Trauma Surgery & Acute Care Open

Balanced resuscitation and earlier mortality end points: bayesian post hoc analysis of the PROPPR trial

Daniel Lammers [1], Omar Rokayak,[1] Rindi Uhlich,[1] Thomas Sensing,[1] Emily Baird,[2] Joshua Richman,[2] John B Holcomb,[1] Jan Jansen [1]

[1]Division of Trauma and Acute Care Surgery, The University of Alabama at Birmingham Hospital, Birmingham, Alabama, USA
[2]Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence to
Dr Daniel Lammers; dtlammer@gmail.com

Received 16 January 2023
Accepted 23 July 2023

To cite: Lammers D, Rokayak O, Uhlich R, *et al*. *Trauma Surg Acute Care Open* 2023;**8**:e001091.

ABSTRACT

Introduction The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial failed to demonstrate a mortality difference for hemorrhaging patients receiving a balanced (1:1:1) vs a 1:1:2 resuscitation at 24 hours and 30 days. Recent guidelines recommend earlier mortality end points for hemorrhage-control trials, and the use of contemporary statistical methods. The aim of this post hoc analysis of the PROPPR trial was to evaluate the impact of a balanced resuscitation strategy at early resuscitation time points using a Bayesian analytical framework.

Methods Bayesian hierarchical models were created to assess mortality differences at the 1, 3, 6, 12, 18, and 24 hours time points between study cohorts. Posterior probabilities and Bayes factors were calculated for each time point.

Results A 1:1:1 resuscitation displayed a 96%, 99%, 94%, 92%, 96%, and 94% probability for mortality benefit at 1, 3, 6, 12, 18, and 24 hours, respectively, when compared with a 1:1:2 approach. Associated Bayes factors for each respective time period were 21.2, 142, 14.9, 11.4, 26.4, and 15.5, indicating 'strong' to 'decisive' supporting evidence in favor of balanced transfusions.

Conclusion This analysis provides evidence in support that a 1:1:1 resuscitation has a high probability of mortality benefit when compared with a 1:1:2 strategy, especially at the newly defined more proximate time points during the resuscitative period. Researchers should consider using Bayesian approaches, along with more proximate end points when assessing hemorrhage-related mortality, for the analysis of future clinical trials.

Level of evidence Level III/Therapeutic.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite the trial being the driving impetus for the adoption of a balanced transfusion strategy for trauma patients during the acute resuscitative period, the original trial failed to demonstrate a statistically significant mortality benefit at 24 hours and 30 days, the studies co-primary end points.

WHAT THIS STUDY ADDS

⇒ Subsequent guidelines suggest that earlier mortality end points should be used when assessing for death secondary to hemorrhage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study, which used a Bayesian approach, demonstrated that there was a high probability of mortality benefit associated with a 1:1:1 vs a 1:1:2 resuscitation strategy at 1, 3, 6, 12, 18, and 24 hours and provides quantifiable data in support of balanced transfusions at each time assessed.

⇒ This analysis supports the use of Bayesian techniques and more proximate end points when assessing hemorrhage-related mortality, which should both be considered for use in future trauma clinical trials assessing blood product resuscitation and hemorrhage.

INTRODUCTION

The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial, published in 2015, was a landmark clinical trial that compared two different trauma transfusion strategies—a '1:1:1' ratio and a '1:1:2' ratio of transfused units of plasma, platelets and red blood cells. This study demonstrated a 4.2% and 3.7% reduction in mortality at 24 hours and at 30 days within the 1:1:1 transfusion cohort, respectively. These differences, however, were not statistically significant at either of the co-primary end points ($p=0.12$ and $p=0.26$, respectively) and the null hypothesis—that there was no treatment effect based on the transfusion strategy used, that is, no mortality benefit—could not be rejected at the level of $p<0.05$.[1] The PROPPR trial was thus, statistically speaking, a 'negative' trial based on the study's primary outcomes.

The PROPPR trial was, however, designed more than a decade ago. Since its design and publication, there have been many methodological advances in clinical trial design and analysis. Two key areas revolve around the optimal timing of mortality outcomes and the increasing popularity of Bayesian analytical frameworks.

Recent data from multiple high-quality studies suggest that the most frequent causes of trauma-related deaths change over time during a patient's resuscitation and hospital course.[2–4] Early deaths are mostly related to hemorrhage, while later deaths are more consistently secondary to traumatic brain injuries and multiorgan failure.[5–8] It makes biological sense that interventions which improve hemorrhage control should be studied over the time period when bleeding occurs. Recently published guidelines for trauma studies—developed at the National Heart, Lung, and Blood Institute (NHLBI) and US Department of Defense (DoD) convened consensus conference—recommend using all-cause mortality

at 3–6 hours from arrival as the optimal study end point when assessing the treatment effects on mortality secondary to hemorrhagic shock.[2–4 9 10]

The aim of this post hoc analysis was to evaluate the effects of a balanced resuscitation strategy (1:1:1) vs a red cell heavy (1:1:2) strategy on mortality at earlier time points while using Bayesian methods. Although a detailed description of Bayesian statistics is outside the realm of this particular paper, a comprehensive comparison of Bayesian and frequentist statistical approaches structured around the PROPPR trial was recently published by our group.[11] Briefly, Bayesian approaches offer an alternative statistical framework that estimates the probability of a treatment effect, as opposed to frequentist statistical methods which most often are used to dichotomize results as 'positive' or 'negative' based on traditionally selected p values.[12 13] This study, therefore, sought to conduct a Bayesian analysis of the data from the PROPPR trial in order to re-evaluate the effects of a 1:1:1 resuscitation strategy versus a 1:1:2 approach on mortality at the 1, 3, 6, 12, 18, and 24 hours resuscitation time points.

METHODS

The PROPPR trial was monitored for safety by an externally appointed board via the NHLBI.[1] This current study, which retrospectively assesses deidentified and publicly available data from the original PROPPR trial, qualified as IRB exempt per local guidelines.

The PROPPR trial

The PROPPR trial enrolled trauma patients from 2012 to 2013 who were predicted to require large volume transfusions at 12 level 1 trauma centers in North America. Patients were randomized to receive a 1:1:1 or 1:1:2 transfusion strategy in order to assess the effects of blood product ratios on mortality. The trial's co-primary end points, chosen jointly by the investigators and regulators, were 24-hour and 30-day mortality. The original study was designed to detect a 10% absolute difference in 24-hour mortality (11% vs 21%) and a 12% absolute difference in 30-day mortality (23% vs 35%). The design and results of the study have been published.[1 14]

Proximate mortality end points

The trauma working group of the NHLBI/DoD consensus conference, which comprised 26 members, recommended a primary outcome of 3–6 hours all-cause mortality for clinical trials assessing hemorrhage control interventions. This selection was guided by goals of patient-centeredness, expected or demonstrated sensitivity to beneficial treatment effects, biological plausibility, clinical and logistical feasibility, and broad applicability.[4] Earlier mortality end points have continued to be recommended as core outcomes for trauma studies.[9 10] In order to illustrate temporal relationships, we chose to evaluate mortality data at 1, 3, 6, 12, 18, and 24 hours from arrival and randomization within the trauma bay.

Bayesian statistical approach in 'plain English'

In brief, this analysis used a multilevel, or hierarchical, non-linear regression model. Hierarchical models allow for individual variables to be analyzed in clusters that can be nestled underneath other variables. The influence of the individual variables on one another within each cluster, as well as between the separate clusters is considered for the statistical analysis. For this study, the individual resuscitation strategy that was received was nestled under each of the hospitals within the study. This offered the opportunity to account for variations in outcomes between the two resuscitation strategies for individual patients and account for variations in outcomes between each of the separate hospitals within the trial.

The Bayesian nature of these models is unique in that it provides the probability that the 1:1:1 resuscitation strategy is superior to the 1:1:2 approach. Based on the data and how the models are analyzed, which is outside the scope of this paper, a series of possible probabilities are provided and termed the posterior probability density distribution. This represents the scope of possible outcomes from the model assessed. While one probability value is determined to be the most likely, a range of possible probabilities are presented to allow for a degree of flexibility within the tested model. Using the associated probability density graphs, numerous hypotheses regarding the degree of differences between the two resuscitation strategies were tested to see how probable each hypothesis was. Detailed descriptions of the statistical analysis are presented in the 'Statistical approach' section.

Statistical approach

Based on the Bayesian hierarchical regression models, which allow for the ability to account for potential site-specific variations in practice patterns, mortality rates between resuscitation groups at each time point were compared. Non-informative priors, which represent an approach that assumes a uniform distribution of possible outcomes for the data given limited prior information, were used for each model in order to minimize the potential risk for subjective bias and provide more conceptually tangible outcomes for the reader. Posterior probabilities and their associated 95% highest density intervals (HDI) for the mortality differences between the two resuscitation strategies were calculated at each time interval and are presented as probability density distributions. This allows the data to be visualized based on the likelihood of occurrence over a range of values. In the context of Bayesian analysis, a 'posterior probability' is the probability of a particular conclusion after considering the actual data in light of prior assumptions. As noted, for this study we assumed a non-informative prior distribution that did not bias the Bayesian analysis toward either study arm.

Model development and optimization resulted in the resuscitative strategy being treated as a population-level, or fixed, effect, while treatment center was imputed as a group-level effect. The models used Markov Chain Monte Carlo modeling (4 chains, 1000 iterations burn-in, and 2000 saved iterations per chain) with a Bernoulli family distribution. The median 2.5th and 97.5th percentiles of the posterior distribution were used to obtain the 95% HDI. All models were created using the BRMS package in R (R Foundation), V.4.0.3.[15 16]

Presentation of results

In order to compare the difference between the two resuscitation strategies, mortality risk ratio (RR) values between the two cohorts were used to provide a more intuitive comparative framework for mortality outcomes. Posterior probabilities were further calculated over a range of RR thresholds to quantify and assess the durability and degree of the reported mortality differences between the groups at each time interval. These RR parameters spanned from a RR <0.5 to a RR >1, with values <1 representing a mortality benefit in favor of the 1:1:1 resuscitative strategy. As RR, by definition, cannot be a negative number, log(RR) was used within the models for comparative purposes in order to account for values over the entire potential

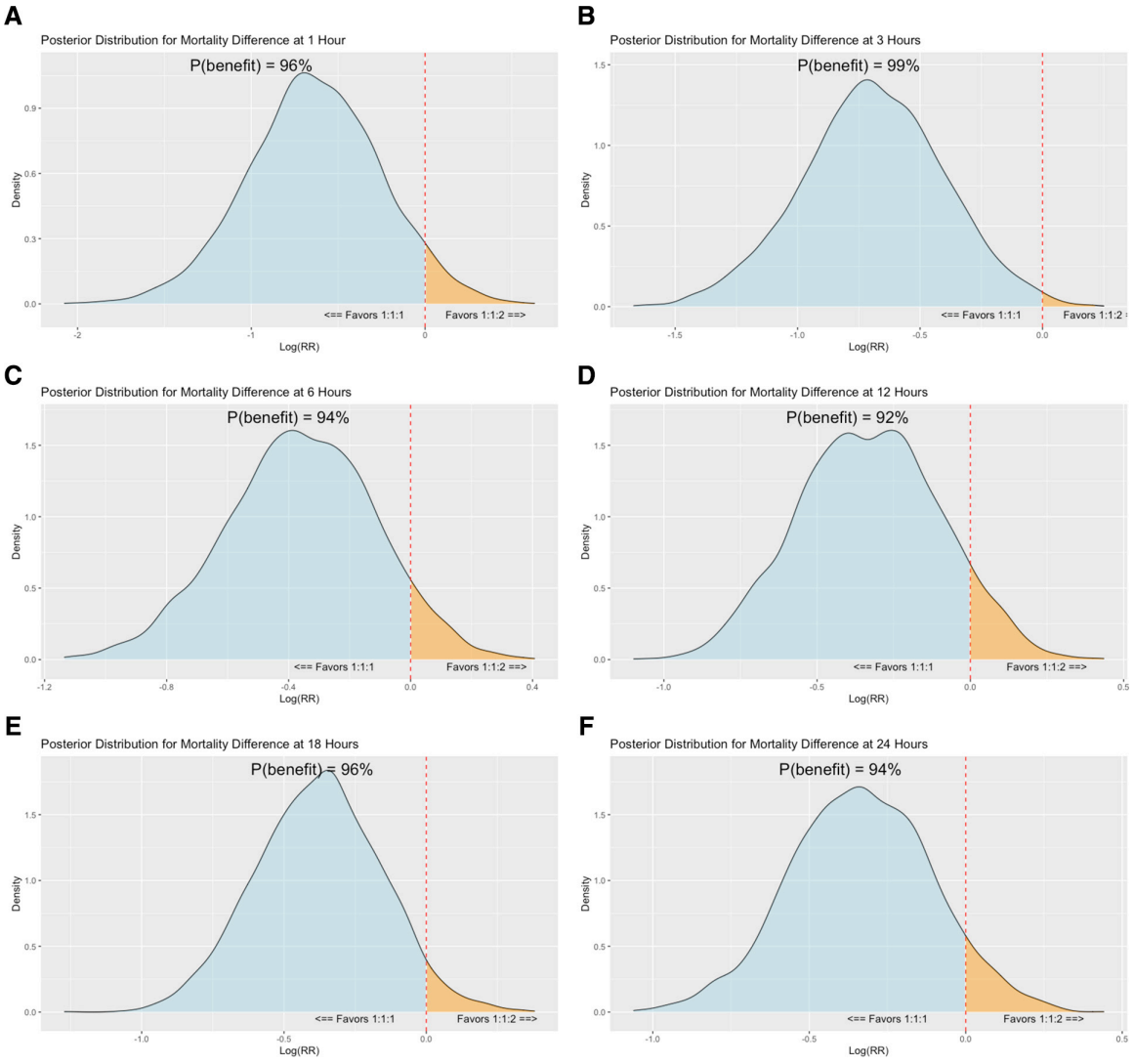

Figure 1 (A–F) Posterior distribution graphs for all-cause mortality comparing 1:1:1 vs 1:1:2 resuscitation strategies at 1 hour (A), 3 hours (B), 6 hours (C), 12 hours (D), 18 hours (E) and 24 hours (F) .

probability distribution. This allowed for the possibility that the 1:1:1 approach could display lower or higher mortality rates compared with the 1:1:2 cohort. For reporting purposes, the RR estimates were obtained by taking the exponential function of log(RR).

In order to further illustrate the results, we also calculated Bayes factors (BFs). BFs act as a likelihood ratio between the competing hypotheses by directly comparing the posterior probabilities of each scenario in ratio form. This strategy represents an alternative way to quantify the support for one of two opposing hypotheses and compute the strength of the associated evidence. These are often interpreted using Jeffrey's Scale of Evidence, which divides the possible BF values into readily interpretable categories, or grades, and translates them into a qualitative judgment based on their associated strength of the evidence. Grades range from 'anecdotal (BF 1–3)' to 'substantial (BF 3–10)', 'strong (BF 10–30)', 'very strong (BF 30–100)' and 'decisive (BF >100)'.[17]

RESULTS

Figure 1 demonstrates the posterior probability density distributions at each time assessed. These graphs demonstrate the posterior probabilities that compare the balanced resuscitation strategy with the 1:1:2 approach. The total area under the curve (AUC) in each graph represents the total (100%) probability in relation to mortality benefit. The vertical line represents a log(RR) of 0, which is equivalent to an RR of 1 corresponding to no difference between treatments. The AUC to the left of the vertical line signifies the probability in favor of a balanced approach over a 1:1:2 strategy for each time point. Based on these findings, the posterior probabilities associated with a mortality benefit (ie, RR <1) represented by the balanced transfusion cohort in the setting of non-informative priors were 94% at 1 hour, 99% at 3 hours, 94% at 6 hours, 92% at 12 hours, 96% at 18 hours, and 94% at 24 hours (table 1).

The associated BF for the balanced approach demonstrating superiority over the 1:1:2 strategy was 21.2 at the 1 hour time point, indicating 'strong' evidence, 142 at the 3 hours time point, indicating 'decisive' evidence, and 14.9, 11.4, 26.4, and 15.5 at the 6 hours, 12 hours, 18 hours, and 24 hours time points, respectively, also indicating 'strong' evidence in support of balanced transfusions when using non-informative priors (table 1).

Under non-informative priors, patients receiving a balanced transfusion demonstrated a mortality RR of 0.53 (95% HDI=0.28–0.98) at 1 hour, 0.50 (95% HDI=0.30–0.80) at

Table 1 Posterior probabilities and BFs favoring the 1:1:1 transfusion strategy

Time period (hour)	P(1:1:1>1:1:2)	BF	Level of evidence*
1	96%	21.2	Strong
3	99%	142	Decisive
6	94%	14.9	Strong
12	92%	11.4	Strong
18	96%	26.4	Strong
24	94%	15.5	Strong

P(1:1:1>1:1:2); posterior probability of balanced transfusion being superior to red cell heavy strategy.
*Based on Jeffery's Scale of Evidence: BFs between 1 and 3 represent anecdotal evidence, 3 and 10 represent substantial evidence, 10 and 30 represent strong evidence, 30 and 100 represent very strong evidence and >100 represent decisive evidence in favor of the alternative hypothesis.
BF, Bayes factor.

3 hours, 0.70 (95% HDI=0.46–1.03) at 6 hours, 0.72 (95% HDI=0.49–1.05) at 12 hours, 0.68 (95% HDI=0.48–0.97) at 18 hours, and 0.71 (95% HDI=0.49–1.04) at 24 hours following arrival to the trauma bay when compared with those who received 1:1:2 resuscitation.

Table 2 shows the posterior probabilities, BFs, and levels of evidence for different RR thresholds, down to an RR of <0.5. The first column (RR <1) demonstrates the results cited above, as well as in figure 1 and table 1. The additional columns correspond to the posterior probability, BF, and level of evidence for correlating reductions in RR. For example, column 2 shows that the posterior probability of a RR <0.9 is 97% (or 'very strong') at 3 hours; and 86% (still 'substantial') at 6 hours. As expected, higher thresholds for RR reduction are associated with lower posterior probabilities and greater uncertainty. In temporal terms, the results show 'strong' to 'decisive' evidence in favor of a 1:1:1 transfusion strategy (ie, RR <1), compared with a 1:1:2 strategy, at all time points within the first 24 hours. However, this relationship does not follow a linear pattern over the course of the first 24 hours. The posterior probability associated with a mortality benefit in the balanced transfusion group decreases from 99% at 3 hours to 92% at 12 hours, before rising to 96% at 18 hours, and then falling again to 94% at 24 hours.

DISCUSSION

Optimal transfusion strategies in trauma remain an area of ongoing research. In this post hoc analysis of the PROPPR trial, we evaluated the study's results in terms of more proximate end points using the powerful capabilities of Bayesian statistics. In doing so, a high probability of mortality benefit associated with a balanced transfusion strategy, as opposed to a 1:1:2 approach, was demonstrated. Furthermore, the high probability of mortality benefit associated with balanced transfusion strategies was demonstrated at each of the early time points assessed.

Adding to the evidence base for balanced transfusion strategies

It is noteworthy that, even at 24 hours (one of the trial's original outcomes), there was a 94% posterior probability of benefit with a 1:1:1 strategy. This contrasts sharply with the 'statistically non-significant' finding (based on a p value of 0.12) of the original analysis, and the authors' conclusion that 'administration of plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours'.[1] While Bayesian and frequentist estimates do not coincide exactly, it is worth considering that rejecting a frequentist null-hypothesis with a two-sided test at $p<0.05$ is equivalent to rejecting the appropriate one-sided test at $p<0.025$ which is, in turn, analogous to a posterior probability >97.5%. This discordance highlights both the potential limitations associated with frequentist-based statistics and the strengths of the Bayesian approach.

Post hoc and 'what-if' analyses of clinical trials should always be viewed cautiously. Nevertheless, it stands to reason that alternative outcome metrics, and a Bayesian analysis, would have

Table 2 Risk reduction threshold analysis assessing the PPs, BFs, and LOEs at each risk level evaluated

Time	Measure	RR <1	RR <0.9	RR <0.8	RR <0.7	RR <0.6	RR <0.5
1 hour	PP (%)	96	92	87	78	63	44
	BF	21.2	11.2	6.6	3.5	1.7	0.8
	LOE	Strong	Strong	Substantial	Substantial	Anecdotal	Anecdotal
3 hours	PP (%)	99	97	94	88	74	51
	BF	142.0	38.2	15.8	7.1	2.8	1.0
	LOE	Decisive	Very strong	Strong	Substantial	Anecdotal	Anecdotal
6 hours	PP (%)	94	86	71	52	26	10
	BF	14.9	5.9	2.5	1.1	0.4	0.1
	LOE	Strong	Substantial	Anecdotal	Anecdotal	Anecdotal	Anecdotal
12 hours	PP (%)	92	83	67	46	23	6
	BF	11.4	4.9	2.0	0.9	0.3	0.1
	LOE	Strong	Substantial	Anecdotal	Anecdotal	Anecdotal	Anecdotal
18 hours	PP (%)	96	90	77	54	29	8
	BF	26.4	9.1	3.3	1.2	0.4	0.1
	LOE	Strong	Substantial	Substantial	Anecdotal	Anecdotal	Anecdotal
24 hours	PP (%)	94	85	68	46	22	5
	BF	15.5	5.6	2.2	0.9	0.3	0.5
	LOE	Strong	Substantial	Substantial	Anecdotal	Anecdotal	Anecdotal

*LOE based on Jeffery's Scale of Evidence.
†RR values in favor of 1:1:1 compared with 1:1:2 resuscitation strategy with lower RR thresholds representing a stronger benefit seen within a balanced approach.
BF, Bayes factor; LOE, level of evidence; PP, posterior probability; RR, risk ratio.

cast a very different light on the results of the PROPPR trial. It should be noted, however, that despite being a 'negative study', the PROPPR trial is one of the most influential and widely cited studies in support of balanced resuscitation strategies. This likely is because of the statistically significant differences in secondary outcomes (ie, death secondary to exsanguination) of the original trial; however, many statisticians believe secondary outcomes should be viewed with caution and skepticism.[18 19] Moreover, this may also be due to an unrecognized 'inherent Bayesian analysis' conducted by readers of the original study, especially when viewing the original Kaplan-Meier survival curves.[1 20]

Support for proximate end points

This study also supports the call for using more proximate mortality end points when evaluating hemorrhage control interventions.[2–4 9 10] This notion reflects data showing that early all-cause mortality following injury is most frequently the result of hemorrhage. This approach avoids the confounding bias of other later causes of mortality, such as traumatic brain injury and multiorgan failure, and the difficulties inherent in using 'disease-specific' mortality, which is often difficult to define.[5–8]

However, the temporal relationship between the posterior probability of benefit and time of death is not as clear-cut as we had hoped. Conceptually, one might envision that the posterior probability of benefit should be highest at 1 hour, and then drop off in a predictable manner. Our data do not show this to be the case. This may be the consequence of relatively few deaths between time periods and the resulting unstable event rates. Alternatively, this may be due to different causes of death (which may or may not be amenable to the intervention under investigation) at 1 hour compared with 18 hours, or even 24 hours. This issue requires further investigation.

The power of Bayesian analytical frameworks

Bayesian analyses are becoming more widely accepted, both for a priori and post hoc analyses of clinical trials.[21–25] Although more difficult to design, these analyses are conceptually attractive, and their output—if presented well—may be easier to comprehend than that of traditional, frequentist evaluations. Bayesian approaches offer results which can be explicitly interpreted as reflecting the weight of evidence, in keeping with intuition, increasing the potential to be more clinically impactful, especially as p values are notoriously misinterpreted throughout the medical field.[20 26 27]

Furthermore, Bayesian studies allow for the ability to assess both the null and alternative hypothesis. In doing so, Bayesian approaches allow researchers the potential to directly quantify the probability of the alternative hypothesis. This is statistically impossible using frequentist methods. Thus, Bayesian techniques offer the potential for more direct and granular inferences to be made, as well as offer the opportunity to directly provide evidence in support of a particular hypothesis as opposed to simply rejecting its null.

Most importantly, Bayesian analyses avoid the dichotomization and oversimplification inherent in frequentist statistics.[12 13] The PROPPR trial is an excellent example of this as we feel that a 94% posterior probability of mortality benefit with balanced transfusion approaches for trauma is sufficient to satisfy most clinicians and is far more informative than a p value of 0.12.

Limitations

Bayesian approaches are not without their limitations.[28] A lack of familiarity with Bayesian concepts within the medical community must be overcome prior to more widespread adoption into clinical practice and incorporation into prospective studies.[29] Furthermore, many currently published Bayesian analyses represent unplanned, post hoc analyses of primary studies, often in an attempt to overcome underpowering. Although these reports add to the interpretation of their associated primary studies, a key take-away should be that more clinical trials should be analyzed primarily using Bayesian techniques as they may overcome many challenges clinical researchers face.[29 30]

CONCLUSION

This analysis provides evidence in support that a 1:1:1 resuscitation has a high probability of mortality benefit when compared with a 1:1:2 strategy, especially at the newly defined more proximate time points during the initial resuscitative period. Researchers should consider using Bayesian approaches, and more proximate end points when assessing hemorrhage-related mortality, for the analysis of future clinical trials.

Acknowledgements The authors would like to thank the University of Alabama at Birmingham Center for Injury Science for their support on this project.

Contributors DL, JR, JBH, JJ contributed to the study design. DL, OR, RU, TS, EB performed the literature search. DL, JR performed the statistical analysis. DL, OR, RU, TS, EB, JR, JBH, JJ critically interpreted the data. DL, OR, RU, TS, EB drafted the manuscript. JR, JBH, JB critically revised the manuscript. All authors approved the manuscript prior to submission. DL will be acting as the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The original PROPPR trial received US Food and Drug Administration, Health Canada, Department of Defense, and site-specific institutional review board approvals prior to initiation.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request.

Author note Media Summary: Bayesian statistics offer an alternative statistical methodology compared with frequentist approaches. Using Bayesian approaches, balanced transfusion strategies were found to be superior to red blood cell heavy approaches for mortality at 1, 3, 6, 12, 18, and 24 hours from point of injury.

ORCID iDs
Daniel Lammers http://orcid.org/0000-0002-9489-3633
Jan Jansen http://orcid.org/0000-0001-8863-4398

REFERENCES

1 Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, *et al*. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015;313:471–82.
2 Holcomb JB, Moore EE, Sperry JL, Jansen JO, Schreiber MA, Del Junco DJ, Spinella PC, Sauaia A, Brohi K, Bulger EM, *et al*. Evidence-based and clinically relevant outcomes for hemorrhage control trauma trials. *Ann Surg* 2021;273:395–401.
3 Fox EE, Holcomb JB, Wade CE, Bulger EM, Tilley BC, PROPPR Study Group. Earlier endpoints are required for hemorrhagic shock trials among severely injured patients. *Shock* 2017;47:567–73.
4 Spinella PC, El Kassar N, Cap AP, Kindzelski AL, Almond CS, Barkun A, Gernsheimer TB, Goldstein JN, Holcomb JB, Iorio A, *et al*. Recommended primary outcomes for clinical trials evaluating hemostatic blood products and agents in patients with bleeding. proceedings of a national heart lung and blood Institute and US Department of defense consensus conference. *J Trauma Acute Care Surg* 2021;91:S19–25.
5 Tisherman SA, Schmicker RH, Brasel KJ, Bulger EM, Kerby JD, Minei JP, Powell JL, Reiff DA, Rizoli SB, Schreiber MA. Detailed description of all deaths in both the shock

and traumatic brain injury hypertonic saline trials of the resuscitation outcomes consortium. *Ann Surg* 2015;261:586–90.
6 Chang R, Kerby JD, Kalkwarf KJ, Van Belle G, Fox EE, Cotton BA, Cohen MJ, Schreiber MA, Brasel K, Bulger EM, *et al*. Earlier time to hemostasis is associated with decreased mortality and rate of complications: results from the pragmatic randomized optimal platelet and plasma ratio trial. *J Trauma Acute Care Surg* 2019;87:342–9.
7 Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, Uribe P, Mallett O, Zubko T, Oetjen-Gerdes L, Rasmussen TE, *et al*. Death on the battlefield (2001–2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg* 2012;73:S431–7.
8 Alarhayem AQ, Myers JG, Dent D, Liao L, Muir M, Mueller D, Nicholson S, Cestero R, Johnson MC, Stewart R, *et al*. "Time is the enemy: mortality in trauma patients with hemorrhage from torso injury occurs long before the "golden hour"" *Am J Surg* 2016;212:1101–5.
9 Gelbard RB, Nahmias J, Byerly S, Ziesmann M, Stein D, Haut ER, Smith JW, Boltz M, Zarzaur B, Callum J, *et al*. Establishing a core outcomes set for massive transfusion: an EAST modified Delphi method consensus study. *J Trauma Acute Care Surg* 2023;94:784–90.
10 Nahmias J, Byerly S, Stein D, Haut ER, Smith JW, Gelbard R, Ziesmann M, Boltz M, Zarzaur B, Biffl WL, *et al*. A core outcome set for resuscitative endovascular balloon occlusion of the aorta: a consensus based approach using a modified Delphi method. *J Trauma Acute Care Surg* 2022;92:144–51.
11 Lammers D, Richman J, Holcomb JB, Jansen JO. Use of Bayesian statistics to reanalyze data from the pragmatic randomized optimal platelet and plasma ratios trial. *JAMA Netw Open* 2023;6:e230421.
12 Bolstad WM, Curran JM. Introduction to Bayesian Statistics.3rd edn. Hoboken, NJ, USA: John Wiley & Sons, 2016.
13 McShane BB, Gal D, Gelman A, Robert C, Tackett JL. Abandon statistical significance. *The American Statistician* 2019;73:235–45.
14 Baraniuk S, Tilley BC, del Junco DJ, Fox EE, van Belle G, Wade CE, Podbielski JM, Beeler AM, Hess JR, Bulger EM, *et al*. Pragmatic randomized optimal platelet and plasma ratios (PROPPR) trial: design, rationale and implementation. *Injury* 2014;45:1287–95.
15 Bürkner PC. Brms: an R package for Bayesian multilevel models using Stan. *J Stat Softw* 2017;80:1–28.
16 Bürkner PC. Advanced Bayesian multilevel modeling with the R package Brms. *ArXiv Prepr ArXiv170511123* 2017.
17 Kass RE, Raftery AE. Bayes factors. *Journal of the American Statistical Association* 1995;90:773–95.
18 Gelbard RB, Cripps MW. Pitfalls in study interpretation. *Surg Infect (Larchmt)* 2021;22:646–50.
19 Freemantle N. Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic *BMJ* 2001;322:989–91.
20 Goodman S. A dirty dozen: twelve P-value misconceptions. *Semin Hematol* 2008;45:135–40.
21 Granholm A, Munch MW, Myatra SN, Vijayaraghavan BKT, Cronhjort M, Wahlin RR, Jakob SM, Cioccari L, Kjær M-BN, Vesterlund GK, *et al*. Dexamethasone 12 mg versus 6 mg for patients with COVID-19 and severe hypoxaemia: a pre-planned, secondary Bayesian analysis of the COVID STEROID 2 trial. *Intensive Care Med* 2022;48:45–55.
22 Zhang C, Jin H, Wen YF, Yin G. Efficacy of COVID-19 treatments: a Bayesian network meta-analysis of randomized controlled trials. *Front Public Health* 2021;9:729559.
23 Song ATW, Rocha V, Mendrone-Júnior A, Calado RT, De Santis GC, Benites BD, Costa-Lima C, Vargas T, Marques LS, Fernandes JC, *et al*. Treatment of severe COVID-19 patients with either low-or high-volume of convalescent plasma versus standard of care: a multicenter Bayesian randomized open-label clinical trial (COOP-COVID-19-MCTI). *Lancet Reg Health Am* 2022;10:100216.
24 Goligher EC, Tomlinson G, Hajage D, Wijeysundera DN, Fan E, Jüni P, Brodie D, Slutsky AS, Combes A. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *JAMA* 2018;320:2251–9.
25 Laptook AR, Shankaran S, Tyson JE, Munoz B, Bell EF, Goldberg RN, Parikh NA, Ambalavanan N, Pedroza C, Pappas A, *et al*. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: a randomized clinical trial. *JAMA* 2017;318:1550–60.
26 Windish DM, Huot SJ, Green ML. Medicine residents' understanding of the biostatistics and results in the medical literature. *JAMA* 2007;298:1010–22.
27 García-Berthou E, Alcaraz C. Incongruence between test statistics and P values in medical papers. *BMC Med Res Methodol* 2004;4:13.
28 Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature* 2019;567:305–7.
29 Clark J, Muhlemann N, Natanegara F, Hartley A, Wenkert D, Wang F, Harrell FE, Bray R, Medical Outreach Subteam of the Drug Information Association Bayesian Scientific Working Group. Why are not there more Bayesian clinical trials? Perceived barriers and educational preferences among medical researchers involved in drug development. *Ther Innov Regul Sci* 2023;57:417–25.
30 Jansen JO, Pallmann P, MacLennan G, Campbell MK, UK-REBOA Trial Investigators. Investigators the URT. Bayesian clinical trial designs: another option for trauma trials *J Trauma Acute Care Surg* 2017;83:736–41.