adverse events. Models were adjusted for Injury Severity Score (ISS), SBP <90 mm Hg and heart rate ≥120 bpm on admission to the ED. We adjusted for SBP and heart rate due their association with both the exposure (RBC category) and outcomes of interest. ISS is the summation of the square of the highest Abbreviated Injury Scale (AIS) score for up to three body regions (out of six total regions) and ranges from 1 (minor injury) to 75 (likely fatal injury). ISS standardizes severity of traumatic injury, and those with major trauma and higher ISS are more likely to need RBCs.

To account for hazard ratio (HR) estimation issues due to monotonic likelihood arising from sparse event counts, a Firth penalized likelihood was used for all models.[7,8] We utilized global tests of interactions with time for all variables in the model as well as tests of interactions with time

for all individual variables, and found no evidence suggesting departure from proportionality as all p-values for the tests of interaction were not significant.

2.3 | Outcomes

Outcomes included acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), infectious complications including superficial, deep and organ/space surgical site infection, severe sepsis, central line-associated bloodstream infection (CLABSI), ventilator associated pneumonia (VAP), and venous thromboembolic events (VTE), the latter of which were further defined as deep venous thrombosis (DVT) or pulmonary embolism (PE). Outcomes were measured throughout the patients' index hospitalization. The outcomes were defined according to the National Trauma Data Standard™ (NTDS) 2021 Data Dictionary which provides a uniform set of trauma registry variables. Data on complications and outcomes were extracted from our institution's trauma registry.

3 | RESULTS

Of the 12,996 trauma patients admitted to our trauma service during the study period with a hospital stay of at least 72 h, 3121 (24.0%) received an RBC transfusion within 24 h of arrival. Of these, 31.4% (981/3121) had MTP activated and were included in the analysis. An additional group of 207 trauma patients who had MTP activated but received no RBC units was also included for comparison. Among the MTP activations, 17.4% received no RBCs, 27.4% 1–3 units, 32.4% 4–9 units, and 22.7% ≥10 RBC units. There was no significant difference in median age ($p = .1863$), or trauma mechanism ($p = .8666$) among the RBC groups, though those transfused at least 10 RBC units were most likely to be male ($p = .0333$) (Table 1). Median was lowest for the group not transfused and highest for the ≥10 units group ($p < .0001$); in addition, the proportion of those with a heart rate of at least 120 bpm was highest for the ≥10 units group (44.9%) and lowest for the non-transfused group (9.7%) ($p < .0001$). Median SBP was lowest for the group that received ≥10 units of RBCs and highest for the non-

TABLE 1 Comparison of demographics, injury, and clinical characteristics[a] among patients with a massive transfusion protocol activation by units of packed red blood cells (RBC) transfused

	0 RBC ($n = 207$)	1–3 RBC ($n = 326$)	4–9 RBC ($n = 385$)	10+ RBC ($n = 270$)	p-value[b]
Median age (years)	35 (24–51)	37 (26–54)	36 (27–54)	33 (26–51)	.2517
Male (%)	155 (74.9)	244 (74.8)	292 (75.8)	225 (83.3)	.0333
Trauma type (%)					
Blunt	97 (46.9)	143 (43.9)	180 (46.8)	123 (45.6)	.8666
Penetrating	110 (53.1)	183 (56.1)	205 (53.2)	147 (54.4)	
Median heart rate (bpm)	91 (76–105)	108 (86–132)	110 (90–130)	115 (92–131)	<.0001
Heart rate ≥ 120 bpm	20 (9.7)	78 (24.2)	147 (38.8)	120 (44.9)	<.0001
Median SBP (mm Hg)	137 (118–157)	108 (86–132)	101.5 (81–126)	94 (74–117)	<.0001
SBP <90 mm Hg (%)	12 (5.8)	93 (28.5)	143 (37.1)	115 (42.6)	<.0001
Median ISS	16 (9–24)	18 (11–29)	22 (14–34)	25.5 (17–38)	<.0001
ISS ≥16 (%)	106 (51.2)	199 (61.0)	281 (73.0)	224 (83.0)	<.0001
Median platelet units transfused (%)	0 (0–0)	0 (0–1)	1 (0–1)	3 (2–5)	<.0001
Median plasma units transfused (%)	0 (0–0)	1 (0–2)	4 (3–6)	12 (8–20)	<.0001
Outcomes					
On ventilator support (%)	101 (48.8)	227 (69.6)	354 (91.9)	265 (98.1)	<.0001
Median ventilator days	5 (2–9)	4 (2–10)	5 (2–10)	7 (3–14)	<.0001
Admitted to ICU (%)	149 (72.0)	293 (89.9)	377 (97.9)	262 (97.0)	<.0001
Median ICU days	6 (4–11)	7 (4–13)	10 (5–17)	15 (7–25)	<.0001
Median hospital LOS	8 (5–15)	11 (7–19)	15 (10–24)	12 (8–20)	<.0001

Abbreviations: ICU, Intensive Care Units; ISS, Injury Severity Score; LOS, Length of Stay; SBP, Systolic blood pressure.

[a]Presented as *n* (%) or median (interquartile range).

[b]Based on Fisher's exact or Kruskal-Wallis test for categorical and continuous variables, respectively.

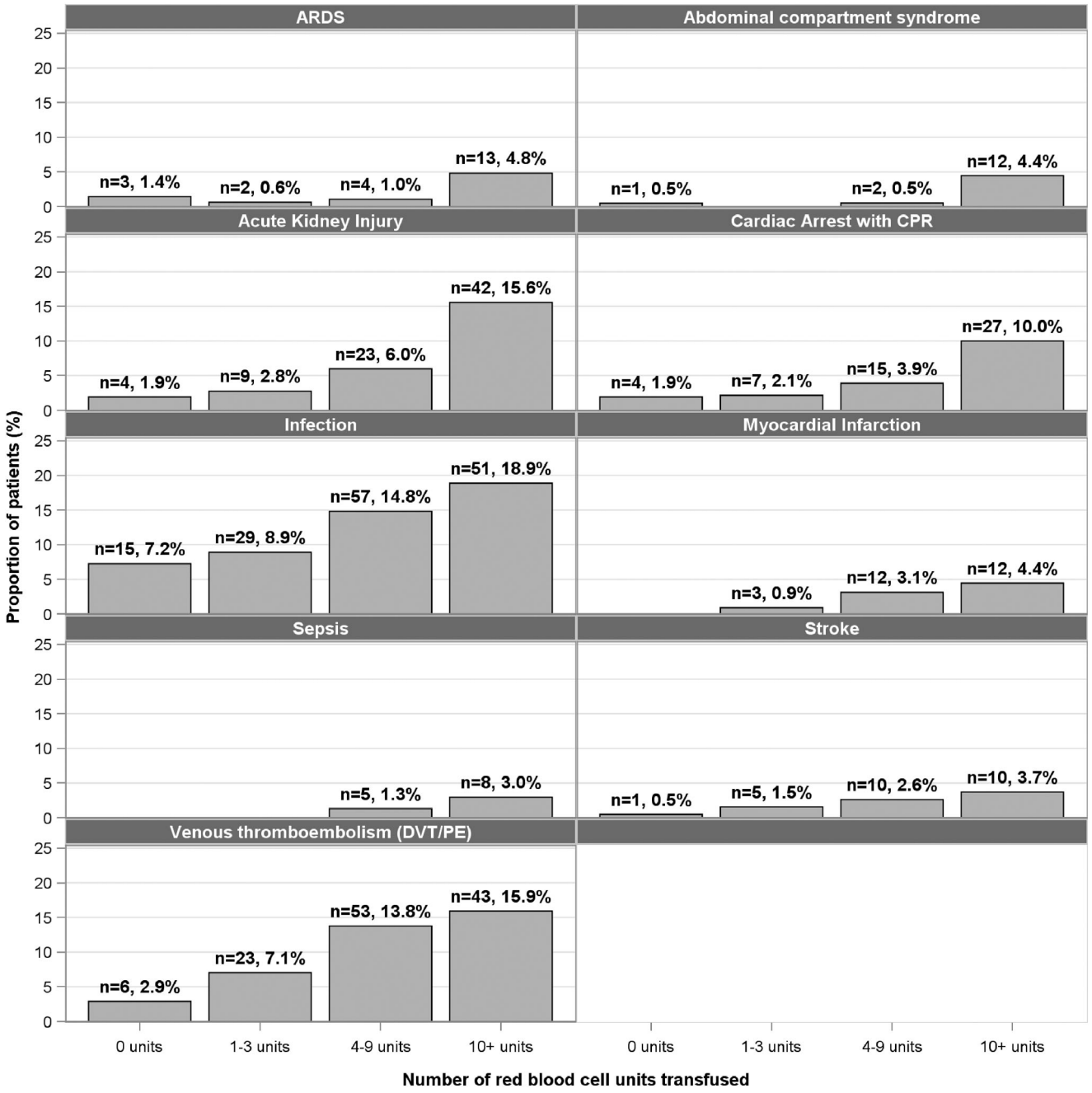

FIGURE 1 Proportion of patients developing complications based on units of RBC transfused

transfused group ($p < .0001$). Patients that received ≥10 units also had the highest median days on ventilator support ($p < .0001$), ICU days ($p < .0001$) and hospital length of stay ($p < .0001$).

Figure 1 depicts the proportion of patients that developed infectious and non-infectious complications based on units of blood transfused. There was a very low incidence of any complication in the 1–3 units group. Only 29/326 (9%) developed infectious complications and none had sepsis. A total of 23/326 patients (7%) had a DVT or PE. Only 2/326 developed ARDS and 9/326 (3%) had AKI.

Examining the risk of infection, compared to the non-transfused group, there was no increased risk of any complication for the 1–3 units group for both crude (unreported) and adjusted models (Table 2). Though the adjusted association for pulmonary embolism was on the precipice of statistical significance (HR 4.42, 95% CI 0.99–41.68), the confidence limits were wide due to the small number of events for the 0-unit transfusion referent group. For the 4–9 units group, there was no significant association except for an 11-fold increased risk of myocardial infarction, which had a very wide confidence

TABLE 2 Adjusted hazard ratios (HRs) and associated 95% confidence limits (95% CIs) for the association between number of packed red blood cell units transfused and nosocomial complications among patients with a massive transfusion protocol activated

	0 RBC ($n = 207$)	1–3 RBC ($n = 326$)		4–9 RBC ($n = 385$)		10+ RBC ($n = 270$)	
Complication	**Risk (%)**	**Risk (%)**	**aHR (95% CI)[a,b]**	**Risk (%)**	**aHR (95% CI)[a,b]**	**Risk (%)**	**aHR (95% CI)[a,b]**
Abdominal compartment syndrome	1 (0.5)	0 (0.0)	0.16 (0.00–3.13)	2 (0.5)	0.58 (0.07–6.83)	12 (4.4)	3.46 (0.67–35.07)
Acute kidney injury	4 (1.9)	9 (2.8)	1.21 (0.41–4.18)	23 (6.0)	2.24 (0.86–7.29)	32 (15.6)	5.50 (2.17–17.62)
Acute respiratory distress syndrome	3 (1.4)	2 (0.6)	0.40 (0.06–2.80)	4 (1.0)	0.63 (0.13–3.86)	13 (4.8)	2.04 (0.50–11.66)
Cardiac arrest	4 (1.9)	7 (2.1)	0.63 (0.16–2.47)	15 (3.9)	1.78 (0.65–5.95)	27 (10.0)	3.80 (1.43–12.47)
Venous thromboembolism	6 (2.9)	23 (7.1)	2.04 (0.89–5.34)	53 (13.8)	3.32 (1.54–8.44)	43 (15.9)	3.41 (1.54–8.81)
Deep vein thrombosis	5 (2.4)	13 (4.0)	1.34 (0.48–4.48)	40 (10.4)	2.72 (1.09–8.61)	39 (14.4)	3.52 (1.39–11.22)
Pulmonary embolism	1 (0.5)	10 (3.1)	4.42 (0.99–41.68)	16 (4.2)	7.53 (1.80–69.50)	7 (2.6)	4.84 (0.97–47.61)
Infection	15 (7.2)	29 (8.9)	0.80 (0.40–1.68)	57 (14.8)	1.21 (0.65–2.40)	51 (18.9)	1.29 (0.68–2.61)
Myocardial infarction	0 (0.0)	3 (0.9)	4.20 (0.40–567.63)	12 (3.1)	11.38 (1.39–1479.47)	12 (4.4)	20.27 (2.47–2639.85)
Sepsis	0 (0.0)	0 (0.0)	0.50 (0.00–94.94)	5 (1.3)	4.50 (0.44–608.98)	8 (3.0)	7.57 (0.74–1031.88)
Stroke	1 (0.5)	5 (1.5)	1.44 (0.23–14.97)	10 (2.6)	3.33 (0.72–31.88)	10 (3.7)	4.33 (0.91–42.11)

Abbreviation: aHR, adjusted hazard ratios.

[a]Estimated from a Cox proportional hazards regression model using the 0 RBC group as the referent.

[b]Adjusted for Injury Severity Score ≥16, pulse <120 beats per minute and systolic blood pressure <90 mm Hg.

interval (HR 11.38, 95% CI 1.39–1479.47) and an over 3-fold adjusted increased risk of VTE (HR 3.32, 95% CI 1.54–8.44). The VTE association was driven in part by a near 8-fold increased risk of PE (HR 7.53, 95% CI 1.09–8.61), although the PE association is based on a small number of events and the confidence limits are wide. For the ≥10 units group, significantly increased adjusted risks of AKI (HR 5.50, 95% CI 2.17–17.62), cardiac arrest (HR 3.80, 95% CI 1.43–12.47), any VTE (HR 3.41, 95% CI 1.54–8.81), and myocardial infarction (HR 20.27, 95% CI 2.47–2639.85) were observed.

4 | DISCUSSION

Uncontrolled bleeding is the most common preventable cause of death for patients with severe injury.[9] Severe bleeding is accompanied by coagulopathy, which is then exacerbated by ongoing blood loss. Resuscitation strategies for acute hemorrhage have evolved over time, and a shift from crystalloid-based therapy to early balanced blood components has led to improved survival. For trauma patients in hemorrhagic shock, under-transfusion can lead to higher mortality and adverse events, while early, balanced blood transfusion and minimized crystalloid use decreases trauma-induced coagulopathy and hemorrhage-related deaths.[10,11]

Despite the benefits of early transfusion for patients in hemorrhagic shock, plasma, platelets, and RBC transfusions have been associated with increased risk of allergic reactions, transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), ARDS, organ failure and death.[12,13] While allergic and febrile reactions are usually benign, they have the potential to cause unnecessary discomfort and can lengthen hospitalization. TRALI and TACO introduce risks for serious cardiopulmonary complications in bleeding patients, although the rate of TRALI is <1:100,000 units transfused.[14] Interestingly, in a secondary analysis of the Pragmatic, Randomized Optimal

Platelet and Plasma Ratios (PROPPR) trial, ARDS was more associated with crystalloid than blood products.[15] Immunosuppression has been documented as another side-effect of transfusion, and could predispose patients to non-transfusion related infection and cancer recurrence, and inhibit wound healing.[16–21] While risk of transfusion-related viral infections in the US has declined, transfusion-associated bacterial infection and sepsis are still reported complications.[22–25]

The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study found that the emergent treatment of trauma patients in hemorrhagic shock is one of the situations subject to potential over-transfusion of blood, as transfusion decisions are often made based on clinicians' judgment.[26] Subsequent studies document an early mortality rate of 10% within 6 h of admission.[27] Although there are clinical decision support tools to assist with rapidly predicting the need for the MTP, these tools tend to over-triage in favor of receiving massive transfusion, and most are not designed to determine the exact amount of blood product required for every bleeding patient.[28–30] For patients with severe traumatic injury and active hemorrhage, the survival benefits of transfusion likely outweigh the risk; however, less is known about potential over-transfusion of blood among patients that are either not hemorrhaging, or stabilized after receiving only a few units.

Despite prior studies showing a positive correlation between transfused volume and morbidity and mortality, our analysis showed that transfusion with small amounts of blood can avoid delayed transfusion among patients that need it, without an increased risk of complications. Most prior studies examining the effects of small volume blood transfusion included general surgery patients or a mixed medical and surgical patient population.[3–6] They do not include acutely injured trauma patients in whom the inflammatory response to injury likely influences immune homeostasis and recovery, as well as post-traumatic outcomes, independent of any blood transfusion. In addition, division of dose groups varies widely across studies, and some do not account for length of time from the initial transfusion to development of the complication, resulting in a time bias.

Several studies have shown that platelets and plasma transfusions, but not RBCs, are independent risk factors for acquiring a nosocomial infection among critically ill patients.[4,31,32] Platelets play a key role in the inflammatory and immune response, and may lead to immunomodulation despite widespread use of blood product leukoreduction.[33] Data from a prospective multicenter cohort study from the Netherlands also found that when administered together with platelets, RBCs did not contribute to the risk of infections.[31] Although our institutional guidelines support a balanced ratio of RBC:plasma:platelets and minimal crystalloid during resuscitation for hemorrhagic shock, data on concomitant plasma and platelet transfusion were not included in our regression models due to a near-direct correlation of the count of RBC units transfused with the count of units of plasma (Spearman's rho = 0.91, $p < .0001$) and platelets (Spearman's rho = 0.81, $p < .0001$) transfused, resulting in issues with collinearity when RBC and either platelets or plasma are in the model together.

There are several limitations to our study. Given the retrospective study design we could not account for differences in resuscitation practices, nor could we control for the decision to transfuse, which was at the trauma surgeon's discretion. Although coding is standardized, there may have been under-reporting of complications and inconsistencies in the capture of complications in our trauma registry. Though our hospital does not routinely screen for VTE, we obtain imaging for confirming venous thromboembolic events based on clinical triggers; therefore, it is possible that there were additional VTEs that were not captured among asymptomatic patients. In addition, we did not collect data on pre-hospital blood transfusions which could have impacted our results. Also, information on the duration of blood product storage was not available, and storage duration has been found to affect immunomodulation with possible undesirable transfusion-related clinical outcomes.[9]

The study period includes the COVID-19 pandemic period, which could have impacted transfusion management and patient outcomes. However, while elective surgeries were temporarily canceled during the pandemic peak, Trauma and Acute Care Surgery was not affected by the restrictions and transfusion management remained the same as the pre-pandemic period. While our hospital did experience a shortage of Type O blood during the Fall of 2021, this mostly impacted non-oncologic elective procedures some of which were canceled to conserve the inventory for emergencies and oncologic cases. Finally, it is possible that our results failed to reach statistical significance due to the small sample size and relatively low number of events in the transfusion groups.

In conclusion, in the absence of highly specific, rapid tools for definitive diagnosis of hemorrhagic shock, early empiric transfusion may subject patients to unnecessary transfusion with blood. However, among patients meeting current clinical triggers for massive transfusion, receiving 1–3 units of allogeneic blood does not appear to be associated with adverse outcomes.

FUNDING INFORMATION

Our work has no outside sources of support or funding to report. This research was presented as a poster at the 80th Annual Meeting of The American Association for the Surgery of Trauma in September 2021.

CONFLICTS OF INTEREST

Dr Holcomb is a consultant with Cellphire, Hemostatics and Arsenal, is Co-founder, Co-CEO and on the Board of Directors of Decisio Health, on the Board of Directors of QinFlow, Zibrio, and Oxyband and a Co-inventor of the Junctional Emergency Tourniquet Tool. Dr. Jansen has received grants from NIH, DoD, and NIHR. He is a consultant for CSL Behring and Cellphire and has received study support from CSL Behring, RevMedX, Infrascan, and Prytime Medical. All other authors: no conflicts of interest to disclose.

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How to cite this article: Gelbard RB, Griffin RL, Reynolds L, Abraham P, Warner J, Hu P, et al. Over-transfusion with blood for suspected hemorrhagic shock is not associated with worse clinical outcomes. Transfusion. 2022;62(S1):S177–S184. https://doi.org/10.1111/trf.16978