Colombian Journal of Anesthesiology
Revista Colombiana de Anestesiología
www.revcolanest.com.co
OPEN
Wolters Kluwer

Mortality in civilian trauma patients and massive blood transfusion treated with high vs low plasma: red blood cell ratio. Systematic review and meta-analysis

Mortalidad en pacientes con trauma civil y transfusión masiva tratados con una relación alta de plasma: glóbulos rojos versus una relación baja. Revisión sistemática y metaanálisis

Henry Oliveros Rodríguez[a], Fernando Ríos[a,b], Cristhian Rubio[c], Daniel Martin Arsanios[a], Andrés Felipe Herazo[a], Luis Mateo Beltrán[a], Paloma García[a], Annie Cifuentes[a], Juliana Muñoz[a], Javier Polanía[a]

[a] School of Medicine, Universidad de La Sabana, Chía, Colombia
[b] Clínica Universidad de La Sabana, Chía, Colombia
[c] Epidemiology Postgraduate Program, Facultad de Medicina, Universidad de la Sabana, Chía, Colombia.

Keywords: Meta-analysis, Massive transfusion, Civilian trauma, Mortality, Plasma, Red blood cells

Palabras clave: Metaanálisis, Transfusión masiva, Trauma civil, Mortalidad, Plasma, Eritrocitos

Abstract

Introduction: Massive bleeding in civilian trauma patients leads to dilutional coagulopathy. Transfusion with high plasma:red blood cell (RBC) ratio has been effective in reducing mortality in war trauma patients. However, in civilian trauma the evidence is controversial.

Objective: To assess the impact on mortality of high vs low plasma:RBC ratio transfusion, in civilian trauma patients with massive bleeding.

Methods: A systematic review and meta-analysis, including observational studies and clinical trials, was conducted. Databases were systemically searched for relevant studies between January 2007 and June 2019. The main outcome was early (24-hours) and late (30-day) mortality. Fixed and random effects models were used.

Results: Out of 1295 studies identified, 33 were selected: 2 clinical trials and 31 observational studies. The analysis of observational trials showed both decreased early mortality (odds ratio [OR] 0.67; 95% confidence interval [CI], 0.60–0.75) and late mortality (OR 0.79; 95% CI, 0.71–0.87) with the use of high plasma:RBC ratio transfusion, but there were no differences when clinical trials were evaluated (OR 0.89; 95% CI, 0.64–1.26). The exclusion of patients who died within the first

How to cite this article: Oliveros Rodríguez H, Ríos F, Rubio C, Arsanios DM, Herazo AF, Beltrán LM, García P, Cifuentes A, Muñoz J, Polanía J. Mortality in civilian trauma patients and massive blood transfusion treated with high vs low plasma: red blood cell ratio. Systematic review and meta-analysis. Colombian Journal of Anesthesiology. 2020;48:126–137.

Read the Spanish version of this article at: http://links.lww.com/RCA/A930.

Correspondence: Universidad de La Sabana, Campus Puente del Común, km 7.5 Autopista Norte de Bogotá, Chía, Colombia.
E-mail: henry.oliveros@unisabana.edu.co

Colombian Journal of Anesthesiology (2020) 48:3

http://dx.doi.org/10.1097/CJ9.0000000000000161

24 hours was a source of heterogeneity. The Injury Severity Score (ISS) altered the association between high plasma:RBC ratio and mortality, with a reduced protective effect when the ISS was high.

Conclusion: The use of high vs low plasma:RBC ratio transfusion, in patients with massive bleeding due to civil trauma, has a protective effect on early and late mortality in observational studies. The exclusion of patients who died within the first 24 hours was a source of heterogeneity.

Resumen

Introducción: El sangrado masivo en los pacientes con trauma civil propicia el desarrollo de coagulopatía dilucional. La transfusión de plasma y glóbulos rojos con una relación alta ha sido efectiva para disminuir la mortalidad en pacientes con trauma de guerra; sin embargo, su evidencia en trauma civil es controversial.

Objetivo: Evaluar el efecto sobre la mortalidad de la transfusión de plasma: glóbulos rojos con relación alta (TPGR-RA) versus baja, en pacientes con sangrado masivo por trauma civil.

Métodos: Se realizó una revisión sistemática y metaanálisis de estudios observacionales y experimentos clínicos publicados en el periodo de enero de 2007 a junio de 2019. El desenlace principal fue mortalidad temprana (24 horas) y tardía (30 días), utilizando el modelo de efectos fijos y aleatorios.

Resultados: De 1.295 estudios identificados se incluyeron 33: dos experimentos clínicos y 31 estudios observacionales. El uso de TPGR-RA mostró una disminución de la mortalidad temprana (OR 0,67; IC 95 %, 0,60–0,75) y tardía (OR 0,79; IC 95 %, 0,71–0,87) cuando se analizaron los estudios observacionales, pero no hubo diferencias cuando se evaluaron los experimentos clínicos (OR 0,89; IC 95 %, 0,64–1,26). La exclusión de pacientes que fallecieron en las primeras 24 horas fue una fuente de heterogeneidad. La gravedad del trauma, ISS (por las iniciales en inglés de *injury severity score*) modificó la asociación entre la TPGR-RA y mortalidad, siendo menor el efecto protector cuando el ISS era alto.

Conclusiones: El uso de TPGR-RA en pacientes con trauma civil y transfusión masiva (TM) tiene efecto protector sobre la mortalidad en los estudios observacionales. La exclusión de pacientes fallecidos en las primeras 24 horas fue causa de heterogeneidad.

Introduction

The main causes of death in trauma patients during the first 24 hours are exsanguination and central nervous system (CNS) injuries. Whenever there massive bleeding involving the CNS, mortality rises to 50% within the first hour.[1] Bleeding results in important physiological changes that may even lead to the lethal triad of acidosis, hypothermia, and coagulopathy.[2] Coagulation disorders are an independent factor for mortality[3] accounting for 30% of the deaths of civilian trauma patients.[4] The initial treatment of trauma patients requires surgical damage control and management of the hemorrhagic shock, in order to reduce blood loss to the minimum and restore tissue perfusion.[5] These interventions include minimizing the use of crystalloids to prevent organ dysfunction associated with fluid overload—such as dilutional coagulopathy—and early use of blood products.[6] These measures are *resuscitation with damage control*, intended to perform a hemostatic resuscitation to prevent death from exsanguination.[7] In trauma patients requiring massive transfusion, the fresh frozen plasma (FFP) to platelets and red blood cells (RBCs) ratio has been studied, which provides the best protective effect. Consequently, there is an increasing number of trials assessing the impact of the FFP:RBC ratio on outcomes such as mortality or multiple organ failure, with controversial results.

Since 2005, the United States Army's Institute of Surgical Research Conference suggested the administration of a high ratio (1:1:1) instead of a low ratio (1:1:2).[8] Later on, the *Prospective, observational, multicenter, major trauma transfusion trial* (PROMMTT)[9] found that the administration of blood products with a high FFP:RBC ratio was associated with decreased mortality during the first 6 hours after the trauma event. In contrast, the clinical trial *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* (PROPPR),[10,11] did not find any mortality reduction at 24 hours and at 30 days; however, there was a lower risk of early death due to exsanguination in patients treated with a high ratio. Moreover, some trials have reported an increase in the number of pulmonary complications and multiple organ failure with a higher FFP input.[12,13]

Notwithstanding, the consensus to intervene early in coagulopathy, with limited crystalloid use and early treatment with blood products,[14] it is not clear however about which plasma: RBC ratio provides the best outcomes. Some observational studies and clinical experiments have compared different FFP:RBC ratios with varying results, attributable to differences in the definition of massive bleeding, early exclusion of deceased patients, and interventions at different time periods.[15,16]

The objective of this systematic review was to assess the impact on early and late mortality of the administration of high vs low FFP:RBC, in patients with civilian trauma massive bleeding, and to determine the sources of heterogeneity of the trials.

Methodology

Selection of trials

A systematic literature review was conducted to identify observational studies and clinical controlled trials that

addressed the research question, with no language restrictions. The PRISMA (*Preferred Reporting Items for Systematic reviews and Meta-Analyses*) recommendations were followed.[17] The systematic review protocol was previously registered in PROSPERO (Record ID 111387).

The quality of the observational studies was assessed with the Newcastle–Ottawa scale (NOS),[18] and in the case of clinical experiments, the Cochrane collaboration instructions were adopted.[19] In order to identify the studies, the following e-databases were consulted, between the first week of 1990 and week 40 of 2019: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update, Embase, PsycINFO, and Lilacs, using the following search strategy: (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). In addition, the structured filters validated for observational studies of the Scottish Intercollegiate Guidelines Network were used, and for controlled clinical trials. The search was manually complemented with the snowball strategy and gray literature search using OpenGrey.

Inclusion criteria for the studies in this review

The studies that met the following criteria were included: clinical controlled trials or observational cohort, case controlled, studies that should include civilian trauma patients, report the FFP:RBC ratio administered, assess the mortality outcome, and embrace the previously established massive transfusion definition of ≥10 units in 24 hours, ≥6 units in 12 hours, or ≥5 units in 4 hours.[20]

Exclusion criteria for the studies

Any studies with the following characteristics were excluded: (a) studies such as case reports or case series; (b) studies using a historical cohort as the comparator; (c) studies that failed to consider the severity of the patients using scales such as the Injury Severity Score (ISS); and (d) studies, including patients with war or military trauma, or that included patients undergoing programmed surgeries.

Data mining

From each study, the information collected included the FFP:RBC ratio used for each one of the comparator groups, the mean age, the severity assessed with the ISS score, and in terms outcomes, mortality at 6, 12, and 24 hours and at 30 days after hospital discharge. Two reviewers (HO, DM) independently checked all the abstracts, taking the exclusion and inclusion criteria into account. Any differences among the studies selected were identified and reconciled, and the studies were independently reviewed as full texts.

Statistical analysis

The quality of the selected observational studies was assessed using the NOS scale,[18] and in the case of clinical experiments, the Cochrane collaboration instructions were followed.[19] Two reviewers (HO, DM) independently assigned a quality score and settled any disagreements by consensus. High-quality studies were those that obtained 7 or more points in NOS. The heterogeneity of the studies was assessed using the Q of Cochran, the I^2, and the Tau index; high heterogeneity was considered as $I^2 > 50\%$. The *odds ratio* (OR) was measured in each study, with their corresponding confidence intervals (CIs). Mortality before 24 hours was considered early and at 30 days late. The FFP:RBC ratio used was taken into account both in the intervention and in the comparator, and the accepted high ratio was that defined for each study. A 1:1 ratio represented the same number of units of FFP and RBC; in contrast, a 1:2 meant twice the amount of RBC per FFP unit, and this latter one was a lower ratio. For the combination of early and late mortality outcomes, it was stratified in accordance with the exclusion of deceased patients at 6, 12, and 24 hours, in order to assess the differential opportunity to receive therapy for survival. The OR values were obtained for each summary measurement through the fixed effects models of the Mantel and Hansen model; the random effects model by inverse variance, charts, and analyses were conducted using the statistical software STATA 15.0 (StataCorp, College Station, TX).

Results

General findings and quality assessment of the trials

With the search strategy, 1295 studies were identified and 74 of them were selected based on title and abstract; 25 failed to meet the inclusion criteria and an additional 16 were excluded due to various reasons; finally, 33 studies were included for analysis (Fig. 1).

Of the studies included, 22 reported mortality in the first 24 hours; in other 22, death was reported at 30 days, and 15 studies reported both outcomes. Most of the studies established as high FFP:RBC ratio cut points above 1:1.5 and 1:2. The quality of the observational studies assessed using NOS[18] was three points for only one study.[21] The rest had scores between 6 and 9, which translates into adequate-good quality. The risk of bias was low in the clinical experiments (Table 1).

Summary measurements of mortality assessment

When analyzing the 31 observational studies (n = 13924), the use of a high FFP:RBC ratio was associated with lower early mortality (OR 0.67; 95% CI, 0.60–0.75) and late (OR 0.79; 95% CI, 0.71–0.87), but with a significant heterogene-

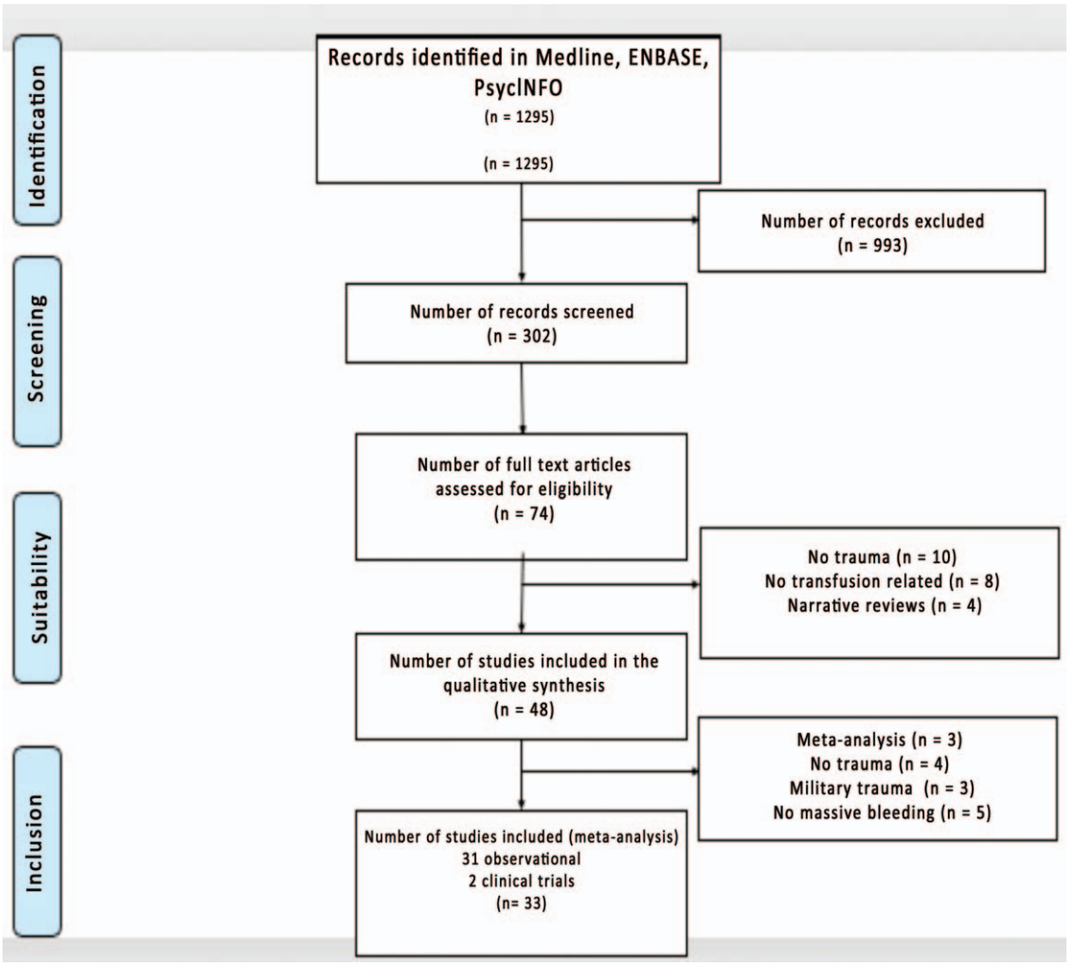

Figure 1. Flowchart identification and selection of the trials that met the inclusion criteria.
Source: Authors.

ity for both estimates, with an $I^2$of 91.9% and 86.3%, respectively. There were no differences between the groups when assessing the clinical (n=749) (OR 0,89; 95% CI, 0.64–1.26) and the heterogeneity was high (I^2 79.8%). The observational studies took into account the potential differences due to the exclusion of deceased patients over the first 24 hours following admission, and hence the summary measurements were stratified (6, 12, and 24 hours and studies that did not exclude the deceased patients). The result was that by not excluding the death over the first 24 hours, the protective effect on early mortality was maintained (OR 0.58; 95% CI, 0.38–0.89), but that was not the case for late mortality (OR 0.72; 95% CI, 0.46–1.11) (Fig. 2).

Heterogeneity assessment

As shown in Table 2, when mortality was stratified in accordance with the exclusion of deceased patients at 6, 12, and 24 hours, the heterogeneity decreased in all categories as compared against the global I^2. Additional stratifications were conducted, keeping in mind the time at which the transfusion was initiated (4, 6, 12, and 24 hours); no reduced heterogeneity was observed in the studies.

Meta-regression

To assess the ISS and age with the association between high FFP:RBC and early and late mortality, a meta-regression was conducted using the random effects model. As shown in Fig. 3, as the ISS value increases, the strength of the association between a high FFP:RBC ratio and mortality reduction. This can be inferred from the value of the slope $\beta_0=1.6$ for early mortality and $\beta_0=1.7$ for late mortality. However, the CIs are wide and contain the zero value.

Publications bias

The publication bias assessment used the funnel chart and Egger's test to determine the asymmetry via lineal

Table 1. Overall characteristics of the studies.

Reference	Outcome mortality	n	Age	ISS	High ratio FFP:RBC	Odds ratio CI (95%)	Quality Newcastle–Ottawa (18)
Holcomb et al[22]	30 days	418	39	33	1:2	1.99 (1.32–2.98)	8
	24 hours	418	39	33	1:2	1.81 (0.16–2.81)	8
Sperry et al[23]	30 days	415	41	34	1:1.5	0.73 (0.45–1.20)	8
	12 hours	415	41	34	1:1.5	0.28 (0.10–0.80)	8
Duchesne et al[24]	24 hours	135	33	27	1:1	0.05 (0.02–0.13)	8
Maegele et al[25]	30 days	713	41	41	1:1	0.51 (0.36–0.71)	8
	24 hours	713	41	41	1:1	0.34 (0.22–0.41)	8
Gunter et al[26]	30 days	259	34	25	2:3	0.43 (0.24–0.76)	6
Kashuk et al[27]	24 hours	140	35	36	1:2	0.54 (0.27–1.06)	6
Teixeira et al[28]	30 days	383	32	31	1:2	0.37 (0.26–0.60)	7
Snyder et al[29]	24 hours	134	39	33	1:2	0.48 (0.24–0.96)	7
Dente et al[30]	30 days	73	35	29	1:1	0.56 (0.20–1.55)	6
	24 hours	73	35	29	1:1	0.37 (0.11–1.23)	6
Zink et al[31]	30 days	452	33	31	1:1	0.43 (0.22–0.83)	6
	6 hours	452	33	31	1:1	0.07 (0.01–0.55)	6
Mitra et al[32]	30 days	331	42	36	1:1.5	0.93 (0.49–1.74)	9
	4 hours	331	42	36	1:1.5	0.32 (0.10–1.08)	9
Shaz et al[33]	30 days	190	37	27	1:2	1.18 (0.66–2.10)	6
	24 hours	190	37	27	1:2	1.8 (0.92–3.54)	6
Lustenberger et al[34]	24 hours	229	40	37	1:1.5	0.08 (0.04–0.16)	7
Spoerke et al[35]	30 days	529	NA	NA	1:4	0.39 (0.25–0.62)	7
	24 hours	529	NA	NA	1:4	0.29 (0.16–0.52)	7
Rowell et al[36]	30 days	704	40	32	1:2	0.71 (0.53–0.96)	9
	24 hours	704	40	NA	1:2	0.54 (0.38–0.76)	9
Peiniger et al[37]	30 days	1250	41.8	42	1:2	2.11 (1.65–2.69)	9
	24 hours	1250	41.8	42	1:2	3.29 (2.52–4.29)	9
Magnotti et al[38]	24 hours	103	38	32	1:2	0.39 (0.17–0.89)	7
Borgman et al[39]	30 days	659	43	34	1:2	0.61 (0.44–0.85)	8
	24 hours	659	43	34	1:2	0.47 (0.33–0.68)	8

Reference	Outcome mortality	n	Age	ISS	High ratio FFP:RBC	Odds ratio CI (95%)	Quality Newcastle–Ottawa (18)
Biasi et al[40]	24 hours	393	39	32	1:3	1.54 (0.93–2.54)	6
Spinella et al[41]	30 days	461	38	40	1:2	0.74 (0.40–1.35)	6
Wafaisade et al[42]	30 days	1362	45	36	1:1	0.66 (0.51–0.85)	8
	24 hours	1362	45	36	1:1	0.51 (0.36–0.73)	8
Brown et al[43]	6 hours	604	43	37	1:1.5	0.37 (0.14–0.95)	6
Sharpe et al[44]	30 days	135	37	32	1:1.5	0.46 (0.23–0.94)	7
Duchesne et al[45]	24 hours	451	38	23	1:2	0.38 (0.22–0.65)	9
Simms et al[46]	3 hours	151	33	29	1:1.4	0.19 (0.08–0.45)	6
Guidry et al[47]	6 hours	234	35	25	1:2	0.63 (0.35–1.14)	9
Nascimento et al[48]	30 days	69	41	35	1:1	4 (1.03–16.3)	*
Kudo et al[49]	30 days	15	60	25	1:1.5	0.8 (0.10–6.35)	7
	6 hours	15	60	25	1:1.5	1 (0.11–8.95)	7
Kim et al[50]	30 days	100	47	32	1:2	0.61 (0.26–1.46)	8
	24 hours	100	47	32	1:2	0.08 (0.02–0.39)	8
Rubén Peralta et al[21]	30 days	77	34	29	1:1.5	0.2 (0.07–0.55)	3
	24 hours	77	34	29	1:1.5	0.15 (0.05–0.45)	3
Stanworth et al[51]	24 hours	298	38	28	1:2	0.35 (0.19–0.65)	9
Holcomb et al[11]	30 days	680	34	26	1:1	0.81 (0.57–1.15)	*
	24 hours	680	34	26	1:1	0.71 (0.47–1.09)	*
Endo et al[52]	30 days	1777	NA	NA	1:1.25	0.85 (0.60–1.21)	8

* RCT = randomized controlled trials.
Source: Authors.

regression. An asymmetry was found mainly for the studies that assessed the late mortality outcome. This asymmetry could be due to a very high heterogeneity, to the quality differences and to the size of the trials (Fig. 4).

Discussion

In this meta-analysis, the use of a high FFP:RBC ratio in civilian trauma patients and massive transfusion was associated with a lower mortality risk over the first 34 hours to 30 days when the observational studies were evaluated. There were no significant differences when conducting clinical experiments. When the outcome was stratified based on the exclusion of deceased patients over the first 24 hours, the protective effect was maintained only for early mortality but not for late mortality; this may be due to the survival bias. Furthermore, the ISS changed the association between a high FFP:RBC ratio and mortality, being lower when the ISS was high.

Resuscitation of severe trauma patients and major bleeding has experienced significant changes, including the restricted use of crystalloids, surgical damage control, and balanced ratio transfusions, that are intended to match the total blood, an approach known as *damage control resuscitation*.[53] This particular strategy has been associated with lower requirements of blood products, decreased inflammation, and probably improved survival.

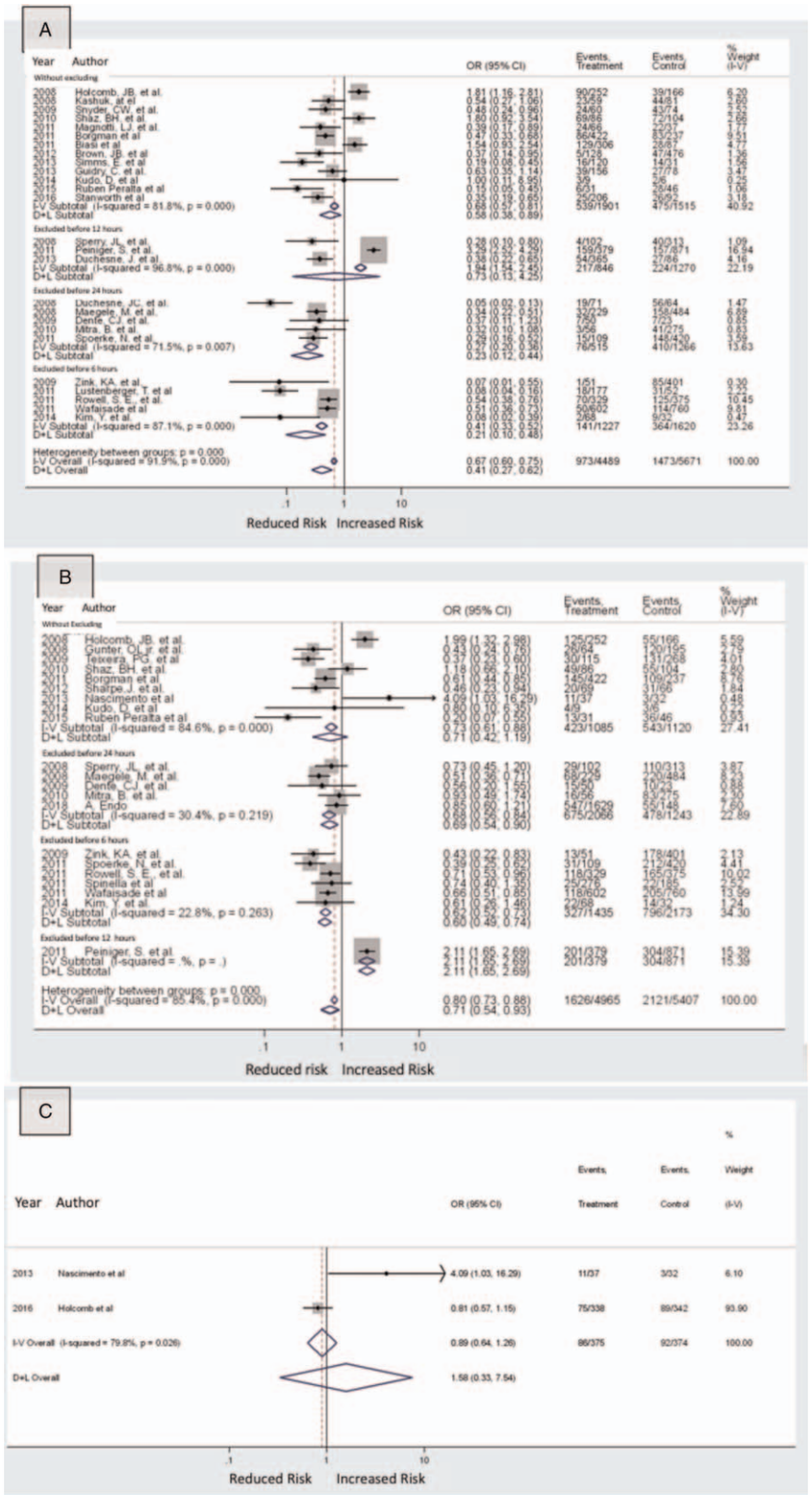

Figure 2. Effect of high vs low FFP:RBC ratio on mortality. (A) Mortality at 24 hours in observational studies. (B) 30-days mortality in observational studies. (C) Mortality in clinical experiments. FFP = fresh frozen plasma, RBC = red blood cell.
Source: Authors.

Table 2. Summary of early and late mortality measurements based on the exclusion of patients with massive bleeding.

Exclusion of deceased	n	OR (95% CI) Fixed effects model	OR (95% CI) Random effects model	I^2%
Without exclusion				
Early mortality	4.096	0.68 (0.57–0.81)*	0.58 (0.38–0.89)*	81.8
Late mortality	2.885	0.73 (0.61–0.88)*	0.71 (0.42–1.19)*	84.6
Excluded at 6 hours				
Early mortality	2.847	0.41 (0.33–0.52)*	0.21 (0.10–0.48)*	87.1
Late mortality	3.608	0.62 (0.52–0.73)	0.60 (0.49–0.74)	22.8
Excluded before 12 hours				
Early mortality	2.116	1.94 (1.54–2.45)	0.73 (0.13–4.25)	96.8
Late mortality	1.250	2.11 (1.65–2.69)	2.11 (1.65–2.69)	0
Excluded before 24 hours				
Early mortality	1.781	0.27 (0.20–0.36)*	0.23 (0.12–0.44)*	71.5
Late mortality	3.309	0.68 (0.56–0.84)*	0.69 (0.54–0.90)*	30.4

*With $P < 0.05$.
Source: Authors.

Despite all of these, the ideal FFP:RBC ratio is still controversial. The literature published between 2007 and 2015, based on observational studies, found that high ratios have a protective effect on mortality and hence the scientific associations issue recommendations based on this guideline.[54] However, these studies must be interpreted with caution because of their design. Rahouma et al[15] suggest some limitations with regards to the survival bias because several studies ignored the exact time of the blood products transfusion; hence, it might be possible that balanced ratios (high) could have been administered to the patients who survived the first hours, that is, the less severe. Our meta-analysis supports the possibility of survival bias in the observational studies, because when the outcomes were stratified in accordance with the exclusion of deceased patients over the first 24 hours, the early mortality protective effect declined and was non-existent for the late mortality.

There are other potential variables apart from the FFP:RBC ratio that may influence the mortality outcome; for instance, the early and timely administration of blood products (FFP in particular). So only by improving the transfusion protocol for patients with massive bleeding, has it been possible to report decreases in mortality from 45% to 19%.[55] These appreciations were tested in a clinical experiment. Holcomb et al in the PROPPR trial[10,11] found no significant differences in mortality at 24 hours and 30 days, though homeostasis was achieved faster and there were less deaths as a result of exsanguination in the group treated with a high ratio. Moreover, the authors claim that about 15% of the deaths were due to traumatic brain injury, which could have contributed to the absence of differences.

The PROPPR trial[11] also showed that the administration of higher than 1:1 ratio had no additional benefit in mortality, which is a consistent finding with the result of this meta-analysis, since we stratified based on different FFP:RBC ratios, we did not identify that as a source of heterogeneity. With regards to other sources of heterogeneity suggested by other authors, such as time of initiation of the administration of blood products,[56] the total number of units transfused, and the amount of crystalloids administered,[44,57] these became study limitations and made it impossible to stratify based on these variables because they were not reported.

Our study has its limitations. First, the volume of crystalloids administered over the first few hours is unknown and this is a risk factor for coagulopathy and death;[52,58] however, this is a limitation typical of

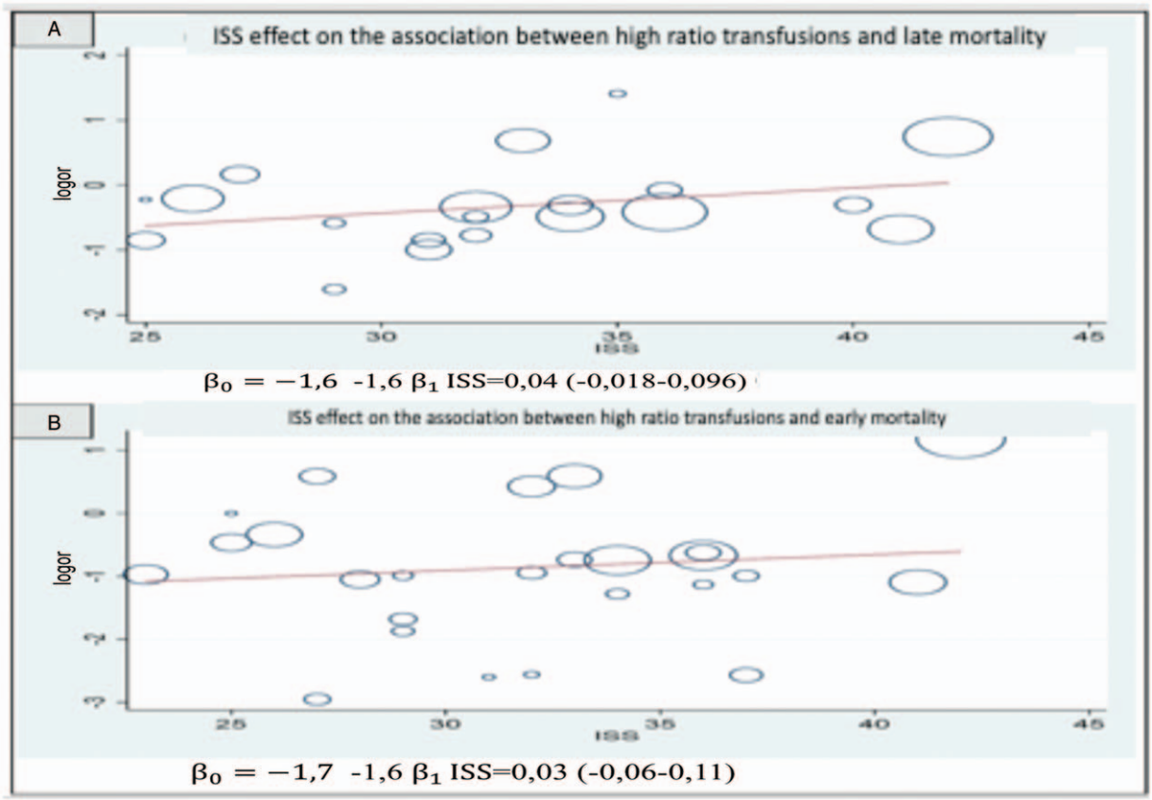

Figure 3. Meta-regression of the ISS effect on the association between high FFP:RBC ratio and mortality. FFP = fresh frozen plasma, ISS = Injury Severity Score, RBC = red blood cell.
Source: Authors.

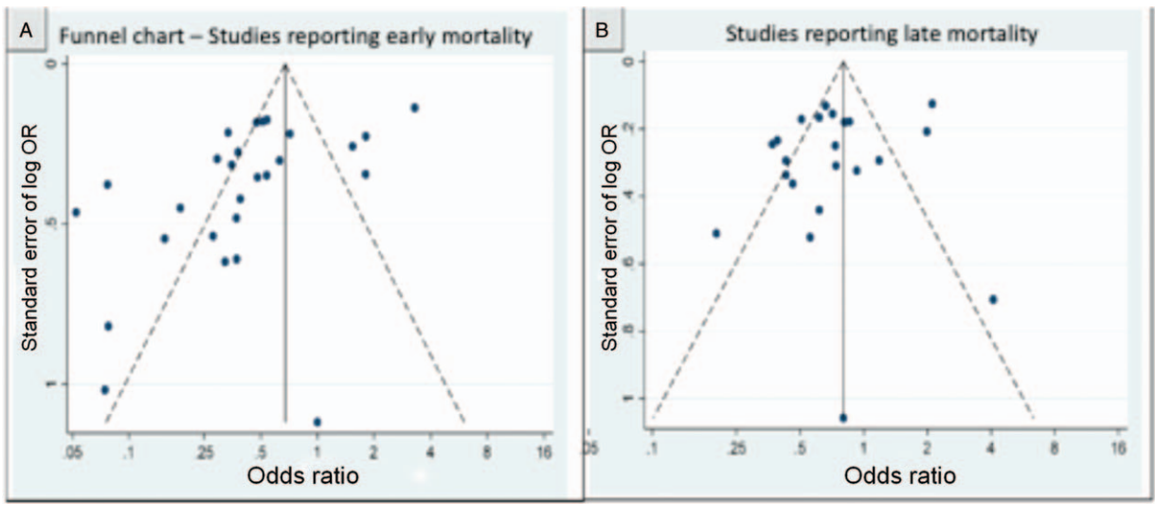

Figure 4. Assessment of publication bias in studies reporting early and late mortality (A and B, respectively).
Source: Authors.

individual studies, since these variables are not reported. Neither is the use of other interventions assessed, such as cryoprecipitates, prothrombin complex concentrate, fibrinogen concentrates, and tranexamic acid. Moreover, the definition of massive transfusion includes a very long period of observation (up to 24 hours), which could delay the onset of adequate therapy and favor the survival bias. This has shorten the time to diagnosis of MT to just a few hours (*critical threshold for the administration of three units in one hour*)[59,60] and to adopt massive bleeding prediction models such as: modified shock index,[61] Assessment of Blood Consumption score ABC[62] Trauma Associated Severe Hemorrhage Score TASH,[63] Schreiber Score[64] Emergency Transfusion Score ETS,[65] and the Prince of Wales Hospital Score PWH.[66] The final goal of this reasoning is to reduce the observation period and start hemostatic resuscitation early.[63]

Although the right blood products ratio continues to be a valid query, its generalized use has been questioned, because of the risk of acute pulmonary injury and multiple organ failure. Along these lines, the proposal is to individualize treatment and direct transfusion support based on a *therapy guided by objectives,* aimed at achieving normal hemostasis, since it has been able to reduce bleeding, decrease the amount of blood products used, and improve other outcomes.[67] To this end, "bedside" coagulation tests are conducted with viscoelastic methods (VEM) and based on the results, the specific blood products used are determined. Some authors suggest a mixed strategy that comprises transfusion therapy with high ratio during the early massive bleeding, and then make some adjustments in accordance with a VEM algorithm (thromboelastography or thromboelastometry).[68]

Conclusion

The use of high FFP:RBC ratio in civilian trauma patients and massive transfusion was associated with a lower mortality risk in the first 24 hours and at 30 days when the observational trials were assessed. There were no significant differences when analyzing the clinical experiments. When the outcomes were stratified in accordance with the exclusion of deceased patients over the first 24 hours, a protective effect was maintained only for early mortality, with no differences in late mortality. The studies identified showed an increased heterogeneity resulting from multiple sources; one of the most relevant ones was the exclusion of patients who die early, before the first 24 hours after the trauma event, which represents a survival bias. Other sources of heterogeneity, such as the severity of the trauma, changed the use of blood products and mortality, as evidenced in the meta-regression.

Funding

The authors have no funding to disclose.

Conflicts of interest

The authors have no conflicts of interest to disclose.

References

1. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma 2006;60 (6 suppl):S3–S11.
2. Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma 2008;65:748–754.
3. MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. J Trauma 2003;55:39–44.
4. Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. J Trauma 2003;54:1127–1130.
5. Ball CG. Damage control resuscitation: history, theory and technique. Can J Surg 2014;57:55–60.
6. Cotton BA, Reddy N, Hatch QM, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg 2011;254:598–605.
7. Duchesne JC, McSwain NE Jr, Cotton BA, et al. Damage control resuscitation: the new face of damage control. J Trauma 2010;69: 976–990.
8. Spinella PC, Perkins JG, Grathwohl KW, et al. Fresh whole blood transfusions in coalition military, foreign national, and enemy combatant patients during Operation Iraqi Freedom at a U.S. combat support hospital. World J Surg 2008;32:2–6.
9. Holcomb JB, Fox EE, Wade CE, et al. The PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study. J Trauma Acute Care Surg 2013;75 (1 suppl 1):S1–S2.
10. Baraniuk S, Tilley BC, del Junco DJ, et al. Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial: design, rationale and implementation. Injury 2014;45:1287–1295.
11. Holcomb JB, Tilley BC, Baraniuk S, et al. 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: the PROPPR randomized clinical trial. JAMA 2015;313:471–482.
12. Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? Crit Care Med 2006;34 (5 suppl):S170–S173.
13. Dunbar N, Cooke M, Diab M, et al. Transfusion-related acute lung injury after transfusion of maternal blood: a case–control study. Spine 2010;35:E1322–E1327.
14. Cohen MJ, West M. Acute traumatic coagulopathy: from endogenous acute coagulopathy to systemic acquired coagulopathy and back. J Trauma 2011;70 (5 suppl):S47–S49.
15. Rahouma M, Kamel M, Jodeh D, et al. 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. Am J Surg 2018;216:342–350.
16. Zehtabchi S, Nishijima DK. Impact of transfusion of fresh-frozen plasma and packed red blood cells in a 1:1 ratio on survival of emergency department patients with severe trauma. Acad Emerg Med 2009;16:371–378.
17. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–605.
19. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142.
20. Chico-Fernández M, García-Fuentes C, Alonso-Fernández MA, et al. Massive transfusion predictive scores in trauma. Experience of a transfusion registry. Med Intensiva 2011;35:546–551.
21. Peralta R, Vijay A, El-Menyar A, et al. Trauma resuscitation requiring massive transfusion: a descriptive analysis of the role of ratio and time. World J Emerg Surg 2015;10:36.

22. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008; 248:447–458.
23. Sperry JL, Ochoa JB, Gunn SR, et al. An FFP:PRBC transfusion ratio ≥1:1.5 is associated with a lower risk of mortality after massive transfusion. J Trauma 2008;65:986–993.
24. Duchesne JC, Hunt JP, Wahl G, et al. Review of current blood transfusions strategies in a mature level I trauma center: were we wrong for the last 60 years? J Trauma 2008;65:272–276.
25. Maegele M, Lefering R, Paffrath T, et al. Red-blood-cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiple injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft fur Unfallchirurgie. Vox Sanguinis 2008;95:112–119.
26. Gunter OL Jr, Au BK, Isbell JM, et al. Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. J Trauma 2008;65:527–534.
27. Kashuk JL, Moore EE, Johnson JL, et al. Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? J Trauma 2008;65:261–270.
28. Teixeira PG, Inaba K, Shulman I, et al. Impact of plasma transfusion in massively transfused trauma patients. J Trauma 2009;66:693–697.
29. Snyder CW, Weinberg JA, McGwin G Jr, et al. The relationship of blood product ratio to mortality: survival benefit or survival bias? J Trauma 2009;66:358–362.
30. Dente CJ, Shaz BH, Nicholas JM, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. J Trauma 2009;66:1616–1624.
31. Zink KA, Sambasivan CN, Holcomb JB, et al. A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. Am J Surg 2009;197:565–570.
32. Mitra B, Mori A, Cameron PA, et al. Fresh frozen plasma (FFP) use during massive blood transfusion in trauma resuscitation. Injury 2010;41:35–39.
33. Shaz BH, Dente CJ, Nicholas J, et al. Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. Transfusion 2010;50:493–500.
34. Lustenberger T, Frischknecht A, Bruesch M, et al. Blood component ratios in massively transfused, blunt trauma patients—a time-dependent covariate analysis. J Trauma 2011;71:1144–1150.
35. Spoerke N, Michalek J, Schreiber M, et al. Crystalloid resuscitation improves survival in trauma patients receiving low ratios of fresh frozen plasma to packed red blood cells. J Trauma 2011;71 (2 suppl 3):S380–S383.
36. Rowell SE, Barbosa RR, Allison CE, et al. Gender-based differences in mortality in response to high product ratio massive transfusion. J Trauma 2011;71 (2 suppl 3):S375–S379.
37. Peiniger S, Nienaber U, Lefering R, et al. Balanced massive transfusion ratios in multiple injury patients with traumatic brain injury. Crit Care 2011;15:R68.
38. Magnotti LJ, Zarzaur BL, Fischer PE, et al. Improved survival after hemostatic resuscitation: does the emperor have no clothes? J Trauma 2011;70:97–102.
39. Borgman MA, Spinella PC, Holcomb JB, et al. The effect of FFP:RBC ratio on morbidity and mortality in trauma patients based on transfusion prediction score. Vox Sanguinis 2011;101:44–54.
40. De Biasi AR, Stansbury LG, Dutton RP, et al. Blood product use in trauma resuscitation: plasma deficit versus plasma ratio as predictors of mortality in trauma (CME). Transfusion 2011 51:1925–1932.
41. Brasel KJ, Vercruysse G, Spinella PC, et al. The association of blood component use ratios with the survival of massively transfused trauma patients with and without severe brain injury. J Trauma 2011;71 (2 suppl 3):S343–S352.
42. Wafaisade A, Maegele M, Lefering R, et al. High plasma to red blood cell ratios are associated with lower mortality rates in patients receiving multiple transfusion (4</=red blood cell units<10) during acute trauma resuscitation. J Trauma 2011;70:81–88.
43. Brown JB, Cohen MJ, Minei JP, et al. Debunking the survival bias myth: characterization of mortality during the initial 24 hours for patients requiring massive transfusion. J Trauma Acute Care Surg 2012;73:358–364.
44. Sharpe JP, Weinberg JA, Magnotti LJ, et al. Accounting for differences in transfusion volume: are all massive transfusions created equal? J Trauma Acute Care Surg 2012;72:1536–1540.
45. Duchesne JC, Heaney J, Guidry C, et al. Diluting the benefits of hemostatic resuscitation: a multi-institutional analysis. J Trauma Acute Care Surg 2013;75:76–82.
46. Simms ER, Hennings DL, Hauch A, et al. Impact of infusion rates of fresh frozen plasma and platelets during the first 180 minutes of resuscitation. J Am College Surg 2014;219:181–188.
47. Guidry C, DellaVope J, Simms E, et al. Impact of inverse ratios on patients with exsanguinating vascular injuries: should more be the new paradigm? J Trauma Acute Care Surg 2013;74:403–409.
48. Nascimento B, Callum J, Tien H, et al. Effect of a fixed-ratio (1:1:1) transfusion protocol versus laboratory-results-guided transfusion in patients with severe trauma: a randomized feasibility trial. CMAJ 2013;185:E583–E589.
49. Kudo D, Sasaki J, Akaishi S, et al. Efficacy of a high FFP:PRBC transfusion ratio on the survival of severely injured patients: a retrospective study in a single tertiary emergency center in Japan. Surg Today 2014;44:653–661.
50. Kim Y, Lee K, Kim J, et al. Application of damage control resuscitation strategies to patients with severe traumatic hemorrhage: review of plasma to packed red blood cell ratios at a single institution. J Korean Med Sci 2014;29:1007–1011.
51. Stanworth SJ, Davenport R, Curry N, et al. Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice. Br J Surg 2016;103:357–365.
52. Endo A, Shiraishi A, Fushimi K, et al. Outcomes of patients receiving a massive transfusion for major trauma. Br J Surg 2018; 105:1426–1434.
53. Stensballe J, Henriksen HH, Johansson PI. Early haemorrhage control and management of trauma-induced coagulopathy: the importance of goal-directed therapy. Curr Opin Crit Care 2017;23:503–510.
54. Cannon JW, Khan MA, Raja AS, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: A practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg 2017;82:605–617.
55. Riskin DJ, Tsai TC, Riskin L, et al. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. J Am College Surg 2009;209:198–205.
56. González EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. J Trauma 2007;62:112–119.
57. Neal MD, Hoffman MK, Cuschieri J, et al. Crystalloid to packed red blood cell transfusion ratio in the massively transfused patient: when a little goes a long way. J Trauma Acute Care Surg 2012;72:892–898.
58. Tapia NM, Suliburk J, Mattox KL. The initial trauma center fluid management of penetrating injury: a systematic review. Clin Orthopaedics Related Res 2013;471:3961–3973.
59. Savage SA, Zarzaur BL, Croce MA, et al. Redefining massive transfusion when every second counts. J Trauma Acute Care Surg 2013;74:396–400.
60. Cantle PM, Cotton BA. Prediction of massive transfusion in trauma. Crit Care Clin 2017;33:71–84.
61. Terceros-Almanza LJ, García-Fuentes C, Bermejo-Aznarez S, et al. Prediction of massive bleeding. Shock index and modified shock index. Med Intensiva 2017;41:532–538.
62. Nunez TC, Voskresensky IV, Dossett LA, et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma 2009;66:346–352.
63. Yucel N, Lefering R, Maegele M, et al. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. J Trauma 2006;60:1228–1236.
64. Schreiber MA, Perkins J, Kiraly L, et al. Early predictors of massive transfusion in combat casualties. J Am College Surg 2007;205: 541–545.

65. Kuhne CA, Zettl RP, Fischbacher M, et al. Emergency Transfusion Score (ETS): a useful instrument for prediction of blood transfusion requirement in severely injured patients. World J Surg 2008;32:1183–1188.
66. Rainer TH, Ho AM, Yeung JH, et al. Early risk stratification of patients with major trauma requiring massive blood transfusion. Resuscitation 2011;82:724–729.
67. Schochl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010;14:R55.
68. Johansson PI, Stensballe J. Effect of haemostatic control resuscitation on mortality in massively bleeding patients: a before and after study. Vox Sanguinis 2009;96:111–118.