The Many Faces of Survivor Bias in Observational Studies on Trauma Resuscitation Requiring Massive Transfusion

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Approximately 10% of military trauma patients and 3% to 5% of civilian trauma patients require massive transfusion, typically defined as greater than 10 units of packed RBCs (pRBCs) within 6 to 24 hours of hospital admission.[1] The protocol for massive transfusion in adult trauma patients is controversial. The traditional approach calls for administration of fresh frozen plasma (FFP) and platelets when there is strong evidence of coagulopathy or after transfusion of greater than 10 units of pRBCs. The competing approach (sometimes called 1:1:1) calls for FFP (prethawed) and platelets to be administered as early as the first unit of pRBCs at an FFP:platelet:pRBC ratio of approximately 1:1:1 to 2 for patients likely to require massive transfusion. Although to our knowledge there have been no published randomized controlled trials to compare the 2 approaches, numerous observational studies have shown an association between 1:1:1 and improved outcome. However, nonexperimental studies are particularly prone to bias, and survivor bias is one of the more serious, interesting, and perhaps less obvious problems in these studies. We have used data from a recent study[2] to illustrate the different types of survivor bias (Figure 1). Understanding them improves the quality of discourse about massive transfusion and may heighten awareness of the presence of survivor bias in other quasi-experimental and experimental studies.

SURVIVOR BIAS 1—PATIENTS HAVE TO SURVIVE LONG ENOUGH TO RECEIVE 1:1:1

In one popular study methodology, investigators select a cohort of trauma patients who required massive transfusion and calculate the transfusion ratio at an assessment time, typically 24 hours. For patients who survive 24 hours, the ratio is based on all transfused products during that time, but for those who die sooner it is based on a shorter time. The investigators then compare overall mortality for patients whose cumulative FFP/platelet:pRBC ratio at 24 hours was high (≥1:1:1 to 2) with that of those whose ratio was low (<1:1:1 to 2). For example, Borgman et al[3] found that for low, medium, and high FFP:pRBC ratios, overall mortality rates were 65%, 34%, and 19%, respectively. In a logistic regression model of these data, the odds ratio for survival with high versus low ratio transfusion was 8.6 (95% confidence interval 2.1 to 35.2). This result, one far beyond reasonable expectation, is best explained by survivor bias. Because most study sites use a traditional transfusion strategy of using mainly pRBC in the first few hours of care and more FFP and platelets after the first few hours, and because many trauma patients die in the first few hours, those who die early are likely to have a low FFP/platelet:pRBC ratio, whereas those who do not die early will more likely have a high transfusion ratio. This creates a situation that confounds the association between transfusion ratio and mortality. Patients did not necessarily die because they did not receive enough FFP and platelets; they did not receive enough FFP and platelets because they died.[4] Ho et al[5] demonstrated that the longer the delay in reaching 1:1:1 to 2, the stronger the bias.

SURVIVOR BIAS 2—EARLY DEATHS THAT MAY BENEFIT FROM 1:1:1 ARE EXCLUDED

In an attempt to minimize survivor bias 1, some investigators eliminate patients who die in the first few hours of care, when it is unlikely that they would have received sufficient FFP to be in the high-ratio group. This period ranged from 30 minutes[6] (to allow time for thawing) to several hours[7] (to allow sufficient time for FFP transfusion to catch up). Eliminating patients who die in the first 30 minutes
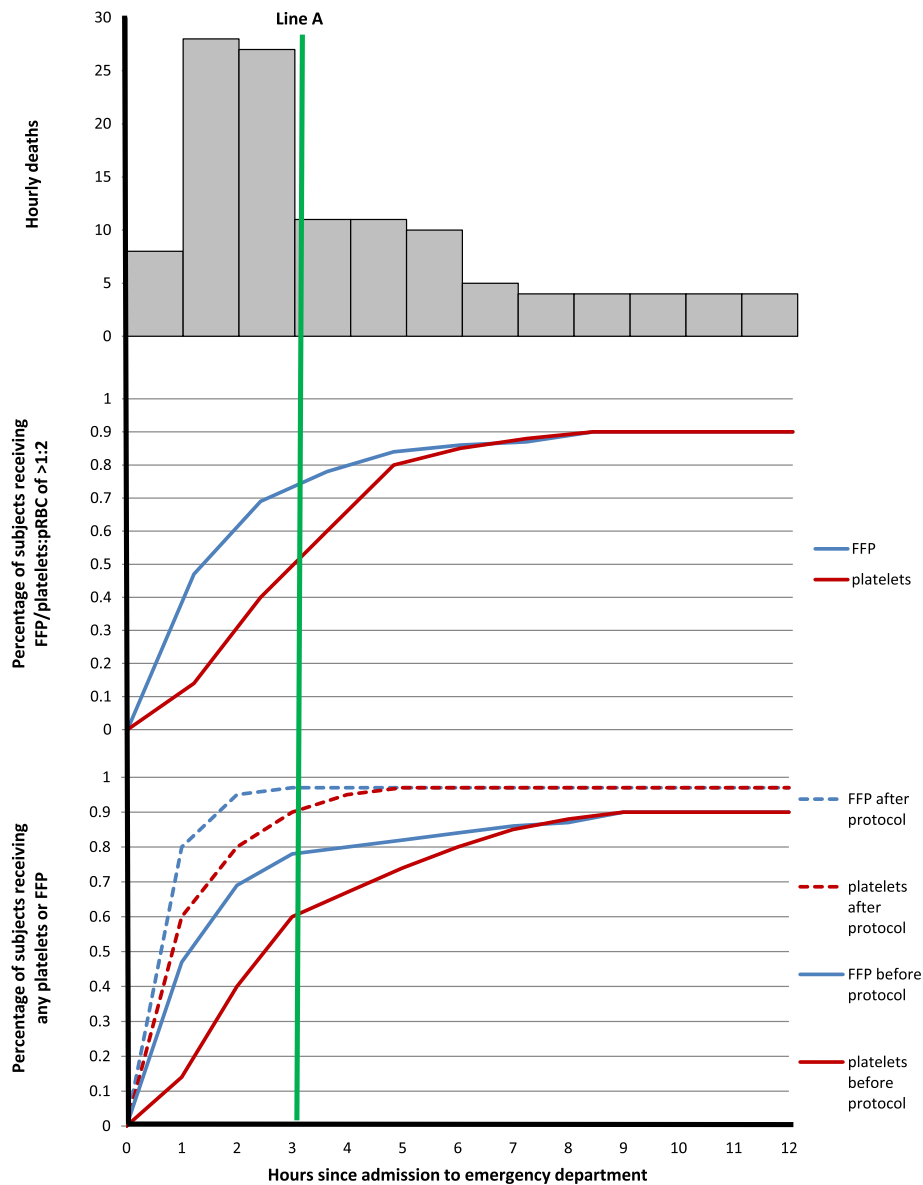
Figure 1. The top panel is a histogram showing the timing of early deaths in the PROMMTT trial.[2] During the initial ∼3 hours of emergency department (ED) admission mortality was high and because of delays in initiating FFP and platelet transfusion, FFP:pRBC and platelets:pRBC ratios were low (middle panel) with only a small percentage of patients achieving ratios of >1:2. Type 1 survivor bias is seen when mortality data from patients to the left of line A are included in the analysis. Most of these early deaths are in the low ratio group creating a bias in favor of "1:1:1." To avoid Type 1 survivor bias an investigator might exclude patients to the left of Line A from the analysis, however doing so leaves a cohort that is less coagulopathic and thus is less likely to show benefit from "1:1:1," creating Type 2 survivor bias. The relatively lower death rate to the right of Line A also makes it more difficult to show a beneficial effect of higher FFP and platelet ratios. The bottom panel illustrates Type 3 survivor bias. The solid curves ("before") represent patients before institution of a "1:1:1" protocol, i.e., they were resuscitated in the "traditional" way. The dashed curves ("after") represent patients enrolled after institution of a "1:1:1" transfusion protocol, emphasizing early use of FFP and platelets. A before-after study may include only those patients who had received at least 1 unit of FFP or platelets. In the before group many of the sickest patients are excluded because they died before they received FFP or platelets, resulting in an after group that, comparatively, has a higher probability of death. Survivor bias 3 makes it more difficult to show that early administration of FFP and platelets is beneficial. Data from PROMMTT[2] also show a spike in multi-organ failure 3–30 days after admission amongst survivors (not shown). Since most (∼90%) of the survivors will have had high FFP/platelet:pRBC ratios, one may conclude that multi-organ failure is associated with use of FFP/platelets, creating Type 4 survivor bias. *FFP*, fresh frozen plasma.