# The Relationship of Blood Product Ratio to Mortality: Survival Benefit or Survival Bias?

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**Background:** Recent studies show an apparent survival advantage associated with the administration of higher cumulative ratios of fresh frozen plasma (FFP) to packed red blood cells (PRBC). It remains unclear how temporal factors and survival bias may influence these results. The objective of this study was to evaluate the temporal relationship between blood product ratios and mortality in massively transfused trauma patients.

**Methods:** Patients requiring massive transfusion (>10 units of PRBC within 24 hours of admission) between 2005 and 2007 were identified (n = 134). In-hospital mortality was compared between patients re-ceiving high (>1:2) versus low (<1:2) FFP: PRBC ratios with a regression model, using the FFP:PRBC ratio as a fixed value at 24 hours (method I) and as a time-varying co-variate (method II).

**Results:** The FFP:PRBC ratio for all patients was low early and increased over time. Sixty-eight percent of total blood products were given and 54% of deaths occurred during the first 6 hours. Using method I, patients receiving a high FFP: PRBC ratio (mean, 1:1.3) by 24 hours had a 63% lower risk of death (RR, 0.37; 95% CI, 0.22–0.64) compared with those receiving a low ratio (mean, 1:3.7). However, this asso-ciation was no longer statistically significant (RR, 0.84; 95% CI, 0.47–1.50) when the tim-ing of component product transfusion was taken into account (method II).

**Conclusions:** Similar to previous studies, an association between higher FFP: PRBC ratios at 24 hours and improved sur-vival was observed. However, after adjust-ment for survival bias in the analysis, the association was no longer statistically signif-icant. Prospective trials are necessary to evaluate whether hemostatic resuscitation is clinically beneficial.

**Key Words:** Hemostatic resuscitation, Plasma, FFP, Transfusion, Survival bias.

"**D**amage control resuscitation" or "hemostatic resuscita-tion" is a resuscitation strategy incorporating aggres-sive management of injury-associated coagulopathy,[1–5] and has been promoted by the surgical services of the US military in recent years. Reserved for the severely injured casu-alty, this strategy includes the utilization of thawed plasma as a primary resuscitation fluid in a 1:1 or 1:2 ratio with packed red blood cells (PRBCs).[6–9] Enthusiasm for this approach has been enhanced by the recent publication of retrospective studies that demonstrated a survival advantage associated with the adminis-tration of relatively higher FFP:PRBC ratios, in both military and civilian patient populations.[10–15]

Although retrospective data demonstrate a relationship between higher cumulative FFP:PRBC ratios and lower mor-

tality at a specific point in time (ratio calculated at 24 hours after admission in most studies), the actual temporal relation-ship between the administration of specific components and mortality has not been elucidated. Plausibly, the apparent survival advantage associated with high FFP:RBC transfu-sion ratios could be the consequence of a survival bias among the cohort studies. Survival bias can occur in studies evalu-ating the effect of a specific treatment on survival when the study design results in a time window between the initiation of subject observation and the initiation of treatment. If an excessive number of deaths occur before the initiation of treat-ment, survival bias can significantly distort the true treatment effect.[16] As component blood products are not administered uniformly and simultaneously in civilian clinical practice, and many deaths occur early, it is possible that the survival advan-tage observed among those receiving a higher FFP:PRBC ratio may simply reflect the fact that they lived long enough to receive the higher ratio of products. In this study, we sought to account for survival bias by investi-gating the relationship between the timing of component blood product transfusion and in-hospital mortality in a massively transfused civilian trauma patient cohort.

## METHODS

Between January 2005 and January 2007, all trauma patients treated at the University of Alabama-Birmingham (UAB) Hospital who were massively transfused were se-lected for inclusion in this study. Massive transfusion was defined as transfusion of 10 or more units of PRBC during the

first 24 hours of hospitalization. UAB is an American College of Surgeons accredited Level I trauma center providing acute trauma care for north central Alabama and surrounding regions, serving a population of over two million. The facility admits over 3,500 patients per year, of whom 15% have Injury Severity Score (ISS) >25.

Demographic and clinical data were retrieved from the trauma registry, as well as individual electronic and paper medical records. A team of physician reviewers recorded the precise times of transfusion events and deaths during the initial 48 hours of hospitalization. These data were obtained primarily from the trauma bay nursing flowsheet, operating room anesthetic record, and intensive care unit nursing flowsheets. Data quality control was performed by comparing the recorded time of blood product administration with time of product release from the blood bank. No significant data inconsistencies were observed.

Initial observations showed that relevant events occurred infrequently beyond the first few hours. Accordingly, events were categorized using the following time intervals from the time of patient arrival: every 30 minutes for the first 2 hours, every 1 hour for 2–6 hours, and every 6 hours for 6–24 hours. For each patient, the cumulative FFP:PRBC ratio up to and including a given time period was calculated using the following formula:

$$FFP:PRBC \ Ratio = F / (B + C),$$

where $F$, $B$, and $C$ were the cumulative numbers of plasma, PRBC, and autotransfused cell saver units administered, respectively. Patients were categorized according to FFP:PRBC ratio. Patients with ratios of 0.5 or greater (≥1:2) were assigned to the "high-ratio" group and patients with ratios less than 0.5 (<1:2) were assigned to the "low-ratio" group. This stratification of patients was based on unpublished data from our own institution, and confirmed by recently published studies showing a ratio of FFP:PRBC of at least 1:2 to be optimal for survival.[12,13] Patients who received no plasma, PRBC, or cell saver (ratio = 0/0) were not categorized in either group until such time as they received at least one unit of a blood product. Any patient who received PRBC or cell saver but no plasma (ratio = 0) was included in the low-ratio group, whereas anyone who received plasma but no PRBC or cell saver (ratio = infinity) was included in the high-ratio group.

Demographic and clinical characteristics were compared between survivors and nonsurvivors using $t$ and $\chi^2$ tests for continuous and categorical variables, respectively. Two approaches were used to evaluate the association between FFP:PRBC ratio and mortality. The first approach used a standard Cox proportional hazards regression model. The primary outcome of interest was in-hospital mortality, with time calculated as the duration between admission to death or discharge. The primary independent variable was the cumulative FFP:PRBC ratio at 24 hours, with adjustment for age, gender, ISS, mechanism of injury (blunt vs. penetrating), associated head injury (as defined by Centers for Disease Control criteria), and admission base deficit, International Normalized Ratio (INR), and thrombocytopenia (platelet count <150,000 per microliter). The second approach was identical to the first, with the exception that the primary independent variable was treated as a time-dependent covariate.[17] That is, the FFP:PRBC ratio is not exclusively considered at a solitary fixed point in time (e.g., 24 hours). Rather, the relationship between in-hospital mortality and FFP:PRBC ratio is modeled over time, taking into account the fact that patients may transition to and from the low- to high-ratio groups at each time interval of interest. This is the preferred approach to correct for survival bias.[16]

## RESULTS

A total of 150 patients received massive transfusion during the study period, and 134 had complete medical records available for review. The remaining 16 patients were excluded from subsequent analysis. A total of 2,620 units of PRBC and cell saver and 1,104 units of FFP were transfused during the 24-hour resuscitation period of interest. Most blood products were transfused early in the hospital course, with 68% of the 24-hour total given in the first 6 hours and 92% in the first 12 hours after arrival to hospital. The first unit of PRBC was given at a median time of 18 minutes (range, 1–348 minutes), whereas the first unit of FFP was given at a median time of 93 minutes (range, 24 minutes–350 minutes).

Overall in-hospital mortality was 50% (67 deaths), with most deaths occurring early in the hospital course. Fifty-four percent of all in-hospital deaths occurred within 6 hours of arrival, and 72% within 24 hours. Median time of death was 293 minutes, or 4.9 hours (range, 61 minutes–119 days). The cause of death was exsanguinating hemorrhage in 45 patients (67.2%), traumatic brain injury in nine patients (13.4%), multisystem organ failure (MSOF) in seven patients (10.4%), and other causes in six patients (9.0%).

Clinical characteristics of survivors and nonsurvivors are presented in Table 1. No significant differences were observed with respect to age, gender, associated head injury, injury mechanism, or admission INR between survivors and nonsurvivors. ISS and admission base deficit were higher and thrombocytopenia more common among nonsurvivors. With respect to subsequent management, nonsurvivors were taken to the operating room faster, received more units of PRBC, and were less likely to receive cryoprecipitate than survivors.

Cumulative FFP:PRBC ratios were calculated at a time point of 24 hours from hospital presentation for each patient. The low-ratio group comprised 74 patients with a mean ratio of 0.27 (1:3.7) ± 0.14. The high-ratio group comprised 60 patients with a mean ratio of 0.76 (1:1.3) ± 0.28. Figure 1 demonstrates the incidence of death associated with ratio group, with patients assigned to groups according to their cumulative FFP:PRBC ratio at 24 hours. The incidence of death was 58% in the low-ratio group compared with 40% in the high-ratio group. Upon Cox regression modeling with

**Table 1** Characteristics of In-Hospital Survivors and Non-Survivors (N = 134)

|  | Survivors (N = 67) | Non-survivors (N = 67) |
|---|---|---|
| Initial presentation |  |  |
| Age, mean | 36.8 | 41.6 |
| Male, % | 64.2 | 77.6 |
| ISS* | 28.7 | 39.4 |
| Blunt injury mechanism, % | 40.3 | 38.8 |
| Head injury, % | 20.9 | 22.9 |
| Base deficit* | −9.5 | −12.6 |
| INR | 1.60 | 1.85 |
| Thrombocytopenia, %* | 11.9 | 29.9 |
| Subsequent management |  |  |
| PRBC units transfused, median* | 15.0 | 18.5 |
| Cell saver units transfused, median | 1 | 2 |
| FFP units transfused, median | 10 | 7.5 |
| Platelet units transfused, median | 2 | 2 |
| Received cryoprecipitate, %* | 56 | 33 |
| Received factor VIIa, % | 7 | 7 |
| Treated operatively, % | 94 | 88 |
| Time from arrival to OR start, median (minutes)* | 86 | 67 |

* $P < 0.05$.
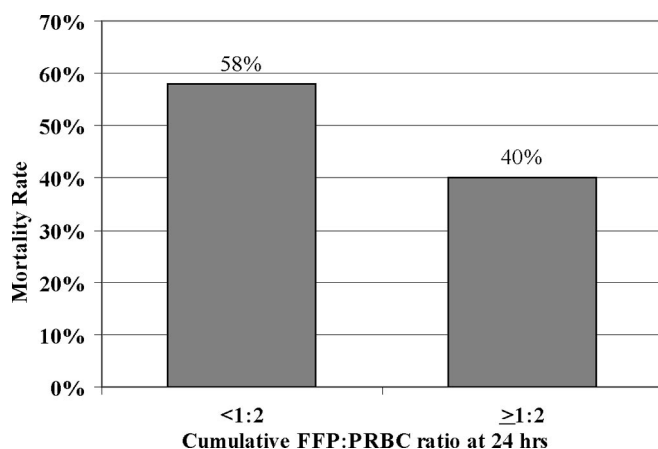


**Fig. 1.** *Comparison of mortality rates between patients receiving a 24-hour cumulative FFP:PRBC ratio of <1:2 versus ≥1:2.*

adjustment for age, gender, ISS, mechanism of injury, associated head injury, and base deficit, INR, and thrombocytopenia at admission, patients in the high-ratio group had a significantly lower risk of death compared with the low-ratio group (RR, 0.37; 95% CI, 0.22–0.64).

FFP:PRBC ratios were additionally calculated for each time interval of interest. Table 2 demonstrates the breakdown of the number of patients in each FFP:PRBC ratio group according to time interval. The number of patients in the high ratio (≥1:2) group was low during the initial time intervals, but increased over time. Conversely, the majority of patients started in the low ratio (<1:2) group, but this number decreased over time. These changes evolved as patients transitioned from the low-ratio group to the high-ratio group.

Table 2 also demonstrates the temporal mortality among each group. During the early time intervals, most deaths occurred in the group receiving a low ratio for that interval, whereas during the later time intervals more deaths occurred in the group receiving a high ratio. Of the 43 deaths in the low-ratio group, 33 (77%) occurred during the first 6 hours and six (14%) occurred after 24 hours. Of the 24 deaths in the high-ratio group, only three (13%) occurred within the first 6 hours, whereas 13 (54%) occurred after 24 hours.

All deaths in both groups during the first 6 hours were as a result of exsanguinating hemorrhage, with the exception of one patient in the low-ratio group who died of traumatic brain injury. The causes of death after 24 hours in the low-ratio group were MSOF in three patients, traumatic brain injury in two patients, and exsanguination in one patient. In the high-ratio group, causes of death after 24 hours were traumatic brain injury in seven patients, MSOF in four patients, respiratory events occurring after a Do Not Resuscitate order in two patients, and exsanguination in one patient. This pattern of mortality demonstrates the potential for survival bias, as the majority of deaths occurred when most patients resided in the low-ratio group, before the accumulation of a substantial number of patients in the high-ratio group.

To adjust for the survival bias apparent in Table 2, Cox regression modeling was again performed, as described above, with the only difference being that the FFP:PRBC ratio was treated as a time-dependent covariate. With this analysis method, the survival advantage associated with the high-ratio group as demonstrated previously was not evident (RR, 0.84; 95% CI, 0.47–1.50) (Fig. 2). Additional adjustment for platelet, cryoprecipitate, and factor VIIa transfusion

**Table 2** Group Sizes* and Numbers of Deaths in Low (<1:2) and High (≥1:2) FFP:PRBC Ratio Groups by Time Interval of Hospitalization

|  | ≤30 min. | >30–60 min. | >60–90 min. | >90–120 min. | >2–3 hrs. | >3–4 hrs. | >4–5 hrs. | >5–6 hrs. | >6–12 hrs. | >12–18 hrs. | >18–24 hrs. | >24 hrs. | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| <1:2 (low ratio) |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No. pts in group | 86 | 102 | 103 | 102 | 95 | 91 | 85 | 87 | 74 | 73 | 74 | 74 | **74** |
| No. deaths during interval | 0 | 0 | 8 | 10 | 9 | 3 | 2 | 1 | 2 | 2 | 0 | 6 | **43** |
| ≥1:2 (high ratio) |  |  |  |  |  |  |  |  |  |  |  |  |  |
| No. pts in group | 1 | 6 | 13 | 20 | 34 | 39 | 46 | 46 | 60 | 61 | 60 | 60 | **60** |
| No. deaths during interval | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 7 | 1 | 0 | 13 | **24** |

* Group sizes exclude patients who have not yet received any blood products (ratio = 0/0).
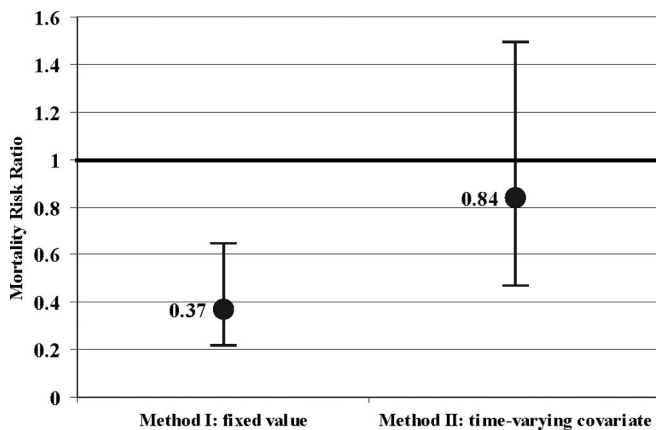
**Fig. 2.** *Comparison of relative risks of mortality for patients receiving a high (≥1:2) versus a low (<1:2) FFP:PRBC ratio, calculated using the fixed ratio at 24 hours (method I, RR 0.37, CI 0.22–0.64) versus the ratio as a time-varying covariate to account for survival bias (method II, RR 0.84, CI 0.47–1.50).*

did not change the substance of the result (RR, 1.07; 95% CI, 0.87–1.31).

## DISCUSSION

The association between FFP:PRBC ratio and mortality has been investigated in several recent studies. Borgman et al.[10] divided 246 massively transfused military casualties into three groups based on cumulative 24-hour FFP:PRBC ratio, and demonstrated that mortality was lowest in the highest ratio group. They observed that deaths occurred earlier for patients receiving lower ratios; median time of death in the low, medium, and high-ratio groups was 2, 4, and 38 hours, respectively. Their military study population differed from the civilian population in several important ways, including a much higher incidence of penetrating trauma (>92%), a lower median ISS of 18, and use of fresh whole blood. In a larger military study that included patients receiving any amount of component blood products, Spinella et al.[18] found that plasma transfusion was associated with better survival, whereas PRBC transfusion was associated with poorer survival. Prethawed plasma for immediate transfusion was not used, and fresh whole blood was excluded from this analysis.

Duchesne et al.[12] investigated the association between FFP:PRBC ratio and mortality in civilian trauma patients, using a similar methodology to Borgman et al. In a cohort of 135 massively transfused civilian patients (>10 units of PRBC transfused in first 24 hours), mortality was significantly lower (26% vs. 87%) in those receiving a cumulative 24-hour FFP:PRBC ratio of ≥1:2 versus <1:2.

Although it is tempting to conclude from these reports that transfusion protocols should incorporate the early targeting of a 1:1 or 1:2 FFP:PRBC ratio to improve mortality in massively transfused patients, it is important to consider inherent limitations in study design. It is notable that no explicit protocol was in place to transfuse to a predetermined

ratio in any of these prior reports. More importantly, the cross-sectional approach to the comparison of high and low ratios fails to account for the ephemeral nature of FFP:PRBC ratios in actual practice. In civilian trauma centers using component therapy, FFP:PRBC ratios change dramatically over the time course of treatment. To date, no study has accurately evaluated this relationship in a temporal fashion. As demonstrated by our data, most patients received PRBC almost immediately on arrival to the trauma bay, followed later by FFP administration. Because of this pattern, the likelihood of a patient achieving a high FFP:PRBC ratio (i.e., the treatment of interest) increased with time, as illustrated by patients crossing over from the low to high-ratio group.

Many deaths occurred early in the hospital course, during the time intervals in which more patients were in the low-ratio group than the high-ratio group. Survival bias was introduced as patients in the low-ratio group died early, which effectively fixed them at a low FFP:PRBC ratio for the remainder of the resuscitation period and prevented them from ever transitioning to the high-ratio group. Therefore, patients receiving a high FFP:PRBC ratio appeared to have a significantly lower risk of death by our first analysis method, which was similar to methods used in other studies.[10–14] However, this association was no longer evident when the temporal nature of the FFP:PRBC ratio was correctly accounted for in the analysis.[16] Therefore, it could be concluded that the nonsurvivors in our study population did not die because they got a lower FFP:PRBC ratio; they got a lower ratio because they died.

In a recent study of 133 massively transfused civilian patients, Kashuk et al.[13] observed a U-shaped curve in which mortality was lowest at a FFP:PRBC ratio of 1:2. Although they defined massive transfusion differently (≥10 units PRBC in 6 hours), their observations were similar to ours in several respects. First, they observed that most blood products were given early; 80% of total transfusion requirement was given in the first 6 hours, compared with 68% in our study. Second, they observed a disproportionate number of very early deaths for patients who received lower ratios. Finally, cumulative FFP:PRBC ratios in their study increased with time. They observed a mean cumulative ratio of 0.38 (1:2.6) at 6 hours and 0.47 (1:2.1) at 24 hours; we observed 0.35 (1:2.9) at 6 hours and 0.42 (1:2.4) at 24 hours. The potential for survival bias was not specifically evaluated.

To date, only Fox et al.[19,20] have directly compared hemostatic resuscitation with standard therapy. They performed a retrospective cohort study comparing outcomes in a small number of military patients with vascular injury before and after institution of a hemostatic resuscitation protocol. Although physiologic parameters were improved after protocol initiation, mortality was actually nil in both groups.

The results of our study should be interpreted in light of several limitations. Because transfusion practices and protocols vary widely, the findings of a single-center study may not be generalizable to other civilian trauma centers. Our

relatively small sample of 134 patients may not have provided adequate statistical power to observe a true survival benefit when incorporating temporal factors. It is also important to note that this study does not provide a direct comparison of hemostatic resuscitation with conventional resuscitation strategies. Similar to many civilian trauma centers, our blood bank does not maintain a supply of thawed plasma for trauma patients, and no specific protocol was in place to target FFP and PRBC administration to a predetermined ratio in our study population.

Although the rationale for hemostatic resuscitation is clear, it is difficult to support this approach with currently published retrospective studies given their inherent limitations and potential for survival bias. Our study highlights the need for well-designed prospective studies to address the important question of whether hemostatic resuscitation results in improved clinical outcomes. It also highlights the difficulties of performing these studies when component therapy is used. It will be vitally important for these studies to track the exact timing of blood product administration to ensure that the assigned resuscitation protocol is being accurately followed and that randomized patients are administered the proper blood product ratio.

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# DISCUSSION

**Dr. Osamu Tasaki** (Osaka, Japan): Dr. Jurkovich, Dr. Kushimoto, ladies and gentlemen. Dr. Snyder and his group presented an important paper focusing on the recent topic in massive transfusion for trauma patients. They used two different statistical methods to evaluate whether high FFP:RBC ratio really results in improved clinical outcomes. Their results showed that the survival advantage associated with higher FFP ratio diminished once the temporal nature of transfusion was taken into account. The time-dependent evaluation in their study was fresh and their findings were clear but I have several questions for Dr. Snyder.

First of all, most patients who died in the first few hours after injury should be lethal cases and not only FFP but any other treatment had no chance to work. Why did you include these patients for your analysis when you evaluated the real impact of blood product transfusion on mortality? And if you exclude these lethal cases of acute death, for example in three hours after injury, is your conclusion still the same as you have presented?

Secondly, the transfusion strategy for trauma patients significantly affects the FFB:RBC ratios. Even if you do not have a strict protocol for massive transfusion, the principle in your department about the use of FFP, platelet concentrates, and cryoprecipitates needs to be addressed for better understanding of your results. And was your strategy the same throughout the study period?

Thirdly, the optimal FFP:RBC ratio for patients requiring massive transfusion is not clarified yet and several previous reports have suggested different optimal rations of one-to-two; two-to-three, or one-to-two by each mathematical method. Your results can change depending on the ratio you

choose. So why did you select the ratio of one-to-two for dividing your trauma patients into two groups?

Lastly, it is very curious that the mortality after 24 hours was significantly higher in the high FFP ratio group as compared with that in the low FFP ratio group. Are these later deaths in higher ratio group due to hemorrhage, sepsis, MODS, or head trauma? Would you clarify the cause of death and speculate if it is some complication of high use of FFP or another bias of other reasons?

I would like to congratulate Dr. Snyder and his colleagues for their important paper with original viewpoint. And I would like to thank AAST and JAAM for the privilege to discuss this paper in the wonderful joint meeting. Thank you.

**Dr. David P. Blake** (Norfolk, Virginia): Yes, sir, thank you very much. It was a very interesting and provocative presentation. I have two questions for the authors; however.

Number 1, did you see any breakout in demographics in terms of mechanism of injury, whether it was blunt or penetrating, in how this difference presented itself?

And, secondly, were there any other confounding variables such as delayed operative management that might have contributed to some of this bias? Thank you.

**Dr. Bryan A. Cotton** (Nashville, Tennessee): I wanted to comment on your title. It says, "Hemostatic Resuscitation." Hemostatic resuscitation is not necessarily or damage control resuscitation is not necessarily a ratio in and of itself. It is a concept of hypotensive resuscitation, less crystalloid, high ratios of plasma/platelets, all those together driving and delivering this. And, again, it's a matter of getting those earlier and getting that lag time eliminated like we talked about earlier.

So given that, did your study population reflect a change in your practice or an implementation/employment of a new protocol using truly damage control resuscitation/hemorrhage resuscitation instead of just a one-to-two ratio in isolation?

Second question is how do you dismiss the apparent survival benefit, at least apparent in your abstract, from zero to six hours which showed that there was actually improved survival with the higher ratios during that first six hours?

**Dr. Samir M. Fakhry** (Fairfax, Virginia): Dr. Snyder, thank you for a very nice presentation and for an elegant study. As you're hearing, it is forcing us to ask the questions that we should be asking as we prepare to do the necessary randomized control trials.

My question to you is if the effect that you're describing is real then it should become more apparent as you look at people who are bleeding more slowly and who are in shock for shorter periods of time. Did you look to see, for example, if this affect existed for patients with blunt trauma versus penetrating, presuming that they bleed more slowly? Did you look to see if the affect persisted for people who were going to the OR early versus those who went to the OR late?

This would be an interesting way to tell whether or not the affect of survival bias is truly the explanation for the divergent results we're getting in the new studies versus the old studies and even among the new studies.

**Dr. Steven M. Steinberg** (Columbus, Ohio): First I would like to thank the Program Committee for putting these very fascinating studies on back-to-back-to-back. It's unusual and thought-provoking. I would like to congratulate Dr. Snyder on an excellent presentation and congratulate the whole group on questioning the dogma. I think it is always good to question dogma. And it's amazing to me how quickly this issue has become dogma in many of our institutions. We're certainly giving high ratio FFP to PRBC transfusions now.

The question I have for Dr. Snyder is how do we get the real answer? You know, what is the truth? Is it only going to be through a randomized prospective trial looking at different ratios of FFP to PRBC? Or is there some other methodology that we might use? Thank you.

**Dr. William R. Fry** (Colorado Springs, Colorado): I am wondering if there is a death bias as well as a survival bias in that it's difficult to say based on what you presented whether or not the injuries were survivable or not.

And as it relates to that, how many of the injuries were treated to control or definitively repair during the course of their treatment before they exsanguinated such that you actually had a coagulopathy rather than the injuries that the patient suffered as the cause of death?

**Dr. John B. Holcomb** (Houston, Texas): I can't resist. Dr. Britt, I would like to congratulate you for a balanced presentation on this topic. I know that was hard to do. And I think the Program Committee did a good job.

For Dr. Snyder, as opposed to talking about his survival bias I think what you clearly show is a mortality bias by not having plasma available early. So you can look at data many ways. It always depends on your vector. And I'm looking at your mortality bias early.

People have looked at the first six hours. We've reported six-hour differences. Dr. Marty Schreiber has a six-hour paper as well showing improved survivals with increased ratios.

And what you pointed out in fact is what Dr. Dutton says, an anesthesiologist, we use what we can get our hands on. Right now at your institution that's lactated ringers, normal saline and red blood cells so that's what you're giving.

I would ask you if you have considered improving through your PI process now that you've identified with data a problem of putting thawed plasma available in the emergency department, like many centers are doing, so that you can bring this survival benefit early to your patients. Thank you.

**Dr. Juan C. Duchesne** (New Orleans, Louisiana): I just wanted to mention that damage control resuscitation definitely will impact survival. And I think one of the issues in your study is the selection bias of having a patient that has a hole in the aorta. That patient, damage control resuscitation is not going to save him. Thank you.

**Dr. Timothy C. Fabian** (Memphis, Tennessee): This is obviously an extremely important issue for trauma care in this country. Dr. Magnotti from our group looked at this. We

wrote an abstract very recently that was strikingly identical to the methodology used today in the UAB paper. We had a very similar number of patients. And our conclusions were essentially identical to what Dr. Snyder brought. I would suggest to you that the jury is clearly still out on this entire issue. I think it will remain out until we can get well-controlled, prospective data set up. And I would challenge the Multi-Institutional Trials Committee to take this on because it has a huge impact on trauma care.

**Dr. Christopher W. Snyder** (Birmingham, Alabama): Thank you all very much for your comments. Dr. Tasaki, thank you for your insightful questions. I would also like to thank your colleague Dr. Ogura for taking the time to review our manuscript.

Regarding your first question, why did we include patients with lethal or non-survivable injuries—we felt that it would be inappropriate to exclude them, since when a patient rolls in to the trauma bay you usually don't have the luxury of knowing whether the injury will be survivable or not. Our study population only included patients who received massive transfusion, so presumably there was some possibility of survival, or we would not have attempted to salvage them with blood products.

Regarding our institution's transfusion practices, we do have a rapid transfusion protocol that was in place throughout the study period. It involves the release of blocks of six units of packed red blood cells with four units of FFP. Regarding use of platelets and cryoprecipitate, a large number of patients received these products, but I could not give you the precise details on how they were distributed. We can include those details in our manuscript.

We chose the ratio of 1:2 FFP to packed red cells based on the published literature and a pilot study at our institution that suggested a survival benefit at a threshold ratio of 1:2. However, we did do the analysis using other ratios as our breakpoint, including 1:1, 1:3 and 1:4, and the results were similar for all of them—no survival benefit when the time-varying nature of the ratio was taken into account.

The late deaths in those who received a high ratio were mainly due to traumatic brain injury and multi-system organ failure; we will include the details in the manuscript.

There were several questions regarding the potential confounding effects of injury mechanism and timing of operative management. There was no difference in distribution of blunt versus penetrating injury between survivors and non-survivors, and our regression models were adjusted for mechanism

of injury. Regarding operative management, around 91 percent of these patients were managed with immediate operation, with a median time of about an hour and 20 minutes from hitting the trauma bay to making an incision in the OR. The non-survivors got to the OR about 20 minutes faster than the survivors, which is likely a reflection of their more severe injuries.

Dr. Cotton, thank you for making the excellent point that hemostatic resuscitation is not just a ratio in isolation. I would respectfully point out, though, that most of the studies being used as evidence that hemostatic resuscitation improves survival were not truly comparing hemostatic resuscitation to standard therapy either. They were just looking back at uncontrolled FFP:PRBC ratios, often in a time when thawed plasma was not even being used.

Our pre-existing massive transfusion protocol and management practices did not change over the course of the study. Regarding our abstract, we may not have presented it clearly enough, but in fact we did not see a significant difference in survival at six hours.

Dr. Holcomb, thank you for your comments and important contributions to this topic. I think that if we at UAB felt confident that thawed plasma and high FFP to PRBC ratios truly improved survival, we would certainly be working to put thawed plasma in our emergency department. However, like Dr. Fabian said, we feel that the jury is still out.

The key finding of our study was that the FFP to PRBC ratio is not constant over the resuscitation period. Instead, it starts out low and increases with time, and a given patient's ratio only becomes fixed at the time of death. In previous studies showing an association between improved survival and higher ratios, their analysis was done as if the ratio was constant over time. I would respectfully contend that it does not matter at what timepoint you make your comparison—6 hours, 12 hours, 24 hours, whatever—if you just look at the ratio at a fixed point in time and don't take the variation over time into account, you are going to get survival bias. In other words, it may look like patients survived because they got a higher ratio, when in fact they got a higher ratio because they survived long enough to get it.

Finally, to respond to Dr. Steinberg's question of how we can address the issue short of doing a randomized trial: I think the main thing is that we need to use statistical methods that account for the time-varying nature of the FFP to PRBC ratio. Unfortunately, to do this you need detailed data on when each unit of product is given, and this data can be difficult to get.