Critical Review Form
Therapy

Holcomb JB, del Junco DJ, Fox EE, et al; PROMMTT Study Group. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013 Feb;148(2):127-36.

Objectives: **"to accurately describe when RBCs, plasma, and platelets were infused and to assess the association between in-hospital mortality and the timing and amount of blood products."**

Methods: **This prospective, multicenter, observational cohort study was conducted at 10 level 1 trauma centers in the United States. Patients aged 16 years or older requiring the highest level of trauma activation who received at least 1 U of PRBCs in the first 6 hours after admission were eligible for enrollment. Prisoners, patients who were transferred, patients who expired within 30 minutes of arrival, pregnant women, patients with > 20% body surface area burns or inhalation injury, and patients receiving > 5 minutes of consecutive chest compressions were excluded. change in clinical practice was recommended as part of this observational study. Following initiation of the study, the authors determined that it would be most productive to only include patients who survived long enough to receive at least 3 blood product units, and this became a further eligibility requirement.**

The primary outcome of interest was in-hospital mortality, which was evaluated based on the independent variables of plasma:PRBC and platelet:PRBC transfusion ratios. Risk of death was assessed beginning at minute 31 or the initiation of a third transfused unit, whichever came last. Cumulative blood product ratios were computed at baseline and over 14 different time intervals: every 15 minutes from minute 31 to one hour, ten 30 minute intervals between 1 and 6 hours, the 18-hour interval from 6 hours to 24 hours, and the 29-day interval from 24 hours to 30 days. Patients were followed up to a period of 30 days, with a separate analysis focusing on the first 24 hours after admission to the ED.

Out of 34362 trauma admissions over "an average" of 58 weeks, data collection was initiated for 12560 patients. There were 1245 patients who were eligible, of whom 905 receive at least 3 units of blood products and were hence included in the analysis. Overall in-hospital mortality was 25%. The median age was 37 years and 75.9% were male. The mechanism of injury was blunt trauma in 64.4% of patients.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	No. This was an observational study in which the interventions of interest were plasma:RBC and platelet:RBC transfusion ratios. No change in intervention was prescribed, but rather these ratios were dictated by standard clinical practice.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	N/A.
3.	Were patients analyzed in the groups to which they were randomized?	Again, this was not a randomized trial and patients were not analyzed based on group assignment. Instead, they were analyzed based on transfusion ratios: $< 1:2$, $\geq 1:2$ to $< 1:1$, $\geq 1:1$. These ratios were analyzed at a variety of time intervals, such that individual patients could be analyzed in different groups at different intervals as their transfusion ratio changed over time. Of note, patients who did not receive at least 3 units of blood product were excluded, and although resonable, this appears to have been an *ad hoc* decision.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Uncertain. Given the nature of the study, including the lack of randomization and the possible switching of patients between groups over time, it would be difficult to compare groups with another in a meaningful way.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes, but this is not likely of any significance given the nature of the study (performance bias).
2.	Were clinicians aware of group allocation?	Yes. Again, this study was not randomized or blinded, but this is not likely of any significance given the nature of the study (performance bias).
3.	Were outcome assessors aware of group allocation?	Yes. The investigators were fully aware of what products were transfused as they needed this information to assign patients to their respective groups at each of the time intervals. Given the

		objectivity of the primary outcome (mortality), it is unlikely that any degree of observer bias would have influenced the results.
4.	Was follow-up complete?	Presumably yes, though this is not specifically mentioned. The primary outcome was in-hospital mortality out to thirty days, so it seems reasonable that the investigators would have access to this information for all patients included in the study.
II.	**What are the results ?**	

1.	How large was the treatment effect?	In the time period from 31 minutes to 6 hours following ED admission, use of a higher (i.e. more balanced) transfusion ratio conferred a significant survival benefit.
		• For the plasma:RBC ratio, the HR was 0.31 (95% CI 0.16-0.58).
		  ○ For a moderate plasma:RBC ratio (≥ 1:2 to < 1:1) the HR was 0.42.
		  ○ For a high plasma:RBC ratio (≥ 1:1), the HR was 0.23.
		• For the platelet:RBC ratio, the HR was 0.55 (95% CI 0.31-0.98).
		  ○ For a moderate platelet:RBC ratio (≥ 1:2 to < 1:1) the HR was 0.66.
		  ○ For a high platelet:RBC ratio (≥ 1:1), the HR was 0.37.
		In the time interval from 6 hours to 24 hours after ED admission, a higher plasma:RBC ratio was associated with improved survival, but a higher platelet:RBC ratio was not.
		• For the plasma:RBC ratio, the HR was 0.34 (95% CI 0.14-0.81).
		  ○ For a moderate plasma:RBC ratio (≥ 1:2 to < 1:1) the HR was 0.79.
		  ○ For a high plasma:RBC ratio (≥ 1:1), the HR was 0.55.
		• For the platelet:RBC ratio, the HR was 0.81 (95% CI 0.46-1.43).
		There was no significant difference in mortality noted based on either plasma:RBC ratio (HR 1.21, 95% CI 0.90-1.61) or platelet:RBC ratio (HR 0.78, 95% CI 0.57-1.06) in the 24 hour to 30 day time interval.

2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	

1.	Were the study patients similar to my patient?	Yes. This study was conducted at several level 1 trauma centers in the US which should see a cohort of patients similar to those seen at our institution (external validity). Around 64% of patients were seen following blunt injury, which seems similar to our injury pattern. Past medical history was not described for this patient population, but given that this was a younger population seen following trauma, there is no reason to suspect any significant difference between these patients and ours with respect to medical history.
2.	Were all clinically important outcomes considered?	No. The authors considered the most important outcomes (i.e. 24-hour and 30-day survival), but did not consider several other important outcomes, such as the amount of blood product required, transfusion-related adverse events (e.g. anaphylaxis, TRALI), ICU LOS, time on the ventilator, and functional outcomes.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a retrospective, purely observation study, and while its results are thought-provoking, it was not designed to change management. The ensuing PROPPR study followed up on this concept and provided better evidence on this topic. What this study suggests is that more balanced resuscitation (plasma:RBC and platelet:RBC ratios closer to 1:1) results in improved mortality over the short term (up to 6 hours), but does not seem to have as much of an effect when monitored out to 30 days.

Limitations:

1. **The authors did not provide the dates of the study.**
2. **This was a retrospective study and hence subject to significant selection bias, resulting in imbalances between groups that could have affected mortality.**
3. **Despite attempt to control for this, survival bias still likely had some effect on the outcomes.**
4. **This study was intended to look at patients receiving mass transfusions, but the median number units blood given at 24 hours only 5-6, suggesting this is not the population the investigators intended to study.**
5. **Patients who did not receive at least 3 units of blood product were excluded, and although reasonable, this appears to have been an *ad hoc* decision.**

Bottom Line:

This retrospective, observation study looking at plasma:RBC and platelet:RBC ratios in trauma patients receiving blood product transfusion found that early in resuscitation, a more balanced transfusion ratio conferred a survival benefit. Looking at mortality 24 to 30 days after ED admission, this survival benefit disappeared (likely as the cause of mortality shifted away from hemorrhage to other causes). Further research is needed at this point, including randomized controlled trials looking directly at outcomes with varying blood product rations.