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Review

Does a balanced transfusion ratio of plasma to packed red blood cells improve outcomes in both trauma and surgical patients? A meta-analysis of randomized controlled trials and observational studies

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ABSTRACT

Background: The effect of high transfusion ratios of fresh frozen plasma (FFP): packed red blood cell (RBC) on mortality is still controversial. Observational evidence contradicts a recent randomized controlled trial regarding mortality benefit. This is an updated meta-analysis, including a non-trauma cohort.

Methods: Patients were grouped into high vs. low based on FFP:RBC ratio. Primary outcomes were 24-h and 30-day/in-hospital mortality. Secondary outcomes were acute respiratory distress syndrome and acute lung injury rates. Random model and leave-one-out-analyses were used.

Results: In 36 studies, lower ratio showed poorer 24-h and 30-day survival ($p < 0.001$). In trauma and non-trauma settings, a lower ratio was associated with worse 24-h and 30-day mortality ($P < 0.001$). A ratio of 1:1.5 provided the largest 24-h and 30-day survival benefit ($p < 0.001$). The ratio was not associated with ARDS or ALI.

Conclusions: High FFP:RBC ratio confers survival benefits in trauma and non-trauma settings, with the highest survival benefit at 1:1.5.

1. Introduction

The use of 1:1 balanced transfusion in massive traumatic hemorrhage has been an important topic over the past decade.[1–4] Until recently the primary method of resuscitation in massive hemorrhage was utilizing crystalloid and packed red blood cells (RBCs) and correcting coagulopathy as it arose. During the wars in Iraq and Afghanistan, the U.S. military utilize whole blood in austere situations for massive blood transfusion due to a rapidly available pool of donors. Initial studies on this transfusion method suggested that whole blood was as good as, and perhaps even superior to, traditional component transfusion practices with regards to coagulopathy in the setting of massive hemorrhage.[5–7] Other studies from civilian trauma suggested an advantage with early transfusion of FFP and platelets.[8–10] In a 2007 landmark retrospective study Borgman and colleagues[11] demonstrated that by attempting to recreate whole blood by balanced transfusion of individual blood products, mortality could be improved in a cohort of hemorrhaging patients in a combat setting. This and other small studies led to a directive within the U.S. military for a balanced, 1:1 ratio of blood products in massive transfusion when feasible.

Over the next several years, balanced transfusion was applied and studied throughout civilian trauma systems in numerous retrospective studies, yielding generally improved mortality when compared to unbalanced transfusion ratios. The practice remained controversial as the studies were retrospective and it was argued that many were subject to a survival bias since less severely injured patients were more likely to receive or achieve balanced

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transfusion.[12] This led to one prospective observational cohort study and one major randomized control trial (RCTs); The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT)[13] study, and The Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients with Severe Trauma (PROPPRR) Trial.[14] The PROMMTT trial included patients who received a much lower number of blood products but still demonstrated increased survival with balanced transfusion early in the hospital course. Interestingly, the PROPPR trial did not demonstrate improved overall 24-h or 30-day mortality but did demonstrate decreased mortality at 24 h from exsanguination. There is very limited information regarding the effectiveness of balanced transfusion in other surgical specialties, likely because the transfusion practices for other surgical subspecialties are not standardized. The goal of this systematic analysis is to compare the effect of balanced, massive transfusion on mortality and secondary outcomes including acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in a large, cohort of surgical patients, including both trauma and non-trauma sub specialties.

2. Methods

2.1. Study selection

A literature review using PubMed, MEDLINE, EMBASE, Web of Science, Science Direct, and Google scholar databases was performed by two independent investigators (MR and MK) up to January 10th, 2016. The following search terms were used:

(trauma OR traumatic OR injur* OR wound*) AND (massive OR major) AND (haemorrhag* OR hemorrhag* OR bleed* OR transfus* OR blood) AND (plasma OR component) AND (mortal* OR death* OR die OR died). Another search conducted by replacement of (trauma OR traumatic OR injur* OR wound*) by surgery in order to recruit non-trauma articles. In addition, upon identifying other meta-analyses or systematic reviews, references were scanned to capture relevant articles and pertinent reviews (i.e., backward snowballing). In case of disagreement a third investigator (MG) was included and an agreement was negotiated.

2.2. Study inclusion criteria

Studies included met the following criteria: (I) design was RCT or observational studies written in English, with more than 20 participants in each arm of the comparison; (II) massive blood transfused patients (all definitions accepted); (III) available mortality data based on the transfused FFP: RBC ratio; (IV) comparisons were made to contemporaneous patient cohorts, not to historical controls; (V) when cohorts overlapped between two studies, the more recent study was included.

2.3. Data extraction

Microsoft Office Excel 2010 (Microsoft, Redmond, Washington) was used for data extraction. Data extraction of all included studies was performed independently by 2 investigators (MR, DJ) and in case of disagreement a third investigator (MG) was included and an agreement was negotiated.

Extracted variables were: study name, publication year, study design, number of patients, sex, mean age, mean injury severity score (ISS), blunt injury percentage, military versus civilian environment, definition of massive transfusion, different FFP: RBC ratio categories, cut-off with different events number and total patients number in each group (then, categories were grouped as being low vs high for each study according to a predetermined ratios (1:1, 1:1.5, or 1:2) for analysis purposes), 24-h mortality, 30-day/in-hospital mortality (if both were available, only in-hospital mortality data were used), morbidity outcomes (including ARDS and ALI), non-significant and significant differences between the different FFP: RBC ratio groups, factors associated with survival in the studied cohorts and lengths of hospital stay (LOS). The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included studies.[15] Only high quality studies, defined as those achieving seven or more stars, were included in this review.

2.4. Study outcomes

Primary outcomes were 24-hr mortality and 30-day/in-hospital mortality for high vs low FFP: RBC ratio in the whole cohort while secondary outcomes were (I) mortality differences in trauma vs. non-trauma patients regarding FFP: RBC ratio, (II) mortality differences around the different cut-off ratios (1:1, 1:1.5, or 1:2) in order to identify the most beneficial ratio, and (III) ALI and ARDS differences between high vs. low ratios.

2.5. Statistical analysis

Review Manager Version 5.3 (RevMan)[16] was used to perform this pairwise meta-analysis, which was performed according to guidelines from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group[17] and from the Preferred Reporting Items for Systematic reviews and Meta-Analysis group (PRISMA).[18] The average of reported means of different studies was gathered for continuous variables.

The estimated survival data were obtained from the relevant articles either directly from published tables or indirectly from Kaplan–Meier curves using a previously described method[19] with aid of GetData Graph Digitizer software (http://getdata-graph-digitizer.com/).

Individual and pooled odds ratio (OR) with 95% confidence intervals (CI) were calculated by means of the DerSimonian-Laird (inverse variance [IV]) method.[20] OR was our measure for mortality as a dichotomous outcome with OR >1 indicating greater risk of an adverse event (i.e. death or complication as ARDS or ALI) happening in the low ratio group. P value < 0.05 was used to indicate statistical significance.

Statistical heterogeneity was tested by the Cochran Q-test, with statistical significance set at the two-tailed 0.10 level, while extent of statistical consistency was measured with I^2 that equals to 100% X (Q-df)/Q; where Q is Cochran's heterogeneity statistic and df is the degrees of freedom.

The fixed-effect model was used in case of low statistical inconsistency ($I^2 \leq 25\%$) while random-effect model, that better accommodates clinical and statistical variations, in case of moderate or high statistical inconsistency ($I^2 > 25\%$). Higher values of I^2 signified increasing levels of heterogeneity between included studies with p-value <0.05 was considered evidence for significant heterogeneity. Publication bias was assessed by funnel plots. Subgroup analysis was performed based on whether studies were conducted in trauma versus non-trauma settings. Sensitivity analysis using leave-one-out analysis was performed by Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ, USA).

3. Results

3.1. Included studies

Initially, 1321 articles were identified through the PubMed search, with an additional 48 articles added through backward

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snowballing. Following review of titles and abstract, only 93 full text articles were assessed for final eligibility, among them only 36 studies (2 RCTs and 34 observational studies)[1–4,11,12,14,21–49] were included on the basis of our pre-defined inclusion/exclusion criteria (Fig. 1). All but two retrospective studies,[32,33] were from trauma settings.

3.2. Demographics of included studies

Total number of patients among the 34 trauma studies was 16,607 and of the 2 non-trauma (i.e. cardiac and vascular) articles was 580 patients. Twenty-eight studies were from civilian hospitals, 4 from military settings, and 4 from combined civilian/military settings. The majority of the included studies (31 studies) defined massive transfusion as 10 units of RBCs/24 h. Twenty-six articles were from the United States, 7 from Europe, 2 from Asia and 1 from Canada (Table 1).

The mean age was 39.1 years (range 23.5–73 years) for the entire cohort, while for trauma-only cases, the mean age was 37.1 years (range 23.5–47 years) versus 66.7 years (range 60.3–73 years) for non-trauma cases. Overall, 63% of trauma was blunt (range 3–100%), 23% of the population was female (range 2–39%), the average ISS was 31.99 (range 14.6–42.5), and the average baseline hemoglobin and platelets values were 10.60 g/dl and 189,100 μL respectively.

A total of 18/36 (50%) studies reported a FFP: RBC ratio of 1:2 while 9 studies reported a ratio of 1:1 (Table 2). A ratio of 1:1.5 was reported in 6 articles and additional 3 studies reported their outcomes regarding various ratios (2:3 in 2 studies; and 1:2.3 in 1 study) (Fig. 1).

While no clear data was reported regarding the use of coagulation studies for guidance of transfusion ratios, both INR and thrombelastography (TEG) were reported in one study. INR only was reported in other five studies. Only two studies showed significant difference in mortality between both groups based on INR values (initially and at 6 h).

3.3. Mortality

3.3.1. Short-term

24-hr morality was described by 22 studies, revealing higher mortality for lower ratios (OR 2.41, CI 1.94–3.01 $p < 0.001$, Fig. 2A and B),[9,15–35] although at varying ratio cut-offs. Ratios of 1:2 were the most commonly reported, with 9 studies showing a deleterious effect with low ratio (OR: 2.85, CI 2.14–3.81). Seven articles reported a ratio of 1:1 (OR: 2.05, CI 1.55–2.71), and only 4 articles described a ratio of 1:1.5 (OR: 3.97, CI 1.37–11.49) (Table 3).

3.3.2. Intermediate-term

30-day/in-hospital mortality data were available from 27 studies (with different ratio cut-offs) and demonstrated higher mortality for lower ratios (OR: 1.74, CI 1.51–2.02, $p < 0.001$, Fig. 2C and D).[7,9,15,18,20–22,25–29,31–33,36–47]

Ratios of 1:2 were the most commonly reported, with 14 studies showing a deleterious effect of ratio less than 1:2 versus higher ratio (OR: 1.77, CI 1.50–2.10, $p < 0.001$). Seven articles reported a ratio of 1:1 (OR: 1.36, CI 1.09–1.69), while only five articles showed 1:1.5 ratios (OR: 2.31, CI 1.14–5.25) which resulted in the highest OR among the various ratios. Fig. 3 shows 24-h and 30-day/in-hospital mortality at different ratios. Funnel plots were created to assess for publication bias (Supplementary Fig. 1).

Lower FFP: RBC ratio was associated with an increase in mortality rate among both trauma and non-trauma groups; however, this was more pronounced among non-trauma patients (OR: 2.60, CI 1.51–4.49 vs OR: 1.71, CI 1.47–1.98 for trauma cases) (Table 3, Supplementary Fig. 2).

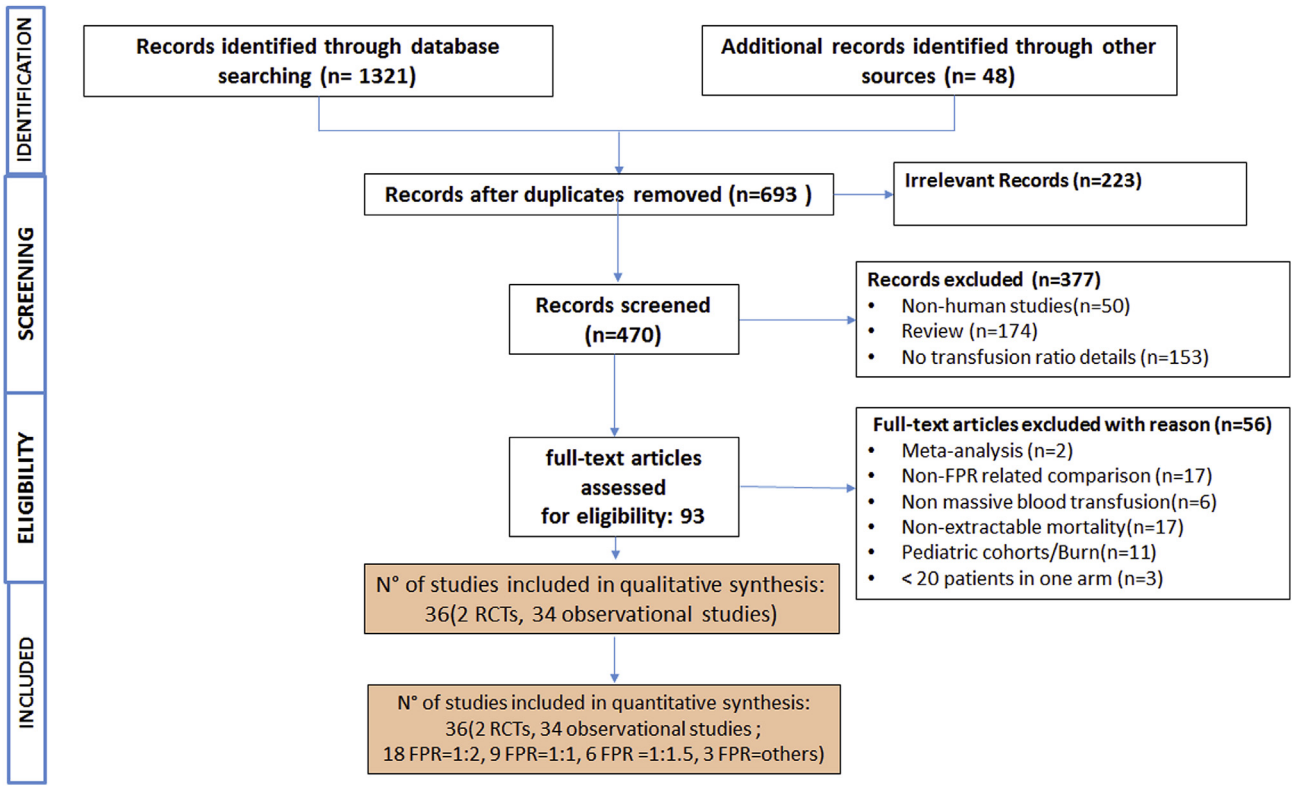

Fig. 1. PRISMA algorithm.

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Table 1
Characteristics of included of included studies.

Study	Year	Country	Centers	Study period	Type of study
Borgman[11]	2007	USA	Brooke Medical Army Center/Iraq	2003–2005	Retrospective
Borgman[1]	2011	Germany	Multi center	2002–2007	Retrospective
Brown[2]	2012	USA	Multi center	2003–2010	Prospective
Brown[21]	2011	USA	Multi center	2005–2006	Retrospective
De Biasi[3]	2011	USA	University of Maryland School of Medicine, Baltimore	2003–2008	Retrospective
Dente[4]	2009	USA	Multi center	2007–2008	Prospective
Duchesene[23]	2008	USA	Multi center	2002–2006	Retrospective
Duchesene[22]	2009	USA	Multi center	2001–2007	Retrospective
Gunter[24]	2008	USA	Multi center	2006–2007	Retrospective
Hardin[25]	2014	USA	Multi center	2003–2009	Retrospective
Holcomb[14]	2015	USA	Multi center	2012–2013	RCT
Holcomb[26]	2008	USA	Multi center	2005–2006	Retrospective
Kashuk[27]	2008	USA	Denver Health Medical Center	2001–2006	Retrospective
Kim[28]	2014	Korea	Ajou University School of Medicine	2010–2012	Retrospective
Lustenberger[29]	2011	Switzerland	University Hospital of Zurich	1996–2006	Retrospective
Maegele[30]	2008	Germany	Cologne-Merheim Medical Center	2002–2006	Retrospective
Magnotti[31]	2011	USA	University of Tennessee Health Science Center,Memphis	2006–2007	Retrospective
Mazzeffi[32]	2016	USA	University of Maryland School of Medicine	2006–2014	Retrospective
Mell[33]	2010	USA	University of Wisconsin	1987–2007	Retrospective
Mitra[34]	2010	Australia	Alfred Hospital	2004–2008	Retrospective
Nascimento[35]	2013	Canadian	Multi center	2009–2011	RCT
Peiniger[36]	2011	Germany	University of Witten	2002–2008	Retrospective
Rowell[37]	2011	USA	Multi center	2005–2007	Retrospective
Sharpe[38]	2012	USA	Multi center	2006–2009	Retrospective
Shaz[39]	2010	USA	Emory University Rollins School of Public Health, Atlanta, Georgia	2007–2009	Retrospective
Snyder[12]	2008	USA	University of Alabama-Birmingham (UAB) Hospital	2005–2007	Retrospective
Sperry[40]	2008	USA	Multi center	2003–2007	Prospective
Spinella[41]	2011	USA	Multi center	2005–2006	Retrospective
Spoerke[42]	2011	USA	Multi center	2005–2007	Retrospective
Stanworth[43]	2015	UK	Multi center	Till 2011	Prospective
Teixeira[44]	2009	USA	Multi center	2000–2005	Retrospective
Undurraga Peri[45]	2015	USA	Multi center	2012–2013	Retrospective
Van[46]	2010	USA	US army institute of surgical research	2003–2008	Retrospective
Wafaisade[47]	2011	Germany	University of Witten/Herdecke, Cologne-Merheim Medical Center	2005–2008	Retrospective
Yang[48]	2015	China	Medical College of Xi'an Jiaotong University	2009–2010	Retrospective
Zink[49]	2009	USA	Oregon Health & Science University	2005–2006	Retrospective

RCT: randomized control trial, USA: United States of America.

Heterogeneity was evident among nearly all of outcomes, except for 30-day/in-hospital mortality for non-trauma studies ($I^2 = 0\%$, $P = 0.32$) and for ALI ($I^2 = 0\%$, $P = 0.73$; Table 3); thus, a random model was commonly adopted in this study.

Sensitivity studies using leave one out analysis of 24-h and 30-day/in-hospital mortality at different ratios were done (Supplementary Fig. 3).

3.4. Morbidity

ARDS data was available from 8 studies[2,14,28,29,35,40,45,46] and ALI data was reported in 2 studies.[14,28] There was no difference in the incidence of ARDS with respect to FFP: RBC ratio (OR: 0.68, CI 0.40–1.16, P = 0.16). Similarly, no differences were observed in the incidence of ALI (OR: 1.23, CI 0.81–1.86, P = 0.34) (Supplementary Fig. 4).

4. Discussion

The ideal ratio for balanced transfusion is a controversial issue with multiple facts and considerations ranging from patient outcomes to allocation of resources.[1,50] In their study Borgman and co-authors[11] found that a higher transfusion ratio of 1:1.4 was significantly associated with improved mortality when compared to a medium (1:2.5) or low (1:8) ratios (19% vs 34% vs 65%, $p < 0.001$, respectively). Recently, the Eastern Association for the Surgery of Trauma (EAST)[51] recommended damage control resuscitation (DCR) that entails transfusion of an equal amounts of RBC, FFP, and PLT during the early, empiric phase of resuscitation with significant outcomes benefit in massively bleeding patients. This has raised interest regarding the most effective transfusion protocol and ratio. The evidence published from 2007 to 2015 supported balanced transfusion with a 24-h and 30-day mortality benefit. However, all of these studies were observational with concerns regarding the quality of the available evidence.[52] Many of these studies were limited by survival bias since the exact timing of blood products transfusion was often unknown. In addition, length time bias is possible as the patients who have had survived were probably less injured, and thus, lived long enough to receive balanced transfusion. This problem has been addressed in two observational studies by Snyder et al. and Sperry et al.,[12,40] who examined blood product ratios as time varying covariates with no survival benefit in contrast to previous results. We included these studies in our analysis, however they were small in size and a larger population will be needed for increasing the power of such findings.

In many centers, providing FFP in a timely manner has resulted in a notable decline in mortality rates. These findings support the argument that changing the transfusion protocol, by adding FFP, could improve outcomes as opposed to changing transfusion ratios. Riskin et al.[53] reported on the mortality rates of trauma patients 2 years before and after the implementation of a rapid massive transfusion protocol (MTP) at a level 1 trauma center. Their main goals were to decrease time to first transfusion, to assign a designated MTP leadership and to utilize a transfusion ratio of 1:1.5. Their hypothesis was proved by a drop in mortality rate from 45% to 19%, shown in massively bleeding patients.[53]

The first multicenter prospective observational cohort study, PROMMTT[13] in 2013 sought to describe the timing of blood

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Table 2
Patient details among FPR 1:2 included studies (n = 18).

Author	Age	Females (%)	Military or Civilian	ISS	% Blunt injury	Exclusion criteria	Non-significant differences between groups	Significant differences between groups	Survival associated factors	Overall mean FU (mean or median)	NOS
Borgman[1]	42	33	Civilian	42.5	92	Death within 60 min of ED admission	Pressor-use, sepsis, single organ failure, MOF, vent-free days, ICU-free days, time to death	ICU LOS, in-hospital LOS, Mortality (6hr, 24hr, 30d and in-hospital)	Higher FPR	D/C	8/9
Brown[2]	40.5	27	Civilian	NR	100	None specified	Male, Mechanism of injury, HR, RR, Temp, units of PRBCs transfused	age, GCS, PT, PTT, Plts, Hemoglobin, base deficit, systolic blood pressure, Units FFP transfused	24-h crystalloid, 24-h PRBC, Low hematocrit, No early laparotomy/ thoracotomy, Initial BD, No 24-h vasopressor use, ISS, APACHE II	D/C	8/9
Dente[4]	36	17	Civilian	29	59	Non-trauma patients	24hrs and in-hospital mortality after penetrating trauma	24hrs and in-hospital mortality after blunt trauma	FPR in blunt trauma	D/C	8/9
Duchesene[22]	30.25	11.25	Civilian	21.8	31.3	Patients < 18 years, who died in the ED, and nonsurvivable head injuries.	Age, Gender,SBP, ISS, Penetrating trauma, Initial (HB,BD, INR), operation time	ICU LOS, FPR	Higher FPR	D/C	9/9
Holcomb[26]	39.8	24.7	Civilian	32.3	65.8	Death within 30 min of ED admission	Gender, blunt trauma, admission HR, pH,Temp,Plt,ISS,AIS	Age, SBP, admission BD, INR, GCS	Higher FPR	30 days	9/9
Kashuk[27]	34.9	NR	Civilian	35.9	59	Severe head injury (1ry cause of death), ED resuscitative thoracotomy, documented severe comorbidities; COPD, CAD, CRF, and liver cirrhosis	NR	RBC transfused at 6 h, INR at 6 h 1.5, ED temperature 34 °C, and age 55 years.	FPR associated with coagulopathy reduction not survival	D/C	7/9
Kim[28]	47	17	Civilian	32	93	Death upon arrival to ED or within an hour	Age, gender, Blunt injury, Arrival-Transfusion (min), RBC-FFP transfusion (min), Colloid (L), Initial (hemoglobin, platelets, INR, pH, lactic acid, base deficit), Initial (SBP HR, RR, temp, GCS).	Units PRBC/24 h, Units FPR at 24 h, Units platelets/24 h, Crystalloids/24 h (L), Initial DBP (mmHg)	Higher FPR	D/C	9/9
Magnotti[31]	38	31	Civilian	31.5	63	None specified	Age, ISS, gender, blunt trauma, admission (SBP, HR,INR, Plt)	Admission (BE, lactate)	Blunt injury, admission BE	D/C	8/9
Mazzeffi[32]	60.3	38.9	Civilian	NR	NR	None specified	Age, gender, weight, DM,Dyslipidemia, Hypertension, hemodialysis, baseline (creatinine, hematocrit, INR) , Infectious endocarditis, CLD, CHF, LVEF, ICU or hospital LOS	Hight, Baseline platelet count, PVD, prior MI, Warfain use, emergency operation, CPB time	Preoperative (platelet count, INR, thienopyridine), CPB time. Patients with a highFPR had improved 30-day survival	30 days/D/C	8/9
Mell[33]	73	13.7	Civilian	NR	NR	Symptomatic patients but intact aneurysms, isolated iliac aneurysms, thoraco-abdominal aneurysms, death prior to operating room arrival	Age, weight, gender,hypertension, PVD, DM, Prior (MI, Stroke), operative time, blood loss, known AAA	COPD	Mortality higher in Age >80,Pre-operative tachycardia, Urine output, FFP: RBC <1:2	55 months	9/9
Peiniger[36]	42	16.7	Civilian	41.7	90	Death within the first hour after admission	Age, ISS, gender, blunt trauma, admission (SBP, HR, Plt, HB)	GCS, BE, MOF, sepsis	High FPR. RISC score	30 days	9/9
Rowell[37]	37.5	NR	Civilian	32	64.4	transferred patients from other hospitals, incarcerated, pregnant, < 16 years, burns, received CPR before ED,	ISS, GCS, BD, Age, AIS head, Temp	SBP (in penetrating trauma), HR (in blunt trauma), INR	Higher FPR	30 days	8/9

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Table 2 (*continued*)

Author	Age	Females (%)	Military or Civilian	ISS	% Blunt injury	Exclusion criteria	Non-significant differences between groups	Significant differences between groups	Survival associated factors	Overall mean FU (mean or median)	NOS
						received ED thoracotomy, death within 30 min					
Shaz[39]	35	18	Civilian	27.7	53.5	Nontrauma patients	ISS, penetrating trauma, admission (HR, Temp, fibrinogen), GCS	Mortality (24 h and 30 days)	Higher FPR	30 days	7/9
Snyder[12]	39.2	29	Civilian	36.5	100	None specified	NR	high survival with higher FPR	Higher FPR	30 days/D/C	7/9
Spinella[41]	38	28.5	Military	35	100	Patients who died within the first hour of admission	Age, ISS, gender, blunt trauma, admission (SBP, HR, GCS, Plt)	BD	Higher FPR	30 days	8/9
Stanworth[43]	38	31	Civilian	28.5	77.4	Patients transferred from another hospital	Gender, blunt trauma, SBP	SBP on admission	Higher FPR	1 year	7/9
Teixeira[44]	32	13	Civilian	NR	NR	Head injury (AIS score of≥ 3)	NR	GCS 8, FPR, Abdominal AIS≥3, Age≥55, SBP<90, Vascular injury	Higher FPR	D/C	8/9
Van[46]	25.7	NR	Military	14.6	41	None specified	CVA, MI, ARDS,PE, DVT	Renal failure	Higher FPR	30 days	8/9

AAA; abdominal aortic aneurysm, AIS; abbreviated injury score, BD; base deficit, BE; base excess, CAD; coronary artery disease, CHF; congestive heart failure, CLD; chronic lung disease, CPB; cardio-pulmonary bypass, COPD; chronic obstructive pulmonary disease, CPR; cardiopulmonary resuscitation, CRF; chronic renal failure, CVA; cerebro-vascular accident, DVT; deep venous thrombosis, D/C; discharge, DM; diabetes mellitus, ED; Emergency department, FPR; fresh frozen plasma: packed red blood cells ratio,GCS; Glasgow coma scale, HB; haemoglobin, HR; heart rate, ISS; injury severity score, LOS; length of hospital stay, MBT; Massive blood transfusion, MI; myocardial infarction, MOF; multi-organ failure, NOS; Newcastle-Ottawa Scale, OEF; Operation Enduring Freedom, OIF; Operation Iraqi Freedom, PE; pulmonary embolus, Plt; platelets, PROPPR; The Pragmatic, Randomized Optimal Platelet and Plasma Ratios, PVD; peripheral vascular disease, RISC; Revised Injury Severity Classification score, rFVIIa; recombinant factor VIIa, SBP; systolic blood pressure, TIC; traumatic induced coagulopathy.

products transfusion and assess the association between in-hospital mortality and the timing and amount of blood products given. This paper was not limited to massive transfusion as it was a feasibility study for a future, larger RCT. The authors found that the majority of patients did not reach a balanced transfusion ratio until about 3–6 h into admission. One of the most important findings of this study was that early balanced transfusion led to a decreased 24-h mortality; a finding described previously by Borgman in 2007. These findings proved that multiple factors could be involved.

In 2015, Holcomb and colleagues published their widely anticipated data from the PROPPR RCT which examined 680 trauma patients who received early balanced massive transfusion. The goal

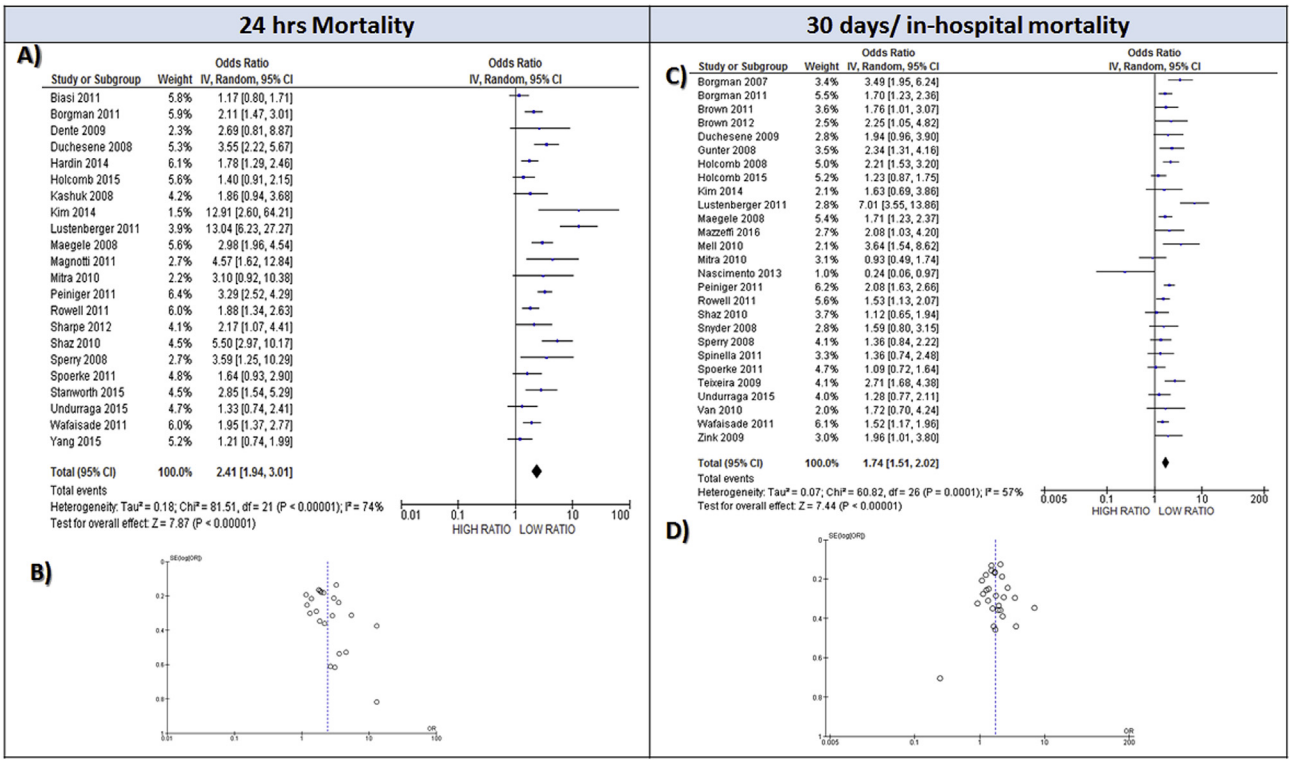

Fig. 2. 24-Hour and 30-day mortality.

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Table 3
All outcomes of interest.

FPR	Outcome	Number of studies	Cases	OR	95% CI	Heterogeneity	Test for overall effect	Outcome higher in
All Studies (All Ratio; NO non-trauma)	24-hrs mortality	22	12178	2.41	1.94–3.01	$P < 0.00001$, $I^2 = 74\%$	Z = 7.87, P=<0.00001	low ratio
All Ratio	In-hospital/30-day mortality	27	13075	1.74	1.51–2.02	P = 0.0001, I2 = 57%	Z = 7.44, P=<0.00001	low ratio
All Ratio (Trauma)	In-hospital/30-day mortality	25	12,495	1.71	1.47–1.98	$P = 0.0001$, $I^2 = 58\%$	$Z = 7.00$, P=<0.00001	low ratio
All Ratio (Non-trauma)	In-hospital/30-day mortality	2	580	2.60	1.51–4.49	P = 0.32, $I^2 = 0\%$	$Z = 3.44$, $P = 0.0006$	low ratio
1:1	24-hrs mortality	7	5265	2.05	1.55–2.71	$P = 0.03$, $I^2 = 57\%$	$Z = 5.00$, P=<0.00001	low ratio
1:1	In-hospital/30-day mortality	7	5266	1.36	1.09–1.69	P = 0.09, $I^2 = 45\%$	Z = 2.74, P=<0.006	low ratio
1:1.5	24-hrs mortality	4	1877	3.97	1.37–11.49	P=<0.0001, $I^2 = 88\%$	$Z = 2.55$, P=<0.01	low ratio
1:1.5	In-hospital/30-day mortality	5	1813	2.31	1.14–5.25	P < 0.001, $I^2 = 84\%$	$Z = 2.40$, P = 0.02	low ratio
1:2	24-hrs mortality	9	3540	2.85	2.14–3.81	$P = 0.01$, $I^2 = 59\%$	$Z = 7.10$, P=<0.00001	low ratio
1:2	In-hospital/30-day mortality	14	6193	1.77	1.50–2.10	$P = 0.08$, $I^2 = 37\%$	$Z = 6.68$, P=<0.00001	low ratio
All Studies	ARDS	8	2678	0.68	0.40–1.16	$P = 0.0003$, $I^2 = 74\%$	$Z = 1.42$, $P = 0.16$	none
All Studies	ALI	2	780	1.23	0.81–1.86	$P = 0.73$, $I^2 = 0\%$	$Z = 0.96$, $P = 0.34$	none

FPR; Fresh frozen plasma: packed RBCs ratio, CI, confidence interval; OR, odds ratio; RD, risk difference.

of this study was to address the primary concerns raised in previous studies. All patients who met rather broad inclusion criteria received blood products within a preset time. The authors found that the effects of a 1:1:1 vs 1:1:2 (FFP:PLT:RBC) transfusion ratio had no difference in overall mortality at 24 h (12.7% vs 17.0%, p = 0.12) or after 30 days (22.4% vs 26.1%, p = 0.26). The authors also pointed out that like many trauma trials, about one third of the deaths reported in this study were from traumatic brain injury, and thus, may have contributed to the absence of a significant difference in overall death rates.[13]

In this meta-analysis, we found that a higher transfusion ratio, regardless of the definition, results in improved survival both at 24 h and 30-days (and/or in-hospital mortality) (OR: 2.41, CI 1.94–3.01 vs. OR: 1.76, CI 1.51–2.05). This further supports the rational for an early 1:1:1 transfusion regimen, which aims to achieve rapid hemorrhage control by replacing the actual composition of blood. Intuitively, the role of early balanced transfusion is most critical within the first hours of admission. As noted in PROMMTT and PROPPR study, 24 h is the cut-off period after which other factors start to affect survival.

Unlike the present analysis, prior meta-analyses[54,55] did not include RCTs; in 2013 Bhangu et al.[54] included six observational studies reporting the outcomes for 1885 patients and reported a survival benefit with high FFP: RBC ratio without identifying additional benefits of 1:1 over 1:2 ratios. In 2011, Rajasekhar et al.[55] published their meta-analysis of 11 observational studies that included 3107 patients and found that there was an insufficient amount of evidence to support the survival advantage of a 1:1 ratio transfusion strategy. Compared to previous studies, this is the largest meta-analysis including; 36 articles, of which 2 are RTCs. The goal of this study was to look into the impact of balanced transfusion on mortality in wide range of surgical specialties. Owing to the nature of the medical question being addressed here, it is difficult to test the efficacy of such emergency transfusion

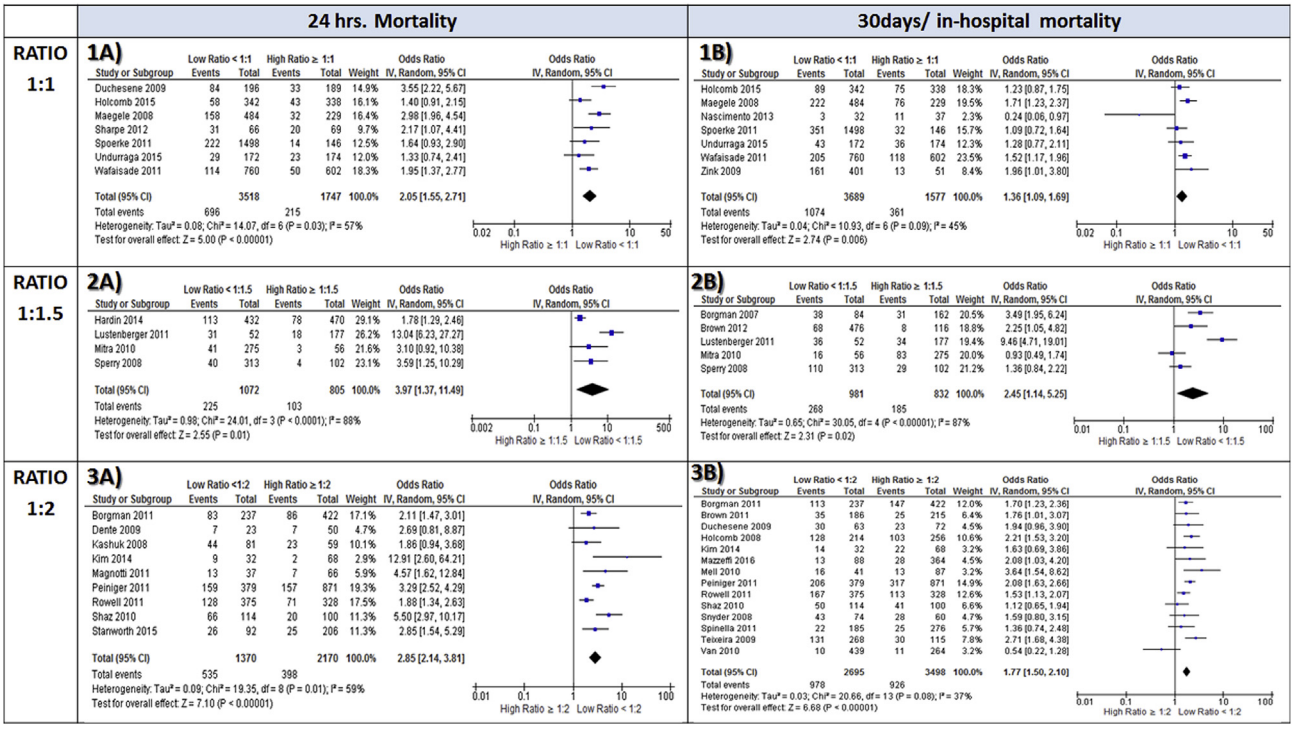

Fig. 3. 24-Hour and 30-day Mortality at different ratios.

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protocols in a controlled setting. Until now, there is still little high-quality evidence available about this topic. Articles about trauma represent the best evidence literature available regarding massive transfusions, and thus, would be the foundation of our study. Instead of attempting to control for the inherent bias present in the observational studies, we tried to be as comprehensive as possible in regards to our inclusions. Our study is the first to examine balanced transfusion in a non-trauma cohort. However, it is important that the readers understand that the primary source of our data is an observational trauma population. The scarcity of balanced transfusion data among non-trauma patients highlights the need for a specific investigation in this area. The non-trauma cohort included in this analysis is derived from two studies comprised of 580 patients about mortality outcomes.

In this analysis, we found that a lower transfusion ratio is associated with an increase in mortality among both groups, however, this was more pronounced among the non-trauma patients (OR: 2.60, CI 1.51–4.49 non-trauma vs OR: 1.71, CI 1.47–1.98 for trauma). Despite the small size of the cohort, these findings could serve as a cornerstone for future studies in this specific area.

One of the concerns raised by opponents to national implementation of balanced transfusion was the possibility for a rise in transfusion associated injuries especially in massively transfused patients. Murad and colleagues, in a meta-analysis of 12,421 patients who received MTP, found that the transfusion of plasma was associated with a higher rate of ALI (OR: 3.00, CI, 1.29–4.75) in surgical patients alone.[56] In contrast, the above mentioned randomized study and others showed that the effect of transfusion ratio does not influence the incidence of ARDS or ALI.[14,35,45] We addressed this contradiction in our analysis and we could not find a significant association. Before rushing into conclusions, it is important to take into consideration the many precipitating factors involved in the development of such critical disease as well as the type of injury. It is probably safer to control for other factors before final judgement could be settled.

The main limitation of this study is that almost all of our data are observational, and thus, survival bias is unavoidable. Adjusting for this bias was challenging as it applied to almost all of the observational data papers. In addition, due to the limited data on MTP in non-trauma patients, our study has a small sample size. This, however, highlights an area of future research and provides a basis for future reviews.

5. Conclusion

The use of high ratio, balanced transfusion will continue to be an important area of discussion and research. Our data suggests that there is a survival benefit at 24 h and 30 days when this practice is followed, with the largest benefit within 24 h. A ratio of 1:1.5 was associated with the highest survival benefit. Furthermore, there is no evidence in our study of increased rates of ALI or ARDS. Ultimately a larger prospective randomized controlled trial with several thousand patients will be required to determine the best ratio of blood products in massive transfusion.

Conflict of interest

The authors declare no financial relationship that may cause a conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amjsurg.2017.08.045.

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