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Timing and volume of transfusion for adult major trauma patients with hemorrhagic shock: a registry-based cohort study

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ABSTRACT

Introduction Transfusion of blood components is vital for the resuscitation of injured patients in hemorrhagic shock. Delays in initiating transfusion have been associated with harm, as has excess transfusion. The aim of this study was to evaluate variables associated with hospital mortality, with a focus on the two modifiable risk factors— time to initiate transfusion and volume of blood components—with hospital mortality.

Methods This was a registry-based cohort study, including all consecutive adult patients presenting with hemorrhagic shock (systolic blood pressure (SBP) ≤90 mm Hg and transfusion of blood components) to a level 1 adult trauma center during a 5-year period (January 1, 2017–December 31, 2021). Associations with hospital mortality were assessed using multivariable logistic regression analysis, with final models developed using backward elimination.

Results There were 195 patients included and there were 49 (25.1%) in-hospital deaths. The median time to first transfusion was 10 (IQR 6–16) minutes. Age (adjusted OR (aOR) 1.06; 95% CI: 1.03 to 1.08), initial SBP (aOR 0.96; 95% CI: 0.3 to 0.98), intracranial bleeding or diffuse axonal injury (aOR 2.63; 95% CI: 1.11 to 6.23), and the volume of blood components in the first 4 hours (aOR 1.08; 95% CI: 1.03 to 1.13) were associated with mortality. Time to transfusion was not associated with in-hospital mortality (aOR 0.99; 95% CI: 0.95 to 1.03). Among the 90 patients who underwent urgent transfer to the operating room or angiography suite, the median time to transfer was 2.38 hours (IQR 1.5–3.7). In this subgroup, age (aOR 1.11; 95% CI: 1.05 to 1.18) and volume of blood components (aOR 1.20; 95% CI: 1.08 to 1.34) were associated with mortality.

Discussion In this setting where times to transfusion are short, further reductions in the time to transfusion are unlikely to improve outcome. In our population, for every unit of blood component transfused, the adjusted odds of death increased by 8%. These findings suggest investigation into strategies to achieve earlier control of hemorrhage.

Level of evidence III.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Time to delivery of blood components may be a modifiable risk factor to improve outcomes. This is commonly achieved through early activation of major hemorrhage protocols and easier access to blood components.

WHAT THIS STUDY ADDS

⇒ In a mature adult trauma center, time to initiating blood component transfusions was short and not associated with hospital mortality. After adjusting for injury and shock severity, the volume of blood components transfused was associated with hospital mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Reducing the need for blood component transfusion should be the target for future interventions.

INTRODUCTION

Providing timely transfusion therapy while simultaneously performing other life-saving interventions is a key challenge during the reception and resuscitation of critically injured patients. Major hemorrhage protocols (MHPs) are designed to provide standardized delivery of blood components and other products directed at hemostasis. Although the content of MHPs may vary between institutions, most prioritize red blood cells (RBCs) for the management of hemorrhagic shock, along with high volumes of fresh frozen plasma (FFP) and platelets. MHPs have become standard practice for most trauma centers, despite some controversies regarding their effectiveness.[1]

In conjunction with other measures of hemorrhage control, the American College of Surgeon Trauma Quality Improvement Program guidelines advise a maximum interval of 10 minutes between activation of an MHP to delivery of an initial set of blood components. Delays to blood components have been associated with a 5% increase in odds of 30-day mortality for every minute in delay (adjusted OR (aOR) 1.05; 95% CI: 1.01 to 1.09).[2] Decreasing the time to delivery of blood components may therefore be a modifiable risk factor to improve outcomes.

In trauma centers, time to transfusion is associated with the location of blood component storage.[3] For patients presenting with hemorrhagic shock, blood components are commonly stored in institutional blood banks and delivered after request, manually or through pneumatic chutes, usually after activation of the MHP. This is the practice in our center, with components sent from the blood bank through a pneumatic chute. An alternative is

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storage of a small supply of universal blood components in the trauma center.[3]

A potential risk of enabling easier access to blood components is avoidable transfusions. Higher transfusion volumes have been associated with worse outcomes, after adjustments for injury severity and shock.[4 5] A restrictive transfusion strategy could therefore be promoted, that is cost-effective, reduces the risk of adverse events specific to transfusion, and introduces no harm.[6] Thus, the aim of this study was to evaluate, among adult patients with hemorrhagic shock after trauma presenting to a level 1 trauma center, the association of two modifiable risk factors—the time to blood component transfusion and volume of blood components—with hospital mortality. The hypothesis was that shorter time to blood component transfusion and lower volumes of blood components during acute resuscitation would be associated with lower mortality. This would inform strategies to reduce time to transfusions and to reduce transfusion volumes during trauma resuscitation.

PATIENTS AND METHODS

Design

This was a registry-based cohort study.

Setting

The state of Victoria, Australia has three major trauma services (MTS) located in metropolitan Melbourne: one pediatric and two adult. The Alfred Hospital is a level 1 adult trauma center and receives the largest number of major trauma patients in Australia. Under the Victorian State Trauma System, all major trauma patients aged 16 years or older are recommended to receive definitive care at an adult MTS. Patients presenting to the Alfred Hospital and with suspected hemorrhagic shock are managed using a ratio-based MHP.[7]

The Alfred Hospital Trauma Registry (AHTR) prospectively records prehospital and hospital data to chronicle trauma activity. Criteria for inclusion in the registry include all major trauma (Injury Severity Score (ISS) >12) presentations, those requiring admission for over 72 hours, all trauma intensive care unit admissions and all deaths after injury.

Patient selection

Patients were identified from the AHTR during a 5-year period (January 1, 2017–December 31, 2021). Eligible patients were adults, presenting directly from the scene of injury, and with hemorrhagic shock. For the purpose of inclusion into the study, hemorrhagic shock was defined by presentation with hypotension (initial systolic blood pressure of ≤90 mm Hg) and transfusion of at least one unit of RBC in the emergency department (ED). We excluded patients where the cause of injury was burns, near-drowning and near-hanging. At the time of recording patient data to the registry, we were blinded to administration of tranexamic acid that was provided as part of the PATCH-Trauma trial.[8]

We performed a subgroup analysis including patients who underwent urgent surgery or angioembolisation. This population was defined as eligible patients who were transferred directly from the trauma center to the operating room or angiography suite.

Exposure variables

The primary exposure variable was the time to blood component transfusion, defined as time from arrival to the trauma center to the start of first transfusion. Data for this variable were extracted using an explicit chart review of transfusion records. The second exposure variable was the volume of blood components (RBC, FFP and platelets) transfused in the first 4 hours after arrival at the trauma center. In Australia, one adult unit of apheresis or pooled platelets is equivalent to platelets derived from four single whole-blood donor units. Prehospital time was defined by time of injury (as estimated by prehospital staff) to time of arrival to the ED.

Outcome

The outcome variable was death, recorded at hospital discharge.

Analysis

Normally distributed continuous variables were presented using mean (SD), ordinal or skewed data were presented using median (IQR), and categorical data presented using count (percentages). The association between exposure variables and the outcome was assessed using univariable logistic regression analysis and presented using ORs with 95% CIs. All variables that demonstrated an association with the outcome ($p<0.10$) were initially entered into a multivariable logistic regression analysis. Backward selection was used, retaining variables that demonstrated significant associations to develop the final models. The results of the multivariable logistic regression analyses were reported using aOR with corresponding 95% CIs. A possible effect modification of time to transfusion with prehospital time was assessed. Post-estimation multicollinearity was assessed using the variance inflation factor (VIF) and goodness of fit assessed using Hosmer-Lemeshow test. A p value of <0.05 was considered statistically significant. All analyses were performed using Stata V.17.0 (College Station, Texas, USA).

RESULTS

There were 285 patients who presented directly from the scene and had an initial systolic blood pressure of ≤90 mm Hg. Of these, 13 patients were excluded for mechanism of injury being burns, near-drowning or near-hanging. A further 77 patients were excluded as they did not receive any blood transfusion within 4 hours of arrival to the ED, and 195 patients were included for analysis. At hospital discharge, there were 49 (25.1%) deaths. Among the 77 patients who did not receive a blood transfusion, there were 9 deaths. Of these, five patients had severe traumatic brain injury (TBI) with fixed and dilated pupils. The other four patients were of older age with a range of 78–97 years. Time to death ranged from 4.3 to 58.9 hours.

Baseline characteristics of patients and univariable associations with death at hospital discharge are listed in table 1. Consistent with the epidemiology of major trauma patients in our setting, patients were young males and blunt trauma was the most common mechanism of injury, with motor vehicle crashes being the most common cause of injury. Age, high ISS, mechanism of injury, the degree of hypotension and tachycardia and intracranial bleeding or diffuse axonal injury demonstrated some association with mortality at hospital discharge.

Transfused blood components and times to initial blood components, and their association with mortality at hospital discharge are listed in table 2. In the first 4 hours, patients received a median of 4 (IQR 2–8) units of red blood cells, 2 (IQR 1–4) units of FFP and 1 (IQR 0–2) adult dose of platelets. The volume of total blood components transfused (OR 1.07; 95% CI: 1.02 to 1.10) was associated with in-hospital mortality. In all cases, RBC was the first blood component transfused. Times to first RBC transfusion in hospital are displayed in figure 1.

Table 1 Baseline characteristics and associations with mortality at hospital discharge

Variable	Summary measure	Association with in-hospital mortality OR (95% CI)	P value
Age (years), mean (SD)	49.7 (21.8)	1.03 (1.02 to 1.05)	<0.001
Male sex (%)	142 (72.8)	0.89 (0.43 to 1.82)	0.75
Injury Severity Score			
<12	30 (15.4%)	Ref	Ref
12–25	52 (26.7%)	1.01 (0.27 to 3.78)	0.99
26–40	48 (24.6%)	2.41 (0.70 to 8.26)	0.16
>40	65 (33.3%)	4.17 (1.30 to 13.37)	0.016
Cause of injury			
Motor car or truck crash	53 (27.2%)	4.19 (0.86 to 20.3)	0.075
Motorcycle crash	24 (12.3%)	1.07 (0.16 to 7.22)	0.94
Pedal cycle crash	9 (4.6%)	2.14 (0.25 to 18.50)	0.49
Pedestrian	37 (19.0%)	4.24 (0.84 to 21.51)	0.081
Low fall	11 (5.6%)	2.81 (0.39 to 20.45)	0.31
High fall	19 (19.7%)	3.46 (0.59 to 20.21)	0.17
Penetrating	25 (12.8%)	0.31 (0.03 to 3.75)	0.36
Other	18 (8.7%)	Ref	Ref
Prehospital time (hrs)	1.9 (1.3–2.9)	1.08 (0.85 to 1.37)	0.53
Initial systolic blood pressure (mm Hg), mean (SD)	70.3 (16.9)	0.96 (0.94 to 0.98)	<0.001
Initial pulse rate (beats/min), mean (SD)	97.7 (33.3)	0.99 (0.98 to 1.00)	0.028
Initial shock index ≥1	156 (80.0%)	1.40 (0.59 to 3.28)	0.45
FAST			0.36
Negative	125 (64.1%)	Ref	
Positive	59 (30.3%)	1.40 (0.68 to 2.88)	
Unknown or equivocal	11 (5.6%)	–	
Intracranial bleeding or diffuse axonal injury	54 (27.8%)	3.65 (1.83 to 7.27)	<0.001

FAST, Focused Assessment with Sonography in Trauma.

The initial multivariable regression model including all variables that demonstrated some association with hospital mortality is listed in online supplemental table 1. After backward selection, with time to first blood component kept in the model, results are listed in table 3. Age (aOR 1.06; 95% CI: 1.03 to 1.08), initial systolic blood pressure (aOR 0.96; 95% CI: 0.3 to 0.98), presence of intracranial bleeding or diffuse axonal injury (aOR 2.63; 95% CI: 1.11 to 6.23), and the total volume of blood components in the first 4 hours (aOR 1.08; 95% CI: 1.03 to 1.13) were associated with hospital mortality. Time to first blood component was not associated with hospital mortality (aOR 0.99; 95% CI: 0.95 to 1.03). Prehospital time (p value for interaction term=0.87) was not an effect modifier. Mean VIF for the model was 1.09, and the p value for the Hosmer-Lemeshow goodness-of-fit statistic was 0.17.

There were 90 patients who underwent urgent transfer to the operating room or angiography suite, of whom 14 (15.6%) died at hospital discharge. The median time to transfer was 2.38 hours (IQR 1.5–3.7). In this population, there were 14 (15.7%) deaths. Variables associated with in-hospital mortality are listed in online supplemental table 2 and a comparison of patients who underwent urgent transfer to the operating room or angiography suite versus those who did not is presented in online supplemental table 3. In the final model, age (aOR 1.11; 95% CI: 1.05 to 1.18) and total blood components within 4 hours (aOR 1.20; 95% CI: 1.08 to 1.34) were associated with mortality (table 4). In this subgroup, time to first blood components was not associated with mortality (aOR 0.96; 95% CI: 0.85 to 1.08). Time to death, subgrouped by transfusion volume, is presented in online supplemental figure 1.

DISCUSSION

Among injured patients presenting with hemorrhagic shock to an adult level 1 trauma center, times to blood component transfusion were short and were not associated with hospital mortality. The volume of blood component therapy was associated with mortality and is potentially a modifiable risk factor. This study suggests that implementation and evaluation of strategies to reduce bleeding and the need for blood component transfusion during trauma resuscitation could improve outcomes.

The setting of this study and restrictions to the included population must be considered when interpreting these results. Mature trauma systems have achieved substantial improvements in outcomes through a system-based approach, resuscitation using trauma teams, and inpatient management using dedicated trauma services.[9–12] In this mature adult trauma center, despite blood components requiring transport from the blood bank, times to transfusion were relatively short. This is likely associated with an established prehospital notification, an MHP that is frequently activated and audited, and a pneumatic tube that transports blood components directly to the trauma center. In such a setting, further incremental improvements in time to transfusion are unlikely to significantly improve patient outcomes.

Table 2 Transfusion of blood components and univariable association with mortality

Variable	Summary measure, median (IQR)	Association with in-hospital mortality OR (95% CI)	P value
RBC units in first 4 hours	4 (2–8)	1.12 (1.05 to 1.21)	0.001
Time to first RBC unit (mins)	10 (6–16)	0.97 (0.93 to 1.01)	0.10
FFP units in first 4 hours	2 (1–4)	1.14 (1.04 to 1.24)	0.004
Time to first FFP unit (mins)	21 (11–29)	0.97 (0.95 to 1.00)	0.068
Platelet (adult units in first 4 hours)	1 (0–2)	1,43 (1.14 to 1.80)	0.002
Time to first platelet unit (mins)	26 (17–45)	1.00 (0.98 to 1.02)	0.87
Total blood components in first 4 hours (units)	8 (4–14)	1.07 (1.02 to 1.10)	0.001

FFP, fresh frozen plasma; RBC, red blood cell.

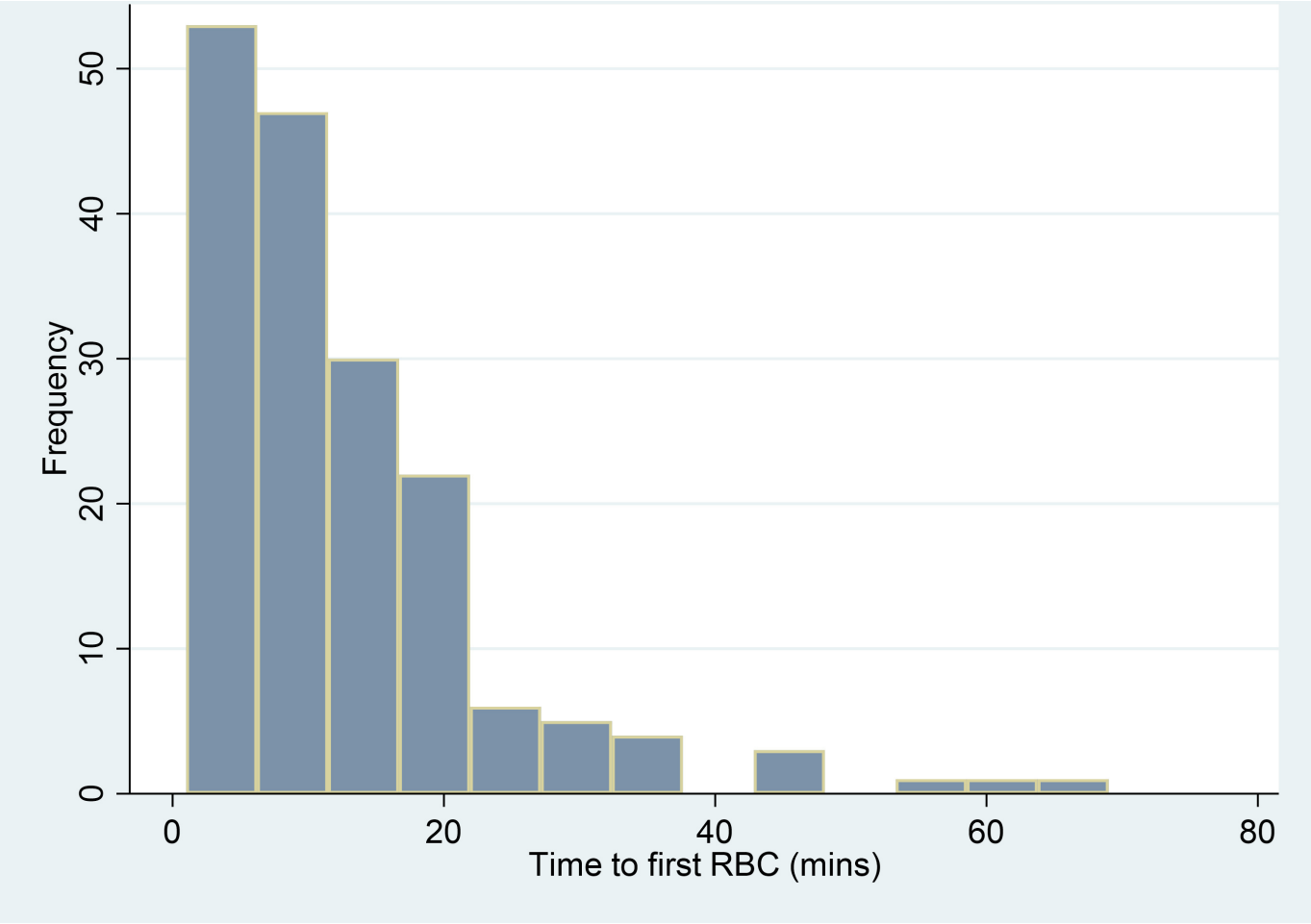

Figure 1 Time to first unit of RBC or any blood component. RBC, red blood cell.

A modifiable risk factor identified in this study was the volume of blood components transfused, with 8% higher odds of death for every unit of blood component transfused in our study. Although transfusion of blood components remains essential for trauma resuscitation, there appears to be a need to implement and assess innovative strategies to reduce blood component transfusion. During trauma reception and resuscitation, such strategies can be broadly categorized to direct control of bleeding using surgical and/or angioembolisation techniques and reduction in blood component requirement through optimization of physiology and coagulation (figure 2). The evaluation of such strategies is therefore a priority target for further research, particularly among discrete subgroups of patients such as those with TBI or penetrating trauma.

Reducing the time to definitive hemorrhage control is another modifiable risk factor. The median time to transfer was 2.38 hours (IQR 1.5–3.7). This was substantially longer than recommended. For example, the Royal Australasian College of Surgeons guideline for emergency operative intervention is 30 minutes and for interventional radiology 60 minutes, to effect hemorrhage control.[13] There are multiple confounders in the association of time to hemorrhage control and outcomes that include detection and characterization of hemorrhage, availability of theater and staff. Therefore, rather than promoting a linear association of time to theater with outcomes, in some cases, it is prudent to accept some delays to surgery to achieve greater understanding on the pathophysiology of bleeding. But

Table 3 Adjusted associations with in-hospital mortality (final model)

Variable	Adjusted OR (95% CI)	P value
Age (years)	1.06 (1.03 to 1.08)	<0.001
Initial SBP (mm Hg)	0.96 (0.93 to 0.98)	0.001
Intracranial bleeding or diffuse axonal injury	2.63 (1.11 to 6.23)	0.028
Total blood components in 4 hours (units)	1.08 (1.03 to 1.13)	0.003
Time to first blood component (mins)	0.99 (0.95 to 1.03)	0.64

SBP, systolic blood pressure.

Table 4 Adjusted association with in-hospital mortality among patients who underwent urgent surgery or angioembolisation

Variable	Adjusted OR (95% CI)	P value
Age (years)	1.11 (1.05 to 1.18)	<0.001
Total blood components in 4 hours (units)	1.20 (1.08 to 1.33)	0.001
Time to first blood component (mins)	0.96 (0.85 to 1.08)	0.49

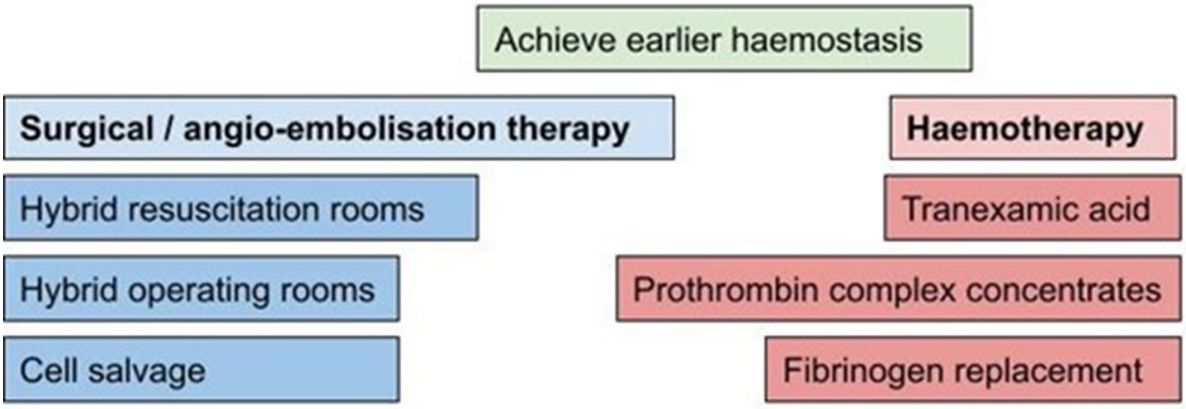

Figure 2 Research priorities to achieve earlier in-hospital hemostasis.

recognition of delays to definitive hemorrhage control demands investigations into strategies to enable earlier therapy.

Hybrid trauma resuscitation bays and operating rooms reduce the time to hemorrhage control by enabling earlier surgery and angiography, while concurrently providing capacity for assessment using imaging and ongoing hemotherapy.[14] Management in hybrid resuscitation bays has been associated with reduced blood component transfusion and lower mortality.[15 16] However, trials are required for definitive evidence on benefits towards patient outcomes and cost-effectiveness. During surgical management, the role of cell salvage during trauma resuscitation remains unknown and requires further assessment.[17 18]

There is substantial potential for adjunct products to reduce blood component transfusion. Early administration of tranexamic acid has been consistently associated with lower mortality, without higher thromboembolic complications.[8 19] Dosing and the effect of tranexamic acid on functional outcomes of patients require further assessment. Similarly, there is some uncertainty regarding the role of prothrombin complex concentrates, with potential benefits unknown, and there have been suggestions of thromboembolic events.[20] Further trials are indicated and are currently enrolling patients. Pre-emptive fibrinogen replacement may also reduce other blood component requirements and although a recent trial did not demonstrate a benefit, further trials are underway.[21]

This study is limited in being conducted in a single adult trauma center. The results, therefore, may not be generalizable to other centers. In particular, the results should not be extrapolated to prehospital care, where early access to blood components may be life-saving. In our center, a ratio-based MHP was used and this practice differs from settings using viscoelastic hemostatic assay (VHA)-based MHPs. However, whether VHA-based resuscitation results in lower blood component transfusions or improved mortality remains unknown.[22] Transfer times to the operating room or angiography suite may be significantly lower at other centers. We did not consider the effect of survival bias in the analyses. The concept of survival bias would posit that some patients would have died prior to the opportunity to be transfused large volumes of blood products. This bias, if present, would shift the association between blood products and mortality towards null, and hence, consolidates the findings of this study. Our study only included patients with hypotension on arrival, and therefore would have excluded patients who may have had occult hemorrhage and presented with a higher blood pressure. Investigations into diagnosis of occult hemorrhagic shock remain a target for future research. We also excluded patients who did not receive a blood transfusion, with the possibility that death could have resulted due to delays in initiation of transfusion, However, our assessment of the subgroup of patients who died without being transfused suggests that death was associated with severe TBI and multitrauma in older patients, and not due to inability to transfuse blood components. Finally, it is acknowledged that in severely injured patients, a massive transfusion is sometimes essential therapy, and a reflection of tissue injury and shock.

As a retrospective analysis, it is possible that unknown confounders were unaccounted for. However, we adjusted for the common variables associated with mortality after major trauma, age, shock severity and injury severity. Finally, in our discussion, we have not considered the potential for prehospital management to improve outcomes. This is an evolving field and contains many more targets for urgent research.

CONCLUSIONS

In a mature adult trauma center, times to blood component therapy were short, and further reductions in times to transfusion are unlikely to be associated with a mortality benefit. Age, shock severity and TBI were identified as non-modifiable risk factors for hospital mortality. The need for high volume of blood product transfusion and the time to operative or angiographic hemorrhage control were potentially modifiable risk factors.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Alfred Hospital Research and Ethics Committee (project ID 253/22). The requirement to seek informed consent from participants was waived by the Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request and subject to Ethics Committee approval.

of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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