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Prevalence of Survivor Bias in Observational Studies on Fresh Frozen Plasma:Erythrocyte Ratios in Trauma Requiring Massive Transfusion

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ABSTRACT

Observational studies on transfusion in trauma comparing high *versus* low plasma:erythrocyte ratio were prone to survivor bias because plasma administration typically started later than erythrocytes. Therefore, early deaths were categorized in the low plasma:erythrocyte group, whereas early survivors had a higher chance of receiving a higher ratio. When early deaths were excluded, however, a bias against higher ratio can be created. Survivor bias could be reduced by performing before-and-after studies or treating the plasma:erythrocyte ratio as a time-dependent covariate.

We reviewed 26 studies on blood ratios in trauma. Fifteen of the studies were survivor bias-unlikely or biased against higher ratio; among them, 10 showed an association between higher ratio and improved survival, and five did not. Eleven studies that were judged survivor bias-prone favoring higher ratio suggested that a higher ratio was superior.

Without randomized controlled trials controlling for survivor bias, the current available evidence supporting higher plasma:erythrocyte resuscitation is inconclusive.

THERE is consensus in trauma management that fresh frozen plasma (FFP) should be given when continuous hemorrhage and coagulopathy are present.[1–4] In recent years, however, the best way of giving FFP in the 2% of civilian and 7% of military trauma patients who require massive transfusion (MT) has been controversial.[5–8] This controversy is between use of conventional fluid and blood management guidelines *versus* the so-called "1:1" strategy in the subset of trauma patients who require MT.[6–8] The definition of MT in the literature varies, but is typically equal to or more than 10 units of packed erythrocytes within 6–24 h of hospital admission.[1–5]

Conventional fluid management in hemorrhagic shock has been to give crystalloid and erythrocytes initially.[9] According to current guidelines, FFP should be considered after 1–1.5 blood volumes have been lost or coagulation tests are raised (international normalized ratio more than 2 or activated partial thromboplastin time more than 1.5×normal), in the presence of excessive microvascular bleeding.[3,4] The decision to give FFP may therefore be made at 0.5–4 h following hospital admission. Furthermore, FFP requires

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thawing, and is sometimes ordered in small quantities (*e.g.*, 10–15 ml/kg or equal to or less than 4 units).[3,4] Whereas group O erythrocytes for severe shock has been readily available for decades, use of universal donor plasma (AB, a rather rare commodity) is only a recent development. The number of units of plasma given compared to that of erythrocytes (P:E) tends therefore to have been far less than one during the initial hours of resuscitation. It just so happens also that hemorrhage and coagulopathy are important causes of death in the first few hours of resuscitation.[7,10] In recent years, many practitioners have argued that conventional transfusion guidelines do not sufficiently address the needs of trauma patients with massive and ongoing bleeding. Based only on anatomic and physiologic parameters identified within minutes of arrival in hospital and on initial response to resuscitation, clinicians can reasonably identify that small subset of patients whose transfusion requirement will likely be substantial,[11,12] and administer prethawed FFP and blood products such that P:E approaches 1:1–2 early in the course of resuscitation.[5–8] This nearly unity ratio is continued but is terminated as soon as hemorrhage is controlled. The emphasis of this so-called "1:1" philosophy is very much on the early (within less than 0.5–1 h of admission) attainment of a P:E ratio of 1:1–2, hence achieving such a ratio at the 24th hour after hospital admission (playing catch-up) does not constitute "1:1."[7]

There has not been a single randomized controlled trial (RCT) to date validating either traditional transfusion guidelines or "1:1" in MT.[7] Proponents of the "1:1" philosophy cite supportive observational studies.[6,7] Opponents counter that observational studies are prone to biases.[6] Without data from RCTs, a 17-member multidisciplinary panel recently would not recommend either for or against transfusion of FFP at a P:E ratio of more than or equal to 1:3 during MT.[2]

There is in particular one type of bias, survivor bias (SB), or immortal time bias, that is universally cited as the flaw that puts the validity of P:E studies in doubt (SB is actually not uncommon in observational studies).[6,8,13] It arises because patients with massive and ongoing hemorrhage often die during the early hours of hospital admission before receiving substantial quantities of FFP (when using traditional transfusion guidelines), and thus are categorized (without randomization) in the low P:E cohort in observational studies, whereas patients surviving long enough to receive sufficient FFP (finally caught up) are categorized in the high P:E cohort.[13] Hence observational studies using data from centers using conventional (as opposed to "1:1") guidelines have a built-in SB favoring the high P:E cohort.[13] In logistic regression analysis, low FFP may similarly emerge as an associative factor in mortality.

To avoid this form of SB, some investigators have excluded those patients who died within half to several hours after hospital admission. Unfortunately, since hemorrhage and coagulopathy are such important causes of mortality during the first few hours in a significant proportion of trauma patients (other causes of early deaths include severe head injury with or without associated hemorrhage, but within the first 6 h, exsanguination is dominant[14]), the practice of including only patients who survive until intensive care unit admission 4–7 h later, for example, excludes a significant portion of patients who had died from exsanguination who potentially could have benefitted from increased FFP therapy. In the process, a much less discussed, albeit important, SB against high P:E is created.[8,10]

As an increasing number of trauma centers appear to be aiming for a "1:1" philosophy based on its effectiveness as reported in observational studies, there still remains concern that many of these studies may be flawed because of SB. Thus we need to pause and ask the important question: How widespread is SB in P:E studies, and are we being too hasty or too cautious on this important resuscitation issue? To answer this we have appraised published P:E studies for the presence of SB. Randomized trials and observational studies are prone to other bias, but SB is our focus here. Also, only studies on P:E ratios in trauma resuscitation were examined; other hemostatic therapies and adjuncts are outside the scope of this review.

It is important to note that for the purpose of this review, high P:E at 24 h and "1:1" are not exactly interchangeable. The former applies to studies in centers that adhered to conventional guidelines (in which FFP typically is started much later than erthryocytes), and P:E was calculated using the cumulative FFP and erythrocytes at the end of 24 h. The latter applies to studies in centers where there was an early aggressive FFP protocol, in which "1:1" means a high P:E that was achieved shortly after hospital admission.

Materials and Methods

The MEDLINE database was searched using OVID interface from 1966 to July 2011, combining the keywords "massive transfusion" and "trauma." All 210 abstracts thus found were reviewed, and the full texts of 75 studies, case series, and reviews were examined. Abstracts that have not been published as full papers were excluded. Also the January 2010-July 2011 issues of J Trauma, Injury, Crit Care Med, Intens Care Med, Crit Care (London), Surgery, Am J Surg, Br J Surg, Can J Surg, J Am Coll Surg, Ann Surg, World J Surg, Anesthesiology, Anesth Analg, Br J Anaesth, Can J Anesth, Transfusion, Vox Sang, and Resuscitation were reviewed. Finally, a search on Google was made ("trauma+ coagulopathy") and the first 100 hits vetted. Bibliographies of all reviewed papers were then searched for more articles.

Any study was included for analysis if it consisted of a comparison between high FFP:packed erythrocyte ratio *versus* low ratio in trauma resuscitation involving MT. MT was defined as equal to or more than 10U erythrocytes over less than or equal to 24 h, or any average of equal to or more than 1U erythrycytes/h within the first 12 h of resuscitation. Case series and reports, nonhuman studies, reviews, commentary

articles, and nontrauma papers were also excluded, although their references were reviewed.

For studies involving the use of warm fresh whole blood (WFWB), the equivalent blood ratios were used, meaning 1 unit of WFWB was considered the same as 1 unit each of FFP, platelets, and packed erythrocytes.

Use of recombinant activated factor VII (rFVIIa) and other prohemostatic nonblood products was noted but was not used as an inclusion or exclusion criterion.

Two of the authors (Drs. Ho and Dion) independently examined the final list of papers chosen for review and drew consensual conclusions. There was no blinding of the names of authors, their affiliations, or the journal titles. RCTs, if there were any, would be judged SB-free.

A study was considered SB-unlikely:

if cohorts after and before the implementation of a MT protocol that called for the early attainment of P:E = 1:1–2 were compared. The cohorts were independent. (Such studies fulfill the objective of comparing "1:1" with conventional fluid and blood product management as the MT protocol typically calls for the early/earlier attainment of equivalent units of FFP and erythrocytes);

or,

if P:E was analyzed as a time-dependent covariate.

A study was considered SB-prone:

if patients were drawn from the same pool and were categorized in the low or high P:E cohort depending on how much blood products they had received up to a fixed time point (*e.g.*, at 24 h or time of death). All patients were included from time of hospital admission or shortly thereafter to that time point. This bias is in favor of high P:E because early deaths were categorized in the low P:E cohort. Such studies are high *vs.* low P:E and do not truly compare "1:1" and conventional fluid/blood management as there is no stipulation on an early attainment of a P:E of 1:1–2; only the summative P:E at the end of 24 house or time of death is considered;

or,

if patients were drawn from the same pool, but only those surviving beyond the first few hours or long enough to be admitted to an intensive care unit were studied. This bias is against high P:E because hemorrhage is a dominant cause of death within the first few hours[14] and patients who had survived that long either had less severe coagulopathy or might have already benefitted from having high P:E management. Here again, such studies do not truly compare "1:1" and conventional management as only the summative P:E at the end of 24 h is considered.

Results

No RCTs were found. Thirty eight (fig. 1) uncontrolled observational trauma studies comparing high *versus* low P:E in MT were identified. The definitions of high and low P:E

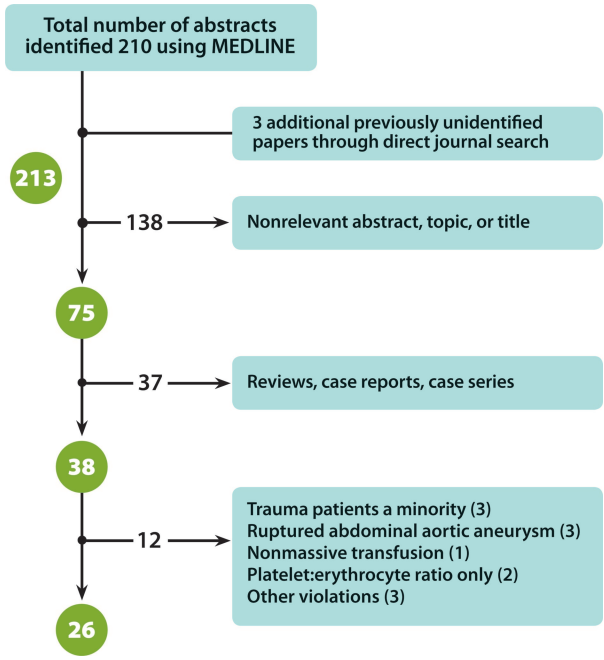

Fig. 1. Breakdown of literature search results.

vary with the studies.[15–52] In general, high P:E is loosely defined as equal to or more than 1:1–2 and low FFP is defined as less than 1:1–2.[15–50] From that list, 12 studies were excluded, three because trauma patients made up only a fraction of the patient population studied,[41–43] three because they involved only patients with ruptured abdominal aortic aneurysm,[44–46] one (involving patients with vascular or extremities injuries) because massively and nonmassively transfused patients were included,[47] one because the patient population was similar to another study already included,[48] two because both the study and control groups were given low FFP,[49,50] and two because only platelet:erythrocyte ratios were examined.[51,52]

A total of 6,655 patients were studied in the 26 reports included in the final analysis (table 1, fig. 2).[15–40] Because overlapping of patients likely occurred in some studies,[19,20,27,29] the total number of patients is probably slightly less. In figure 2 we provide a breakdown of the studies based on civilian or military, effect of high P:E/"1:1," and whether they were SB-prone (favoring high P:E or against high P:E) or SB-unlikely. Mortality is typically reported as in-hospital or 30-day mortality.

Military trauma (4 studies)[15–18] and civilian trauma (22 studies)[19–40] have been grouped separately (table 1, fig. 2).

In terms of the crucial result of interest the following was found:

(A) Of the four military studies,[15–18] all showed that high P:E was superior and all were SB-prone favoring high P:E [Van *et al.*'s[18] study actually only showed a trend ($P = 0.07$)];

Table 1. Studies Comparing High and Low Fresh Frozen Plasma:Packed Erythrocyte Ratios for Trauma Patients Requiring Massive Transfusion

Reference	Study Design	Results	Survivor Bias Y/N
Military			
Borgman 2007;[15] Iraq/ United States	Registry review. 246 combat casualties Nov. 2003–Sept. 2005 who were given ≥10 U erythrocytes or WFWB in first 24 h. Three groups analyzed according to P:E ratio of low 1:12–1:5, intermediate 1:3–1:2.3 and high 1:1.7–1:1.2.	High P:E increases survival to hospital discharge mainly from reducing death from hemorrhage. Survival of low *vs.* intermediate *vs.* high P:E was 11/31 (45%) *vs.* 35/53 (66%) *vs.* 131/162 (81%), respectively, $P < 0.001$. After excluding those given rFVIIa, the results became 74% *vs.* 61% *vs.* 85%, respectively, still significant.	Yes, SB prone, favoring high P:E.
Stinger 2008;[16] Iraq/ United States	Retrospective review of data in Jan. 2004–Oct. 2008 from military trauma registry. 252 patients received ≥10 U packed erythrocytes in first 24 h.	High fibrinogen cohort receiving a P:E of 11.2/15.9 (0.7) plus cryoprecipitate 9.3 U and 2.9 U of WFWB per patient *vs.* a low fibrinogen cohort receiving a P:E of 3.5/15.9 (0.2) plus 0.77 U of cryoprecipitate and 0.6 U of whole blood; survival to hospital discharge in high P:E group was 152/200 (76%) *vs.* low P:E group of 25/52 (48%), $P < 0.001$.	Yes, SB prone, favoring high P:E.
Spinella 2009;[17] Afghanistan/Iraq/ United States	Retrospective review of data for Jan. 2004–Oct. 2007 from military hospitals; 354 patients received WFWB, most had ≥10 U erythrocytes in first 24 h.	Among survivors, the P:E was 0.75 (0.56–0.95), and among non-survivors, the P:E was 0.58 (0.40–0.89), $P = 0.003$, despite a much higher use of rFVIIa in the latter. Amount of WFWB used relatively small. 24-h and 30-day survival rates significantly higher in those given WFWB. Patients given whole blood possibly got plasma earlier.	Yes, SB prone, favoring high P:E.
Van 2010;[18] Iraq/ United States	247 soldiers with isolated extremity injury massively transfused.	High P:E was associated with a trend toward decreased mortality 17.2% *vs.* 6.9%, $P = 0.07$; and a trend toward increased complications 20.7% *vs.*. 26.4%, $P > 0.05$. Higher prevalence of rFVIIa in high P:E cohort.	Yes, SB prone, favoring high P:E.

(*continued*)

Table 1. Continued

Reference	Study Design	Results	Survivor Bias Y/N
Civilian			
Maegele 2008;[19] Germany	Registry review of 2002–2006 data from German Trauma Registry; 713 civilians with ISS >16 received ≥10 U packed erythrocytes between admission to hospital and ICU admission. Only patients alive long enough to go to ICU were analyzed.	Survival rate at 6 h: P:E >1.1 *vs.*. 0.9–1.1 *vs.* <0.9 was 96.5% *vs.* 90.4% *vs.* 75.3%; survival rate at 24 h for the same P:E was 89.7% *vs.* 83.3% *vs.* 67.4%; 30-day survival for the same P:E was 75.7% *vs.* 64.9% *vs.* 54.5%; in-hospital survival for the same P:E was 69.6% *vs.* 64% *vs.* 54.1%. All significant.	Yes, SB prone, against high P:E.
Duchesne 2008;[20] United States	Retrospective chart review of Jan. 2002–Dec. 2006 of trauma data; 135 civilians receiving >10 U packed erythrocytes and who survived surgery. Resuscitation followed conventional guidelines.	Mortality in patients who received >10 U erythrocytes 26% *vs.* 87.5% when P:E was 1:1 *vs.* 1:4 ($P = 0.0001$). A ratio of 1:4 was consistent with increased risk of mortality (relative risk: 18.88; 95% CI: 6.32–56.36; $P = 0.001$), when compared with a ratio of 1:1.	Yes, SB prone, against high P:E.
Gonzalez 2007;[21] United States	Retrospective cohort review of trauma database over 51 months ending Jan. 2003; 97 civilians given ≥10 U packed erythrocytes in first 24 h who survived to ICU admission were identified. Patients were admitted to ICU at a mean of 6.8 h after admission.	Survivors and nonsurvivors received a P:E of 6:11 and 4:13, respectively, prior to ICU admission. There was more blunt trauma and worse coagulopathy on admission, but ISS was lower, amongst survivors, and their INR on intensive care unit admission was better.	Yes, SB prone, against high P:E.
Sperry 2008;[22] United States	7-center Nov. 2003–Mar. 2007 data reviewed retrospectively; 415 blunt trauma patients transfused ≥8 U erythrocytes in first 12 h divided into >1:1.5 and <1:1.5 ratios. Median transfusion of 14 U erythrocytes. Patients with isolated head injury excluded.	24-h survival P:E of high ≥1:1.5 *vs.* low <1:1.5 was 72/102 (71%) *vs*. 203/313 (65%); high *vs*. low P:E: multiorgan failure was 64% *vs.* 54%; infection rate was 58% *vs.* 43%; respiratory distress syndrome was 47% *vs.* 24%; 24-h erythrocyte requirement was 16 ± 9 *vs.* 22 ± 17.	Yes, SB prone, favoring high P:E.
Holcomb 2008;[23] United States	Retrospective review of data from July 2005–June 2006 from 16 civilian trauma centers; 466 trauma patients who received ≥10 U packed erythrocytes in first 24 h. 65% blunt injury; patients divided into groups according to P:E and subgroups according to FFP/platelets: erythrocytes.	30-day survival: P:E ≥1:2 *vs.* <1:2 was 165/252 (66%) *vs.* 112/214 (52%); high platelets and FFP to erythrocytes was 110/151 (73%) *vs.* low ratios 56/131 (43%). Higher rFVIIa use in higher ratio cohorts. High plasma + high platelet ratios was associated with less truncal blood loss, higher 6-h, 24-h, and 30-day survival, and more ICU, ventilator, and hospital-free days ($P < 0.05$), with no change in multiple organ failure deaths.	Yes, SB prone, favoring high P:E.*

(*continued*)

Table 1. Continued

Reference	Study Design	Results	Survivor Bias Y/N
Kashuk 2009;[24] United States	Retrospective review of prospective uncontrolled data between 2001 and 2006 in hospital. 133 trauma patients receiving >10 U of packed erythrocytes in first 6 h.	High P:E reduced coagulopathy; a U-shaped mortality at hour 6 against the P:E suggested the ideal ratio is not 1:1 but 1:2. Survival probability according to ratio of 1:1 *vs.* 1:2–1:3 *vs.* ≥1:5 = 43% *vs.* 72% *vs.* 9%, respectively.	Yes, SB prone, favoring high P:E.
Teixeira 2009;[25] United States	Retrospective review of cross-referenced databases; 6 yr of data; 383 civilians receiving >10 U erythrocytes in first 24 h. Severe head injuries excluded.	Survival to hospital discharge: High P:E (>1.3) *vs.* medium P:E (>1.8 ≤1.3) *vs.* low P:E (≤1:8) was 58/226 (74%) *vs.*. 48/95 (51%) *vs.* 6/62 (10%). Differences significant.	Yes, SB prone, favoring high P:E.
Mitra 2010;[26] Australia	Retrospective review of blood bank and hospital databases at 1 hospital; 331 patients received ≥5 U packed erythrocytes first 4 h in July 2004–Aug. 2008.	Survival rate at 24 h: P:E of >1: 1.5 *vs.* 1:1.5–1.25 *vs.*. 1:1.25–3.5, and <1:3.5 was 94.7%, 88.3%, 81.8%, and 82%. For those who survived to ICU, high P:E patients required longer ventilation and intensive care stay.	Yes, SB prone, favoring high P:E.
Borgman 2011;[27] Germany	Retrospective analysis of a Trauma Registry; 659 patients across Germany who scored high in likelihood of requiring ≥10 U erythrocytes in the emergency department and/or operating room. Deaths within 1 h of admission to emergency excluded.	P:E of mean 1:0.95 was associated with improved survival, with an odds ratio of 2.5 (90% CI 1.64–4), when compared with a P.E. of mean 1:5.6. 14.1% of patients in the high P:E group received rFVIIa *vs.*. 6.1% in the low P:E group $P < 0.05$.	Yes, SB prone, favoring high P:E; and SB likely, against high P:E.
Shaz 2010;[28] United States	Single hospital. Retrospective review of clinical and blood bank data before implementation of "1:1" (n = 84; Feb. 2005–Jan. 2007) *vs.* prospective uncontrolled data after "1:1" (n = 132; Feb. 2007–Jan. 2009). MT = ≥10 U packed erythrocytes/24 h.	No difference in survival, ICU and hospital lengths of stay between the 2 groups. Erythrocytes, cryoprecipitate, platelets, and FVIIa use were similar between groups but FFP use was higher in post-"1:1"group (P:E was 0.5 ± 0.2 *vs.* 0.3 ± 0.2). When all patients were analyzed together, 24-h and 30-day survivals were best with P:E ≥0.5, platelet: erythrocytes ≥1, cryoprecipitate: erythrocytes ≥1.	Yes, despite being a before and after study. SB prone favoring high P:E.

(*continued*)

Table 1. Continued

Reference	Study Design	Results	Survivor Bias Y/N
Duchesne 2011;[29] United States	Same center as Duchesne,[20] 12 months of data Jan.–Dec. 2006 using pre-"1:1" protocol *vs.* 12 months of data Jan.–Dec. 2007 post-"1:1" protocol. 118 civilians receiving >10 U erythrocytes during and after surgery.	30-day survival: post-"1:1" cohort 48:61 (78.6%) *vs.* pre-"1:1" 34/57 (59.6%), $P < 0.02$. Hospital length of stay was also significantly lower in the post-"1:1" group. Much less use of crystalloid in the post-"1:1" group. No mention of rFVIIa.	No, SB unlikely (before-and-after study). Yes, SB prone, against high P:E.
Gunter 2008;[30] United States	2 yr before establishment of "1:1" 140 civilians, data collected retrospectively *vs.* 2 yr of data after implementation of "1:1" 119 civilians, data collected prospectively.	30-day survival: P:E >1:1.5 *vs.* <1:1.5 was 38/64 (59%) *vs.* 74/195 (38%), $P = 0.008$; platelet:erythrocyte >1:1.5 *vs.* 1:<1.4 was 39/63 (62%) *vs.* 76/196 (39%), $P = 0.001$; 30-day survival for post-"1:1" *vs.*. pre-"1:1" groups was 61/119 (51%) *vs.* 53/140 (38%), $P = 0.02$.	No, SB unlikely (before-and-after study).
Riskin 2009;[31] United States	Retrospective chart review comparing cohorts 2 yr pre- and post-"1:1"; 77 trauma patients requiring ≥10 U packed erythrocytes in first 24 h.	30-day survival rate of post-"1:1" *vs.* pre-"1:1" was 30/37 (81%) *vs.* 22/40 (55%), $P = 0.02$. P:E was 1:1.8 in pre- and post-"1:1" cohorts, but mean time to first FFP was 254 and 169 min ($P = 0.02$), respectively.	No, SB unlikely (before-and-after study).
Dente 2009;[32] United States	Prospective review of 73 trauma patients' data collected over 1 yr after starting "1:1" in Feb. 2007, compared with 2 yr before implanting "1:1"; data from comparable group of 84 civilians retrospectively collected from registry.	Post-"1:1" patients received a mean of 23.7 U erythrocytes and 15.6 UFFP transfusions *vs.* pre-"1:1" patients' 22.8 U erythrocytes ($P = 0.67$) and 7.6 U FFP ($P < 0.001$). Crystalloid use dropped drastically. 24-h survival was 83% in post-"1:1" group *vs.* 64% in pre-"1:1" group ($P = 0.008$), and at 30 days 66% *vs.* 45% ($P = .04$). Use of rFVIIa similar in both groups.	No, SB unlikely (before-and-after study).
Cotton 2009;[33] United States	Retrospective review of Trauma Registry data on civilians given ≥10 U erythrocytes during first 24 h collected Aug. 2004–Jan. 2006 pre-"1:1" *vs.* prospectively collected uncontrolled data Feb. 2006–Jan. 2008 post-"1:1".	30-day survival: post-"1:1" *vs.* pre-"1:1" was 72/125 (57%) *vs.* 53/141 (38%), $P = 0.001$. High P:E associated with significantly less blood product use, less pulmonary and multiorgan failure, abdominal compartment syndrome, open abdomens, and septic shock; no difference in renal failure or systemic inflammatory response syndrome.	No, SB unlikely (before-and-after study).

(*continued*)

Table 1. Continued

Reference	Study Design	Results	Survivor Bias Y/N
Zaydfudim 2010;[34] United States	Single hospital. Retrospective review of registry data before implementation of "1:1" (n = 39; Feb. 2004–Jan. 2006) *vs.*. prospective uncontrolled data after implementation of "1:1" (n = 36; Feb. 2006–Jan. 2008).	30-day survival in post-"1:1" *vs.* pre-"1:1" cohorts was 19/36 (53%) *vs.* 12/39 (31%), $P = 0.02$; cardiac dysfunction and abdominal compartmental syndrome were significantly lower in post-"1:1" patients despite much higher ISS. P:E as measured at 24 h were similar.	No, SB unlikely (before-and-after study).
de Biasi 2011;[35] United States	Retrospectively reviewed 835 trauma patients from 2003 to 2008 of which 307 received ≥10 U packed erythrocytes in the first 24 h of admission.	Mortality with 0–2, 3–6, or >6 deficit units of FFP at 3 h was 39.3, 44.1, and 64.1% ($P < 0.003$) and at 24 h was 37.6, 48.1 and 60.4% ($P < 0.007$). No statistically significant mortality reduction was seen with increased P:E ratios alone, indicating that FFP deficit (erythrocyte units minus FFP units) given may be the more critical and sensitive indicator.	No, SB unlikely (P:E is time-dependent covariate).
Scalea 2008;[36] United States	*Prospective uncontrolled cohorts; 806 trauma civilians admitted to ICU between July 2004 and Nov. 2006, single-center study; 81 patients received ≥10 U erythrocytes in 24 h.*	*Logistic regression in massive transfusion cohort found no significant effect on in-hospital mortality for either P:E as a continuous variable odds ratio OR, 1.49; 95% CI, 0.63–3.53; P = 0.37, or 1:1 ratio as a binary variable OR, 0.60; 95% CI 0.21–1.75; P = 0.35.*	*Yes, SB prone, against high P:E.*
Snyder 2009;[37] United States	*Retrospective review of trauma registry data in Jan. 2005–Jan. 2007. 134 patients with complete data who received >10 U erythrocytes during the first 24 h. See Discussion section.*	*When total blood use after 24 h was compared, survival was 60% in high P:E ≥1. group vs. 42% in low P:E <1:2 group; this difference became nonsignificant when data was analyzed in a time-dependent manner: hourly in first 2 h, then hourly for 4 h, then 6-hourly for 16 h. Adjustment for platelets, cryoprecipitate and rFVIIa administration did not significantly change the results.*	*No, SB unlikely (P:E is time-dependent covariate).*
Magnotti 2011;[38] United States	*Single hospital; retrospective review of trauma registry Mar. 2006–Dec. 2007. 103 patients given ≥10 U packed erythrocytes within 24 h. Resuscitation protocol appears to be high P:E.*	*Patients receiving P:E ≥1:2 had improved survival 62% vs. 41%; P < 0.002, but when excluding patients during the first 6 h, difference disappears. When treating P:E as a time-dependent covariate, the hazard ratio of high plasma was 0.58 (95% CI 0.279–1.114; P = 0.098). high P:E associated with reduced mortality between 0–6 h after admission to hospital. No mention of rFVIIa.*	*No, criteria SB unlikely; and yes, SB prone, against high P:E.*

(*continued*)

Table 1. Continued

Reference	Study Design	Results	Survivor Bias Y/N
Dirks 2010;[39] Denmark	*Single hospital; 2001–2002 pre-"1:1", n = 97 vs. 2005–2007 post-"1:1",* n = *156; patients had >10 U erythrocytes in first 24 h. In both cohorts, FFP transfusion trigger was INR >1.2 or aPTT >35 s and prethawed FFP was available and used.*	*No difference in 30-day mortality in pre- and post-"1:1" groups; time to first unit of FFP in pre-"1:1" protocol 28 min. and in post-"1:1", 3 min. The pre-"1:1" patients were not managed according to conventional transfusion protocol but were given early FFP.*	*No, SB unlikely (before-and-after study).*
O'Keeffe 2008;[40] United States	*Single hospital system; 2003–2004 pre-"1:1" n = 46 vs. 2004–6 post-"1:1", n = 132; patients had >10 U erythrocytes in first 24 h.*	*No difference in 24-h mortality in pre- and post-"1:1"groups; P:E actually decreased in the post-"1:1" group (2.07 vs. 1.78); time to 1st units of plasma earlier in the post-"1:1" group; use of erythrocytes, plasma, platelets was less but of rVIIa was higher in post-"1:1"group. Mortality after 24 h significantly less in post-"1:1" group.*	*No, SB unlikely (before-and-after study).*

Italicized text is for studies that did not show an association between reduced mortality and high P:E.

* Only one patient who died during the first 30 min of admission was excluded; it is unlikely that such a short exclusion time could have eliminated survivor bias.

aPTT = activated partial thromboplastin time; CI = confidence interval; FWB = fresh whole blood; ICU = intensive care unit; INR = international normalized ratio; ISS = injury severity score; MT = massive transfusion; P:E = ratio of number of units of fresh frozen plasma (FFP) to the number of units of packed erythrocytes; rFVIIa = recombinant activated factor VII; SB = survivor bias; U = units; WFWB = warm fresh whole blood.

(B) Among 22 civilian studies,[19–40] seven studies[29–35] (n = 1,259) judged SB-unlikely showed "1:1" as superior, four studies[37–40] (n = 668) judged SB-unlikely showed "1:1"/high P:E as not superior, seven studies[22–28] (n = 2,603) judged SB-prone (favoring high P:E) showed high P:E as superior, three studies[19–21] (n = 945) judged SB-prone (against high P:E) showed high P:E as superior, and one study[36] (n = 81) judged SB-prone (against "1:1") showed "1:1" as not superior;

(C) Studies with SB favoring high P:E and showing an association between high P:E and increased survival accounted for 11 of the 26 studies analyzed.

Overall, of 26 studies on high *versus* low P:E ratios, 21 found an association between high P:E (*i.e.*, 1:1–2)/"1:1" and improved survival but only 10 (all civilian) of them were either SB-unlikely (7) or had a bias against high P:E (3). Five (all civilian) of the 26 studies found no such favorable association but one of them had a built-in bias against high P:E and one had a control group whose transfusion management was closer to "1:1" than to conventional practice (Dr. Jesper Dirks, Clinical Associate Professor, Department of Anesthesia, Centre of Head and Orthopedics, Copenhagen University Hospital, Copenhagen, Denmark, personal e-mail communication, June 2011). In other words, only 10 of the 26 studies showed high P:E as superior and were SB-free or had SB against high P:E. No association between high P:E and reduced short-term survival has been reported.

Discussion

Our review discovered that SB is rather prevalent in studies on blood product ratios in trauma requiring MT. The positive association between high P:E and improved survival in SB-prone (favoring high P:E) studies may be partly or wholly factitious. On the other hand, the SB-stigma should not apply to all P:E studies. In fact, 10 studies that found a positive association between "1:1"/high P:E and improved survival were SB-free or had SB against high P:E,[19–21,29–35] one study that did not find such a positive association had a bias against "1:1,"[35] and no study found "1:1" or high P:E to have been associated with decreased survival.

Study Design Strategies to Prevent SB

Including only patients who have survived the initial few hours when FFP administration typically lags is one technique of avoiding SB in favor of "1:1."[53,54] The exact number of hours to exclude is highly variable. For example, mean time to first FFP (not necessarily P:E equals 1:1–2 status) before and after implementation of a "1:1" policy at Stanford Medical Center was 254 and 169 min, respectively.[31] On the other hand, at the R. Adam Cowley Shock Trauma Center,

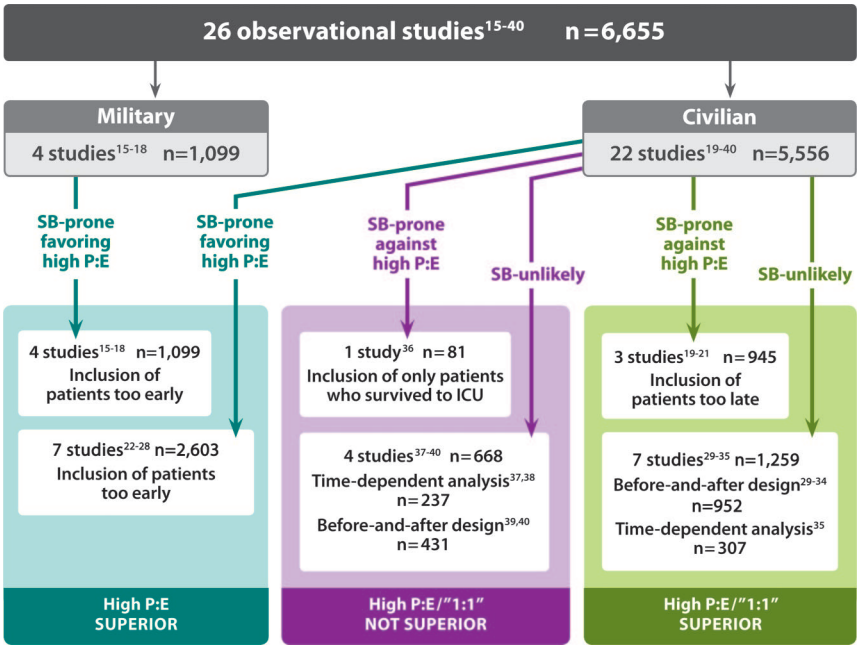

Fig. 2. Breakdown of studies analyzed according to setting, fresh frozen plasma use, outcome, and survivor bias. Studies that show a positive association between "1:1" and improved survival and that are either survivor bias-unlikely or survivor bias-prone against "1:1" are indicated by *thick arrows*. ICU = intensive care unit; P:E = plasma to erythrocyte ratio; SB = survivor bias.

where "1:1" has been standard practice for a longer time,[8,35,36] the mean time to achieving nearly 1:1–2 blood product ratios would be shorter. One group excluded deaths within the first 30 min of admission to hospital but only one patient was excluded.[23] This was probably insufficient to significantly reduce SB that favors high P:E.

Including only patients who have survived to reach the intensive care unit may eliminate SB that favors high P:E. The price to pay, unfortunately, is that any benefits of high P:E become harder to observe. About 10–20% of trauma deaths are possibly preventable and 10–80% of them are due to hemorrhage, mostly occurring within 6 h of admission and with coagulopathy playing a major role.[10,14] Including only those patients who survive surgery to be admitted to the intensive care unit (some 4.5–7 h after admission[20,21,36,49]), as in Scalea *et al.*'s,[36] Gonzalez *et al.*'s[21] and Duschene *et al.*'s[20] studies, would exclude patients who might have serious hemostatic issues (and have succumbed), and in whom "1:1" might have helped. Instead, such a study would have focused only on those who might have less serious hemostatic issues (and have survived), and in whom the benefits of "1:1," if there had been any, would not have been uncovered.[8,10] Furthermore, if a center already had "1:1" in place, as might have been the case at the A. Adams Cowley Shock Trauma Center,[35,36] studying only survivors beyond the first few hours of admission meant that some of the studied patients might have already enjoyed the benefits of "1:1," had there been any.

Clearly, the longer the period of exclusion since admission in such observational studies, the less SB against conventional plasma management (in centers without a "1:1" policy) there is, but the higher the potential bias against high P:E or "1:1" (regardless of whether the transfusion protocol is conventional or "1:1").

Another strategy for avoiding SB is to populate the low and high FFP cohorts with independent subjects. This has been done by taking data collected after implementation of a "1:1" protocol and comparing them with a historical cohort. This strategy avoids a Hawthorne effect that can be associated with RCTs. However, comparing 2-yr cohorts before and after implementing "1:1" ignores secular trends[8] and possibly allows the benefits of other advances in resuscitation to be credited to "1:1." For instance, many centers have seen a dramatic decrease in 24-h crystalloid use as they have transitioned to a "1:1" policy. It is unclear if the potential benefit of "1:1" is from more FFP or less crystalloid, or both.

Another way of avoiding SB is to model the relationship between mortality and P:E ratio over time, and treating the P:E ratio as a time-dependent covariate.[35,37,38] This is a recommended technique of avoiding SB in observational studies.[53,54] Snyder *et al.* compared mortality of patients who had had high P:E at the end of 24 h and those who had had low P:E and found the former to be associated with increased survival.[37] This advantage became statistically insignificant when they divided the 24-h study period into 0.5–6 h subintervals and calculated the P:E and the mortality rates of the high P:E and low P:E groups within each subinterval.[37] deBiasi *et al.* also did not find the mortality of high P:E and low P:E to be different but found that a high FFP deficit (not a low P:E) in relationship to erythrocytes was associated with higher mortality.[35] This study has been put into the category of studies that have found a positive association between high

P:E and improved survival (see table 1 and fig. 2) because the study's conclusion calls for equal number of FFP and erythrocytes units.

In "1:1," Is It the Ratio, or the Timing, That Matters?

In one before-and-after study in which the cohort after the implementation of a "1:1" MT protocol was found to have significantly better survival, the cumulative P:E at 24 h after admission was 1:1.8 both before and after adoption of "1:1."[31] The only difference was that "1:1" (the "after" group) resulted in earlier administration of the first unit of FFP [169 (95% CI: 130–209) min], whereas clinicians using traditional resuscitation principles (the "before" group) started late with FFP [254 (185–323) min; $P = 0.04$] but played "catch-up." In that study, platelets were also started significantly earlier in the post-MT group.[31] The early use of WFWB was associated with a survival advantage in one study.[16] In Dirks' comparison of trauma patients before and after institution of a "1:1" protocol, there was no difference in mortality.[39] They used international normalized ratio more than 1.2 or activated partial thromboplastin time more than 35 s as a FFP-transfusion trigger, and had on standby prethawed FFP during both the pre- and post-MT periods (Dr. Jesper Dirks, Clinical Associate Professor, Department of Anesthesia, Centre of Head and Orthopedics, Copenhagen University Hospital, Copenhagen, Denmark, personal e-mail communication, June 2011). First exposure to FFP was 28 min after admission even in the pre-"1:1" cohort, possibly accounting for the lack of clinical outcomes difference. These studies[16,31,39] suggest that if "1:1" is indeed superior, it might be due to the earlier, not just the increased, use of FFP. As such, it is worth emphasizing that studies examining the cumulative P:E at 24 h after admission do not shed enough light on the "1:1" paradigm as they do not factor in the timing at which P:E equal to 1:1–2 was reached. It is possible that in future studies the 6-h period/endpoint after admission will be more revealing.

End-points

The reviewed studies typically used 24 h-, 30 day-, and in-hospital mortality as end-points. Since uncontrolled hemorrhage is an important cause of early death, and "1:1" emphasizes early aggressive use of FFP, it makes sense to measure mortality at 6 h. In Holcomb *et al.*'s (SB-prone favoring high P:E) study, the Kaplan–Meier survival curve diverges mainly during the initial 6 h of admission, after which the curves were largely parallel and much flatter.[23] Later end-points are also important to determine if early and increased use of FFP actually leads to increased or decreased overall exposure to blood products, which could be reflected in the incidences of transfusion-related acute lung injury, respiratory distress syndrome, and multiorgan failure. The issue of competing mortality risks has received less attention in transfusion studies. All clinicians recognize that trauma patients largely die from hemorrhage, head injury, and multiorgan failure/sepsis, and some patients have multiple causes of death. These events, although related to the initial injury, occur at distinctly different time points, and the effect of competing mortality risks must be accounted for.

Notable Studies Not Included in Our Analysis

Several MT studies on P:E that are of interest were excluded from this review because nontrauma patients were included. In Johannson *et al.*'s. (SB-unlikely) study, P:E at 24 h after and before implementation of "1:1" were 1:1.3 and 1:1.6, respectively, but the post-"1:1" group received FFP earlier and had better survival.[41] Rose *et al.* found in their (SB-prone favoring high P:E) study an association of P:E ratio more than 1.1 with improved survival in elective and emergent nontrauma and trauma patients requiring MT.[42] Johannson *et al.* found in a (SB-prone favoring high P:E) study that MT patients whose mean P:E was 1:1.25 had a survival rate of 50%, whereas those whose PE was 1:2.5 had a survival rate of 7.7%.[43] A further three MT observational (SB-unlikely) studies involved patients with ruptured abdominal aortic aneurysm showed that after implementation of "1:1" survival improved.[44–46]

Military versus *Civilian*

Military and civilian injuries share many similarities, but there are some notable differences. A civilian must wait for an ambulance but a soldier injured on the battlefield usually receives immediate basic care from a fellow soldier and then a combat medic[55] before embarking on an arduous journey to the nearest combat support hospital. Blood products at the combat hospital are usually available in adequate amounts, and not infrequently augmented by WFWB. Since 2004 many deployed hospitals have used thawed AB plasma and erythrocytes as the primary initial resuscitation fluids. With planning and routine use, WFWB is available within 30 min of a request but can sometimes take up to 2 h. Some civilian trauma centers have followed this practice, and thawed AB plasma has become available in recent years. Because of the higher energy transfer and predominance of multiple penetrating injures, combat casualties have a higher chance of requiring MT, placing greater burdens on the blood bank and operating room logistics and personnel. Despite these differences, survival after combat injury and massive hemorrhage is at least equivalent and in many cases superior to those seen in civilian centers. So far, all four military studies[15–18] have all included patients from the time of hospital admission or shortly thereafter, and are therefore SB-prone, favoring high P:E. Future observational military studies should use time-dependent analysis to avoid SB.

In summary, we have outlined criteria for identifying SB when appraising observational studies on the use of FFP in trauma requiring MT and have applied them to published studies to discover that SB is common. Trauma management is complex and it takes the combined merit of many interventions to bring about measurable improvements. The pres-

ence of SB in part may explain the rather big reduction in mortality associated with high P:E in some studies. On the other hand, the bias cannot be used to dismiss all of the available data to date. Doing so is cherry-picking and spoils the debate. Uncontrolled observational studies are prone to other biases and confounders that diminish their validity. In closing, therefore, we emphasize the need for good RCTs to answer this question. To this end, the multicenter Prospective Randomized Optimum Platelet and Plasma Ratio trial comparing blood product ratios in trauma patients predicted to require MT will start enrolling patients in 2012,‡‡ and the Trauma Formula-driven *versus* Lab-guided study (ClinicalTrials.gov Identifier: NCT00945542) comparing "1:1" *versus* conventional resuscitation in patients with hemorrhagic shock is currently enrolling patients, as is the Early Whole Blood in Patients Requiring Transfusion After Major Trauma trial (ClinicalTrials.gov Identifier: NCT01227005).§§

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§§ http://www.clinicaltrials.gov/ct2/results?term=trauma+AND+plasma. Accessed June 28, 2011.

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