Does the evidence support the importance of high transfusion ratios of plasma and platelets to red blood cells in improving outcomes in severely injured patients: a systematic review and meta-analyses

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BACKGROUND: Deaths by exsanguination in trauma are preventable with hemorrhage control and resuscitation with allogeneic blood products (ABPs). The ideal transfusion ratio is unknown. We compared efficacy and safety of high transfusion ratios of FFP:RBC and PLT:RBC with low ratios in trauma.
STUDY DESIGN AND METHODS: Medline, Embase, Cochrane, and Controlled Clinical Trials Register were searched. Observational and randomized data were included. Risk of bias was assessed using validated tools. Primary outcome was 24-h and 30-day mortality. Secondary outcomes were exposure to ABPs and improvement of coagulopathy. Meta-analysis was conducted using a random-effects model. Strength and evidence quality were graded using GRADE profile
RESULTS: 55 studies were included (2 randomized and 53 observational), with low and moderate risk of bias, respectively, and overall low evidence quality. The two RCTs showed no mortality difference (odds ratio [OR], 1.35; 95% confidence interval [CI], 0.40-4.59). Observational studies reported lower mortality in high FFP:RBCs ratio (OR, 0.38 [95% CI, 0.22-0.68] for 1:1 vs. <1:1; OR, 0.42 [95% CI, 0.22-0.81] for 1:1.5 vs. <1:1.5; and OR, 0.47 [95% CI, 0.31-0.71] for 1:2 vs. <1:2, respectively). Meta-analyses in observational studies showed no difference in exposure to ABPs. No data on coagulopathy for meta-analysis was identified.
CONCLUSIONS: Meta-analyses in observational studies suggest survival benefit and no difference in exposure to ABPs. No survival benefit in RCTs was identified. These conflicting results should be interpreted with caution. Studies are mostly observational, with relatively small sample sizes, nonrandom treatment allocation, and high potential for confounding. Further research is warranted.

Trauma is responsible for one in 10 deaths worldwide and is the leading cause of mortality in individuals younger than 35 years of age.[1,2] Hemorrhage accounts for 40% of all trauma deaths.[3] Bleeding is exacerbated by acute trauma coagulopathy (ATC),[3,4] which is present before resuscitation in 25% of patients.[4,5] Deaths by exsanguination and coagulopathy are potentially preventable with rapid hemorrhage control and proper resuscitation strategies.[5]

Resuscitation strategies targeted at ATC have demonstrated a lower risk of death from exsanguination, possibly mediated by early reversal of coagulopathy with subsequent decreased bleeding.[5,6] However, the intrinsic mechanisms

of ATC are still controversial, such as the balance between inhibition of procoagulant pathways and fibrinolysis.[7] Due to this uncertainty, the amount of fresh-frozen plasma (FFP) and platelets (PLTs) that should be used in relation to the amount of red blood cells (RBCs) transfused or the importance of other clotting factor concentrates are unknown. The principle of damage control resuscitation, which is characterized by early administration of blood products using a FFP:PLTs:RBCs ratio of 1:1:1, aims to prevent and correct the ATC while minimizing the use of crystalloids. These principles have demonstrated improved outcomes compared to traditional resuscitation practices.[7–9]

However, several studies have questioned the principle of 1:1:1 ratio, reporting improved outcomes with other fixed transfusion ratios of FFP:PLTs:RBCs, FFP:RBCs, or PLTs:RBCs[9] or using viscoelastic methods[10-13] such as thromboelastography (TEG [Haemonetics Corporation]) and rotational thrombelastometry (ROTEM [Tem Innovations GmbH]) to direct resuscitation. These tests provide global information on the dynamics of clot development, stabilization, and dissolution, reflecting in vivo hemostasis and provide a more goal-directed approach to transfusion.[12] Currently, there are no data supporting the optimal approach, with centers using massive transfusion protocols (MTPs) with different fixed transfusion ratios on admission, followed by transfusion guided by laboratory tests or TEG/ROTEM.[14–17] Other centers use a more goal-directed approach with TEG/ROTEM assessment at admission, using other concentrate of clotting factors, such as prothrombin complex concentrate (PCC; Octaplex), fibrinogen concentrate, and antifibrinolytic drugs.[13–17] We sought to review the evidence supporting different transfusion ratios of FFP and PLTs to RBCs or FFP or PLTs to RBCs. Specifically, we aimed to compare the effects of high transfusion ratio of FFP and/or PLTs to RBCs to low ratios on in-hospital mortality, exposure to allogeneic blood products, and coagulopathy.

MATERIALS AND METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] Meta-analyses were performed according to the guidelines from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.[19]

Studies

This review included prospective and retrospective cohort studies with a control group (e.g., observational studies comparing high vs. low transfusion ratios) and randomized controlled trials (RCTs). To be included, studies should have reported at least one outcome of interest. We excluded observational studies that addressed other approaches such as transfusion guided by viscoelastic methods or studies that addressed the use of other concentrate of clotting factors. Case reports, case series, and conference proceedings were also excluded.

Participants

Studies were included if they were conducted in adult trauma patients (≥15 years old) with an important risk of bleeding as per each study definition. Studies should have included patients who received at least 1 unit of RBCs within the first 24 hours postadmission.

Interventions

Intervention was the resuscitation of trauma patients using a high fixed transfusion ratio of FFP and PLTs to RBCs or FFP or PLTs to RBCs, as defined in each study. The control was a low fixed transfusion ratio of FFP and PLTs to RBCs or FFP or RBCs to RBCs, also defined and compared in each study.

Outcome measures

The primary outcome was in-hospital mortality assessed at two time points: at 24 hours of admission and at 30 days of admission. Secondary outcomes were: 1) cumulative number of allogeneic RBCs, FFP, and PLT units transfused in 24 hours postadmission and 2) effect on the ATC, represented by values of international normalized ratio (INR), fibrinogen, and TEG or ROTEM variables, all measured within 24 hours postadmission.

Search methods

We searched Medline (from 1946 to July 31, 2018), Embase (1947 to July 31, 2018), Cochrane Controlled Trials Register (from inception to July 31, 2018), ClinicalTrials.gov (http://www.clinicaltrials.gov), and Google Scholar (first 200 hits). The search was not restricted by date, language, or publication status. Search terms were defined a priori and by reviewing the MeSH terms of articles identified in preliminary literature searches. The search strategy was based on the Medline search strategy and was modified as necessary for the other databases. A sensitive search strategy combining MeSH headings and the keywords "transfusion ratios/component transfusion/balanced resuscitation/hemostatic resuscitation/bleeding/trauma coagulopathy/trauma induced coagulopathy/acute coagulopathy of trauma and shock/acute trauma coagulopathy" AND "injury/trauma" was used.

Data abstraction

Two review authors (RS, PPD) not blinded to journal, institutions, or authors independently examined all abstracts of the studies identified by the search and determined the eligibility of each study. Any disagreements were resolved by consensus or with another review author (LTDL or AAM). Titles and abstracts of every record retrieved were screened to determine which of the studies should be undergo a full-text review. Full texts of the studies with questionable eligibility or considered eligible were retrieved in this phase for evaluation. The reference lists of the retrieved articles were also searched for additional citations. Only published data were included. Investigators were not

contacted for obtaining further data. Data were also collected independently by two review authors (RS and AAM).

Risk of bias assessment and GRADE profile

Risk of bias was assessed by two review authors (LTDL and RS) for each included study. Any disagreement was resolved through discussion and consensus with a third author (BN). Each included study was classified as RCT or observational cohort study, and the risk of bias was assessed differently according to each type of study design. For RCTs, the Cochrane Collaboration's tool[20] was used, which assesses bias in the domains of sequence generation, allocation concealment, blinding of outcomes, incomplete outcome data, selective outcome reporting, and baseline imbalances. For cohort studies, risk of bias was assessed using the Newcastle–Ottawa Scale (NOS),[21] which defines patient groups as comparable in either the design or analysis when the effect of the exposure is adjusted for confounders. This tool assesses risk of bias in the domains of selection of exposed and nonexposed cohorts, comparability of cohorts, assessment of outcomes, and adequacy of follow-up. For observational studies score of 3 or less was considered high risk of bias, 4 to 6 was considered moderate risk of bias, and 7 or more was low risk of bias. Quality of evidence for mortality and exposure to allogeneic blood products was evaluated using GRADE criteria, which included evaluation of each outcome for five criteria: risk of bias, inconsistency, imprecision, indirectness, and publication bias. It was classified as high, moderate, low, or very low (www.gradepro.org, Version 3.6.1, McMaster University 2014).

Statistical analyses

Studies were combined in meta-analyses if there was enough clinical and methodologic homogeneity. Studies were analyzed separately according to their design (observational or randomized). Clinical and methodologic heterogeneity across the studies was assessed by examining the details of the subjects, the baseline data, the interventions, and the outcomes to determine whether the studies were sufficiently similar. Statistical heterogeneity was determined using the I^2 statistic and the chi-square test. High values of both tests ($I^2 > 40\%$, a nonsignificant chi-square [$p < 0.05$], respectively) demonstrate high levels of inconsistency and heterogeneity. Heterogeneity was further investigated observing the variations in the effect sizes across studies and overlapping of confidence intervals (CIs), which were used while performing the GRADE profile. Pooling of overall estimates was performed using generic inverse variance weighting methods. With these methods, each study estimate of the relative treatment is given a weight that is equal to the inverse of the variance of the effect estimate (i.e., one divided by the standard error squared). Studies were grouped according to the transfusion ratios of FFP: PLTs:RBCs, FFP:RBCs, or PLTs:RBCs reported for conducting meta-analyses. Before-and-after studies were removed from the pooled analyses to avoid secular trends in practice patterns.

Review Manager 5.3 software (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, 2015) was used to carry out quantitative analyses. A random-effects model was used as this approach accommodates clinical and statistical variations. Heterogeneity was explored. Odds ratio (OR) and 95% CI were used as statistical measures for mortality as a dichotomous outcome. Mean and standard deviation (SD) was the statistical measure used to describe exposure to allogeneic blood products and coagulopathy. Studies that reported transfusion data in medians and interquartile ranges (IQRs) and mean and SD were estimated using the sample size, median, and the IQR as demonstrated in the method published by Wan.[22]

RESULTS

Included studies (Fig. 1)

The electronic search identified 814 potentially relevant studies of which 73 were selected for full-text review and from these 55 studies met the inclusion criteria.[23-77] There was excellent agreement between the reviewers for study inclusion (Cohen's Kappa, 0.88).[78]

Clinical characteristics

RCTs (Table S1, available as supporting information in the online version of this paper.)

Two RCTs[23,24] were included (n = 749 patients). The study conducted by Holcomb and colleagues[23] was a multicenter trial and the study conducted by Nascimento and colleagues[24] was a single-center feasibility trial. The Injury Severity Score of participants across both studies ranged from 26 to 41, and the age ranged from 34 to 41 years. Most participants were male.

Observational cohort studies (Table S1)

Fifty-three observational cohort studies[25-77] were included (n = 27,228 patients). Thirty-one were retrospective,[26,29,34,36,38,42,44–47,49–54,56–62,65,66,68–70,72–74,76,77] 13 were prospective,[25,27,28,30,31,35,37,40,41,55,67,70,71] and nine had a before-and-after design.[31,32,39,43,48,63,64,68,75] Nineteen studies were multicenter,[27–29,32,37,41,46,49–51,54–57,60,69,70,72,74] and 34[25,26,30,31,33–36,38–40,42–45,47,48,52,53,58,59,61–68,71,73,75–77] were conducted in single trauma centers. The mean ± SD age of patients across all studies was 38.3 ± 6.8 years and the mean ± SD Injury Severity Score was 31.6 ± 6.2. Most patients were male (mean ± SD 76.5% ± 9.2%).

Interventions

RCTs (Table S1)

The PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial[23] assessed the ratio of 1:1:1 versus 1:1:2 (FFP:PLTs:RBCs) and the feasibility trial[24] assessed the ratio of 1:1:1 versus laboratory-guided transfusion.
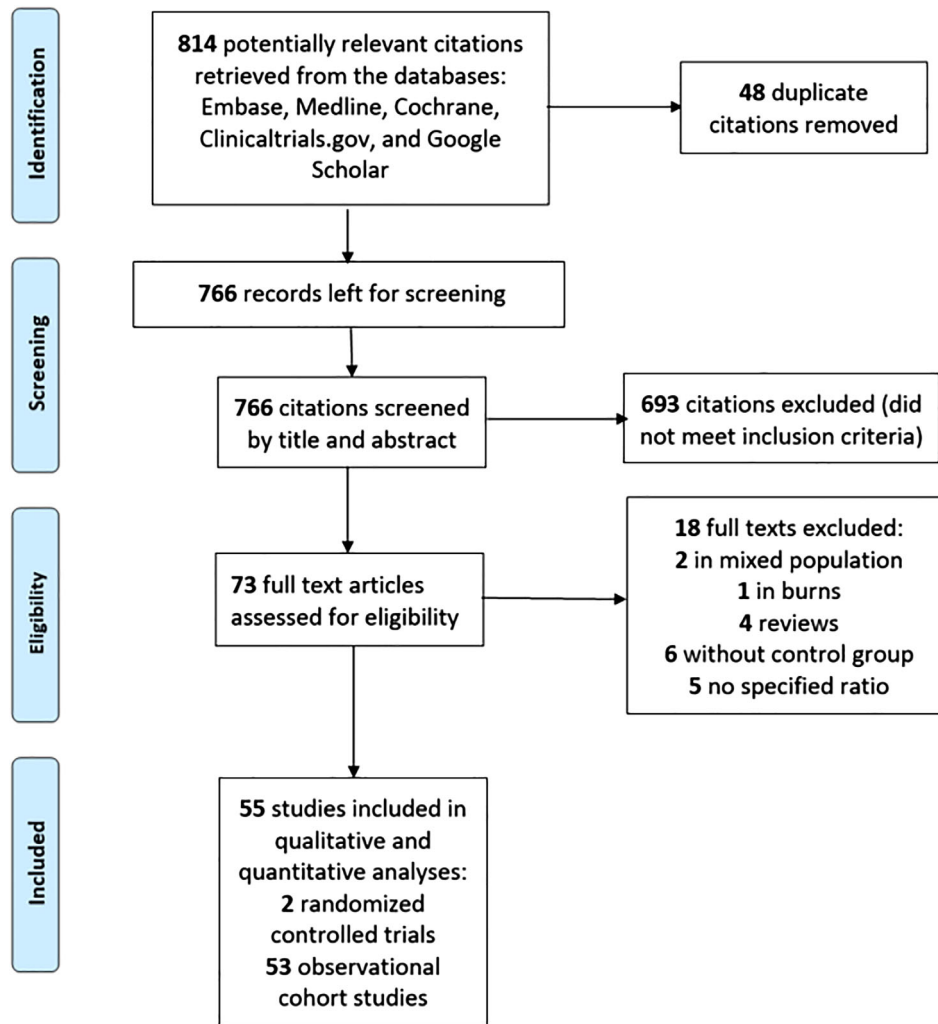
Fig. 1. PRISMA flow chart of study selection. [Color figure can be viewed at wileyonlinelibrary.com]

Observational cohort studies (Table S1)
Different fixed transfusion ratios were evaluated across the studies. Thirty-three studies[28–30,33–40,42,46,48,51–53,55–59,61,62,64,66,67,70–73,76,77] addressed FFP:RBCs, two[54,65] addressed PLT:RBCs, and 14[26,27,41,43–45,47,49,50,60,63,68,74,75] addressed both FFP:RBCs and PLTs:RBCs. Four studies[32,43,63,69] examined fibrinogen:RBCs or cryoprecipitate:RBCs and three[25,31,32] examined FFP:PLTs:RBCs. Ratios of FFP:RBCs and PLTs:RBCs ranged both from 1:1 to 1:8 and from 1:1 to 1:9, respectively.

Risk of bias
RCTs (Table S2, available as supporting information in the online version of this paper)
Both studies had low risk of bias in all domains assessed. We did not penalize the studies due to lack of blinding because blinding intervention is not feasible in this setting.

Observational cohort studies (Table S2)
The NOS[21] scores were more than 6 for all studies.

OUTCOMES

Mortality
RCTs (Table S3, available as supporting information in the online version of this paper)
The PROPPR trial[23] assessed two different ratios of FFP:PLTs:RBCs (high, 1:1:1 vs. low, 1:1:2) and reported no difference in 24-hour and 30-day mortality. However, there was a lower rate of death from exsanguination at 24 hours (9.2% vs. 14.6% in 1:1:2 group; difference, −5.4% [95% CI, −10.4% to −0.5%]; p = 0.03). The other study, a feasibility trial[24] not powered for mortality, reported no difference in 28-day mortality between both groups (1:1:1 vs. laboratory-guided transfusion), with a relative risk of 2.27 (95% CI = 0.98-9.63).

Observational cohort studies (Table S3)

Fifty studies[25–32,34–36,38–54,56–77] reported 24-hour and/or 30-day mortality. Only six studies[30,40,54,57,66,76] scored nine in the NOS and demonstrated a low risk of bias. Overall,

these 50 studies had an adequate balance of risk factors across the two groups and accounted for confounders in their analyses. They reported that higher transfusion ratios were associated with higher rates of survival. Only one
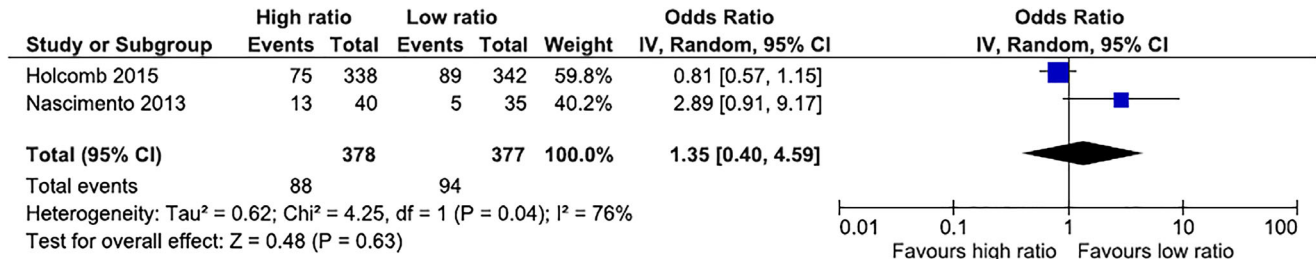
Fig. 2. Thirty-day mortality in RCTs. High ratios in both studies were 1:1:1 (FFP:PLTs:RBCs in Holcomb's and RBCs:FFP:PLTs in Nascimento's trial). Low ratio in Holcomb's trial was 1:1:2 (FFP:PLTs:RBCs) and in Nascimento's trial it was 1.8:1:0.7 (RBCs:FFP:PLTs). [Color figure can be viewed at wileyonlinelibrary.com]

Fig. 3. Twenty-four-hour mortality in non-RCTs according to the FFP:RBC ratio assessed. [Color figure can be viewed at wileyonlinelibrary.com]

retrospective study[40] using regression analyses with Cox proportional hazard models reported no difference in mortality within the first 6 hours after admission across three ratios of FFP:RBCs (1:1.5, 1:1.5-1:2, and <1:2; p = 0.535).

Exposure to allogeneic blood products

RCTs (Table S3)

The PROPPR trial[23] reported that the 1:1:1 ratio group received more FFP (median of 7 units vs. 5 units, p < 0.001) and PLTs

(12 units vs. 6 units, p < 0.001). However, patients received similar amount of RBCs (9 units) within the first 24 hours in both arms. Nascimento and coworkers[24] demonstrated no difference in the amount of transfused RBCs, FFP, and PLTs across groups.

Observational cohort studies (Table S3)

Twenty-nine studies[25,28,31,32,34,35,37,39,41–46,48,49,51,52,55,58,61–63,65,67,68,70,73,74] reported comparisons between the number of units transfused in the high- and low-transfusion-ratio groups. Of these, 11

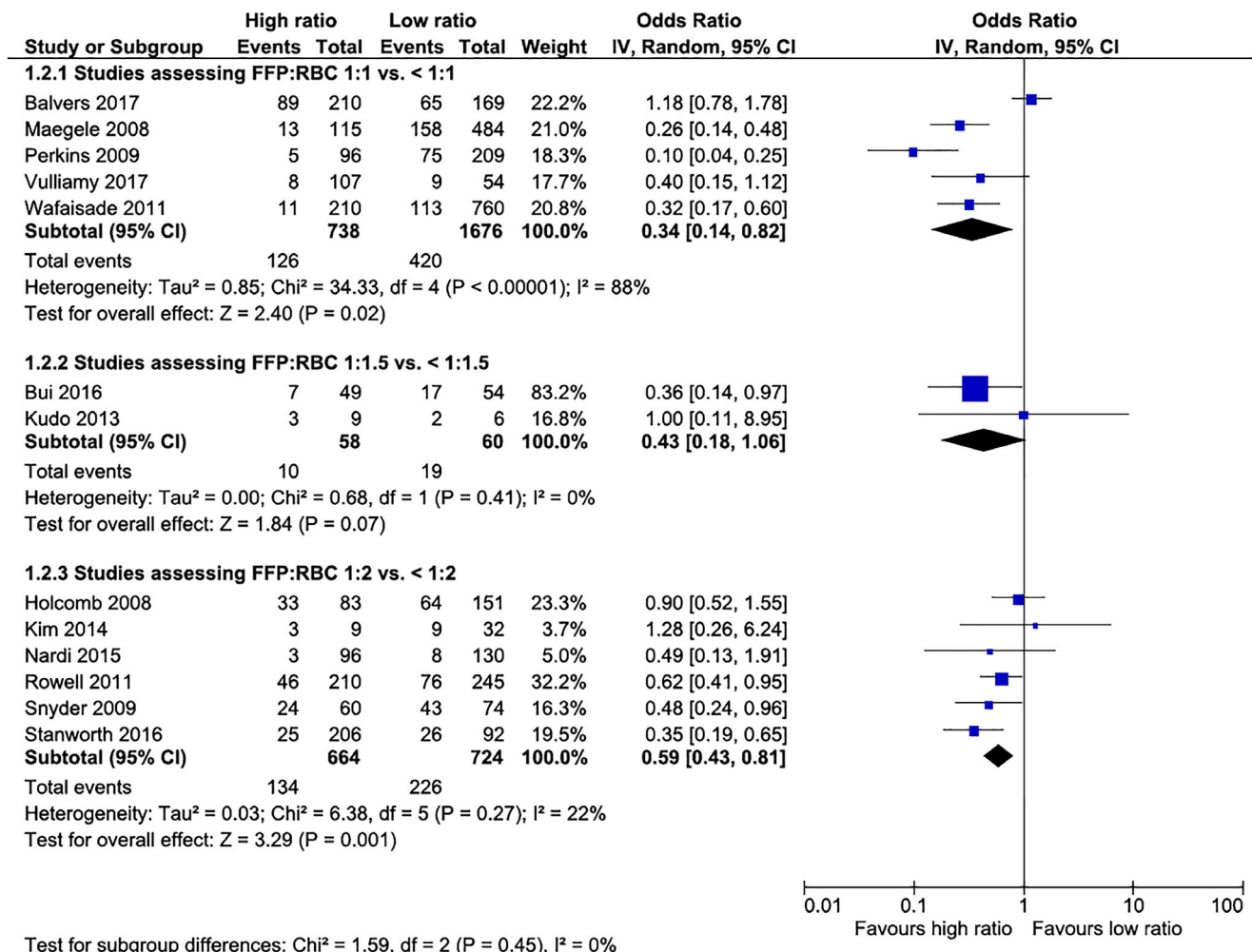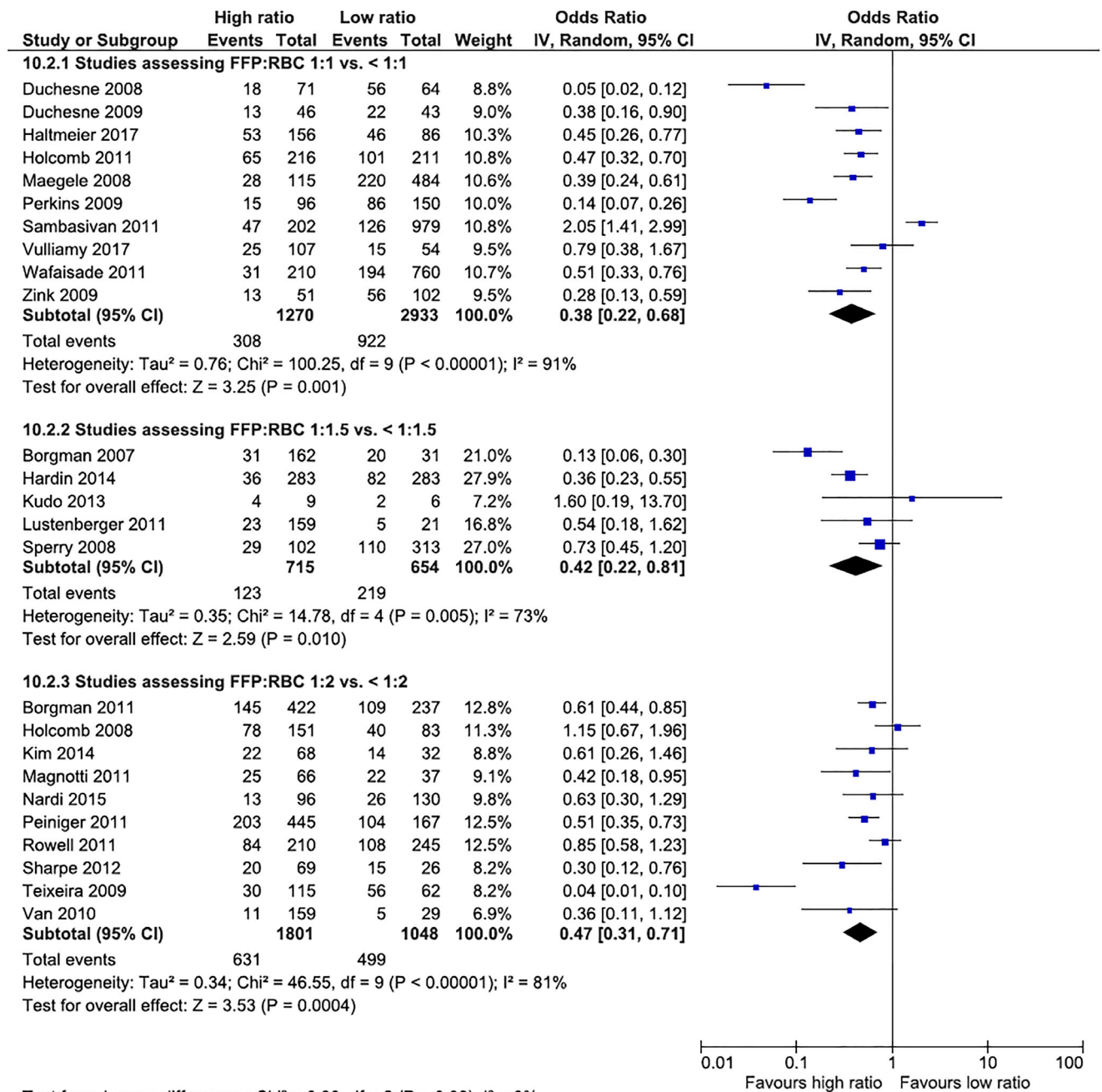**Fig. 4. Thirty-day mortality in non-RCTs according to the FFP:RBC ratio assessed. [Color figure can be viewed at wileyonlinelibrary.com]**

studies[24,28,34,42,43,52,55,58,62,67,68] reported a statistical difference in RBC transfusion, 20[24,28,31,32,35,37,44–46,49,51,52,55,62,66–68,70,73,74] reported a statistical difference in FFP transfusion, and 14[24,31,32,35,41,44,45,51,52,55,62,70,73,74] reported a statistical difference in PLT transfusion. A composite outcome of exposure to blood products (RBC + FFP + PLT + fibrinogen products) was reported in only one study.[27]

Coagulopathy

RCTs (Table S3)
The PROPPR trial[23] reported significant difference in achievement of clinical hemostasis in the 1:1:1 ratio group compared to 1:1:2 (86% vs. 78%, p = 0.006). However, laboratory coagulopathy was not assessed in this trial. The feasibility trial[24] assessed values of INR, PLT count, and fibrinogen and reported no significant differences.

Observational cohort studies (Table S3)
Nine studies[24,28,34,36,44,53,64,67,69] assessed laboratory coagulation variables. Prothrombin time (PT) and INR were assessed in seven studies[28,34,36,44,53,64,67] and showed conflicting results. Bui and coworkers[30] reported a nonsignificant difference in values of INR before and after resuscitation (0.09 ± 0.5 to −0.07 ± 0.13, p = 0.37). Kutcher and colleagues[35] reported that values of PT normalized in 60 and 20% of patients receiving high and low transfusion ratios, respectively. Sperry and coworkers[70] reported no difference between values of INR on admission and after resuscitation (1.76 ± 2 vs. 1.89 ± 1 p = 0.45). Conversely, Kashuk and colleagues[73] reported significant increased values of INR 6 hours postresuscitation with higher FFP:RBCs ratio (1.4 ± 0.5 vs. 2.4 ± 9.1, p not reported). ROTEM variables were assessed in a single study[37] that showed a nonsignificant trend in the proportion of patients developing coagulopathy according to the number of RBC units transfused (40% on admission, 58% after 4 units of RBCs, and 81% after 8 units of RBCs), as measured by clotting amplitude at 5 minutes. Furthermore, the authors reported that FFP and PLTs did not improve coagulation variables; however,

therapy combining FFP, PLTs, and cryoprecipitate improved ROTEM values.

Meta-analyses (Figs. 2–4 and Table 1)

Studies addressing mortality and exposure to allogeneic blood products were combined for the purpose of meta-analyses (Figs. 2–4). Studies addressing coagulopathy and other transfusion ratios with fibrinogen or cryoprecipitate, for example, were not included in meta-analyses as insufficient data were available to be pooled. Furthermore, before-and-after studies were not included in the quantitative analyses. Publication bias was not assessed with funnel plots, as the number of studies on each analysis was less than 10. However, the included studies had a mix of small and large sample sizes, with both positive and negative results, which denotes low probability of publication bias. For exposure to allogeneic blood products, studies were combined according to the blood product assessed (FFP:RBCs or PLTs:RBCs) and according to the ratio assessed (Table 1). Four groups of studies were identified according to the fixed transfusion ratios reported, as follows: 1) studies that reported FFP:RBC ratio of 1:1 versus less than 1:1; 2) studies that reported FFP:RBC ratios of 1:1.5 versus less than 1:1.5; 3) studies that reported FFP:RBC ratios of 1:2 versus less than 1:2; and studies that reported PLT:RBC ratio of 1:2 versus less than 1:2. The latter group was represented by only two studies.[55,60] All mortality and transfusion analyses were conducted separately for each study group.

Mortality in the two RCTs was not significantly different (Fig. 2). For observational cohort studies, mortality was lower in the intervention groups in all three different transfusion ratios of FFP:RBCs assessed (1:1 vs. <1:1, 1:1.5 vs. < 1:1.5, and 1:2 vs. <1:2; Fig. 3). For both 24-hour and 30-day mortality, results were similar, with a survival benefit in the intervention group for the three ratios assessed, demonstrating a dose effect, with increasing ORs from 1:1, 1:1.5, and 1:2 FFP:RBC transfusion ratios.

TABLE 1. Meta-analyses on the exposure to allogeneic blood products in the included studies

Transfusion ratio	Blood product exposure (units)	Pooled mean difference	95% CI	p (overall effect)	I^2
RCTs					
FFP:PLTs:RBCs 1:1:1 vs. <1:1:1	RBCs	−0.65	−1.75 to 0.45	0.25	0%
FFP:PLTs:RBCs 1:1:1 vs. <1:1:1	FFP	1.91	0.92 to 2.90	0.0002	0%
FFP:PLTs:RBCs 1:1:1 vs. <1:1:1	PLTs	3.28	−2.66 to 9.23	0.28	87%
Observational cohort studies					
FFP:RBCs 1:1 vs. <1:1	RBCs	−0.68	−2.68 to 1.33	0.51	59%
FFP:RBCs 1:1 vs. <1:1	FFP	8.88	3.76 to 14.0	0.0007	95%
FFP:RBCs 1:1 vs. <1:1	PLTs	0.80	−0.75 to 2.36	0.31	84%
FFP:RBCs 1:1.5 vs. <1:1.5	RBCs	−0.26	−6.28 to 5.76	0.93	98%
FFP:RBCs 1:1.5 vs. <1:1.5	FFP	9.65	5.35 to 13.95	< 0.0001	98%
FFP:RBCs 1:1.5 vs. <1:1.5	PLTs	1.04	−0.48 to 2.55	0.18	88%
FFP:RBCs 1:2 vs. <1:2	RBCs	−1.12	−4.27 to 2.03	0.48	91%
FFP:RBCs 1:2 vs. <1:2	FFP	9.24	3.95 to 14.53	0.0006	98%
FFP:RBCs 1:2 vs. <1:2	PLTs	7.82	−2.83 to 18.47	0.15	98%
PLTs:RBCs 1:1 vs. <1:1	RBCs	−0.39	−5.121 to 4.32	0.87	86%

We did not find a difference in the number of units of RBCs and PLTs transfused across groups in the RCTs (Table 1). However, greater rates of FFP transfusion were evident in the high-ratio groups, as expected. In the observational cohort studies, exposure to FFP in all three fixed transfusion ratios assessed was also higher in the intervention groups. Conversely, no difference was found for RBCs and PLTs across all three ratios.

GRADE evidence profile (Tables S4 and S5, available as supporting information in the online version of this paper)

Overall, the evidence was of low quality for both mortality and exposure to allogeneic blood products (see details for each item addressed in the tables).

DISCUSSION

Main findings

This systematic review summarizes the evidence pertaining to the use of high transfusion ratios compared to low transfusion ratios in bleeding adult trauma patients. The evidence is represented by two RCTs and 53 observational studies. The randomized data reported no difference in mortality (with one of the RCTs not powered to detect mortality difference). Additionally, low-quality observational evidence suggests a survival benefit in all high transfusion ratios assessed (FFP:RBCs of 1:1 vs. <1:1, 1:1.5 vs. <1:1.5, and 1:2 vs. <1:2 and PLT: RBCs 1:2 vs. <1:2) in pooled analyses of observational studies for 24-hour and 30-day mortality (primary outcome). Low-quality evidence demonstrated no difference in exposure to allogeneic blood products within the first 24 hours. As expected, there was increased number of FFP and PLT units transfused in all three fixed ratios groups. Laboratory measures of coagulopathy were reported in a few studies and reported inconsistent results, however, demonstrating an overall trend to improvement of coagulation tests.

Treatment of severely bleeding and coagulopathic trauma patients has evolved considerably over the past two decades. MTPs have been adopted for the treatment of this population.[79] Additionally, in limited military observational data, the concept of component therapy with higher fixed transfusion ratios of FFP and/or PLTs to RBCs has shown a survival benefit leading to an extension of its use to civilian trauma population and other settings.[80] Currently, most trauma centers use MTPs designed to achieve administration of high amounts of FFP and PLTs early in the resuscitation process.[79] The evolving knowledge on fixed component transfusion ratios provided the rationale for three important studies[23,24,41] that explored the feasibility of 1:1:1 ratio, time to achieve a balanced amount of blood products, and clinical outcomes. The PROMMTT study,[41] a multicenter, prospective observational cohort study, was designed to assess the timing of transfusion of blood products and its association with

in-hospital mortality. In this study, most patients achieved a balanced transfusion between 3 and 6 hours postadmission. Authors reported a decreased 24-hour mortality, which corroborates with previous data.[77] The second study, a RCT,[24] showed that 1:1:1 ratio of FFP:PLTs:RBCs was feasible; however, the authors reported a high rate of wastage of FFP. The trial was not powered to detect mortality difference. The PROPPR trial[23] was the first RCT to assess 1:1:1 ratio of FFP and PLTs to RBCs, compared to 1:1:2 ratio, and assess mortality as primary outcome. The study did not show mortality difference at 24 hours or 30 days postadmission. However, PROPPR addressed several limitations from previous RCTs, such as lack of blinding treatment assignment, survival and selection biases, and small sample sizes. An important limitation was that the trial was not powered to detect a smaller, but still clinically meaningful, difference. As a consequence, the trial did not exclude a potential benefit of the 1:1:1 ratio of less than 10% for 24-hour mortality. A difference in mortality due to exsanguination was identified. The authors recommended a 1:1:1 ratio to be used while patients are still actively bleeding and then transitioning to a lab-guided strategy once bleeding is controlled. These well-designed studies corroborated with previous evidence which emphasized that clinicians should use a higher rate of FFP:RBCs and PLTs:RBCs while activating their MTPs.

More recently, clinicians are evaluating a targeted goal-direct approach.[81] Conventional laboratory tests such as PT and INR, initially used to guide transfusion, have now been replaced by viscoelastic tests in some American and European centers.[81] TEG and ROTEM can identify the specific coagulation defects and guide the clinicians to transfuse the most appropriate blood products.[14,81] Several studies in trauma and nontrauma settings have demonstrated that these tests are able to identify the nuances of ATC and predict need for massive transfusion.[82] An RCT[83] that assessed trauma patients randomized to either TEG-directed therapy, or conventional coagulation assays, demonstrated that the former resulted in similar numbers of RBCs but less FFP and PLTs transfused within the first 2 hours of resuscitation, and 28-day survival improved. In cardiac surgery, a meta-analysis[84] of 8332 patients (nine RCTs and seven observational studies) reported a significant decrease in the odds of receiving allogeneic blood products, decreased reoperations due to postoperative hemorrhage, decreased postoperative acute kidney injury, and fewer thromboembolic events. It is expected that the role of TEG and ROTEM to target specific coagulation defects in different clinical and surgical settings will be defined within the near future.

In parallel, the use of FFP in trauma resuscitation has been done in the prehospital setting. Recently, two RCTs[85,86] using FFP during transport of bleeding trauma patients demonstrated a survival benefit, calling attention for a possible advantage in using FFP or other clotting factors very early after injury. Additionally, plasma has been replaced or

supplemented with other concentrate of clotting factors in other clinical/surgical settings in some European countries. Some centers have been adopting different plasma-derived and recombinant coagulation factor preparations, such as PCC (Octaplex), fibrinogen concentrate (RiasTAP), and other coagulation factors.[14,16,87] The use is variable in different clinical settings, including trauma. For example, in a retrospective study,[87] bleeding trauma patients receiving PCC and/or fibrinogen concentrate without FFP were matched to similar patients receiving FFP without coagulation factor concentrates. Patients receiving PCC were transfused with less allogeneic blood products and had less multiple organ failure but had no survival benefit. Further evidence of non-FFP/PLT use has been growing and experimental research is under way, such as in transfusion of cold-stored and frozen PLTs,[88,89] fibrinogen concentrate administration,[14–17,90,91] and cryoprecipitate[14–17,92] and the use of antifibrinolytic drugs such as tranexamic acid.[14–17,93–95]

Strengths and weaknesses of this review and future research

This is the first meta-analyses to report exposure to allogeneic blood products in resuscitation using fixed component transfusion ratios. This review also updates the evidence previously published in other systematic reviews.[96–99] In addition, this is the first review assessing transfusion ratios of FFP and PLT in trauma patients exclusively and to use the GRADE profile to assess the evidence in trauma patients. The main limitation of the review is that most data are observational and thus survival bias, confounding, and publication bias are unavoidable. Furthermore, retrospective data included different definitions of high and low fixed transfusion ratios, which limited the analysis and pooling of the data between which constitutes high and low ratios uniformly across the studies. Therefore, due to the variability of the definition and center-specific transfusion protocols with differences in blood and blood products' availability and patient's characteristics, we followed what the authors defined as high and low ratios based on their settings, adopting a very pragmatic methodologic approach to our current analyses. Future research is strongly warranted, including well-designed prospective or RCTs to generate a more robust knowledge on which population will best benefit from fixed component transfusion, including which component and at which ratio will it be beneficial for important outcomes. Future studies are needed to address substitutes of component therapy, such as whole blood, cryoprecipitate, fibrinogen concentrate, Factor XIII, PCC, and antifibrinolytic drugs or a combination of these. Moreover, the goal-directed approach offered by TEG and ROTEM still needs its place established in trauma and other perioperative and clinical settings, and studies should include meaningful clinical outcomes as primary endpoints.

CONCLUSIONS

Randomized data have not shown a mortality benefit from a higher transfusion ratio of 1:1:1 compared with 1:1:2 or standard care. Additionally, low quality observational evidence demonstrates a survival benefit, and conflicting results on exposure to allogeneic blood products and improvement of coagulopathy in patients who received high-transfusion ratios. However, these results should be interpreted with extreme caution, as the research in this area is limited by relatively small sample sizes, lack of clinical trials, and the observational nature of most studies with nonrandom treatment allocation and the high probability for confounding. Additionally, fixed transfusion ratios may be potentially replaced in the future with a more targeted approach with different plasma-derived and recombinant coagulation factor preparations using viscoelastic tests and decreasing the use of allogeneic blood products. Ultimately, larger prospective RCTs with several thousands of patients would be required to determine the best transfusion ratio or determine if the goal-directed approach is the answer, which might not be ever feasible due to challenges in timely recruitment of severely bleeding trauma patients and costs involved. Currently, a balanced approach to transfusion while patients are actively bleeding is accepted by American and European guidelines.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Characteristics of the studies included in the systematic review

Table S2. Main findings of the included studies in the systematic review

Table S3. Risk of bias assessment of the studies included in the systematic review

Table S4. GRADE quality assessment profile for mortality and summary of findings

Table S5. GRADE quality assessment profile for exposure to allogeneic blood products and summary of findings.