Pre-hospital transfusion of red blood cells. Part 2: A systematic review of treatment effects on outcomes

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Summary
The primary aim of this systematic review is to describe the effects of prehospital transfusion of red blood cells (PHTRBC) on patient outcomes. Damage control resuscitation attempts to prevent death through haemorrhage in trauma patients. In this context, transfusion of red blood cells is increasingly used by emergency medical services (EMS). However, evidence on the effects on outcomes is scarce. PubMed and Web of Science were searched through January 2019; 55 articles were included. No randomised controlled studies were identified. While several observational studies suggest an increased survival after PHTRBC, consistent evidence for beneficial effects of PHTRBC on survival was not found. PHTRBC appears to improve haemodynamic parameters, but there is no evidence that shock on arrival to hospital is averted, nor of an association with trauma induced coagulopathy or with length of stay in hospitals or intensive care units. In conclusion, PHTRBC is increasingly used by EMS, but there is no strong evidence for effects of PHTRBC on mortality. Further research with study designs that allow causal inferences is required for more conclusive evidence. The combination of PHTRBC with plasma, as well as the use of individualised transfusion criteria, may potentially show more benefits and should be thoroughly investigated in the future. The review was registered at Prospero (CRD42018084658).

KEYWORDS
damage control resuscitation, emergency medical service, major haemorrhage, mortality, outcome, prehospital transfusion, red blood cells

1 INTRODUCTION

Haemorrhage is a potentially preventable cause of death after major trauma.1-3 Topical treatment is not always sufficient to control haemorrhage, since it is often non-compressible.3-5 The lethal triad of acidosis, hypothermia and coagulopathy is related to haemorrhagic shock, especially when blood loss is treated with liberal crystalloid fluid replacement.6 In damage control resuscitation (DCR), blood products are preferred over crystalloids as fluid replacement, while a degree of hypotension is accepted until haemorrhage control has been achieved.6-11

Through transfusion of red blood cells (RBC), the infusion of large volumes of crystalloids may be avoided, as RBC provide a more effective volume expansion. Haemostasis and thrombosis are promoted12 and oxygen carrying capacity restored.13

In an effort to decrease mortality through haemorrhage after major trauma, prehospital transfusion of red blood cells (PHTRBC) is increasingly performed. Military medical teams have been transfusing blood products...
prior to arrival at a surgical unit for years.14,15 This may partially explain survival differences between civilian casualties who require massive transfusion (60%) and military casualties (93%).16 More recently, civilian emergency medical services (EMS) have also started to carry blood to the scene and transfuse their patients in the prehospital setting.17,18

In part 1 of this series, we described the availability and frequency of PHTRBC around the world, and demonstrated that varying transfusion criteria are being used.19 However, to date, little is known concerning the effects on patient outcomes. We have therefore conducted a systematic review with the aim to evaluate the effect of PHTRBC in patients treated by EMS on multiple outcomes including mortality, haemodynamic parameters, and the need for further in-hospital transfusions.

2 | METHODS

The review was registered at Prospero (website: https://www.crd.york.ac.uk/prospero, identification number: CRD42018084658). This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.20

2.1 | Information sources, search strategy and study selection

PubMed and Web of Science were searched through January 2019. The search strategy and the process of selection of studies were described previously.19 For the purpose of this systematic review, only the manuscripts reporting outcome measures after PHTRBC (data on the haemodynamic state, coagulopathy, 24 hours RBC transfusion requirement, length of stay in hospital/intensive care unit [ICU], mortality, or occurrence of complications) were included. For a comprehensive overview of studies reporting outcomes after PHTRBC, controlled studies as well as observational studies were considered for this systematic review.

2.2 | Data extraction

A standardised data extraction sheet was developed, and after testing this on the first 20 articles, it was refined. The setting and type of transport the EMS used (civilian or military, scene or interfacility) and patient characteristics were extracted. Data regarding the effects of prehospital transfusion were collected, including haemodynamic data, coagulopathy, 24 hours RBC transfusion requirement, length of stay in hospital/ICU, mortality and occurrence of complications. Descriptions of problems that arose during PHTRBC are summarised in the text.

Bias was assessed using the Newcastle-Ottawa Scale.21

2.3 | Data synthesis

A priori, we had planned a random-effects meta-analysis of the available evidence. However, no controlled studies were identified, and the observational studies carry a risk of residual confounding even if matching or regression-based techniques were used to control for confounding. Moreover, a high heterogeneity among the studies precluded meaningful pooling of data: Civilian and military studies are not comparable due to fundamental differences in patients, mechanisms of injury and medical facilities. Also within these two groups, differences between patient populations and patient selection, differences between healthcare systems and EMS systems (eg, logistics, staff, equipment, treatment options, response and transport times to definitive care), differences in the type of blood products used (RBC only or a combination of blood products), differences in transfusion criteria, as well as differences in outcome measures are too great to allow a meaningful combined analysis. A meta-analysis was therefore not performed.

3 | RESULTS

3.1 | Selection of articles

The search in PubMed and Web of Science yielded 2172 hits after removal of duplicates. In our scoping review, 71 articles were included.19 In total, 55 of these studies reported one or more outcome measure, and were included in this review (Figure 1).

Forty-one of these studies discussed PHTRBC in civilian medical services, 14 of which allowed comparisons of PHTRBC with a control population. Notably, four articles primarily dealt with a different study topic, but were included as they additionally provided valuable information regarding PHTRBC22-25 (Table 1).

WHAT IS KNOWN ABOUT THE TOPIC

- Prehospital transfusion of red blood cells is increasingly used in the setting of damage control resuscitation, and transfusion criteria vary widely.
- Transfusion of red blood cells is common practice in hospitals to save exsanguinating patients. In this setting, red blood cells are often transfused along with other blood products such as plasma.

WHAT IS NEW

- Literature does not show consistent evidence for beneficial effects of PHTRBC on mortality, shock on arrival to hospital, trauma induced coagulopathy, length of stay in hospitals or intensive care units.

WHAT ARE THE FUTURE KEY QUESTIONS FOR FUTURE WORK ON THE TOPIC

- Can individualised transfusion criteria provide additional benefit?
- Can the combination of PHTRBC with other blood products, such as plasma, reduce mortality in severely bleeding patients in the prehospital setting?
We included 14 articles discussing PHTRBC in military medical services, of which four studies had a control population. Four articles reported prehospital transfusion as an additional topic, while primarily discussing another aspect of their study70,71,74,76 (Table 1).

No randomised trials were identified; all studies were observational. The potential overlap of patients in different manuscripts was substantial (Tables 2 and 3). The bias assessment of the studies is shown in Table 4.

### 3.2 Patient characteristics

In total, 47 civilian studies reported on trauma patients. Blunt injury was most prevalent in the included studies, ranging from 55% to 100% of trauma patients.18,22,24-31,33,35,36,38,41-43,49,52-55,57,58,61 The mean or median injury severity score (ISS) varied from 18 to 43 (Table 1).18,22-31,33,35,37,41-44,49,53,54,57 The most frequent mechanisms of injury were motor vehicle collisions (42%-88%)30,33,35,38,41-44,49,54,61 and falls from a height (3.4%-13%).30,33,35,38,49,54,61

In military services, penetrating injuries were reported by 68% to 100% of studies62,64,65,67-69,71-76 and the mean or median ISS varied from 15 to 45 (Table 1).62,64,65,68,70-72 The most frequently reported mechanisms of injury were explosions (1%-87%)62,64,65,67-69,71-74,76 and gunshot wounds (13%-100%).64-69,71-73,76

Data on non-trauma patients were reported in 16 civilian studies and made up 3% to 100% of these study cohorts.32,40,43,51,54-56,59,61 Suspected gastro-intestinal bleeding or ruptured aortic aneurysm were the most often reported non-traumatic diagnoses in transfused patients. Only one article reported on non-trauma patients attended to by military services; the two patients were transferred between facilities and suffered from obstetric haemorrhage or respiratory disease, they accounted for 2% of transfused patients.69

### 3.3 Outcome—Mortality

#### 3.3.1 Civilian

Unadjusted data from one study suggested that less PHTRBC patients died compared with non-receivers,37 while another unadjusted study found no difference.32

In propensity score-matched trauma patients, Brown et al28,29 found a significant advantage of PHTRBC on either 24 hours or...
| First author (y) | Region | Study period | Primary goal | Study group | Control group | Control for confounding | patients transfused (n) | Type of transport (% trauma) | Mechanism of injury | ISS |
|------------------|--------|--------------|--------------|-------------|---------------|-------------------------|-----------------------|---------------------------|--------------------------|-----|
| **Civilian services** | | | | | | | | | | |
| Henriksen H (2016) | Texas USA | 2012-2013 | To investigate the association between PHTRBC and PHT-plasma and hemostatic function | Receivers of PHTRBC and/or PHT-plasma | Receivers of in-hospital transfusion | Adjusted data | 75 | Scene (100%) | PHTR: Blunt: 55% Penetrating: 45% Control: Blunt: 75% Penetrating: 25% P = .002 | PHT: 29 (17-41) Control: 26 (17-34) P = .106 |
| Holcomb J (2017) | USA (9 trauma centers) | 2015 | To study the effect of PHTRBC and/or PHT-plasma on in-hospital mortality | Severe injured recipients of PHTRBC and/or plasma | No prehospital blood products | Propensity score | 142 | Scene (100%) | PHTR: Blunt: 79.1% Penetrating: 20.9% Matched control: Blunt: 72.7% Penetrating: 27.3% | PHT: 24 (10-34) Control: 22 (10-34) |
| **Retrospective comparative studies** | | | | | | | | | | |
| Brown JB-a (2015) | USA (9 institutions) | 2003-2010 | To characterise the association of pre-trauma center RBC with mortality and TIC in severely injured patients with blunt trauma | Receivers of pre-trauma center RBC | No prehospital transfusion | Propensity score | 50 | Scene + interfacility (100%) | Blunt: 100% Penetrating: 0% (per exclusion) | PHTRBC: 34 (18-43) Control: 30 (23-43) P = .81 |
| Brown JB-b (2015) | Pennsylvania USA | 2007-2012 | To evaluate the association of pre-trauma center RBC with outcomes | Receivers of pre-trauma center RBC | No prehospital transfusion | Propensity score | 240 matched (71 scene) | Scene + interfacility (100%) | PHTRBC: 18 (10-29) Matched Control: 17 (9-27) P = .05 | PHTRBC: 24 (12-29) Control: 22 (11-33) P = .998 |
| Griggs JE (2018) | Kent Surrey & Sussex UK | 2010-2015 | To compare mortality for patients with suspected traumatic haemorrhage receiving PHTRBC compared to crystalloid | Code-Red patients receiving PHTRBC | Code-Red patients receiving crystalloids | Adjusted data | 92 | Scene (100%) | PHTRBC: Blunt: 95% Penetrating: 5% Matched Control: Blunt: 99% Penetrating: 1% MVC: 58% Fall: 9% | Mean (SD) PHTRBC:32 (12) Matched Control: 21 (14) P = .67 |
| Holcomb JB-b (2015) | Texas USA | 2011-2013 | To evaluate effect of PHTRBC and/or PHT-plasma on survival and blood product use | Receivers of PHTRBC and/or PHT-plasma | Receivers of in-hospital transfusion | Adjusted data | 132 | Scene (100%) | PHTR: Blunt: 77% Penetrating: 23% Control: Blunt 83% Penetrating 17% P = .447 | PHTRBC: 22 (12-29) Control: 22 (11-33) P = .998 |
| Kim BD (2012) | Minnesota USA | 2009-2011 | To analyse the effect of PHT-plasma on coagulopathy | Receivers of PHT-plasma + PHTRBC | Receivers of PHTRBC only | no | 59 (of whom 50 RBC only) | Scene + interfacility (100%) | Plasma: Blunt: 67% Penetrating: 33% PHT: 82% P = .317 | Plasma: 27 PHTRBC: 23 P = .918 |
| Miller B (2016) | Tennessee USA | 2007-2013 | To examine the impact of PHTRBC on mortality | Receivers of PHTRBC | No prehospital transfusion | Propensity score | 231 (195 matched) | Scene (100%) | PHTRBC: Blunt: 78% Penetrating: 22% Matched control: Blunt: 90% Penetrating: 10% P < .001 | PHTRBC: 34 (22-43) Matched control: 32 (22-43) P = .903 |
| Parker ME (2017) | Minnesota USA | 2010-2014 | To examine PHT of plasma and/or RBC on outcomes in exsanguinating GI bleeding | Receivers of PHTRBC and/or PHT-plasma | No | No | 112 | Interfacility (0%) | n/a | n/a |
| Peters J (2017) | Nijmegen Rotterdam The Netherlands | 2007-2015 | To establish the efficacy and safety of the PHTRBC by HEMS | Receivers of PHTRBC | Receivers of crystalloids only | Matched | 73 (50 matched) | Scene (100%) | PHTRBC: Blunt 9.3% Penetrating: 7% MVC 70% Fall from height 10% Matched control: Blunt: 94% Penetrating: 6% MVC 68% Fall from height 12% | PHTRBC: 34 (9-75) Control: 35 (18-75) P = .242 |

(Continues)
| First author (y) | Region | Study period | Primary goal | Study group | Control group | Control for confounding | patients transfused (n) | Type of transport (% trauma) | Mechanism of injury | ISS |
|------------------|--------|--------------|--------------|-------------|---------------|-------------------------|-----------------------|---------------------------|-----------------|-----|
| Price DD (1999)  | Oregon USA | 1989-1995 | To evaluate the efficacy of early blood transfusion | Receivers of PHTRBC during air transport | Receivers of cryoprecipitate in ground transport | Matched | 84 | n/d (100%) | PHTTRBC: Blunt 64.8% Penetrating: 35.2% MVC: 42.6% Falls: 11.7% | 27 (19-41) |
| Rehn M (2018)    | London UK | 2009-2015 | To investigate the effect of PHTRBC on overall blood product use | “Code Red” patients after implementation of PHTRBC | “Code Red” patients before implementation of PHTRBC | Adjusted data | 128 | Scene (100%) | PHTTRBC: Blunt 68.6% Penetrating: 31.4% MVC: 43.2% Falls: 12.4% Other blunt: 13.9% | 25 (23-43) |
| Rehn M (2019)    | London UK | 2009-2015 | To investigate the effect of PHTRBC on mortality | “Code Red” patients after implementation of PHTRBC | “Code Red” patients before implementation of PHTRBC | Adjusted data | 239 | Scene (100%) | PHTTRBC: Blunt 146 (61%) Penetrating 93 (39%) Control: Blunt 189 (62%) Penetrating: 111 (37%) | n/d |
| Sumida MP (2000) | Tennessee, Connecticut USA | 1995-1996 | To analyse the effect of PHTRBC on physiologic parameters and outcome | Receivers of PHTRBC | Receivers of cryoprecipitate only | no | 17 | Scene+ interfacility (100%) | PHTTRBC: 28 Control: 27.8 P = .957 | 110 |

Prospective not-comparative studies

| Chang R (2018) | USA (9 trauma centers) | 2015 | To describe the phenotype and laboratory coagulation abnormalities of clinically evident coagulopathy bleeding (CC) after trauma | Highest-risk trauma patients, CC+ | CC- | Adjusted data | PHTRBC in CC+ vs CC- (44%) vs 82 (8%) P < .001 | Scene (100%) | Overall: CC+ vs CC-: Blunt: 28 (68%) vs 79 (21%) Penetrating: 12 (30%) vs 16 (41%) Both: 1 (2%) vs 21 (2%) Injury type P = 0.09 | CC+32 (25-41) CC-: 17 (8-27) P < .001 |
| Reed M (2017)  | Scotland | 2013-2015 | To evaluate the prehospital activation of Code Red | Patients for whom a pre-hospital Code Red was activated | None | n/a | 16 | n/d (100%) | Overall: Blunt: 44 (83%) Penetrating: 9 (17%) | 24 (14-37) |
| Sherren PB (2013) | Greater Sydney Area, Australia | n/s (5 y) | To describe PHTRBC | Missions involving PHTRBC | None | n/a | 147 | n/d (100%) | Blunt: 93.9% Penetrating: 6.1% MVC: 79 Fall from height: 3.4% Other: 11.6% | RTS: 5.967 (4.083-6.904) |
| Weaver AE (2012) | London UK | 2012 | To examine the impact of on-scene PHTRBC for seriously injured patients | Receivers of PHTRBC | None | n/a | 50 | Scene (100%) | n/d | n/d |

Retrospective not-comparative studies

| Berns KS (1998) | Minnesota USA | 1993-1996 | To document the development of protocols for and to review the experience with PHTRBC | Receivers of PHTRBC | None | n/a | 94 | Scene+ interfacility (48%) | n/d | n/d |
| Bodnar D-b (2014) | Greater Brisbane Australia | 2011-2012 | To describe the characteristics, clinical interventions and the outcomes of PHTRBC patients | Receivers of PHTRBC | None | n/a | 71 | Scene (100%) | Blunt: 73.2% Penetrating: 26.8% MVC: 6.7% | Mean (SD) 32.1 (15.2) |
| Dalton AM (1993) | Oregon, Washington USA | 1985-1992 | To show that PHTRBC is safe and practical | Receivers of PHTRBC with MAST | Receivers of PHTRBC without MAST | n/a | 112 | n/d (100%) | Overall: Blunt: 86% Penetrating: 14% MVC: 72% | Mean: MAST: 33 non-MAST: 31 |
| Fahy AS (2017) | Minnesota USA | 2002-2014 | To report our experience with a prehospital transfusion protocol in pediatric patients | Pediatric trauma patients receiving PHTRBC and/or plasma | Pediatric non-trauma patients receiving PHTRBC and/or plasma | n/a | 28 | Scene+ interfacility (57%) | Blunt: 88% Penetrating: 12% MVC: 63% Gunshot wounds: 13% | 24 (range 9-66) |

(Continues)
**TABLE 1 (Continued)**

| First author (y) | Region | Study period | Primary goal | Study group | Control group | Control for confounding | patients transfused (n)* | Type of transport (% trauma) | Mechanism of injury | ISS |
|-------------------|--------|--------------|--------------|-------------|--------------|------------------------|------------------------|---------------------------|-------------------|-----|
| Heschl S (2018)   | Victoria Australia | 2011-2015 | To describe the characteristics of PHTRBC | All cases where approval for PHTRBC was sought by paramedics | None | n/a | 142 | Scene (9.6%) | Blunt/penetrating: n/d, MVC: 8.8%, Crush/fall/other: 11.8% | 36.5 (15.8) |
| Higgins GL (2012) | Maine USA | 2007-2008 | To describe PHTRBC with respect to safety and efficacy and improvement in condition | Receivers of PHTRBC | None | n/a | 45 | scene+ interfacility (71%) | n/d | n/d |
| Hooper N (2017)   | Southwest UK | 2015-2016 | To describe experience with PHTRBC | Receivers of PHTRBC | None | n/a | 62 | n/d (84%) | n/d | n/d |
| Knoak C (2018)    | Western Canada | 2013-2017 | To describe the implementation and stewardship of a prehospital blood transfusion program | Receivers of PHTRBC | None | n/a | 274 | scene+ interfacility (74%) | n/d | n/d |
| Krugh D (1994)    | Ohio USA | 1991-1993 | To describe and review the implementation of an off-site blood product storage program | Receivers of PHTRBC | None | n/a | 8 | n/d (50%) | n/d | n/d |
| Lyon R (2017)     | Kent Surrey & Sussex UK | 2013-2014 | To describe the characteristics of receivers of PHTRBC and evaluate their subsequent in-hospital needs | Receivers of PHTRBC | None | n/a | 147 | scene (97%) | Blunt: 128 (87%) Penetrating: 14 (10%) MVC: 103 (73%) Fall from height: 17 (11.6%) | 33 (SD 13.4) |
| Maher P (2017)    | Washington, USA | 2015 | To describe the development of a HEMS transfusion program | Receivers of PHTRBC or plasma | None | n/a | RBC 13 FFP 3 | scene+ interfacility (85%) | n/d | n/d |
| Mena-Munoz J (2016) | Pennsylvania Ohio Maryland USA | 2003-2012 | To characterise receivers of out of hospital transfusion of blood products (mostly RBC and/or plasma) during critical care transport | Receivers of out of hospital blood products | None | n/a | 1440b | Scene + interfacility (19%) | n/d | n/d |
| Mix FM (2018)     | Minnesota, USA | 2011-2015 | To determine whether opportunities for blood product administration by ground ALS ambulances exist | Adult trauma patients with potential need for prehospital blood administration | None | n/a | 28 | Scene (100%) | Blunt: 26 (9.3%) Penetrating: 2 (7%) | n/d |
| Potter D (2019)   | Minnesota USA | 2003-2012 | To summarize our initial experience with PHTRBC and PHT-plasma in pediatric trauma patients | Receivers (<18 y) of PHTRBC and/or PHT-plasma | None | n/a | 16b | scene + interfacility (100%) | Blunt: 87.5% Penetrating: 12.5% | Mean 30 (range 9-66) |
| Raitt IE (2018)   | Thames Valley UK | 2014-2016 | To review the appropriateness of PHTRBC and to identify outcomes | Receivers of PHTRBC | None | n/a | n/a | Scene (9.5%) | Blunt: 53 (9.4%) Penetrating: 7 (11%) MVC 42 (6.7%) Fall 8 (13%) | ISS 34 (21-43) |
| Sunde GA (2015)   | Bergen Norway | 2014 | To describe our preliminary results after implementing PHTRBC and PHT-plasma | Receivers of PHTRBC and/or PHT-plasma | None | n/a | 4a | scene (7.5%) | Blunt: 67% Penetrating: 33% | n/d |

(Continues)
| First author(s) | Region | Study period | Primary goal | Study group | Control group | Control for confounding | patients transfused (n) | Type of transport (% trauma) | Mechanism of injury | ISS |
|----------------|--------|--------------|--------------|-------------|---------------|------------------------|-----------------------|---------------------------|---------------------|-----|
| Thiels CA (2016) | Minnesota USA | 2002-2014 | To report our experience with prehospital blood product transfusion | Non-trauma patients receiving PHTRBC and/or plasma | Trauma patients receiving PHTRBC and/or plasma | no | PHTRBC 654 | Scene + interfacility (36%) | n/d | n/d |
| Wheeler R (2012) | New England USA | 2005-2009 | To determine factors associated with hypothermia | Trauma patients transported by HEMS, hypothermic on arrival | Non-hypothermic trauma patients, transported by HEMS | n/a | 30 | Scene (100%) | n/d | (Mean ± SD): Hypothermic: 26.07 ± 11.86 Non-hypoth: 15.33 ± 11.39 |
| Garner AA (1999) | Sydney Australia | 1997 | Case report | n/a | 1b | Scene (100%) | Blunt: 100% | 43 (n = 1) |
| Lawton LD (2012) | Queensland Australia | n/s | Case report | n/a | 1b | Scene (100%) | Blunt: 100% | n/d |
| Macnab AJ (1996) | British Columbia Canada | 1996 | Case report | n/a | 1 | Interfacility (0%) | n/a | n/a |
| Trembley AL (2016) | Minnesota Wisconsin USA | 2016 | Description of implementation of protocol | n/a | n/a | n/a | n/d | Scene + interfacility (n/d) | n/d |
| Vartanian, L (2017) | Texas, USA | 2016 | Description of implementation of protocol | Receivers of PHTRBC and/or plasma | None | n/a | 12 | n/d (67%) | Blunt: 7 (67%) Penetrating: 1 (12%) MVC: 5 (62%) Fall: 1 (8%) | n/d |

**Military services**

| Propective comparative studies | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Vitalis V (2017) | French armed forces Sahel | 2016-2017 | To evaluate the practices of battlefield transfusion (RBC, plasma, FWB) | Severely injured receivers of PHT-RBC or plasma or FWB | No battlefield transfusion | No | 7b (4 of whom RBC) | POI + Role 1 | Overall: Blunt: 1 (4%) Penetrating: 27 (96%) Explosion: 16 (57%) Active external haemorrhage: 12 (43%) |

| Retrospective comparative studies | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Howard, JT (2017) | US military Afghanistan | 2001-2014 | To evaluate potential influences on KIA mortality | Casualties who needed and received PHT | Casualties who needed but did not receive PHT | Adjusted data | 75c | Prehospital helicopter transport to FST or CSH | Overall: Explosion: 65.1% Gunshot: 22.5% Blunt or other: 11.4% | n/d |
| O'Reilly DJ-b (2014) | UK MERT-E Afghanistan | 2006-2011 | To evaluate the effect of PHTRBC/PHT-plasma on mortality | Receivers of PHTRBC and PHT-plasma | Matched patients where no PHT available | Propensity score | 97b | POI + Role 1 | PHT: Blunt: 1% Penetrating: 99% Burn: 0% Explosive: 51.5% Gunshot wound: 47.4% Matched control: Blunt: 3.1% Penetrating: 96.9% Burn: 0% Explosive: 49.5% Gunshot wound: 47.4% | PHT: 16 (9-25) Control: 16 (9-24.5) P = .686 |
| Shackelford S (2017) | UK MERT, US Air Force Pedro, US DUSTOFF, Afghanistan | 2012-2015 | To examine the association of PHTRBC and/or PHT-plasma and time to initial transfusion with injury survival | Receivers of PHTRBC and/or PHT-plasma | no PHT | frequency matched | 55b | POI to role 2 or 3 | PHT: Explosives 8.4% Gunshot wound 16% ≥1 Amputation: 73% Hemorrhagic torso injury: 56% Control: Explosives: 71% Gunshot wound: 29% P = .05 ≥1 Amputation: 27% P < .001 Hemorrhagic torso injury: 35% P = .004 | PHT: 29 (17-36) Control: 28.6 (24.0-33.2) P = .88 |
| First author (y) | Region | Study period | Primary goal | Study group | Control group | Control for confounding patients transfused (n) | Type of transport (% trauma) | Mechanism of injury | ISS |
|------------------|--------|--------------|--------------|-------------|---------------|-----------------------------------------------|-----------------------------|-------------------|-----|
| Aye Maung N (2015) | UK army, Afghanistan | 2012-2014 | To explore the utility and feasibility of forward transfusion of RBC | Missions where blood components were carried | None | n/a | 2 | POI + Role 1 | 100% (n = 2) | n/d |
| Malby RF (2013) | US Army, Afghanistan | 2012 | Process improvement initiative of blood product transfusion on Urgent helicopter evacuation casualties | Receivers of PHTRBC and/or PHT-plasma | None | n/a | 15 | POI + Role 1 | 87% Gunshot wound: 13% | n/d |
| Barkana Y (1999) | Israel Defense Force Medical Corps, Israel | 1994-1996 | To characterise the different aspects of PHTRBC and to evaluate its potential effect on the morbidity and mortality | Receivers of PHTRBC | None | n/a | 40 | POI + Role 1 | Blunt: 22.5% Penetrating: 77.5% Explosion: 47.5% Gunshot wounds: 22.5% Explosion + gunshot wounds: 7.5% MVC: 20% Fall from height: 2.5% | 18 (11.5-25) |
| Chen J (2017) | Israeli Air Force, Israel | 2003-2010 | To describe PHTRBC, and to evaluate adherence to clinical practice guidelines | Receivers of PHTRBC | None | n/a | 89 | Scene+ interfacility | Blunt: 69% Non-combat: 31% Gunshot wounds: 26% Explosions: 24% Stab wound: 4% Plane crash: 2% Fall from height: 2% | n/d |
| Edgar IA (2014) | US and UK military, Afghanistan | 2011 | To compare initial management and early outcomes in patients suffering bilateral lower limb amputations and differences related to the type of aeromedical evacuation assets | Surviving adult male patients with bilateral traumatic lower limb amputations transferred by MERT in a CH-47 Chinook helicopter | Vs those evacuated by PEDRO in an HH-60 Pavehawk helicopter. | n/a | n/d | POI to Role 3 | Only patients with bilateral lower limb amputations | NISS MERT: 27 (range 19-41) PEDRO: 27 (range 22-59) P = 1 |
| Morrison JL (2013) | US and UK military Afghanistan | 2008-2011 | To characterise and compare mortality among casualties evacuated with conventional military retrieval (CMR) to those evacuated with an advanced medical retrieval (AMR) capability | Casualties evacuated from POI by an AMR capability | Vs those evacuated by a med-led CMR capability | n/a | 16 | POI to role 3 | AMR: Blast: 70.4% Gunshot: 24.3% Other: 5.3% CMR: Blast: 60.8% P < .001 Gunshot: 34.9% Other: 4.3% Mean (SD): AMR: 16 (17) CMR: 15 (16) P = .122 |
| O'Reilly DJ-a (2014) | UK MERT-E Afghanistan | 2008-2011 | To present the initial experience of military PHTRBC and PHT-plasma | Receivers of PHTRBC and/or PHT-plasma | None | n/a | 31 | POI to role 2 or 3 | Blunt: 1.0% Penetrating: 99% Burn: 0.3% Explosive: 72.9% Gunshot wound: 25.8% | 20 (16-29) |
| Powell-Dunford N (2014) | US Army, Afghanistan | 2012 | To enumerate the specific risks and risk management strategies of en route transfusion | Receivers of PHTRBC and/or PHT-plasma | None | n/a | 63 (54 of whom RBC) | n/d | Explosion: 74% Gunshot wound: 26% | n/d |
| Shlaifer A (2017) | Israeli Defense Forces, Israel | 2013-2016 | To describe feasibility, safety, adverse reactions, and adherence to clinical practice guidelines in PHT-plasma | Receivers of PHT-plasma. Among them 9 receivers of PHTRBC | None | n/a | 9 | POI + Role 1 | Penetrating: 68.5% Blunt: 15.2% Burn: 1.1% Blast: 1.1% Combination: 14.1% | ISS 1-8: 10.9% ISS 9-14: 20.7% ISS 16-24: 28.3% ISS 25-40: 40.1% |

(Continues)
30 day mortality in two different studies, with 50 and 240 transfused patients, respectively. Rehn et al. found a lower prehospital mortality in trauma patients transported from the scene. After adjustment, Holcomb et al. found lower odds of mortality in critical trauma patients who received PHTRBC and/or plasma at 6 hours. However, in six other studies reporting matched or adjusted data, no significant effect on mortality was found, either at 3 hours, 24 hours, 28 days, or 30 days post-infusion, for in-hospital mortality or overall mortality (Table 5). Conversely, Kim et al. found significantly lower mortality at 24 hours and a lower mortality overall for patients transfused with both PHT-plasma and PHTRBC compared with patients receiving PHTRBC only. These studies varied in patient and injury characteristics, type of transport (from scene/inter-facility), type of blood products used (RBC only or a combination of blood products), transfusion criteria as well as outcome measures, and therefore, data could not be meaningfully combined in a meta-analysis.

### 3.3.2 Military

In military services, almost all studies included patients who possibly received other prehospital blood products besides RBC. Two retrospective studies compared trauma PHT recipients to non-receivers, and found significantly lower mortality in PHT patients (either overall, 24 hours or 30-day mortality) (Table 5). One of these studies subsequently focused on those patients who survived the first 24 hours; the beneficial effect on 30-day mortality was no longer present. This concurs with a large retrospective study (with a partially overlapping study population), where the odds for “killed in action” (KIA) mortality (death before arrival at treatment facility) was 83% lower for casualties who needed and received prehospital transfusion, compared with patients who needed but did not receive a prehospital transfusion.

### 3.4 Outcome—Shock after transfusion

#### 3.4.1 Civilian

Six observational studies compared vital parameters or POCT results before and after transfusion. Five of these noted significant beneficial effects of PHTRBC (decrease in heart rate [HR] and shock index [SI]; rise in systolic, diastolic, or mean arterial blood pressures; less hypotensive episodes (ie, SBP < 90 mmHg) or less “haemodynamic instability” (Table 5). Studies comparing vital parameters in PHTRBC patients vs non-receivers report conflicting results: significantly lower occurrence of hypotension, a higher DBP, and a higher BE and pH have been reported in PHTRBC patients, but in contrast, significantly lower SBP and a lower pH have also been found. Other studies found no significant differences in either SBP, HR, DBP, pH, BE, lactate, change in mean BP or HR or occurrence of “shock on admission.” Compared PHTRBC with PHTRBC + PHT-plasma and found no significant
| Country       | Region               | First author (y)                                      | Comments                                           |
|--------------|----------------------|-----------------------------------------------------|----------------------------------------------------|
| Australia    | (Greater) Brisbane   | Bodnar D-b (2014)                                    |                                                   |
|              |                      | Lawton LD (2013)                                     | Case report                                       |
|              | (Greater) Sydney     | Garner AA (1999)                                     | Case report                                       |
|              |                      | Sherren PB (2019)                                    | Exact period not specified                        |
|              | Victoria             | Heschl S (2018)                                     |                                                   |
| Canada       | Br. Columbia         | Macnab AJ (1996)                                     | Case report                                       |
|              | W. Canada            | Krook C (2018)                                      | Shock Trauma Air Rescue Society (STARS)           |
| NL           | Nijmegen, R'dam      | Peters J (2017)                                     |                                                   |
| Norway       | Bergen               | Sunde GA (2015)                                     |                                                   |
| UK           | Kent, Surrey & Sussex| Griggs JE (2018)                                    |                                                   |
|              |                      | Lyon R (2017)                                        |                                                   |
|              | London               | Rehn M (2018)                                        |                                                   |
|              |                      | Rehn M (2019)                                        |                                                   |
|              |                      | Weaver AE (2012)                                     |                                                   |
| Scotland     | Reed M (2017)        |                                                   |                                                   |
| South West   | Hooper N (2017)      |                                                   |                                                   |
| Thames Valley| Raitt JE (2018)      |                                                   |                                                   |
| USA          | Alabama              | Chang R (2018)                                       | 9 trauma centers                                  |
|              |                      | Holcomb J (2017)                                     | 9 trauma centers                                  |
|              | Arizona              | Chang R (2018)                                       | 9 trauma centers                                  |
|              |                      | Holcomb J (2017)                                     | 9 trauma centers                                  |
|              | California           | Brown JB-a (2015)                                    | 9 institutions                                    |
|              |                      | Chang R (2018)                                       | 9 trauma centers                                  |
|              |                      | Holcomb J (2017)                                     | 9 trauma centers                                  |
|              | Connecticut          | Sumida MP (2000)                                     |                                                   |
|              | Illinois             | Brown JB-a (2015)                                    | 9 institutions                                    |
|              | Maryland             | Chang R (2018)                                       | 9 trauma centers                                  |
|              |                      | Holcomb J (2017)                                     | 9 trauma centers                                  |
|              |                      | Mena-Munoz J (2016)                                  |                                                   |
|              |                      | Berns KS (1998)                                      | Mayo HEMS                                         |
|              |                      | Brown JB-a (2015)                                    | 9 institutions; Trauma only                       |
|              |                      | Chang R (2018)                                       | 9 trauma centers                                  |

(Continues)
| Country   | Region       | First author (y)       | Comments                                                                 |
|-----------|--------------|------------------------|---------------------------------------------------------------------------|
| Minnesota |             | Fahy AS (2017)          | Mayo One, Mayo Pediatric/Neonatal Transport: Pediatric patients only      |
|           |             | Holcomb J (2017)        | 9 trauma centers                                                          |
|           |             | Kim BD (2012)           | Mayo HEMS; Trauma only                                                    |
|           |             | Mix FM (2018)           | Mayo HEMS and ground EMS; Trauma only                                     |
|           |             | Parker ME (2017)        | Mayo HEMS; GI bleed only                                                  |
|           |             | Potter D (2015)         | Mayo HEMS; Pediatric patients only                                        |
|           |             | Thiel CA (2016)         | Mayo HEMS                                                                 |
|           |             | Trembley AL (2016)      | North Memorial Air Care: Description of protocol                           |
| New England|             | Brown JB-a (2015)       | 9 institutions                                                            |
|           |             | Higgins GL (2012)       |                                                                           |
|           |             | Wheeler R (2013)        |                                                                           |
|           |             | Chang R (2018)          | 9 trauma centers                                                          |
|           |             | Holcomb J (2017)        | 9 trauma centers                                                          |
| Ohio      |             | Knigh D (1994)          |                                                                           |
|           |             | Mena-Munoz J (2016)     |                                                                           |
| Oregon    |             | Chang R (2018)          | 9 trauma centers                                                          |
|           |             | Dalton AM (1993)        |                                                                           |
|           |             | Holcomb J (2017)        | 9 trauma centers                                                          |
|           |             | Price DD (1999)         |                                                                           |
| Pennsylvania |         | Brown JB-a (2015)       | 9 institutions                                                            |
|           |             | Brown JB-b (2015)       | STAT MedEvac                                                               |
|           |             | Mena-Munoz J (2016)     |                                                                           |
| Tennessee |             | Miller B (2016)         |                                                                           |
|           |             | Sumida MP (2000)        |                                                                           |
|           |             | Brown JB-a (2015)       | 9 institutions                                                            |
|           |             | Chang R (2018)          | 9 trauma centers                                                          |

(Continues)
differences in SBP, HR, lactate, BE or pH. Brown et al. measured base deficit and lactate levels on arrival to hospital, and used these to calculate the odds of shock. They found that in PHTRBC patients, these odds were significantly lower than in matched control patients (Table 5).

### 3.4.2 Military

In military EMS, three observational studies analysed the change in vital parameters after transfusion, all showing improvements (significant rise in SBP and improvement in SI; fall in HR; or a SBP closer to physiologically normal values as the prehospital transfused volume increased).

Only one study comparing PHTRBC patients to controls found a significant difference reporting a lower HR. No significant differences were found for SBP, pH, BE, or "shock on arrival" (Table 5).

### 3.5 Outcome—24-hour RBC Requirement

#### 3.5.1 Civilian

In the first 24 hours after admission to hospital, civilian patients received a median of 0 to 14 U of RBC, and paediatric patients received a mean of 3.6 U. Five analyses found the RBC requirement in-hospital or in the first 24 hours to be significantly higher for PHTRBC patients, whereas five others found it to be significantly lower. One of these studies noted that taking the prehospital transfused volume into account, the cumulative 24 hours RBC requirement was not significantly different. Two other studies found no significant difference in in-hospital or 24 hours RBC requirement in either PHT vs control or in PHTRBC vs PHTRBC+PHT plasma (Table 5).

#### 3.5.2 Military

Median RBC requirement in the first 24 hours after arrival to hospital was 5 to 10 units, one study reporting a median of 15 units of RBC/fresh whole blood in 24 hours. One study focusing on double amputees showed that an increased volume of prehospital transfused blood was significantly associated with a decreased transfusion requirement in the emergency department. However, three comparative studies observed (an almost) significantly higher 24 hours or in-hospital transfusion requirement in PHTRBC patients (Table 5).

### 3.6 Outcome—Signs of trauma-induced coagulopathy (TIC) on arrival to hospital

Three civilian studies compared the international normalised ratio (INR) of patients who received PHTRBC vs patients who did not. One study reported that PHTRBC patients had significantly lower odds of TIC on arrival to hospital, while two other studies did not find an
| Subject                  | First author (y)                  | Comments            | 94 | 95 | 96 | 97 | 98 | 99 | 00 | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|--------------------------|-----------------------------------|---------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| UK-MERT Afghanistan      | Aye Maung N (2015)                |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Edgar IA (2014)                  |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Morrison JJ (2013)               |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | O’Reilly DJ-b (2014)             |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | O’Reilly DJ-a (2014)             |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Shackelford S (2017)             |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| USA Afghanistan          | Edgar IA (2014)                  | Pedro               |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Howard, JT (2017)                | All helicopters     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Malsby RF (2013)                 | Dustoff             |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Morrison JJ (2013)               | Pedro/Dustoff       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Shackelford S (2017)             | Pedro/Dustoff       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Powell-Dunford N (2014)          | Medevac helicopter  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | West BC (2004)                   | Case report         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| France Sahel             | Vitalis V (2017)                 |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Israel                   | Barkana Y (1999)                 |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Chen J (2017)                    |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|                          | Shlaifer A (2017)                |                     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

Abbreviations: MERT, Medical Emergency Response Team; UK, United Kingdom; USA, United States of America.
TABLE 4 Risk of bias assessment, Newcastle-Ottawa Scale

| First author (y) | Selection | Comparability | Outcome |
|------------------|-----------|---------------|---------|
| Civilian services |           |               |         |
| Prospective comparative studies |   |   |         |
| Henriksen H (2016) | ★★★ | ★★ | ★     |
| Holcomb J (2017) | ★★★★★ | ★★ | ★     |
| Retrospective comparative studies |   |   |         |
| Brown JB-a (2015) | ★★★★★ | ★★ | ★     |
| Brown JB-b (2015) | ★★★★★ | ★★ | ★     |
| Griggs JE (2018) | ★★★★★ | ★★ | ★     |
| Holcomb JB-b (2015) | ★★★★★ | ★★ | ★     |
| Kim BD (2012) | ★★★★ | ★ | ★     |
| Miller B (2016) | ★★★★ | ★ | ★     |
| Parker ME (2017) | ★★★★ | ★ | ★     |
| Peters J (2017) | ★★★★ | ★ | ★     |
| Price DD (1999) | ★★★★★ | ★ | ★     |
| Rehn M (2018) | ★★★★★ | ★ | ★     |
| Rehn M (2019) | ★★★★★ | ★ | ★     |
| Sumida MP (2000) | ★★★★ | ★ | ★     |
| Military services |           |               |         |
| Prospective comparative studies |   |   |         |
| Vitalis V (2017) | ★★★★★ | ★ | ★     |
| Retrospective comparative studies |   |   |         |
| Howard, JT (2017) | ★★★ | ★ | ★     |
| O’Reilly DJ-b (2014) | ★★★★★ | ★ | ★     |
| Shackelford S (2017) | ★★★★★ | ★ | ★     |

The high heterogeneity of the studies was a second factor, which impedes the interpretation of the reported data. As we had expected, patients transported by civilian and military services differed considerably with respect to injury type, injury severity and mortality rates. However, also within these groups, heterogeneity in injury type, injury severity, type of transport, transfusion criteria and type of intervention prevented meaningful meta-analysis. Differences between study outcomes might at least in part be explained by these factors.

3.7 | Outcome—Length of stay in ICU/in hospital

Three civilian studies compared length of stay (LOS) in ICU and LOS in hospitals for PHTRBC patients and their matched controls. No significant differences were found.22,32,34

Only one military study describes LOS, finding a median hospital LOS of 30 days for both PHTRBC patients and controls.65

3.8 | Outcome—Safety/adverse events

Most studies on civilian EMS (11) reported no transfusion reactions occurring.30,35,38,40,43-45,47,49,55,60 A lung injury associated with a transfusion was reported,32 and there was one possible adverse reaction in a trauma patient who developed shortness of breath, which was interpreted as secondary to volume overload.42 A case report has described two “near miss” incidents where haemolysis of donor cells occurred during transport, when the units had not been packed correctly.29

Patients transfused before arrival to hospital were more likely to be hypothermic23 and have lower calcium levels,49 but there was no significant difference in the occurrence of acute respiratory distress syndrome (ARDS) in PHTRBC, non-PHTRBC and PHTRBC+PHT-plasma patients.22,29

As in civilian services, seven military studies have reported no adverse reactions to PHTRBC.62,64,66,67,74,75 One possible transfusion reaction is described, in which a patient developed a fine rash on their trunk after one unit of RBC.68 Seven incidents were reported where the blood products were found to have an out-of-standard temperature.66

4 | DISCUSSION

This systematic review summarises the literature regarding the effects of PHTRBC on several outcome measures.

Overall, evidence of an effect of PHTRBC on outcomes is of limited quality. Notably, no controlled studies were identified, and all studies were observational. Therefore, all reported treatment effects must be interpreted with care. Confounding is likely—and residual confounding cannot be excluded in those studies that attempted to control for confounding—such that causal inferences on the effect of PHTRBC on outcomes are essentially not possible.77 Nonetheless, in the absence of controlled trials, these studies represent the best available evidence and may at least provide some insight about possible associations between PHTRBC and outcomes.

The high heterogeneity of the studies was a second factor, which impedes the interpretation of the reported data. As we had expected, patients transported by civilian and military services differed considerably with respect to injury type, injury severity and mortality rates. However, also within these groups, heterogeneity in injury type, injury severity, type of transport, transfusion criteria and type of intervention prevented meaningful meta-analysis. Differences between study outcomes might at least in part be explained by these factors.

4.1 | Mortality

Results on overall mortality are conflicting, and we found no consistent evidence for any effects of PHTRBC on survival. Recently, Rijnhout et al78 published a meta-analysis on the effects of prehospital transfusion on mortality. In line with our results, these authors did not observe an effect of PHTRBC (without simultaneous transfusion of plasma) on mortality. For the 24 hours mortality, an odds ratio of 0.92 was reported, with a broad 95% confidence interval (0.46-1.85) that does not exclude clinically important effects of PHTRBC in either direction, which indicates an inconclusive result.79 Importantly, heterogeneity was high (I² 80%), similar to the heterogeneity that we observed in explorative analyses. While quantitative heterogeneity was lower for long-term survival, qualitative heterogeneity, along with limited quality and a substantial potential for residual confounding in the observational studies, prompted us to question whether it was appropriate to report a pooled effect.
| First author (y) | Mortality (n [%]) | Shock on arrival to hospitala | 24 h RBC requirement (U) | ICU/hospital LOS (d) | TICb | Adverse events |
|------------------|------------------|------------------------------|--------------------------|---------------------|------|----------------|
| **Civilian services** |                  |                              |                          |                     |      |                |
| **Prospective comparative studies** |                  |                              |                          |                     |      |                |
| Henriksen H (2016)26 | PHT vs control 6 h: 10 (13.3%) vs 15 (8.3%) | SBP: 90 (77-113) vs 100 (80-125) | 10 (4-15) vs 4 (2-9) | n/d | rTEG MA: 62 vs 64 P = .02 |
|                  | 24 h: 12 (16%) vs 19 (10.4%) | DBP: 59 (50-69) vs 60 (48-76) | P < .001 | n/d | G-value: 8.1 vs 8.69 P = .009 |
|                  | In-hospital: 20 (26.7%) vs 38 (20.9%) | HR: 111 (90-133) vs 108 (85-130) | n/d | n/d | ACT: 121 vs 121 |
|                  |                              | pH: 7.21 (7.06-7.32) vs 7.27 (7.18-7.33) | n/d | n/d | R-time: 0.8 vs 0.8 K-time: 1.65 |
|                  |                              | BE: 6 (7-10 - 3) vs 4 (10 - 1) | n/d | n/d | vs 1.4 Angle: 70 vs 73 Ly30: 1 vs 1.4 |
|                  |                              | n/d | n/d | n/d | Adjusting for PH-RBC, |
|                  |                              | n/d | n/d | n/d | PHT-plasma associated with |
|                  |                              | n/d | n/d | n/d | increased rTEG MA: 1 U |
|                  |                              | n/d | n/d | n/d | increase in PH-plasma |
|                  |                              | n/d | n/d | n/d | was associated with |
|                  |                              | n/d | n/d | n/d | (β coefficient) |
|                  |                              | n/d | n/d | n/d | 13.95 mm (95% CI 3.13-24.77) |
|                  |                              | n/d | n/d | n/d | P = .012 |
|                  |                              | n/d | n/d | n/d |                  |
|                  |                              | n/d | n/d | n/d |                |
|                  |                              | n/d | n/d | n/d |                |
| **Retrospective comparative studies** |                  |                              |                          |                     |      |                |
| Brown JB-a (2015)28 | PHT vs control, matched 3 h: 4 (9.3%) vs 8 (12.1%) OR 0.74 (95% CI 0.24-2.26) P = .60 | Admission hypotension: 60% vs 74% OR 0.02 (95% CI 0.01-0.69) P = .04 | 14.0 (7.0-21.7) vs 8.3 (3.4-18.5) P = .03 | n/d | INR > 1.5 OR = 0.01 (95% CI 0.01-0.95) P = .05 |
|                  | 24 h: 5 (11.6%) vs 10 (15.2%) OR 0.74 (95% CI 0.25-2.17) P = .58 | BE: 10 (−5-12) vs −9 (−7-12) | n/d | n/d | Scene only: OR = 0.08 (95% CI 0.01-1.35) P = .079 |
|                  | 30d: 8 (18.6%) vs 14 (21.2%) OR 0.85 (95% CI 0.32-2.28) P = .75 | HR: 0.11 (95% CI 0.02-0.54) P < .01 | n/d | n/d |                  |
|                  |                              | n/d | n/d | n/d |                |
| Brown JB-b (2015)29 | PHT vs control, matched 24 h: 53 (22%) vs 86 (18%) OR 0.16 (95% CI 0.01-0.96) P = .22 | SBP: 106 (80-132) vs 110 (91-130) | 5 (2-11) vs 4 (2-9) P = .06 (95% CI 0.01-0.96) P = .22 | n/d | INR > 1.5 OR = 0.01 (95% CI 0.01-0.95) P = .05 |
|                  | In-hospital: 74 (31%) vs 115 (24%) P = .03 24 h survival: "Shock on admission": 139 (58%) vs 226 (47%) P < .01 | TIC: 113 (47%) vs 149 (31%) matched scene patients: Matched scene patients: 8 (2-18) vs 9 (3-13) AOR 4.91 (95% CI 1.51-16.04) P = .01 | n/d | n/d | Scene only: OR = 0.08 (95% CI 0.01-1.35) P = .079 |
|                  |                              | "Shock on admission": 139 (58%) vs 226 (47%) P < .01 | n/d | n/d |                  |
|                  |                              | 0.87-2.24 P = .17 | n/d | n/d |                |
|                  |                              | n/d | n/d | n/d |                |

(Continues)
| First author (y) | Mortality (n [%]) | Shock on arrival to hospitalb | 24 h RBC requirement (U) | ICU/hospital LOS (d) | TICa | Adverse events |
|------------------|------------------|-----------------------------|-------------------------|---------------------|------|----------------|
| **Griggs JE** (<2016)30 | PHTRBC vs control | 6 h: 10 (10%) vs 19 (18%) P = .2 | n/d | 3 (1-8) vs 4.5 (2-9) (no analysis) ≥ 4 units RBC in 24 h: 41 (40%) vs 62 (60%) P = .02 | n/d | No immediate transfusion complications |
| **Holcomb JB-b (2015)31** | PHT vs control | 6 h: 12% vs 10% P = .425 | Adjusted: OR 0.23 (95%CI 0.106-0.506) P = .088 | 6 h RBC: 0 (0-4) vs 1 (0-5) P = .370 | n/d | ACT: 113 (105-128) vs 121 (105-128) P = .546 |
| **Kim BD (2012)32** | PHT-plasma+RBC vs PHTRBC: | 6 h: 11% vs 4% P = .422 | | 12.7 vs 11.4 P = .694 | ICU: 6.3 vs 7.7 P = .672 | |
| **Miller B (2016)33** | PHTRBC vs control, matched: | 24 h: 39 (20%) vs 31 (16%) P = .291 | | 6 (2-12) vs 3 (0-8) P < .001 | n/d | |

### TABLE 5 (Continued)

| First author (y) | Mortality (n [%]) | Shock on arrival to hospital | 24 h RBC requirement (U) | ICU/hospital LOS (d) | TIC | Adverse events |
|------------------|------------------|-----------------------------|-------------------------|---------------------|------|----------------|
| **In-hospital survival** | **AOR 1.06** (95% CI 0.42-2.61) P = .90 | **AOR 0.28** (95% CI 0.09-0.85) P = .03 | Matched scene patients: | **AOR 0.24** (95% CI 0.07-0.80) P = .02 | **Matched scene patients:** | **Matched scene patients:** |
| **24 h: 23 (32%) vs 37 (6%) P = .33** | | | **≥ 4 U lower requirement:** | | **PH transfusion reactions:** | **None** |
| **In-hospital: 26 (37%) vs 48 (44%) P = .68** | **24 h survival:** AOR 6.31 (95% CI 1.88-21.14) P < .01 | **Shock on admission:** | | | **IH transfusion reactions:** | **1** |
| **In-hospital survival:** AOR 4.32 (95% CI 0.76-24.72) P = .10 | | **≥ 10 units PRBC in 24 h:** | | | | |

**PH transfusion reactions:**
- ARDS: 11% vs 8%
- ARF: 0% vs 4%
- Change in INR*: 0.9 vs 0.2

**Arrival aPTT:** 51 vs 35 P = .037
| First author (y) | Mortality (n [%]) | Shock on arrival to hospital | 24 h RBC requirement (U) | ICU/hospital LOS (d) | TIC | Adverse events |
|-----------------|------------------|----------------------------|-------------------------|---------------------|-----|----------------|
| Parker ME (2017)
32 | PHT vs control: 30d: 13% vs 12% P = 1.00 | Pre vs post transport (mean SD): HPT: HCO3 (mmol/L): 23.20 ± 5.14 vs 22.41 ± 4.35 P = .27. Hemodynamic instability 55 (49%) vs 20 (18%) P < .001 Control: HCO3 (mmol/L) 23.67 ± 6.89 vs 21.90 ± 4.15 P = .29 Hemodynamic instability (%) 47 vs 18 P = .005 | PHTRBC vs control: 24 h: 19 (30%) vs 16 (32%) P = .531 30d: 22 (45%) vs 20 (40%) P = .547 | PHT vs control: Any RBC in-hospital: 96 (86%) vs 40 (82%) P = .6 In-hospital RBC: 4.0 (2.0-6.0) vs 3.0 (2.0-6.0) P = .84 | Hospital: 5.0 (4.0-8.0) vs 6.0 (4.0-8.0) P = .52 ICU: 2.0 (1.0-2.0) vs 2.0 (1.0-3.0) P = .69 | Pre vs post transport (mean ± SD): TRALI: 1 PHT: INR 2.01 ± 1.51 vs 1.56 ± .83 P = .01 Control: INR 1.94 ± 0.97 vs 1.62 ± 1.37 P = .32 |
| Peters J (2017)
33 | PHTRBC vs control, matched: 24 h: 19 (30%) vs 16 (32%) P = .531 30d: 22 (45%) vs 20 (40%) P = .547 | BE = −9.9 (−25.0 to −0.7) vs −6.6 (−23.2 to −0.6) P = .628 Lactate (mmol/L): 3.6 (0.8-21) vs 3.2 (1.1-14.2) P = .142 | 1443 mL (range: 0-19 315 mL) vs 2240 mL (range: 0-15 000 mL) P = .004 24 h RBC including PH volume: 1958 mL (range: 270-20 580) vs 2240 mL (range: 0-15 000) P = .888 | n/d | INR: 1.3 (range 1-10) vs 1.3 (range 1-3.1) P = .529 TIC: 14(40%) vs 10(26%) P = .188 |
| Price DD (1999)
34 | PHTRBC vs control, matched: Overall: 45% vs 40% P = .52 | HR: 113/min (SD 23) vs 98/min (SD 43) P = .002 SBP: n/sign DBP: 69 mmHg (SD 19) vs 49 mmHg (SD 30) P = .003 | In-hospital RBC (mean (SD)): 1414 mL (SD 1660) vs 1007 mL (SD 935) P = .023 | ICU/hospital: n/sign n/d n/d | PH transfusion reactions: none IH transfusion reactions: 1 |
| Rehn M (2018)
35 | PHTRBC vs control: n/d | n/d | Total RBC (pre-hospital + in-hospital): 4 (2-6) vs 6 (4-12) Univariate − 0.624 (95% CI) | n/d | PH/IH transfusion reactions: none |

(Continues)
| First author (y)          | Mortality (n [%]) | Shock on arrival to hospital | 24 h RBC requirement (U) | ICU/hospital LOS (d) | TIC \( ^a \) | Adverse events |
|---------------------------|-------------------|------------------------------|--------------------------|----------------------|-------------|---------------|
| **Rehn M (2019)\(^{36} \)** | **PHTRBC vs control:**<br>Overall: 143 (60%) vs 187 (62%)<br>Univariate: OR 0.90 (95% CI 0.64-1.28) \( P = .554 \)<br>Multivariate: OR 0.92 (95% CI 0.64-1.32) \( P = .648 \)<br>**Prehospital:** 66 (28%) vs 126 (42%)<br>Univariate: OR 0.53 (0.36-0.76) \( P < .001 \)<br>Multivariate: OR 0.52 (95% CI 0.35-0.78) \( P = .001 \) | n/d | 0 (0-5) vs 7 (4-12) | n/d | n/d | n/d |
| **Sumida MP (2000)\(^{37} \)** | **PHTRBC vs control:**<br>Overall mortality Frequency ratio: 1.2 vs 1.4 (Live-1 Die-2) \( P = .01 \) | Change in mean BP: 5.5 vs 15.6 \( P = .227 \)<br>Change in mean HR: 7.6 vs –3.0 \( P = .159 \)<br>pH (mean): 7.23 vs 7.37 \( P = .008 \)<br>Bic (mean): 14.6 vs 21.4 \( P = .0001 \) | n/d | n/d | n/d | n/d |

**Prospective not-comparative studies**

| Chang R (2018)\(^{25} \)** | n/d for PHTRBC CC+ patients had increased mortality at all time points (all \( P < .001 \)) | n/d for PHTRBC | n/d for PHT | n/d for PHTRBC | CC+ vs CC-:<br>Received PHTRBC (n[]): 18 (44%) vs 82 (8%) \( P < .001 \)<br>Transfused prehospital plasma: 18 (44%) vs 104 (11%) \( P < .001 \) | n/d |
| Reed M (2017)\(^{24} \)** | n/d for PHTRBC | n/d for PHTRBC | n/d | n/d | Coagulopathic patients received more blood component units prehospital (data not provided) \( P < .01 \) | n/d |
| Sherren PB (2013)\(^{38} \)** | Dead on scene: 22 (15%) | n/d | n/d | n/d | Transfusion reactions: none | n/d |

(Continues)
| First author (y) | Mortality (n [%]) | Shock on arrival to hospital | 24 h RBC requirement (U) | ICU/hospital LOS (d) | TIC | Adverse events |
|------------------|-------------------|----------------------------|-------------------------|---------------------|-----|---------------|
| Weaver AE (2012) | 60d: 52%          | pH (mean): 7.07 BE (mean): −12.0 | Mean: 10.5 n/d n/d n/d | n/d | n/d | n/d |
| Retrospective not-comparative studies | | | | | | |
| Berns KS (1998) | Overall: 45% Trauma only: 52% | n/d | n/d | ICU (mean): 12 Hospital (mean): 20 | n/d | Complications: none |
| Bodnar D-b (2014) | Trauma only: Dead on scene: 7 (9.9%) | Mean (SD): 7.93 (7.18) | ICU: 5.5 (2.0-16.25) Hospital: 15.0 (1.0-38.5) | n/d | n/d |
| Dalton AM (1993) | 24 h: 46 (41%) Overall: 51 (46%) | Volume of blood and change in SBP: P = .20 | n/d | n/d | PH transfusion reactions: 1 (DIB) |
| Fahy AS (2017) | Trauma vs non-trauma | Lactate (mean ± SD): 2.4 ± 0.6 vs 3.2 ± 0.8 P = .09 | In-hospital RBC (mean [range]): 4.3 (0-8) vs 12.3 (0-82) P = .03 | Hospital LOS (mean): 13.4 vs 8.9 P = .12 | (mean (SD) INR 1.25 ± 0.4 vs 1.3 ± 0.3 P = .69 PT: 29.9 ± 4.5 vs 31.5 ± 9.6 P = .58 TEG: K 2.8 ± 2.8 vs 2.9 ± 1.1 P = .94 Angle: 61 ± 15.3 vs 54.5 ± 9.2 P = .43 R: 4.9 ± 1.7 vs 9.6 ± 9.6 P = .04 MA: 55 ± 14.7 vs 59.8 ± 4.8 P = .55 Ly30: 0.75 ± 0.8 vs 0.03 ± 0.05 P = .08 |
| Heschl S (2018) | Trauma only: Dead on scene: 13 (9.6%) | Changes during treatment: arrival at scene - start transfusion - arrival hospital: HR: 116 (100-130) to 119 (103-132) to 112 (96-130) P < .001 SBP: 90 (80-110) to 80 (65-91) to 94 (71-110) P < .001 SI: 1.27 (1.00-1.57) to 1.50 (1.20-1.80) to 1.23 (0.98-1.49) P = .004 | n/d | n/d | Complications: none |

(Continues)
| First author (y) | Mortality (n [%]) | Shock on arrival to hospital | 24 h RBC requirement (U) | ICU/hospital LOS (d) | TIC | Adverse events |
|------------------|-------------------|-----------------------------|-------------------------|---------------------|-----|----------------|
| Higgins GL (2012) | Prior to discharge: 31% | Pre- vs post-transfusion: SBP < 90 mmHg: 71% vs 29% | n/d | n/d | n/d | Transfusion reactions: none, Complications: none |
| Hooper N (2017) | Before arrival to hospital: 18% | n/d | n/d | n/d | n/d | n/d |
| Krook C (2018) | Overall prehospital: 33 (12%) | n/d | n/d | n/d | n/d | adverse reactions: none |
| Krugh D (1994) | 5 (62.5%) | Mean (range) ± SD pH: 7.15 (6.60-7.42) ± 0.17 | ICU: 6 (2-17) Hospital: 18 | n/d | n/d | Complications: none,Ionized calcium (mean): 1.1 mmol/L; Lower with increasing volume of PRBCs transfused P = .03 |
| Lyon R (2017) | Dead on scene: 38 (26%), After arrival to hospital: 6 h: 16% 28-d: 30% | Mean (range) ± SD pH: 7.15 (6.60-7.42) ± 0.17 | ICU: 6 (2-17) Hospital: 18 | n/d | n/d | |
| Maher P (2017) | PHTRBC: 5 (38%) PHT-plasma: 1 (33%) Scene transports: 2 (22%) Interfacility transports: 4 (37%) | n/d | n/d | n/d | n/d | |
| Mena-Munoz J (2016) | In-hospital 30d: Overall: 22.5% (CI 20.4%-25.0%) PHTRBC vs no-PHTRBC: 201 (28%) vs 252 (27%) OR 0.77 (0.53-1.13) Transfused > 700 mL vs < 350 mL: 48 (47%) vs 161 (23%) OR 2.11 (95% CI 1.46-2.76) | Overall: Lactate 2.4 (1.4-4.8) Odds of in-hospital transfusion after PHTRBC: OR = 2.00 (95% CI 1.46-2.76) Overall: Hospital: 7 (3-14) ICU: 4 (1-9) Overall: PTT: 321 (27.3-38.6) INR: 1.4 (12-1.8) | n/d | n/d | n/d |
| Mix FM (2018) | n/d | n/d | n/d | n/d | |
| Potter D (2015) | Prior to discharge: 4 (25%) | Mean (range) Arrival Lactate: 3.6 mg/dL (1.1-7.1) | Mean 3.6 (range 0-13) Hospital: mean 9.3 (range 1-45) Overall vs PHT-plasma+RBC vs PHTRBC: | n/d | n/d | |

(Continues)
| First author (y) | Mortality (n [%]) | Shock on arrival to hospital | 24 h RBC requirement (U) | ICU/hospital LOS (d) | TIC | Adverse events |
|------------------|------------------|-----------------------------|------------------------|---------------------|-----|----------------|
| Raitt JE (2018)  | On scene: 9 (14%) | n/d                         | 5 (range 1-29)         | n/d                 | n/d | n/d            |
|                  | In-hospital: 11 (19%) | n/d                         |                        |                      |     | Transfusion reactions: none |
|                  | n/d               |                             |                        |                      |     | Complications: none |
| Sunde GA (2015)  | On scene: 2 (50%) | n/d                         |                        |                      |     | Minor allergic reaction after additional in-hospital plasma: 1 (0.1%) |
|                  | After arrival |                             |                        |                      |     | Volume overload: none |
|                  | n/d               |                             |                        |                      |     | TRALI: none |
| Thiels CA (2016) | Overall: 30d: 18.0% | n/d                         | Overall: Hemodynamically unstable on admission: 124 (64%) | | | Hemolytic transfusion reaction: none |
|                  | Non-trauma vs trauma: | n/d | Non-trauma vs trauma: | Hospital LOS (mean ± SD): | | |
|                  | 1d: 5% vs 10% P = .002 | n/d | 7.1 ± 8.7 vs 8.2 ± 10.8 | 9.4 ± 11.2 vs 12.2 | | |
|                  | 30d: 16% vs 22% P = .03 | n/d | | ± 19 | | |
|                  | Surgical vs Medical vs GI-bleed: | n/d | Surgical vs Medical vs GI-bleed: | 12.1 ± 13.9 vs 9.5 | | |
|                  | 1d: 6% vs 6% vs 2% P = .045 | n/d | 7.4 ± 8.3 vs 8.2 | ± 11.6 vs 6.1 ± 6.9 | | |
|                  | 30d: 15% vs 21% vs 13% P = .12 | n/d | P = .51 | ± .97 P = .03 | | |
| Wheeler R (2013) | n/d | n/d | n/d | Hypothermia vs non-hypothermia (mean ± SD): | n/d | PHTRBC vs controls: |
|                  |                   |                             |                        | ICU: 8.96 ± 8.72 vs 7.10 ± 8.51 | | |
|                  |                   |                             |                        | Hospital: 18.20 ± 23.81 vs 8.67 ± 12.82 | | |
| Case reports     |                   |                             |                        |                        | | |
| Garner AA (1999) | n = 1, survived | n/d | 56 (n = 1) | ICU: 88 (n = 1) | n/d |                  |
| Lawton LD (2012) | n = 1, survived until ICU admission | n/d | n/d | n/d | n/d |                  |

(Continues)
| First author (y) | Mortality (n [%]) | Shock on arrival to hospital | $24\ h\ RBC$ requirement (U) | ICU/hospital LOS (d) | TIC$^a$ | Adverse events |
|------------------|------------------|-----------------------------|------------------------------|---------------------|--------|---------------|
| n = 1, survived until hospital admission | n/d | n/d | n/d | n/d | n/d | Hemolysis of donor red cell units during transit: 2 incidents because of improper packaging or cooling |
| Macnab AJ (1996)$^{59}$ | n/d | n/d | n/d | n/d | n/d | Adverse effects: none |
| Description of protocol | | | | | | |
| Trembley AL (2016)$^{60}$ | n/d | n/d | n/d | n/d | n/d | Complications: none |
| Vartanian, L (2017)$^{61}$ | Before hospital arrival: 1 (8%) | n/d | n/d | n/d | n/d | |
| Military services | | | | | | |
| Prospective comparative studies | | | | | | |
| Vitalis V (2017)$^{62}$ | PHT vs control: 24 h: 2 (28.6%) vs 3 (14%) (no analysis performed) | n/d | | Total in-hospital RBC: 1 (0.25-5.5) vs 0 (0-2) | n/d | n/d |
| Retrospective comparative studies | | | | | | |
| Howard, JT (2017)$^{63}$ | Needed & received PHT vs needed but no PHT: KIA: AOR 0.17 (95% CI 0.06-0.51, $P = .002$) | n/d | n/d | n/d | n/d | n/d |
| O’Reilly DJ-b (2014)$^{64}$ | PHT vs control, matched: $30d$: 8 (8.2%) vs 19 (19.6%) $P = .013$ | | SBP: 132 (111-145) vs 131 (114-150) $P = .145$ | In-hospital RBC: 2 (1-8.5) | n/d | n/d |
| | | | HR: 92 (74-115) vs 105 (82-128) $P = .041$ | Total RBC: 4 (2-10) | | n/d |
| Shackelford S (2017)$^{65}$ | PHT vs control, matched: $24\ h$: 3 (5%) vs 69 (20%) | | pH: 7.28 (7.17-7.38) vs 7.29 (7.24-7.34) $P = .65$ | | | n/d |
| | | | BE: −7 (−11 − −4) vs −6.2 (−7.9 − −4.4) $P = .37$ | Shock on arrival: 42 (76%) vs 206 (69%) | | |
| | | | $24\ h\ RBC/WB$: 15 (8-23) vs 11 (8.5-13.5) $P = .002$ | Hospital: 30 (21-30) vs 30 (27-33) $P > .99$ | INR: 1.40 (1.2-1.7) vs 1.26 (1.16-1.36) $P = .008$ | n/d |

(Continues)
| First author (y) | Mortality (n [%]) | Shock on arrival to hospital* | 24 h RBC requirement (U) | ICU/hospital LOS (d) | TIC* | Adverse events |
|------------------|-------------------|-------------------------------|--------------------------|---------------------|------|----------------|
| Aye Maung N (2015) | Overall: 0% (n = 2) | Changes during treatment: radial pulse returned (n = 2) | n/d | n/d | n/d | Adverse events: none |
| Malsby RF (2013) | 24 h: 2 (33%, n = 6) | BE (n = 5): -7 (-7 - -4) Pre- vs post-transfusion: SBP 99 (80-116) vs 120 (104-134) HR 132 (128-138) vs 123 (112-138) | 10 (3.5-14.5) (n = 7) | n/d | n/d | Adverse reactions: none |
| Barkana Y (1999) | In-hospital: 16% | SBP on arrival: 110 | *Emergency phase RBC*: 5 (0-4) | n/d | n/d | Adverse reaction: 1 (rash) |
| Chen J (2017) | Overall: 10 (11%) On arrival to hospital: 7 (8%) 24 h: 9 (10%) In-hospital: 3 (3%) | Scene vs hospital arrival: SBP: 119 (90-130) vs 120 (80-130) P = .49 DBP: 70 (60-80) vs 70 (60-80) P = .23 | n/d | n/d | n/d | Adverse reactions: none Immediate transfusion-related complications: none Technical problems: none |

(Continues)
| First author (y) | Mortality (n [%]) | Shock on arrival to hospital | 24 h RBC requirement (IU) | ICU/hospital LOS (d) | TIC<sup>a</sup> | Adverse events |
|------------------|-------------------|-----------------------------|-------------------------|---------------------|----------------|----------------|
| Edgar IA (2014)<sup>70</sup> | After arrival, in-hospital: 4.5% (n/s for PHTRBC) | HR: 119 (100-130) vs 108 (90-120) P < .01 | MERT vs PEDRO: SBP: 130 (111-170) vs 157 (146-198) P = .0849 | MERT vs PEDRO: RBC in ED: 5 (2-14) vs 12 (6-21) (no analysis) | n/d | n/d |
| Morrison JJ (2013)<sup>71</sup> | AMR vs CMR: overall: 9.1% vs 9.2% P = .536 (n/s for PHTRBC) | n/d | n/d | n/d | n/d | n/d |
| O'Reilly DJ-a (2014)<sup>72</sup> | Overall: 62 (20%) | n/d | 7 (1-15) total RBC: 8 (3-18) | n/d | n/d | Adverse effects: none |
| Powell-Dunford N (2014)<sup>73</sup> | 24 h: 8 (13%) | BE: –9 (–14 to –6) | Pre vs post-transfusion: SBP: 86 (70-104) vs 108 (85-127) P = .001 | INR: 1.2 (1.1-1.4) | n/d | Adverse reaction: none |
| Shlaifer A (2017)<sup>74</sup> | In-hospital: 11 (12%) (n/s for PHTRBC) | n/d | n/d | n/d | Adverse event to FDP: 1 (chills and shivering) |
estimate. Nonetheless, despite these limitations, the data by Rijnhout et al can be considered hypothesis generating and do suggest that the combination of PHTRBC and plasma may potentially be beneficial for long-term survival, warranting further investigation. Similarly, a recent systematic review by Shand et al reported high heterogeneity and the authors could not draw conclusions about the effect of prehospital transfusion of any blood component on outcome.\textsuperscript{80} Previous systematic reviews have summarised the evidence up to 2015\textsuperscript{81} and 2016,\textsuperscript{82} however, numerous studies have been published thereafter such that a more up to date systematic review is warranted.

4.2 | Haemodynamics, coagulopathy, 24-hours RBC requirement and LOH/ICU stay

Observational studies in both civilian and military services found that after PHTRBC, SBP recovers, HR decreases and SI improves. However, these improvements could be due to the administration of analgesia or fluids in general or merely be time-dependent effects. Outcomes of comparative studies in both military and civilian services reporting on haemodynamics, coagulopathy or 24-hour RBC requirement are conflicting and could not confirm an effect of PHTRBC on any of these variables.

A large majority of patients in both civilian and military observational studies required transfusion after arrival to hospital, which may be seen as confirmation of the appropriateness of prehospital transfusions. Some studies reported a higher 24 hours RBC requirement in PHTRBC patients, while others reported this to be lower. A higher 24 hours RBC requirement may suggest that the patients who were bleeding most severely had been identified correctly in the prehospital setting as requiring PHTRBC. These patients, in turn, also have a higher demand for blood products when at the hospital. An explanation of a lower 24 hours RBC requirement in PHTRBC patients could be that these patients bled less through prevention of coagulopathy and thus required less transfusion. However, there is thus far no evidence that PHTRBC generally reduces the occurrence of TIC. In some cases, the PHTRBC patients may merely have received the blood they needed earlier, resulting in a lower 24 hours in-hospital RBC requirement. There is currently no evidence that PHTRBC has influence on LOS in hospital and LOS in ICU.

4.3 | Adverse events

There have been few instances of transfusion reactions being reported after PHTRBC. Fortunately, transfusion reactions in the general population are rare, with urticaria occurring in 1% to 3% of patients, febrile non-haemolytic transfusion reaction and cardiac overload in <1%, and all other transfusion reactions in <0.1%.\textsuperscript{83}

4.4 | Strength and limitations

We performed a thorough search with broad inclusion criteria. The eligibility of studies was assessed independently by two authors. It is
5 | CONCLUSION

This systematic review revealed that despite increasing use of PHTRBC by civilian EMS, high-quality evidence for beneficial effects is still lacking. In the absence of high-quality data, it seems reasonable to assume that massively bleeding patients may benefit from PHTRBC. This assumption is supported by several observational studies that do suggest possible beneficial effects on mortality. This may especially be true when PHTRBC is combined with plasma administration. PHTRBC also appears to improve haemodynamic parameters, but there is no evidence that shock on arrival to hospital is averted, nor of an association with TIC or LOS in either hospitals or ICUs. Few adverse events have been reported. Given that prevention is generally better than treatment, prevention of haemorrhagic shock through compression of external bleeding, stabilisation of pelvic fractures, prevention of hypothermia and the administration of tranexamic acid should still remain a priority in trauma patients, even when PHTRBC is available.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Kauvar DS, Wade CE. The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. Crit Care. 2005;9(suppl 5):S1-S9. https://doi.org/10.1186/cc7379.
2. Pannell D, Brisebois R, Talbot M, et al. Causes of death in Canadian forces members deployed to Afghanistan and implications on tactical combat casualty care provision. J Trauma. 2011;71(5 suppl 1):S401-S407.
3. Eastridge BJ, Hardin M, Cantrell J, et al. Died of wounds on the battlefield: causation and implications for improving combat casualty care. J Trauma. 2011;71(1 suppl):S4-S8. https://doi.org/10.1097/TA.0b013e3182417c97.
4. Kelly JF, Ritenour AE, McLaughlin DF, et al. Injury severity and causes of death from operation Iraqi freedom and operation enduring freedom: 2003–2004 versus 2006. J Trauma. 2008;64(2 suppl):S21-S26; discussion S26-7. https://doi.org/10.1097/TA.0b013e318160b9fb.
5. Eastridge BJ, Mabry RL, Seguin P, et al. Death on the battlefield (2001–2011): implications for the future of combat casualty care. J Trauma Acute Care Surg. 2012;73(6 suppl 5):S431-S437. https://doi.org/10.1097/TA.0b013e3182755d6c.
6. Chatrath V, Khetarpal R, Ahuja J. Fluid management in patients with trauma: restrictive versus liberal approach. J Anesth Clin Pharmacol. 2015;31(3):308-316. https://doi.org/10.4103/0970-9185.161664.
7. Hodgetts TJ, Mahoney PF, Kirkman E. Clinical developments damage control resuscitation. World. 2007;153:299-300.
8. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma: Injury Infect Crit Care. 2007;62(2):307-310. https://doi.org/10.1097/TA.0b013e3180324124.
9. Beelekey AC. Damage control resuscitation: a sensible approach to the exsanguinating surgical patient. Crit Care Med. 2008;36(7 suppl):S267-S274. https://doi.org/10.1097/CCM.0b013e318177da7d.
10. Gerhardt RT, Strandenes G, Cap AP, et al. Remote damage control resuscitation and the Solstrand conference: defining the need, the language, and a way forward. Transfusion. 2013;53(suppl 1):9s-16s. https://doi.org/10.1111/trf.12030.
11. Harris T, Davenport R, Mak MBK. The evolving science of trauma resuscitation. Emerg Med Clin North Am. 2018;36(1):85-106.
12. Litvinov RI, Weisel JW. Role of red blood cells in haemostasis and thrombosis. ISBT Sci Ser. 2017;12(1):176-183. https://doi.org/10.1111/vox.12331.
13. Schober P, Schwarte LA. From system to organ to cell: oxygenation and perfusion measurement in anesthesia and critical care. J Clin Monit Comput. 2012;26(4):255-265. https://doi.org/10.1007/s10877-012-9350-4.
14. Cap AP. The school of hard knocks: what we’ve learned and relearned about transfusion in a decade of global conflict. Transfus Med. 2014;24(3):135-137. https://doi.org/10.1111/tme.12127.
15. Hooper T, Nadler R, Butler FK, Badloe JF, Glassberg E. Implementation and execution of military forward resuscitation programs: reply. Shock. 2014;41(suppl 1):102-103. https://doi.org/10.1097/SHK.0000000000000139.
16. Jansen JO, Morrison JJ, Midwinter MJDH, et al. Changes in blood transfusion practices in the UKrole 3 medical treatment facility in Afghanistan, 2008–2011. Transfus Med. 2014;24(3):154-161. https://doi.org/10.1111/tme.12093.
17. Bodnar D, Rashford S, Williams S, Enright-Mooney E, Parker L, Clarke B. The feasibility of civilian prehospital trauma teams carrying and administering packed red blood cells. Emerg Med J. 2014;31(2):93-95. https://doi.org/10.1136/emermed-2012-201969.
18. Holcomb JB, Donathan DP, Cotton BA, et al. Prehospital transfusion of plasma and red blood cells in trauma patients. Prehosp Emerg Care. 2015;19(1):1-9. https://doi.org/10.3109/10903127.2014.923077.
19. van Turenhout EC, Bosser SM, Loer S, Giannakopoulos GF, Schwarte LA, Schober P. Pre-hospital transfusion of red blood cells...
33. Peters JH, Smulders PSH, Moors XRL, et al. Are on-scene blood transfusions by a helicopter emergency medical service useful and safe? A multicentre case-control study. Eur J Emerg Med. 2017;26:128-132. https://doi.org/10.1016/j.ejmej.2016.07.002.

34. Price DD, Norton RL, Zechnich AD, Eldurkar J, Chok J, Mann NC. Out-of-hospital blood administration for critically injured patients transported by helicopter. Ann Emerg Med. 1999;34(4):550-551. https://doi.org/10.1016/S0196-0644(99)80280-7.

35. Rehn M, Weaver AE, Esthelby S, Roislien J, Lockey DJ. Pre-hospital transfusion of red blood cells in civilian trauma patients. Transfus Med. 2018;28(4):277-283. https://doi.org/10.1111/tme.12483.

36. Rehn M, Weaver A, Brohi K, et al. Effect of prehospital red blood cell transfusion on mortality and time of death in civilian trauma patients. Shock. 2019;51(3):284-288. https://doi.org/10.1097/SHK.0000000000001166.

37. Sumida MP, Quinn K, Lewis PL, et al. Prehospital blood transfusion versus crystalloid alone in the air medical transport of trauma patients. Air Med J. 2000;19(4):140-143. https://doi.org/10.1067/maj.2000.110128.

38. Sherren PB, Burns B. Prehospital blood transfusion: 5-year experience of an Australian helicopter emergency medical service. Crit Care. 2013;17(suppl 2):P295-P295. https://doi.org/10.1186/cc12233.

39. Weaver A, Esthelby S, Norton J, Lockey D. The introduction of on-scene blood transfusion in a civilian physician-led pre-hospital trauma service. Scand J Trauma Resusc Emerg Med. 2013;21(Suppl 1):S27. https://doi.org/10.1186/1757-7241-21-s1-s27.

40. Berns KS, Zietlow SP. Blood usage in rotor-wing transport. Air Med J. 1998;17(3):105-108. https://doi.org/10.1016/s1067-991x(98)90104-3.

41. Bodnar D, Rashford S, Hurn C, et al. Characteristics and outcomes of patients administered blood in the prehospital environment by a road based trauma response team. Emerg Med J. 2014;31(7):583-588. https://doi.org/10.1136/emermed-2013-202395.

42. Dalton AM. Use of blood transfusions by helicopter emergency medical services: is it safe? Injury. 1993;24(8):509-510. https://doi.org/10.1016/0020-1383(93)90023-Y.

43. Fahy AS, Thiels CA, Polites SF, et al. Prehospital blood transfusions in pediatric trauma and nontrauma patients: a single-center review of safety and outcomes. Pediatr Surg Int. 2017;33(7):787-792. https://doi.org/10.1007/s00383-017-4092-5.

44. Hesch S, Andrew E, de Wit A, et al. Prehospital transfusion of red cell concentrates in a paramedic-staffed helicopter emergency medical service. Emerg Med Australas. 2018;30(2):236-241. https://doi.org/10.1111/ememmed-2017-2039.

45. Higgins GL 3rd, Baumann MR, Kendall KM, et al. Red blood cell transfusion: experience in a rural aeromedical transport service. Prehosp Disaster Med. 2012;27(3):231-234. https://doi.org/10.1017/s1059-051x.000000001166.

46. Hooper N, Baskerville M, Pynn H, Hooper T. Prehospital blood—developing a service. Dent Traumatol. 2017;19(3):229-240.

47. Krook C, O'Doherty B, Martin D, et al. Blood on board: the development of a prehospital blood transfusion program in a Canadian helicopter emergency medical service. CJEM. 2018;21:1-9. https://doi.org/10.1017/cem.2018.457.

48. Krugh D, Julius C, Quinlin B, et al. Emergency transfusion during medical air transport: development of an off-site storage and transfusion program. Lab Med. 1994;25(5):318-322. https://doi.org/10.1093/labmed/25.5.318.

49. Lyon RM, de Sausmarez E, McWhirter E, et al. Pre-hospital transfusion of packed red blood cells in 147 patients from a UK helicopter emergency medical service. Scand J Trauma Resusc Emerg Med. 2017;25(1):12. https://doi.org/10.1186/s13049-017-0356-2.

50. Maher P, Utarnachitt R, Louzon MJ, Gary R, Sen N, Hess JR. Logistical concerns for prehospital blood product use by air medical services. Air Med J. 2017;36(5):263-267. https://doi.org/10.1016/j.amj.2017.05.003.

51. Mena-Munoz J, Srivastava U, Martin-Gill C, Suffoletto B, Callaway CW, Guyette FX. Characteristics and outcomes of blood product transfusion during critical care transport. Prehosp Emerg Care. 2016;20(5):586-593. https://doi.org/10.1080/10903127.2016.1163447.

52. Mix FM, Zielinski MD, Myers LA, et al. Prehospital blood product administration opportunities in ground transport ALS EMS—a descriptive study. Prehosp Disaster Med. 2018;33(3):230-236. https://doi.org/10.1017/s1049023x18000274.

53. Potter DD, Berns KS, Elserber TD, Zietlow SP. Prehospital use of blood and plasma in pediatric trauma patients. Air Med J. 2015;34(1):40-43. https://doi.org/10.1016/j.amj.2014.07.037.
54. Raitt JE, Norris-Cervetto E, Hawksley O. A report of two years of prehospital blood transfusions by Thames Valley air ambulance. Dent Traumatol. 2018;20(3):221-224.

55. Sunde GA, Vikenes B, Strandenes G, et al. Freeze dried plasma and fresh red blood cells for civilian prehospital hemorrhagic shock resuscitation. J Trauma Acute Care Surg. 2015;78(6):526-530. https://doi.org/10.1097/TA.0000000000000633.

56. Thielis CA, Aho JM, Fahy AS, et al. Prehospital blood transfusions in non-trauma patients. World J Surg. 2016;40(10):2297-2304. https://doi.org/10.1007/s00268-016-3572-4.

57. Garner AA, Bartolacci RA. Massive prehospital transfusion in multiple blunt trauma. Med J Aust. 1999;170(8):394.

58. Lawton LD. Air medical services must be prepared for massive transfusion. Air Med J. 2012;31(3):138-140. https://doi.org/10.1016/j.jamj.2011.09.001.

59. Macnab AJ, Pattman B, Wadsworth LD. Potentially fatal hemolysis of cross-matched blood during interfactivity transport: standards of practice for safe transport of stored blood products. Air Med J. 1996;15(2):69-72.

60. Trembley AL 2nd, Witthuhn S, Cohen S, Conterato M. Implementing protocols to administer blood products in the prehospital setting. Jems. 2016;41(5):48-51.

61. Vartanian L, Nealy W, Uhl N. Blood use in the field: developing protocols for prehospital transfusions. EMS World. 2017;46(3):20-25.

62. Vitalis V, Carfantan C, Moncriol A, et al. Early transfusion on battlefield before admission to role 2: a preliminary observational study during “Barkhane” operation in Sahel. Injury. 2018;49(5):903-910. https://doi.org/10.1016/j.injury.2017.11.029.

63. Howard JT, Kotwal RS, Santos-Lazada AR, Martin MJ, Stockinger ZT. Reexamination of a battlefield trauma golden hour policy. J Trauma Acute Care Surg. 2018;84(1):11-18. https://doi.org/10.1097/ta.0000000000001727.

64. O‘Reilly DJ, Morrison JJ, Jansen JO, et al. Initial UK experience of prehospital blood transfusion in combat casualties. J Trauma Acute Care Surg. 2014;77(3 suppl 2):S66-S70. https://doi.org/10.1097/ta.0000000000000342.

65. Shackelford SA, Del Junco DJ, Powell-Dunford N, et al. Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. Jama. 2017;318(16):1581-1591. https://doi.org/10.1001/jama.2017.15097.

66. Aye Maung N, Doughty H, MacDonald S, Parker P. Transfusion support by a UKRole 1 medical team: a 2-year experience from Afghanistan. J R Army Med Corps. 2016;162(6):440-444. https://doi.org/10.1136/jramc-2015-000489.

67. Malsby RF 3rd, Quesada J, Powell-Dunford N, et al. Prehospital blood product transfusion by U.S. Army MEDDEVAC during combat operations in Afghanistan: a process improvement initiative. Mil Med. 2013;178(7):785-791. https://doi.org/10.7205/MILMED-D-13-00047.

68. Barkana Y, Stein M, Maor R, Lynn M, Eldad A. Prehospital blood transfusion in prolonged evacuation. J Trauma. 1999;46(1):176-180.

69. Chen J, Benov A, Nadler R, et al. Prehospital blood transfusion during aeromedical evacuation of trauma patients in Israel: the IDF CSAR experience. Mil Med. 2017;182(51):47-52. https://doi.org/10.7205/milmed-d-16-00081.

70. Edgar IA, Thompson CJ, Hunter S, Burgess AJ, Lambert AW. Does the method of aeromedical evacuation from the point of wounding to a field hospital have an effect on subsequent blood product usage and patient physiology? J R Nav Med Serv. 2014;100(1):12-17.

71. Morrison JJ, Oh J, DuBose JJ, et al. En-route care capability from point of injury impacts mortality after severe wartime injury. Ann Surg. 2013;257(2):330-334. https://doi.org/10.1097/SLA.0b013e31827efc6f.

72. O’Reilly DJ, Morrison JJ, Jansen JO, Apodaca AN, Rasmussen TE, Midwinter MJ. Prehospital blood transfusion in the En route management of severe combat trauma: a matched cohort study. J Trauma Acute Care Surg. 2014;77(3):S114-S120. https://doi.org/10.1097/TA.0000000000000328.

73. Powell-Dunford N, Quesada JF, Malsby RF, et al. Risk management analysis of air ambulance blood product administration in combat operations. Aviat Space Environ Med. 2014;85(11):1130-1135. https://doi.org/10.3357/ASEM.3851.2014.

74. Shlaifer A, Siman-Tov M, Radomiliensky I, et al. Prehospital administration of freeze-dried plasma, is it the solution for trauma casualties? J Trauma Acute Care Surg. 2017;83(4):675-682. https://doi.org/10.1097/ta.0000000000001569.

75. West BC, Bentley R, Place RJ. In-flight transfusion of packed red blood cells on a combat search and rescue mission: a case report from operation enduring freedom. Mil Med. 2004;169(3):181-183.

76. Howard JT, Kotwal RS, Santos-Lazada AR, Martin MJ, Stockinger ZT. Reexamination of a battlefield trauma golden hour policy. J Trauma Acute Care Surg. 2018;84(1):11-18. https://doi.org/10.1097/ta.0000000000001727.

77. Vetter TR, Mascha EJ. Bias, confounding, and interaction: lions and tigers, and bears, oh my! Anesth Analg. 2017;125(3):1042-1048. https://doi.org/10.1213/ANE.0000000000002332.

78. Rijnhout TWH, Wever KE, Marinus RHAR, Hoogerwerf N, Geeraedts LMGJ, Tan ECTH. Is prehospital blood transfusion effective and safe in haemorrhagic trauma patients? A systematic review and meta-analysis. Injury. 2019;50:1017-1027. https://doi.org/10.1016/j.injury.2019.03.033.

79. Schober P, Bossers SM, Schwarte LA. Statistical significance versus clinical importance of observed effect sizes: what do P values and confidence intervals really represent? Anesth Analg. 2018;126(3):1068-1072. https://doi.org/10.1213/ANE.0000000000002798.

80. Shand S, Curtis K, Dinh M, Burns B. What is the impact of prehospital blood product administration for patients with catastrophic haemorrhage: an integrative review. Injury. 2019;50(2):226-234. https://doi.org/10.1016/j.injury.2018.11.049.

81. Smith IM, James RH, Dretzke J, Midwinter MJ. Prehospital blood product resuscitation for trauma. Shock. 2016;46(1):3-16. https://doi.org/10.1097/SHK.0000000000000569.

82. Huang GS, Dunham CM. Mortality outcomes in trauma patients undergoing prehospital red blood cell transfusion: a systematic literature review. Int J Burns Trauma. 2017;7(2):17-26.

83. Roback J, Grossman B, Harris T, eds. AABB Technical Manual. Bethesda, MD: American Association of Blood Banks Press; 2011.