ORIGINAL RESEARCH

Efficacy and Safety of Prehospital Blood Transfusion in Traumatized Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Approximately five million individuals have traumatic injuries annually. Implementing prehospital blood-component transfusion (PHBT), encompassing packed red blood cells (p-RBCs), plasma, or platelets, facilitates early hemostatic volume replacement following trauma. The lack of uniform PHBT guidelines persists, relying on diverse parameters and physician experience.

Aim: This study aims to evaluate the efficacy of various components of PHBT, including p-RBCs and plasma, on mortality and hematologic-related outcomes in traumatic patients.

Methods: A comprehensive search strategy was executed to identify pertinent literature comparing the transfusion of p-RBCs, plasma, or a combination of both with standard resuscitation care in traumatized patients. Eligible studies underwent independent screening, and pertinent data were systematically extracted. The analysis employed pooled risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous variables, each accompanied by their respective 95% confidence intervals (CI).

Conflicts of interest: The authors declare no conflict of interest.

Keywords: meta-analysis; prehospital blood transfusion; systematic review; traumatized patients

Abbreviations:
ATC: acute traumatic coagulopathy
CI: confidence interval
FWB: fresh whole blood
INR: international normalized ratio
ISS: Injury Severity Score
LTOWB: low-titer O whole blood
MD: mean difference
NIH: National Institutes of Health
PAMPer: Prehospital Air Medical Plasma
PHBT: prehospital blood-component transfusion
p-RBC: packed red blood cells
PRISMA: Preferred Reporting Item for Systematic Reviews and Meta-Analysis
PTC-RBC: pre-trauma center transfusion of red blood cells
RBC: red blood cells
RCT: randomized controlled trial
RR: risk ratio
SD: standard deviation
TIC: trauma-induced coagulopathy

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Results: Forty studies were included in the qualitative analysis, while 26 of them were included in the quantitative analysis. Solely P-RBCs alone or combined with plasma showed no substantial effect on 24-hour or long-term mortality (RR = 1.13; 95% CI, 0.68 - 1.88; P = .63). Conversely, plasma transfusion alone exhibited a 28% reduction in 24-hour mortality with a RR of 0.72 (95% CI, 0.53 - 0.99; P = .04). In-hospital mortality and length of hospital stay were mostly unaffected by p-RBCs or p-RBCs plus plasma, except for a notable three-day reduction in length of hospital stay with p-RBCs alone (MD = -3.00; 95% CI, -5.01 to -0.99; P = .003). Hematological parameter analysis revealed nuanced effects, including a four-unit increase in RBC requirements with p-RBCs (MD = 3.95; 95% CI, 0.69 - 7.21; P = .02) and a substantial reduction in plasma requirements with plasma transfusion (MD = -0.73; 95% CI, -1.28 to -0.17; P = .01).
Conclusion: This study revealed that plasma transfusion alone was associated with a substantial decrease in 24-hour mortality. Meanwhile, p-RBCs alone or combined with plasma did not significantly impact 24-hour or long-term mortality. In-hospital mortality and length of hospital stay were generally unaffected by p-RBCs or p-RBCs plus plasma, except for a substantial reduction in length of hospital stay with p-RBCs alone.

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Introduction

Globally, an alarming 5.1 million individuals have traumatic injuries annually.[1] These traumatic incidents frequently lead to death due to major hemorrhage, a circumstance that could have been averted in approximately 29% of civilian and 24% of military casualties.[2,3] Implementing prehospital blood-component transfusion (PHBT), encompassing packed red blood cells (p-RBCs), plasma, or platelets, alongside the independent administration of crystalloids, has significantly enhanced remote damage control. This approach facilitates early hemostatic volume replacement following trauma. Previous literature has demonstrated that PHBT involving solely p-RBCs led to decreased prehospital mortality. However, it did not exert a discernible impact on in-hospital mortality.[4] Overall, PHBT has been shown to diminish the consumption of blood products during the hospitalization period and exerts a favorable impact on coagulopathy.[5,6]

Several decades ago, the exclusive option for transfusion was fresh whole blood (FWB), which, when utilized, demonstrated a reduction in mortality, particularly in challenging environments such as the battlefield.[7] During the early 1970s, FWB was substituted by blood components, primarily due to the extended storage capabilities of the latter.[8] The superior capacity for oxygen transport, hemostatic functions, and preserved platelet functionality render blood components more suitable for utilization in civil settings or challenging environments.[7] Nevertheless, only a limited number of helicopter Emergency Medical Services are equipped to transport cold-stored whole blood. In contrast, the United States Army employs warm FWB in combat hospitals through a walking blood bank.[9–11]

Acute traumatic coagulopathy (ATC) poses a substantial threat to trauma patients, often manifesting prior to volume resuscitation, even in the prehospital phase. Combined with hypothermia and acidosis, it forms the "lethal triad" in trauma care, linked to poor survival.[12–14] Early hemostatic resuscitation targets ATC, potentially enhancing patient outcomes.[12–14]

The Prehospital Air Medical Plasma (PAMPer) trial established that prehospital plasma resuscitation led to a nearly 10% reduction in 30-day mortality for severely injured patients at risk of hemorrhagic shock compared to standard care resuscitation.[15] The ideal prehospital blood product for resuscitating hemorrhagic shock from trauma remains uncertain. Both prehospital p-RBCs and plasma may enhance outcomes in in-hospital damage control resuscitation compared to using either product alone.

In a previous meta-analysis, simultaneous administration of p-RBCs and plasma via prehospital PHBT showed a substantial reduction in long-term mortality odds for hemorrhagic trauma patients.[16] However, due to predominantly poor-quality evidence, firm conclusions on survival advantage cannot be definitively drawn. Coagulopathy-related outcomes were not assessed, and recent high-quality studies may impact current inconclusive evidence.[17–19] Lack of uniform PHBT guidelines persists, relying on diverse parameters and physician experience.[16,20] This study aims to comprehensively evaluate the efficacy of various components of PHBT, including p-RBCs and plasma, on mortality, hematologic, and coagulopathy-related outcomes.

Methods

This meta-analysis followed the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and implemented the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[21,22]

Literature Search

The various electronic databases were searched extensively, including Cochrane Library (Wiley; Hoboken, New Jersey USA); PubMed (National Center for Biotechnology Information, National Institutes of Health; Bethesda, Maryland USA); Scopus (Elsevier; Amsterdam, Netherlands); Web of Science (Clarivate Analytics; London, United Kingdom); and EMBASE (Elsevier; Amsterdam, Netherlands). Two reviewers independently searched each database using the research key terms provided in Supplementary Table 1 (Supplementary Material available online only). This extensive search was conducted from inception until January 2024. Additionally, reference lists of eligible articles and previous meta-analyses were examined manually to identify relevant citations.

Eligibility Criteria

Two reviewers evaluated the retrieved studies independently and meticulously examined their eligibility according to the predetermined criteria: (1) included studies on traumatized patients; (2) studies comparing the prehospital transfusion of p-RBCs, plasma, or a combination of both with the standard resuscitation care following local protocols in each study as a control (typically crystalloid); and (3) studies assessing any of the following outcomes for the mentioned interventions: mortality, units required of RBCs, plasma, or both during 24 hours, shock, international normalized ratio (INR), hemoglobin, length of hospital stay, or trauma-induced coagulopathy (TIC).

Numerous studies were excluded from analysis due to exclusion criteria: (1) non-comparative studies; (2) studies not published

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in English; (3) editorial letters, abstracts, or comments only; and (4) incorporation of unpublished data.

The primary outcomes of this study were 24-hour and long-term mortality and units required of RBCs, plasma, or both during the 24-hour period. Twenty-four-hour mortality was characterized by patients who passed away within 24 hours after the injury, including those who died at the prehospital scene or during transport. Long-term mortality was specified as mortality ≥ 30 days or during the hospital stay. The secondary outcomes were shock on admission, INR, hemoglobin, length of hospital stay, or TIC.

Data Gathering

Data were extracted in offline data extraction sheets. Extracted data included the study ID, publication year, study location, study arms, sample size, gender distribution, participant ages, study inclusion criteria, cause of injury, Injury Severity Score (ISS), conclusions, and primary outcomes. Data in formats (such as median or range) were translated to mean, standard deviation (SD) using Cochrane Handbook Standard Deviation guidelines.[21]

Risk of Bias Assessment

The quality of the trials was evaluated and included in this study using the Cochrane Risk of Bias Assessment Tool 1 (ROB1), specifically designed for interventional studies.[23] This tool considers factors such as random sequence generation, allocation concealment, blinding of investigators and participants, attrition bias, selective reporting, and other biases. Each aspect was carefully examined to assess potential biases within the included studies. Additionally, the quality assessment of the cohort and case-control studies included in the analysis was evaluated using the National Institutes of Health (NIH; Bethesda, Maryland, USA) tool.[24]

Data Synthesis

Different statistical methods were utilized based on outcome types: mean differences (MD) with SD were pooled using the inverse variance method for continuous outcomes, while risk ratios (RR) with 95% confidence intervals (CI) were employed using the Mantel-Haenszel method for dichotomous outcomes. A fixed-effect model was initially used for homogeneous studies, but a random-effects model was applied for heterogeneous ones. Sensitivity analysis was also applied to resolve heterogeneity if the random-effect model proved ineffective in addressing it. Statistical heterogeneity was evaluated through I^2 and Chi^2 tests, with a P value <.10 indicating heterogeneity and $I^2 \geq 50\%$ suggesting high heterogeneity. Review Manager (RevMan; The Cochrane Collaboration; London, United Kingdom) version 5.4 was used to conduct all the analyses.

Results

Literature Search Results

Following an initial search across four databases (Cochrane, Scopus, Web of Science, and PubMed), a total of 10,865 papers met the initial inclusion criteria; after 3,174 duplicate papers were removed, the remaining 7,691 articles for the title and abstract screening. The inclusion and exclusion criteria were applied, making 61 articles available for full-text examination. Finally, 40 unique studies were included in this systematic review;[4–6,15,17–20,25–56] of them, 26 studies were eligible for meta-analysis.[4–6,15,17–20,25–42] The PRISMA diagram depicting this selection process is shown in Figure 1.

Characteristics of the Included Studies

This systematic review included 40 studies encompassing 23,387 patients. Two were case-control studies,[22,49] 15 were randomized controlled trials (RCTs),[15,17–20,27,33,35–38,40,46,48,56] and the rest were cohort studies. The majority of studies were conducted in the United States, with most of them evaluating the different components of blood transfusion in prehospital settings in traumatized civilian patients. The mean ISS for patients in the included studies ranged from 10 in Gruen, et al[36] to 45.5 in Gaessler, et al.[52] Inclusion criteria varied among studies; however, the majority of them included traumatized hypotensive patients < 90mmHg with tachycardia >108 beats per minute. The baseline and summary of the included studies are shown in Supplementary Table 2 (Supplementary Material available online only).

Quality Assessment Findings

Regarding included RCTs, the following studies showed a high risk in randomization and allocation processes: Crombie, et al; Deeb, et al; Jost, et al; Stassen, et al; and Ziegler, et al.[19,35,38,46,56] As to two case-control studies, both of them were of fair quality according to the NIH tool.[25,49] In the cohort studies, 17 were of fair quality, four were of good quality, and two were of poor quality. Supplementary Figure 1 and Supplementary Table 3 and Table 4 show the quality assessment summary (Supplementary Material available online only).

Outcomes: Mortality

24-Hour Mortality—Packed RBCs were compared to control at this time point in six studies encompassing 3,396 patients. However, no substantial difference was noted between any of them (RR = 1.13; 95% CI, 0.68 - 1.88; P = .63).[4–6,20,25,38] Furthermore, the addition of plasma to p-RBCs was more used in the literature than p-RBCs alone (eight studies encompassing 5,672 patients).[17,19,20,26,28,32,34,39] However, this did not also substantially impact the mortality compared to the control group (RR = 1.13; 95% CI, 0.51 - 2.48; P = .76). Transfusion of plasma was assessed in ten studies, including 2,650 patients.[15,18,20,27,33,35–37,40,41] Unlike the previous two interventions, plasma transfusion significantly decreased 24-hour mortality outcome compared to the control (RR = 0.72; 95% CI, 0.53 - 0.99; P = .04). All of the studies pooled in the previous subgroups were heterogeneous (Chi^2-P < .10); however, the heterogeneity was resolved in the plasma subgroup by excluding Kim, et al[41] (Chi^2-P = .45; I^2 = 0.0%) and the pooled analysis also favored plasma subgroup over control (RR = 0.63; 95% CI, 0.52 - 0.76; P < .001); Figure 2 and Supplementary Figure 2, respectively (Supplementary Material available online only).

Long-Term Mortality (≥ 30 Days)—In this outcome, the analysis revealed the same pattern noted in the 24-hour mortality outcome, with only plasma transfusion showing a substantial reduction in mortality compared to control (RR = 0.75; 95% CI, 0.63 - 0.89; P < .001). Pooled RRs for p-RBCs and p-RBCs plus plasma were as follows: RR = 1.13; 95% CI, 0.77 - 1.65; P = .53 and RR = 0.92; 95% CI, 0.56 - 1.50; P = .73, respectively. Eight studies encompassing 2,040 patients assessed plasma versus control, and they were homogenous (Ch^2-P = .32; I^2 = 14.0%).[15,18,20,27,33,35,36,40] The other two subgroups showed marked heterogeneity among their pooled studies (Chi^2-P < .10). However, the heterogeneity was resolved this by sensitivity analysis as follows. In the p-RBCs subgroup, heterogeneity was resolved after excluding Deeb, et al[38] (Chi^2-P = .41; I^2 = 0.0% and RR = 0.96; 95% CI, 0.85 - 1.08;

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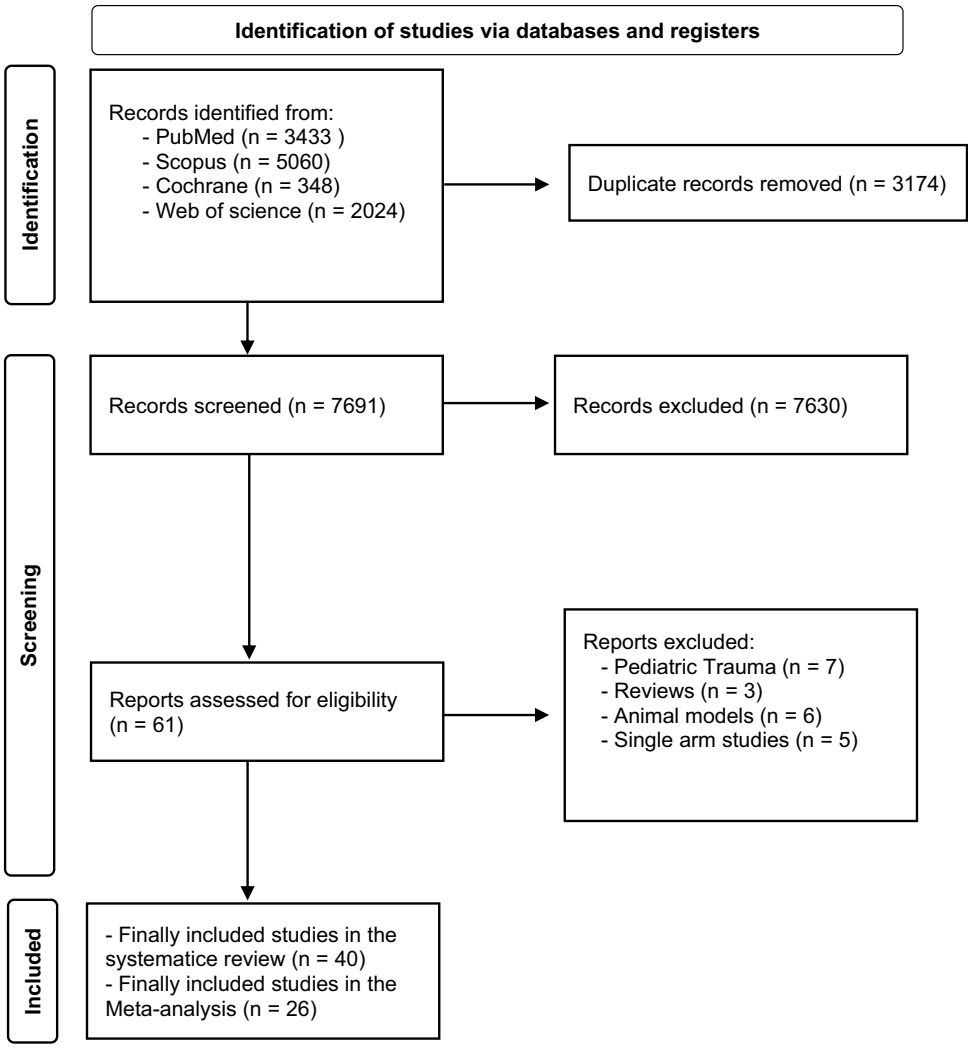

Figure 1. PRISMA Flow Chart.

P = .49). In the p-RBCs plus plasma subgroup, the heterogeneity was resolved after excluding Shackelford, et al[26] (Chi^2-P = .13; I^2 = 52.0% and RR = 1.11; 95% CI, 0.73 - 1.69; P = .64); Figure 3 and Supplementary Figure 3, respectively (Supplementary Material available online only).

Up to Six-Hour Mortality—Packed RBCs plus plasma subgroup was assessed in five studies encompassing 2,020 patients.[17,19,32,34,39] Pooled RR did not favor this intervention over the control group (RR = 1.07; 95% CI, 0.57 - 2.01; P = .83). Also, the pooled studies were heterogenous with Chi^2-P = .003; I^2 = 75.0%, but the heterogeneity was resolved in the sensitivity analysis after excluding Holcomb, et al[32] (Chi^2-P = .15; I^2 = 44.0%). However, no substantial difference was noted between the p-RBCs plus plasma subgroup and control after the later sensitivity analysis (RR = 0.85; 95% CI, 0.50 - 1.43; P = .54). As to p-RBCs and plasma-only subgroups, each of them was assessed in two studies encompassing patients in p-RBCs and patients in plasma subgroups. Still, no substantial difference was noted between these two groups. Pooled estimates for p-RBCs and plasma compared to controls were: RR = 1.62; 95% CI, 0.19 - 13.95; P = .66 and RR = 1.85; 95% CI, 0.46 - 7.46; P = .39, respectively. Pooled studies were heterogenous in the p-RBCs subgroup while they were homogenous in the plasma subgroup (Chi^2-P = .66; I^2 = 0.0%); Supplementary Figure 4 and Figure 5, respectively (Supplementary Material available online only).

Overall Mortality—In this outcome, only two studies were eligible for meta-analysis under the plasma-only subgroup.[41,42] They only included 155 patients, and the analysis showed a higher risk for mortality in the plasma subgroup over the control (RR = 2.45; 95% CI, 1.11 - 5.39; P = .03). These studies were homogenous (Chi^2-P = .29; I^2 = 11.0%); Supplementary Figure 6 (Supplementary Material available online only).

In-Hospital Mortality—In this outcome, the p-RBCs plus plasma subgroup was only eligible for meta-analysis, with three studies encompassing 3,542 patients comparing this intervention to the control.[28,34,39] The analysis revealed no substantial difference between the compared groups (RR = 1.82; 95% CI, 0.54 - 6.12; P = .33). These studies were heterogeneous (Chi^2-P < .001; I^2 = 95.0%), and the heterogeneity could not be resolved (Figure 4).

Outcomes: Length of Hospital Stay

In this outcome, p-RBCs and p-RBCs plus plasma subgroups were assessed in two studies.[17,26] In these studies, p-RBCs substantially

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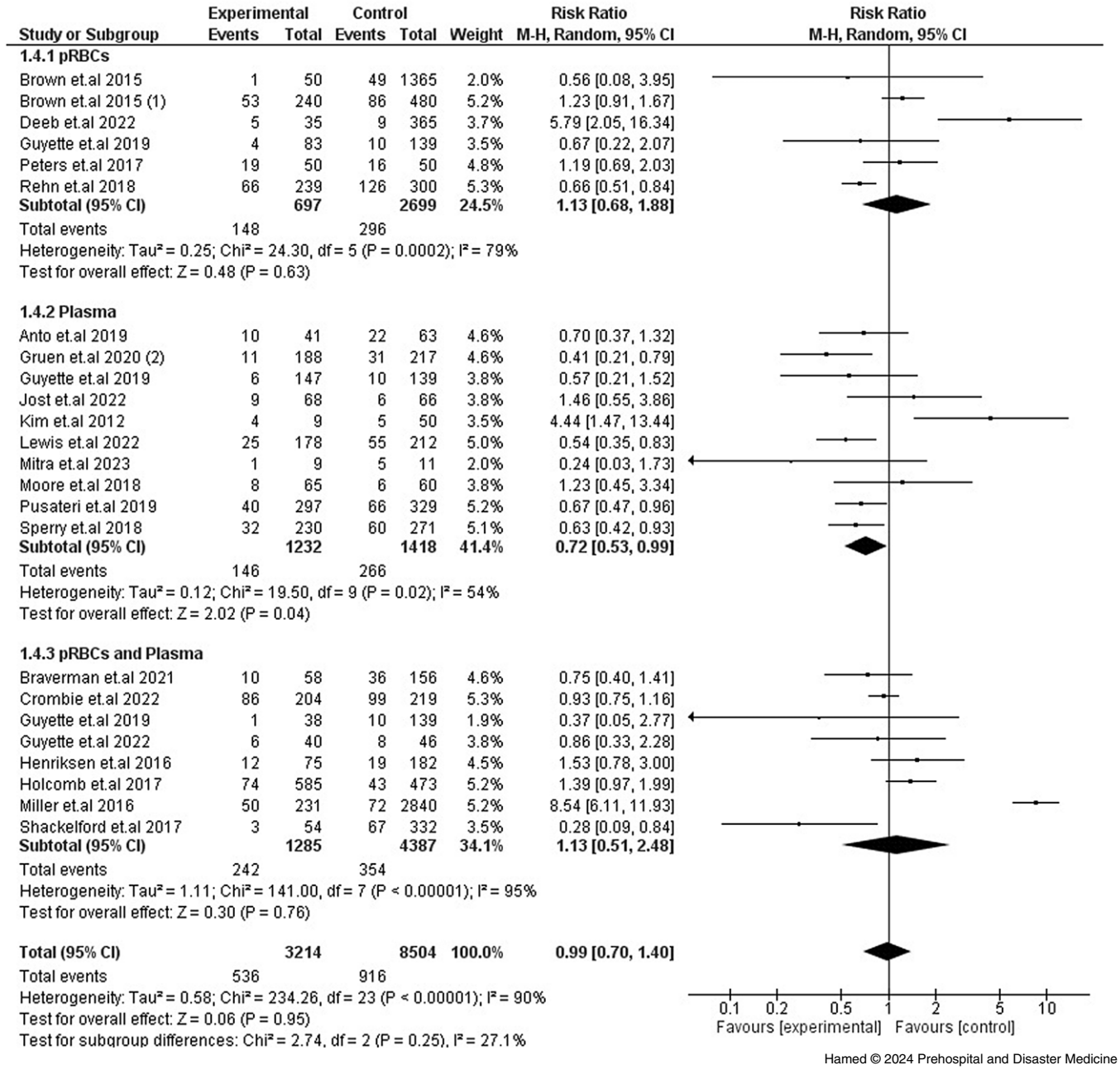

Figure 2. Forest Plot of 24-Hour Mortality.

reduced the length of hospital stay (MD = -3.00; 95% CI, -5.01 to -0.99; P = .003) while p-RBCs plus plasma did not (MD = -3.67; 95% CI, -9.12 to 1.78; P = .19). The plasm-only subgroup was eligible for meta-analysis and was evaluated in five studies encompassing 663 patients. However, no substantial difference was found between the plasma and control groups (MD = 1.03; 95% CI, -1.88 to 3.94; P = .49). Pooled studies in this subgroup were homogenous (Chi^2-P = .17; I^2 = 38.0%); Supplementary Figure 7 (Supplementary Material available online only).

Outcomes: Hematological Parameters

24-Hour Required RBCs—Packed RBC intervention was evaluated in five studies encompassing 2,848 patients.[5,6,20,25,38] The pooled analysis showed that p-RBCs required more RBC units than the control (MD = 3.95; 95% CI, 0.69 - 7.21; P = .02). Yet, the pooled studies were heterogenous (Chi^2-P < .001; I^2 = 86.0%). Conversely, plasma transfusion (seven studies with 2,141 patients) significantly reduced the 24-hour RBCs required compared to the control group (MD = -0.73; 95% CI, -1.28 to -0.17; P = .010), and the pooled studies were also homogenous (Chi^2-P = .30; I^2 = 17.0%). Four studies with 1,802 patients assessed p-RBCs plus plasma versus control did not find substantial differences between either (MD = 1.76; 95% CI, -0.11 to 3.62; P = .07). Pooled studies for this subgroup were heterogeneous (Chi^2-P < .001; I^2 = 89.0%), but it was resolved after excluding Guyette, et al[17] in the sensitivity analysis (Chi^2-P = .20; I^2 = 38.0%). After resolving heterogeneity, the pooled analysis showed that p-RBCs plus plasma had substantially

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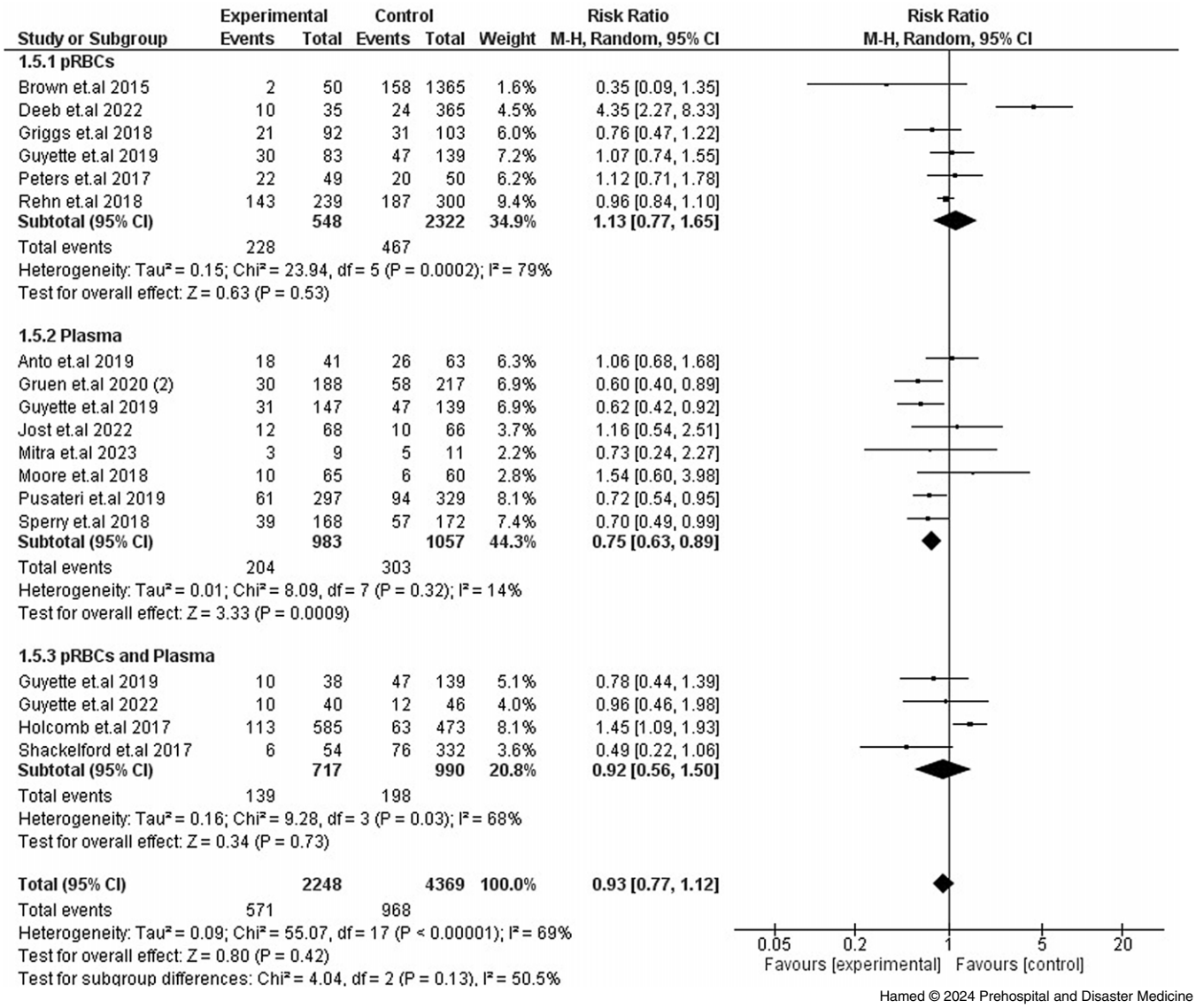

Figure 3. Forest plot of Long-Term Mortality (≥ 30 Days).

higher RBCs requirement than the control with MD = 2.46; 95% CI, 1.55 - 3.37; and P < .001 (Figure 5 and Supplementary Figure 8, respectively; Supplementary Material available online only).

24-Hour Required Plasma— Three studies encompassing 2,357 patients were eligible for meta-analysis of p-RBC intervention versus control.[5,6,20] The pooled analysis showed that p-RBCs had higher plasma requirements than the control (MD = 0.66; 95% CI, 0.09 to 1.22; P = .02). The pooled studies were homogenous (Chi^2-P = .54; I^2 = 0.0%). Plasma transfusion (seven studies with 2,141 patients) did not change the 24-hour plasma requirement compared to the control group (MD = -0.42; 95% CI, -1.06 to 0.22; P = .20). Pooled studies for this subgroup were heterogeneous (Chi^2-P < .001; I^2 = 75.0%), but it was resolved after excluding Pusateri, et al[27] in the sensitivity analysis (Chi^2-P = .69; I^2 = 0.0%). Yet, there was no significant difference between the compared groups. Four studies with 1,802 patients assessed p-RBCs plus plasma versus control and found a substantial difference between showing higher plasma requirements in p-RBCs plus plasma subgroup (MD = 1.27; 95% CI, 0.22 - 2.31; P = .02). Pooled studies for this subgroup were heterogeneous (Chi^2-P < .001; I^2 = 86.0%), but it was resolved after excluding Guyette, et al[17] in the sensitivity analysis (Chi^2-P = .62; I^2 = 0.0%). After resolving heterogeneity, the pooled analysis showed higher plasma requirements in the p-RBCs plus plasma subgroup with MD = 1.82; 95% CI, 1.33 - 2.31; and P < .001 (Figure 6 and Supplementary Figure 9, respectively; Supplementary Material available online only).

24-Hour Required Platelet—Packed RBC transfusion showed higher platelets requirements than the control group with MD = 0.35; 95% CI, 0.16 - 0.53; and P < .001. However, the plasma subgroup and p-RBCs plus plasma subgroups did not show a substantial difference when compared to the control group

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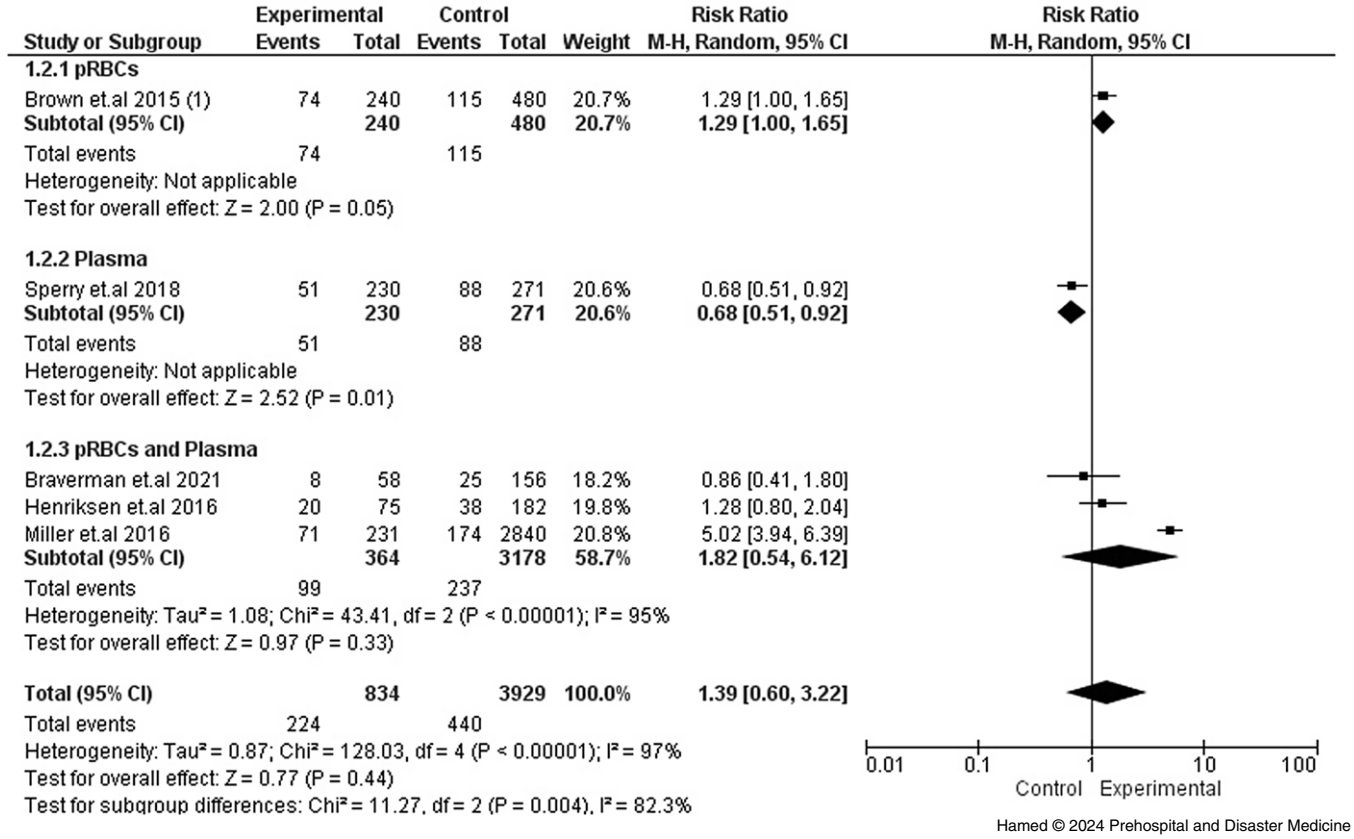

Figure 4. Forest Plot of In-Hospital Mortality.

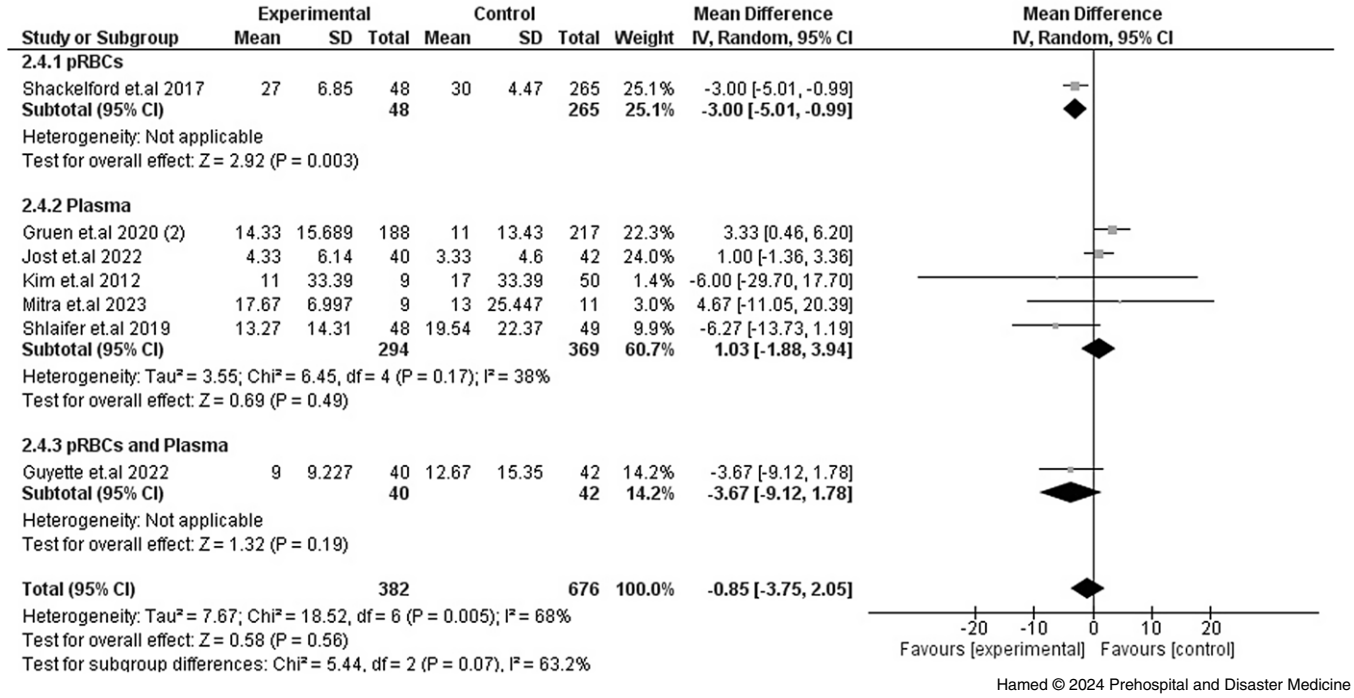

Figure 5. Forest Plot of 24-Hour Required RBCs.

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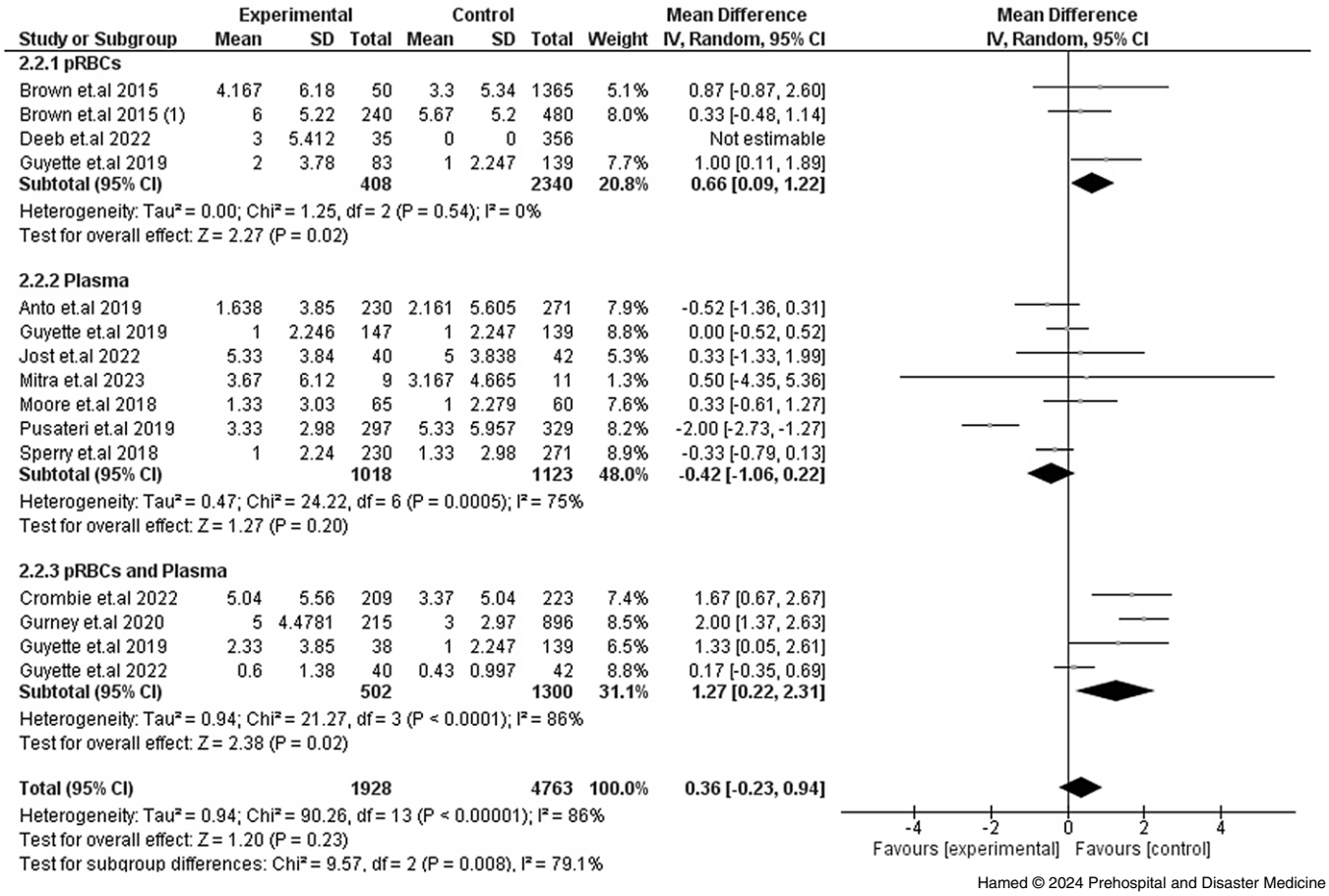

Figure 6. Forest Plot of 24-Hour Required Plasma.

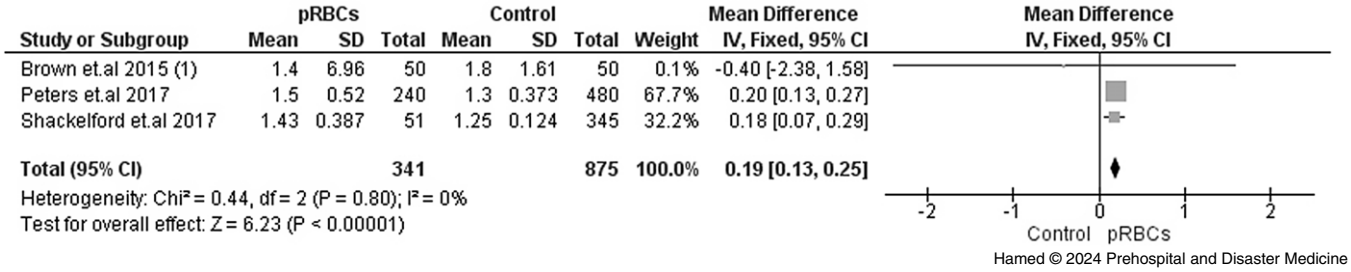

Figure 7. Forest Plot of INR Assessed on Admission with p-RBCs Transfusion.

(MD = -0.16; 95% CI, -0.75 to 0.44; P = .60 and MD = -0.15; 95% CI, -0.39 to 0.10; P = .24, respectively); Supplementary Figure 10 (Supplementary Material available online only).

Outcomes Assessed on Admission with p-RBCs Transfusion

Packed RBCs significantly increased the INR compared to the control group with MD = 0.18; 95% CI, 0.07 - 0.29; and P < .001. This outcome was assessed in three studies encompassing 1,216 patients, and they were homogenous (Chi^2-P = .80; I^2 = 0.0%);[5,25,26] Figure 7.

Both shock and hemoglobin were also assessed on admission; however, no substantial difference was noted between RR = 1.05; 95% CI, 0.94 - 1.18; P = .40 and MD = -0.26; 95% CI, -0.56 to 0.05; P = .10. The studies that assessed the latter two outcomes were homogenous (Chi^2-P > .10); Supplementary Figure 11 and Figure 12, respectively (Supplementary Material available online only).

Trauma-Induced Coagulopathy (TIC)

The TIC was evaluated in two studies with 1,199 patients.[5,25] Packed RBCs showed a substantially higher RR for TIC compared to the control group (RR = 1.52; 95% CI, 1.27 - 1.82; P < .001). Pooled studies were homogenous (Chi^2-P = .94; I^2 = 0.0%); Supplementary Figure 13 (Supplementary Material available online only).

Discussion

This quantitative analysis examined the effects of prehospital blood transfusion interventions among 26 studies in trauma patients. While p-RBCs alone or combined with plasma did not

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significantly impact 24-hour or long-term mortality, plasma transfusion alone was associated with a substantial decrease in 24-hour mortality. Up to six-hour mortality showed no significant differences among interventions, and overall mortality demonstrated a higher risk with plasma transfusion alone. In-hospital mortality and length of hospital stay were generally unaffected by p-RBCs or p-RBCs plus plasma, except for a substantial reduction in length of hospital stay with p-RBCs alone. Hematological parameters analysis revealed increased RBC requirements with p-RBCs, reduced requirements with plasma transfusion, and significantly higher requirements for plasma with p-RBCs plus plasma. Additionally, p-RBCs increased the INR, indicating potential coagulopathy and TIC risk was higher with p-RBCs transfusion.

Over the preceding two decades, the landscape of trauma resuscitation has undergone a substantial transformation, primarily directed toward mitigating coagulopathy by minimizing reliance on crystalloid-based resuscitation. The approach has observed a pivotal shift, emphasizing the early implementation of ratio-based "damage control resuscitation" upon the patient's arrival at the definitive trauma care facility.[8,57,58] Nevertheless, with these advancements, patients still have elevated mortality rates attributed to hemorrhage within the initial hours of admission.[8,59–61] A heightened emphasis on the consequences of hemorrhage and early fatalities resulting from this cause has been underscored, as evidenced by recent advocacy for the goal of achieving zero preventable deaths, as articulated by the National Academies of Sciences, Engineering, and Medicine (NASEM; Washington, DC USA).[62] The historical application of whole-blood transfusion in military medicine for addressing hemorrhagic shock and coagulopathy has been extensive. Notably, the adoption of whole-blood resuscitation has witnessed a growing trend in civilian health care settings, particularly in the past five years. In-hospital administration of low-titer anti-A and anti-B group O whole blood has attained recognition as standard care in over 70 high-volume trauma centers throughout the United States.[63,64]

Administering whole blood in the prehospital environment for managing hemorrhagic shock is appealing and represents a coherent extension of the observed survival benefits associated with individual blood components when administered promptly, near the time of injury, within the prehospital setting.[15,26] High-level data concerning the safety and efficacy of whole blood administration in the prehospital setting are scarce. The current knowledge is limited, necessitating a definitive trial to substantiate and warrant the early post-injury utilization of this invaluable resource.

Guyette, et al's 2019 study revealed compelling findings indicating that any blood product resuscitation was linked to lower mortality compared to resuscitation with crystalloid alone.[20] Notably, similar reductions in mortality were observed for p-RBCs and plasma individually. However, the combined administration of p-RBCs and plasma demonstrated a markedly greater reduction in mortality than either p-RBCs or plasma alone.[20] Conversely, among patients meeting the criteria for blood product administration, crystalloid infusion exhibited a dose-response increase in mortality.[20] In cases where only crystalloid was administered, smaller volumes of up to 500mL were associated with the lowest unadjusted mortality when compared to scenarios with no crystalloid or larger volumes.[20] However, their data and findings were limited by their small sample size. These findings did not align with current results that showed a decrease in mortality only with plasma-only transfusion (long-term and 24-hour mortality).

In a 2022 study by Guyette, et al, a single-center, prospective, cluster-randomized trial for injured air medical patients compared prehospital and in-hospital low-titer O whole blood (LTOWB) resuscitation to standard care. Inclusion criteria were based on prehospital vital signs, and primary outcomes focused on feasibility.[17] The trial was halted at 77% enrollment, reporting a 28-day mortality of 26%. Prehospital LTOWB did not show a statistical mortality benefit at 28 days compared to standard care.[17] However, LTOWB patients had lower red cell transfusion requirements and a reduced incidence of abnormal thromboelastographic measurements without documented transfusion reactions. However, in this study, the whole blood, which included p-RBCs plus plasma, did not substantially differ regarding RBC daily requirements.

Including the prior study in this analysis introduced heterogeneity in the requirements for RBCs. A notable shift was observed upon its exclusion in the sensitivity analysis, indicating higher RBC requirements in the whole blood group. This discrepancy can be rationalized by recognizing the limitations inherent in the single-institution cluster-randomized pilot design of the earlier study, which inherently lacked the necessary power for a conclusive clinical outcome comparison.[17] The sensitivity analysis underscores the impact of study design on outcomes and emphasizes the importance of considering the robustness of individual studies in meta-analytic approaches.[17] Notably, resuscitation practices in the prehospital and early hospital settings exhibit substantial variability nationwide. The study's sample size was small, and lower-than-anticipated adherence to the protocol was observed, potentially introducing differences in comparison arms that could confound any demonstrated outcome variances.[17]

In two studies by Brown, et al, the first involved 1,415 severely injured patients with blunt trauma, 50 of whom received pre-trauma center transfusions of p-RBCs (PTC RBC).[5,6] The PTC RBC group exhibited significantly reduced 24-hour mortality (95% reduction), 30-day mortality (64% reduction), and odds of traumatic-induced coagulopathy (88% reduction). The second study, involving 240 treated patients matched with 480 controls, found that PTC RBC transfusion was associated with increased 24-hour survival, lower odds of shock, and reduced 24-hour RBC requirement.[5,6] The observed discrepancy between pooled analysis and Brown, et al's findings may stem from several factors. Notably, their studies featured a notable imbalance in the comparison arm, with only 50 patients out of 1,415 receiving the intervention. This mismatch could introduce selection bias and compromise the robustness of the comparison. Furthermore, the cohort designs employed in both studies might not effectively control for potential confounding variables, potentially influencing the outcomes. In this qualitative analysis, both of Brown et al.'s studies were deemed of fair quality, suggesting that methodological limitations might contribute to the differences in results.

Regarding prehospital plasma-only transfusion, Jost, et al (PREHO-PLYO study) affirmed the practicability and safety of emergency medical response teams administering prehospital plasma in its lyophilized form.[35] This mode of delivery did not have an adverse impact on the duration of care or other treatment modalities.[15,33] The RePHILL trial, a multicenter study involving four prehospital services, assessed the use of prehospital RBCs and freeze-dried plasma in trauma resuscitation.[19] Adult patients with hypotension presumed to be due to hemorrhagic shock were randomized to receive RBCs and plasma or crystalloid resuscitation. No substantial differences were

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observed in the primary composite outcome of mortality at hospital discharge or failure to reach lactate clearance, as well as secondary outcomes.[19] Prior studies (PAMPer and COMBAT) on prehospital plasma showed varied results, with one indicating a 9.8% absolute risk reduction in mortality at 30 days, possibly influenced by transport mechanisms and prehospital times.[15,33] The RePHILL trial emphasized the importance of an adequate time window for prehospital interventions to be effective.[19] In this meta-analysis, plasma transfusion without p-RBCs significantly decreased long-term and 24-hour mortality.

As previously indicated, the present observations concerning shock, INR, and hemoglobin levels upon admission did not exhibit substantial differences between prehospital p-RBCs transfusion and standard care protocols. This correlation is consistent with prior research findings documented in the existing literature.[5,6,25,26]

The prior meta-analysis conducted by Rijnhout, et al is consistent with current findings concerning the implications of p-RBCs and their correlation with long-term and 24-hour mortality outcomes.[16] Despite this concordance, disparities arise when comparing the effects of the combination of p-RBCs and plasma versus a control group. Rijnhout, et al observed a reduction in mortality with this combination, while this study did not yield statistically substantial differences.[16] Notably, their investigation encompassed a smaller cohort, incorporating nine studies across all subgroups, in contrast to the 26 studies encompassed in the analysis. The augmented sample size in the study strengthens the robustness of current evidence.

Clinical Implications

This analysis has elaborated on the potential practical applications of the current findings, focusing on how they could influence prehospital trauma care protocols. Specifically discussed is how these results support the use of plasma in emergency settings and the potential for updated clinical guidelines that could enhance patient outcomes.

Research Implications

Future trials are suggested that could explore the optimal transfusion strategies in different trauma scenarios and emphasize the need for more high-quality, large-scale studies to validate these conclusions.

Limitations

This meta-analysis faces limitations stemming from the mixed study design, incorporating both scene and inter-facility transports, as observed in the study by Sperry, et al.[15] Additionally, the absence of reported key study characteristics, such as the ISS, poses a potential confounder, hindering a comprehensive understanding of the impact of prehospital blood transfusion. The diverse nature of transfusion strategies across studies and the logistical challenges associated with storing and transporting blood components further underscore the complexity of drawing definitive conclusions from the available data. To address these limitations, future research in this field should strive for standardized study designs, comprehensive reporting of key variables, and uniformity in transfusion protocols to enhance the reliability and applicability of findings in prehospital blood transfusion studies.

Conclusion

The current study revealed that p-RBCs alone or combined with plasma did not significantly impact 24-hour or long-term mortality; plasma transfusion alone was associated with a substantial decrease in 24-hour mortality. In-hospital mortality and length of hospital stay were generally unaffected by p-RBCs or p-RBCs plus plasma, except for a substantial reduction in length of hospital stay with p-RBCs alone. Hematological parameters analysis revealed increased RBC requirements with p-RBCs, reduced requirements with plasma transfusion, and significantly higher requirements for plasma with p-RBCs plus plasma. Future high-quality trials are essential, necessitating the stratification of substantial confounding factors and fostering greater uniformity in transfusion protocols.

Supplementary Materials

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