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High ratio of plasma to red cells in contemporary resuscitation of haemorrhagic shock after trauma: a secondary analysis of the PATCH-trauma trial

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Abstract

Background Plasma transfusion is recommended as an initial intervention in most major haemorrhage protocols for trauma resuscitation. With availability of newer blood components, therapeutic agents and investigations for coagulopathy, the marginal benefits of high ratios of plasma to red cells is uncertain. The aim of this study was to report the association of high ratios of plasma: red cells and 28-day mortality in patients with major trauma.

Methods The PATCH-Trauma trial enrolled critically bleeding patients at high risk of trauma induced coagulopathy and randomised them to receive prehospital tranexamic acid or placebo. The sub-group of patients who were managed with massive transfusions in hospital (> 4 units of red cells in first 4 h) were included for this post-hoc analysis. Associations of high ratios of plasma (more than 1 unit of plasma for every 2 units of red cells) and 28-day mortality were reported using multivariable logistic regression analysis after adjustment for potential confounders including age, neurological injury, injury severity, coagulopathy and administration of platelets, fibrinogen concentrates, cryoprecipitate and tranexamic acid.

Results Among 1310 patients enrolled in the PATCH-trauma trial, 372 patients were included for this analysis; 213 (57.3%) received high ratios of plasma: red cells and 116 (31.4%) deaths were recorded at 28 days. High ratios of plasma: red cells were associated with lower mortality (adjusted odds ratio; aOR 0.50; 95%CI: 0.26–0.96). Older age (aOR 1.02; 95%CI: 1.01–1.03), initial Glasgow Coma Scale 3–8 (aOR 6.57; 95%CI: 2.92–14.80) and trauma induced coagulopathy (aOR 5.64; 95%CI: 2.87–11.1) on hospital arrival were associated with higher mortality.

Conclusions Among patients with critical bleeding managed with massive transfusions, high ratios of plasma: red cells were associated with lower mortality, after controlling for potential confounders. Ongoing provision of early plasma for management of critical bleeding is indicated with consideration to prehospital plasma.

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Keywords Wounds and injuries, Plasma, Blood transfusion, Blood component transfusion, Death, Shock, hemorrhagic, Emergency medicine, Emergency medical services

Introduction

Injury is the leading cause of death among young people with the most common mechanisms being transport injuries, unintentional injuries, interpersonal violence, self-harm and conflict. In 2019, there were 1.49 million deaths worldwide in people aged 10–24 years of which over 40% were due to injuries [1]. The leading causes of death in injured patients were traumatic brain injury and haemorrhage, the latter being the most common preventable cause of death.

In the setting of critical bleeding, acute traumatic coagulopathy or trauma induced coagulopathy often develop secondary to tissue injury and shock and is associated with high early mortality [2]. Early this century, the US Army recommended transfusion of plasma: red cell ratio at a ratio of 1:1 based on data from patients admitted to a single combat support hospital in Iraq to prevent and proactively manage trauma induced coagulopathy [3]. The PROPPR trial then compared a ratio of 1:1:1 to 1:1:2 (plama: platelets: red cells) and while the trial concluded similar mortality at 24 h at 30 days in the two study arms, there was reduced death from haemorrhage at 24 h with higher ratios of plasma and platelets to red cells [4]. A high ratio of plasma: red cells has since been incorporated into major haemorrhage protocols, although low levels of certainty and concerns about survivor bias in observational studies persist [5]. Rather than mandating a 1:1 ratio of red cells to plasma, guidelines therefore recommend a ratio greater than 1:2.

Over the last decade, a range of strategies have been incorporated into major haemorrhage protocols. Prehospital blood components are increasingly available [6]. Precise assessment and management of coagulopathy using viscoelastic haemostatic assays are becoming more common [7]. Tranexamic acid has been confirmed in several studies to reduce in-hospital mortality [8–10]. Cryoprecipitate, fibrinogen and other coagulation factor concentrates have been studied and are being used sporadically [11–13]. In addition, recognition of the importance of early control of haemorrhage has enabled greater access to haemostatic dressings, tourniquets, pelvic binders, damage control surgery and interventional radiology [14–16]. An alternative to fixed-ratio based transfusion strategy is one that is based on point-of-care tests such as viscoelastic haemostatic assays (VHA). While VHA use has been associated with lower blood component usage, associations with patient outcomes remain equivocal [17, 18]. As such, at least for the initial resuscitation of patients, fixed-ratio strategies are commonly used.

Therefore, currently, clinicians have a multitude of potential interventions to use in a critically bleeding patient, most of which are supported by evidence with some degree of uncertainty. In the contemporary management of patients with critical bleeding, therefore, the marginal benefit of early, high-volume plasma, may have changed due to fewer preventable deaths. Two decades after the concept of 1:1 ratio of plasma: red cells was proposed, and with other products and blood components available, the aim of this study was the explore the association of high ratio of plasma to red cells and mortality in patients being managed with massive transfusions.

Methods

This was a post-hoc analysis of a sub-group of patients enrolled in the PATCH-Trauma trial, in which patients were recruited by 15 emergency medical services in Australia, New Zealand, and Germany from 2014 to 2021. The protocol for the PATCH-Trauma trial was designed by the trial management committee, endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group, was approved by the human research ethics committee responsible for each participating site, and previously published [19]. Briefly, eligible patients were adults (≥ 18 years of age) enrolled at the scene of trauma and planned for transport to participating trauma centres. All participating trauma centres were tertiary level hospitals with capacity to provide massive blood and blood component transfusions.

Patients were eligible for inclusion in the PATCH-Trauma trial if they were assessed as being at high risk for trauma induced coagulopathy and if the first dose of tranexamic acid or placebo could be administered within 3 h after injury and before hospital admission. Prehospital assessment of coagulopathy risk was performed with the use of the Coagulopathy of Severe Trauma (COAST) score, with a score of 3 of greater considered to be of high risk and eligible for enrolment. COAST scores range from 0 to 7, with 1 point assigned for each of the following variables: entrapment in a vehicle, systolic blood pressure of less than 100 mm Hg, body temperature of less than 35 °C, suspected pneumothorax, and suspected intraabdominal or pelvic injury. Additional points are assigned if the systolic blood pressure is less than 90 mmHg or if the body temperature is less than 32 °C [20].

Inclusion criteria

For this analysis, we included patients who were managed with a massive transfusion, defined as >4 units of red cells within 4 h after arrival to hospital [21, 22].

Thus, patients who died pre-hospital or prior to administration of 5 units of red cells were excluded. While this criterion would have excluded some patients with critical bleeding, it was designed to exclude mortality bias, where patients classified as having been managed with low ratios of plasma: red cells died prior to the opportunity to receive plasma, rather than death being due to low plasma volumes.

Exposure variable

The primary exposure variable was a high ratio of plasma: red cells at 4 h after arrival to hospital. This was defined as administration of at least 1 unit of plasma for every 2 units of red cells. Thus, any ratio lower than 1:2 (for example, 1:2.5) was considered to be a low ratio.

Explanatory variables

The initial vital signs including blood pressure, pulse rate, temperature and Glasgow Coma Scale (GCS) were as recorded by emergency medical services and before any intervention including sedation or intubation. Coagulopathy was defined as international normalized ratio (INR) > 1.5 on initial blood test on arrival to hospital [23]. Fibrinogen units were defined as equivalence to whole blood cryoprecipitate units, or if fibrinogen concentrate was administered, 1 g was considered equivalent to 3 units of cryoprecipitate.

Outcome variable

The primary outcome was death at 28 days after injury. We also reported time to death in the 28-day period.

Statistical analysis

Continuous variables with normal or near-normal distribution were summarised using mean (standard deviation; SD) and compared using Student's t-test. Ordinal or variables with skewed distribution were summarised using medians (inter-quartile range; IQR) and compared using the Wilcoxon Rank Sum test. Categorical variables were compared using the chi-square test.

Time to death were displayed using Kaplan-Meier graphs for high and low ratios of plasma: red cells (univariable analysis). The univariable association of potentially confounding variables with the outcome were assessed using logistic regression and reported using odds ratios with 95% confidence intervals (95%CI). Variables that demonstrated some univariable association with the outcome ($p < 0.10$), along with the primary exposure variable, were entered into a multivariable logistic regression model, with results reported using adjusted odds ratios (aOR) and 95%CI. There was no backward elimination performed. Cases with missing data were handled using listwise deletion. The quality of fit of the model was reported using Hosmer-Lemeshow p-value. Variance inflation factors (VIF) for each variable, and the mean VIF were calculated to detect and report potential multicollinearity. Finally, the marginal association of each category of plasma: red cell ratios with the outcome variable were displayed. P-values of < 0.05 were defined to be statistically significant. All analyses were conducted using Stata v 18.0 (College Station, TX, USA).

Results

From 1310 patients enrolled in the PATCH-Trauma trial, there were 372 patients included in this study (Fig. 1). Of these, 213 (57.3%) were managed with a high ratio of plasma: red cells. Among those managed with low ratio, 74 patients received ratios of 1:3 – 1:2, 47 received ratios of 1:3 – 1:4 while 38 patients received less than 1 unit of plasma for every 4 units of red cells. Baseline

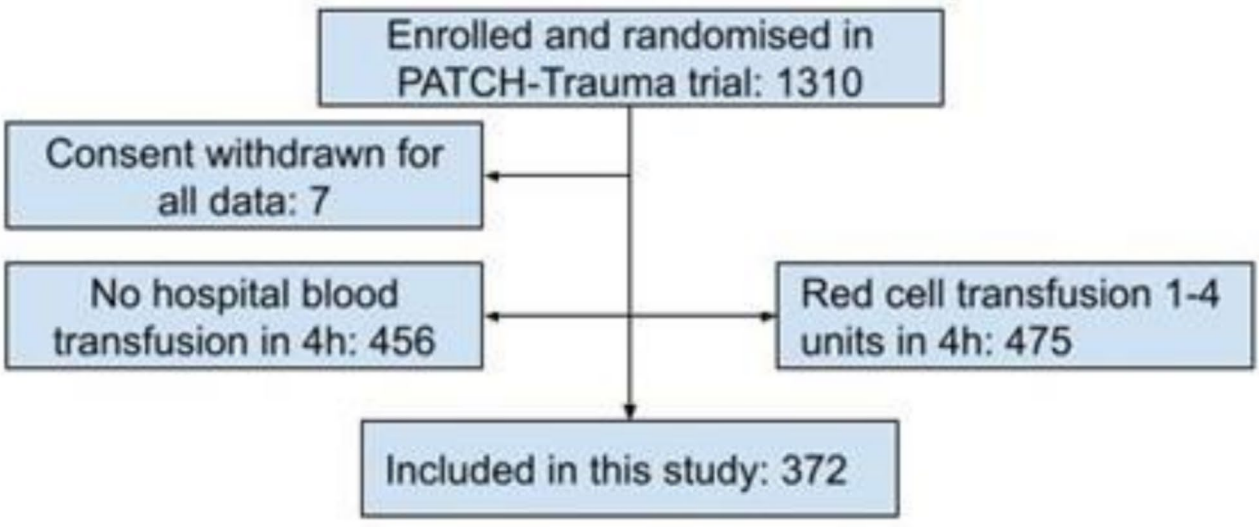

Fig. 1 Inclusion of patients

characteristics of patients are listed in Table 1. Patients managed with a high ratio presented with significantly lower temperature, and a higher proportion were coagulopathic and received greater volume of platelet transfusion. All other demographic, injury severity and management characteristics were similar.

There were 116 (31.4%) deaths recorded at 28 days from injury. Time to death, sub-grouped by high ratio of plasma: red cells is illustrated in Fig. 2. The univariable associations with mortality at 28 days are listed in supplementary Table 1. On univariable analysis, age (OR 1.02; 95%CI: 1.01–1.03), initial (pre-hospital and pre-intubation) GCS 3–8 (OR 4.64; 95%CI: 2.79–7.70), with GCS 13–15 as the reference category, initial temperature (OR 0.78; 95%CI: 0.65–0.94), coagulopathy (initial INR > 1.5) on arrival to hospital (OR 5.99; 95%CI: 3.58-10.00), head or neck injury (OR 1.47; 95%CI: 1.53–3.77), injury severity score (ISS) > 45 (OR 3.59; 95%CI: 1.76–7.30) and the number of units of platelets transfused (OR 1.12; 95%CI: 1.00-1.25) were significantly associated with the outcome. In addition, initial pulse rate and ISS 26–45 demonstrated some association ($p < 0.10$) with 28-day mortality and were entered into the multivariable model.

Results of the multivariable model are listed in Table 2. Following adjustment for potential confounders, a high ratio of plasma: red cells was associated with lower 28-day mortality (aOR 0.50; 95%CI: 0.26–0.96). Older age (aOR 1.05; 95%CI: 1.03–1.07), initial GCS 3–8 (aOR 6.57; 95%CI: 2.92–14.80) with GCS 13–15 as the reference group and coagulopathy on arrival to hospital (aOR 5.64; 95%CI: 2.87–11.1) were associated also associated with 28-day mortality. The *p*-value for the Hosmer-Lemeshow goodness of fit statistic was 0.31. Mean VIF was 1.39, with maximum VIF of 2.22. The predicted mortality after adjustment for potential confounders for each category of plasma: red cell ratio is illustrated in Fig. 3.

Discussion

Among patients with critical bleeding managed with massive transfusions, a high ratio of plasma: red cells (> 1:2) was independently associated with lower mortality, after controlling for potential confounders including age, neurological injury, injury severity, coagulopathy and administration of platelets, fibrinogen concentrates, cryoprecipitate and tranexamic acid. These findings indicate the continuing benefit of provision of plasma for the management of patients with critical bleeding. The benefits of plasma appear to prevent early death with separation of the Kaplan Meier graphs at 1–2 days, and further trials to assess the effects of early plasma in the prehospital phase of care are indicated.

Table 1 Patient characteristics and management sub-grouped by high plasma: red cell ratio

	High ratio *n* = 213	Low ratio *n* = 159	*p*-value
Age (years)- mean (SD)	44.0 (SD 19.1)	41.4 (17.6)	0.18
Sex			
- **Male**	151 (70.9%)	120 (75.5%)	0.33
- **Female**	62 (29.1%)	39 (24.5%)	
Mechanism of injury			
- **Blunt**	194 (91.1%)	144 (90.6%)	0.87
- **Penetrating**	19 (8.9%)	15 (9.4%)	
Initial Glasgow Coma Scale			
- **3–8**	101 (47.4%)	72 (45.3%)	0.57
- **9–12**	21 (9.9%)	20 (12.6%)	
- **13–15**	91 (42.7%)	68 (42.8%)	
Initial SBP (mmHg)- mean (SD)	69.1 (SD 30.6)	67.7 (31.2)	0.66
Initial pulse rate (beats/min) – mean (SD)	116.1 (SD 26.4)	118.8 (SD 32.8)	0.37
Initial temperature (°C)- mean (SD)	35.2 (SD 1.3)	35.6 (SD 1.2)	0.006
Coagulopathy (INR > 1.5)	81 (38.1%)	36 (22.6%)	0.002
Head of neck AIS > 2	104 (48.8%)	64 (40.3%)	0.08
Injury severity score			
- **0–25**	43 (20.3%)	36 (22.6%)	0.41
- **26–45**	111 (52.4%)	89 (56.0%)	
- **> 45**	58 (27.4%)	34 (21.4%)	
Tranexamic acid	139 (65.3%)	84 (52.8%)	0.016
Prehospital red cells	148 (69.5%)	104 (65.4%)	0.41
Prehospital plasma	14 (6.6%)	13 (8.2%)	0.56
Platelet units (median; IQR)	1 (1–3)	1 (0–2)	< 0.001
Fibrinogen units (median; IQR)	3 (0–8)	2 (0–10)	0.19

SD: Standard deviation; SBP: Systolic blood pressure; C: Celsius; AIS: Abbreviated injury scale; IQR: Interquartile range

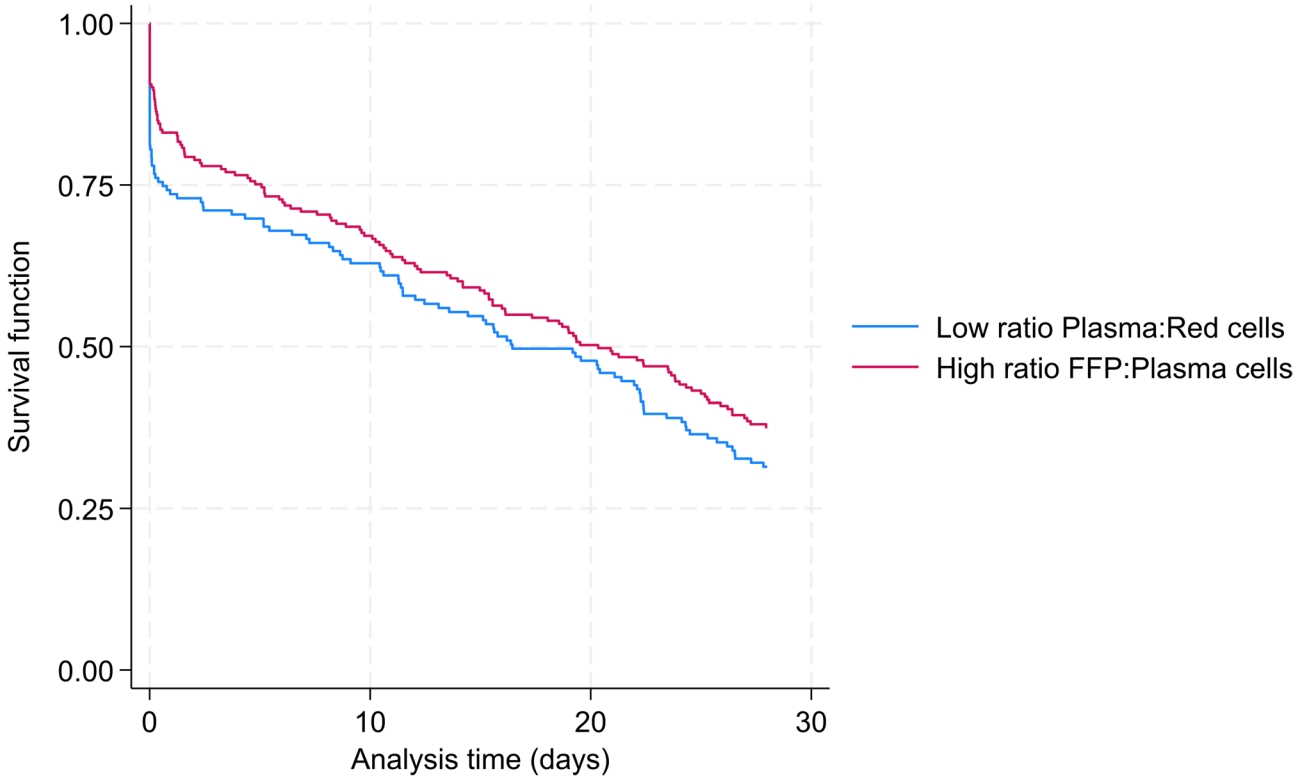

Fig. 2 Time to death sub-grouped by high ratio of plasma: red cells (univariable analysis)

Table 2 Multivariable associations with 28-day mortality

	Adjusted Odds ratio (95%CI)	*p*-value
Age	1.05 (1.03–1.07)	< 0.001
Initial GCS		
- **3–8**	6.57 (2.92–14.80)	< 0.001
- **9–12**	0.63 (0.17–2.37)	0.50
- **13–15**	Ref	
Initial pulse rate (beats/min)	1.00 (0.99–1.01)	0.77
Initial temperature (°C)	1.03 (0.91–1.18)	0.62
Coagulopathy (INR > 1.5)	5.64 (2.87–11.1)	< 0.001
Head or neck AIS > 2	1.47 (0.68–3.14)	0.33
Injury severity score		
- **0–25**	Ref	0.45
- **26–45**	1.46 (0.54–3.94)	0.32
- **> 45**	1.80 (0.57–5.75)	
Platelet units	1.13 (0.96–1.32)	0.15
High ratio plasma: blood cells	0.50 (0.26–0.96)	0.038

The benefits of plasma are likely to be multi-facetted. Plasma contains procoagulant and anti-fibrinolytic factors, and transfusion of plasma may replenish coagulation factors and proteins lost through acute bleeding [24]. Plasma transfusion appears to mitigate the harmful dilutional and inflammatory effects of crystalloid or colloid resuscitation [25]. Additionally, the endothelial glycocalyx is a carbohydrate-rich layer coating the vascular endothelium, forming physical barrier between blood and vessel wall, maintaining blood fluidity and regulates vascular permeability. Disruption of the glycocalyx have been observed after severe trauma and associated with organ failure [26]. Resuscitation with plasma may partially restore the endothelial glycocalyx after severe injury [27].

Major challenges for the delivery of plasma in prehospital settings or even in the early periods of in-hospital trauma resuscitation are the requirements for freezing fresh plasma, thawing and warming prior to use. Extended life plasma (thawed plasma) can mitigate some of these challenges, but results from trials have been inconclusive to date and there is potential for wastage [28–30]. Dried plasma products present attractive options with long shelf lives and simpler reconstitution. However, there have been few trials to date and further assessment in critically bleeding populations is indicated [31].

A key feature of this study was restriction of the population to patients who had in-hospital massive transfusion for critical bleeding. This population remains challenging to identify prospectively. For example, in the population of the CRASH-2 trial, only 51% of patients were transfused any blood components; in the COMBAT and PAMPeR trials, 21% of patients received massive transfusions; and even from the PATCH-Trauma trial that used inclusion criteria designed to detect more patients

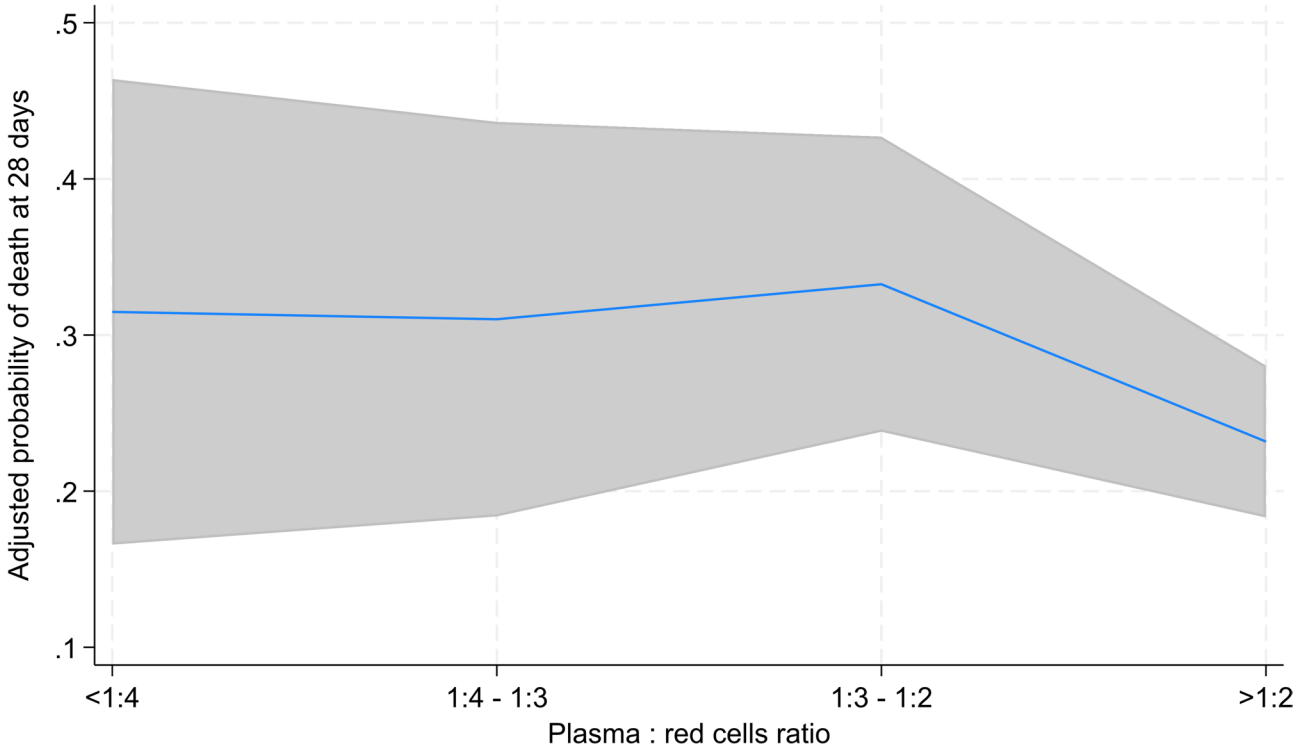

Fig. 3 Adjusted probability of death at 28 days. * Shaded area = 95%CI

with trauma induced coagulopathy, the eligible population for this study was 29% of the trial sample size [8, 10, 29, 30]. Thus, trials to examine interventions in critically bleeding patients require large sample sizes to account for patients with clinical features that mimic haemorrhagic shock. Among such patients, the intervention cannot be beneficial as the underlying condition (critical bleeding) is not present. Therefore, such studies require large sample sizes that are usually feasible only through multi-centre trials, requiring collaborative efforts across different jurisdictions and ideally, multiple countries. In the absence of adequate power to account for patients with critical bleeding and coagulopathy, this form of confounding by indication may lead to type II errors, potentially denying patients life-saving interventions.

This study is limited in being a secondary analysis, which risk identifying between-group differences even if none exists. The effect of survival bias, prominent in most observational studies examining ratios of blood components, was reduced through restriction of the population, but may not have been eliminated [32]. While we adjusted for variables potentially associated with the outcome, the possibility of unknown confounders remains. The population included had a low proportion of patients with penetrating trauma, and the results may be different among other populations. Furthermore, the management of critical bleeding is a rapidly evolving frontier and innovative solutions such as whole blood transfusion and novel oxygen carriers such as OMX may be superior options to plasma or other component transfusions [33, 34].

Conclusions

Transfusion of high ratios of plasma to red cells continues to demonstrate beneficial outcomes in the setting of critical bleeding after trauma. Despite new interventions being available, based on current evidence, plasma should be considered an essential therapy for the management of patients in haemorrhagic shock due to trauma. The provision of plasma to prehospital and forward settings appears indicated and requires ongoing implementation and evaluation.

Abbreviations

AIS	Abbreviated injury scale
aOR	adjusted odds ratio
CI	Confidence interval
GCS	Glasgow coma scale
INR	International normalized ratio
IQR	Interquartile range
ISS	Injury severity score
SBP	Systolic blood pressure
SD	Standard deviation
VIF	Variance inflation factors

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13049-025-01476-2.

Supplementary Material 1

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Author contributions
BM: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing; MCR: Conceptualization, Funding acquisition, Writing – review & editing; SB: Funding acquisition, Writing – review & editing; BD: Writing – review & editing; MM: Funding acquisition, Writing – review & editing; RLG: Funding acquisition, Methodology, Supervision, Writing – review & editing.

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Data availability
The data for this manuscript can be made available on reasonable request from the authors. The data will be published in a public repository after all secondary analyses are complete.

Declarations

Ethics approval and consent to participate
The PATCH-Trauma trial was approved by The Alfred Hospital Research and Ethics Committee project ID HREC/13/Alfred/9 (Local Reference: Project 214/13). The study is also approved in other Australian states and their respective ethics committees. Specifically, New South Wales (2019/ETH00262), Queensland (HREC/14/QRBW/501), South Australia (490.14-HREC/15/SAC/14), Tasmania (Project ID 14471), Northern Territory (Reference ID 2016–1683). In New Zealand, Northern A Health and Disability Ethics Committee provided approval with project reference 14/NTA/123/AM11. In Germany, Witten/Herdecke University has provided ethics approval, project reference F-48/2020.

Consent for publication
All authors are in agreement with the submitted version.

Competing interests
The authors declare no competing interests.

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