Published in final edited form as:

J Trauma Acute Care Surg. 2018 October ; 85(4): 691–696. doi:10.1097/TA.0000000000002020.

A COMPARISON OF RESUSCITATION INTENSITY (RI) AND CRITICAL ADMINISTRATION THRESHOLD (CAT) IN PREDICTING EARLY MORTALITY AMONG BLEEDING PATIENTS: A MULTICENTER VALIDATION IN 680 MAJOR TRANSFUSION PATIENTS

David E Meyer, MD, MS,

University of Texas Health Sciences Center and McGovern School of Medicine, Houston, TX

Bryan A Cotton, MD, MPH,

University of Texas Health Sciences Center and McGovern School of Medicine and The Center for Translational Injury Research, Houston, TX

Erin E Fox, PhD,

The Center for Translational Injury Research, Houston, TX

Deborah Stein, MD, MPH,

The University of Maryland School of Medicine, Baltimore, MD

John B Holcomb, MD,

University of Texas Health Sciences Center and McGovern School of Medicine and The Center for Translational Injury Research, Houston, TX

Mitchell Cohen, MD,

The University of Colorado School of Medicine, Denver, CO

Kenji Inaba, MD, and

The Keck School of Medicine and Los Angeles County Hospital, Los Angeles, CA

Elaheh Rahbar, PhD

The Department of Biomedical Engineering at the Wake Forest University School of Medicine, Winston-Salem, NC

On behalf of the PROPPR Study Group

Abstract

Corresponding Author: David E Meyer, MD, MS, McGovern Medical School at UTHealth, 6431 Fannin; MSB 4.292, Houston, TX 77030, Office: 713 500-7240, Fax: 713 500-0505, david.e.meyer@uth.tmc.edu.

The authors disclose no conflicts of interest.

Presented at the 31st EAST Annual Scientific Assembly, January 9–13, 2018 in Lake Buena Vista, FL.

Author Contribution: BAC, EEF, DMS, JBH, MJC, KI, and ER contributed to study conception and design. BAC, EEF, DMS, JBH, MJC, KI, and ER contributed to acquisition of data. DEM, BAC, and ER contributed to analysis and interpretation of data. DEM, BAC, and ER contributed to drafting the manuscript. DEM, BAC, and ER contributed to critical revision.

BACKGROUND—To address deficiencies associated with the classic definition of massive transfusion, Critical Administration Threshold and Resuscitation Intensity were developed to better quantify the overall severity of illness and predict the need for transfusions and early mortality. We sought to evaluate these as more appropriate replacements for MT in defining mortality risk in patients undergoing major transfusions.

METHODS—Patients predicted to receive MT at 12 Level-1 trauma centers were randomized in the PROPPR trial. MT: 10U RBC in 24 hours; CAT+: 3U RBC in the first hour; and RI: total products in the first 30 minutes (1U RBC, 1U plasma, 1000mL crystalloid, 500mL colloid each valued at 1U). RI was evaluated as a continuous variable and dichotomized as RI4+, where RI $\geq$ 4 U. Each metric was evaluated for its ability to predict mortality at 3, 6, and 24 hours, and at 30 days.

RESULTS—Of the 680 patients, 301 patients met MT definition, 521 were CAT+, and 445 were RI4+. Of those that died, 23% never reached MT threshold, but all were captured by CAT+ and RI4+. The 3-hr (9 vs. 9%), 6-hr (14 vs. 14%), 24-hr (17 vs. 18%), and 30-day mortality rates (28 vs. 29%) were similar between CAT+ and RI4+ patients. When RI was evaluated as a continuous variable, each unit increase was associated with a 20% increase in hemorrhage-related mortality (OR 1.20, 95% CI [1.15–1.29], $p < 0.05$).

CONCLUSION—Both RI and CAT are valid surrogates for early mortality in patients undergoing major transfusion, capturing patients omitted by the MT definition. CAT+ showed the best sensitivity; RI4+ demonstrated better specificity and good PPV and NPV. While CAT+ may be suited for patients receiving a RBC-dominant resuscitation, RI4+ is more comprehensive. RI can also be used as a continuous variable to provide quantitative as well qualitative risk of death.

LEVEL OF EVIDENCE—Level III, Prognostic

Keywords

resuscitation intensity; critical administration threshold; massive transfusion; trauma; hemorrhage

BACKGROUND

Identifying trauma patients who are at risk of refractory traumatic coagulopathy has been the subject of much research over the last two decades. Critical to defining this patient population is the concept of massive transfusion (MT), traditionally defined as the need for 10 or more units of red blood cells (RBCs) within a 24-hour period. This original MT definition and the subsequent research (aimed at identifying patients who will require MT), has resulted in faster delivery and administration of blood products. This has translated to tangible survival benefits.^{1,2,3} However, the traditional definition of MT is an arbitrary and antiquated measurement with substantial limitations and survival biases.⁴ It is a measurement that gained popularity when resuscitation of hemorrhagic shock was often performed predominantly with crystalloid solutions and RBCs, with the use of plasma or platelets limited or completely absent during the resuscitation. By definition, MT does not account for the use of plasma, platelets, colloid solutions, or crystalloid solutions that might be used in a more contemporary resuscitation. With the advent of damage control resuscitation (DCR) and a renewed emphasis on balanced blood product resuscitation, MT is

becoming less useful as a surrogate measurement for transfusion need and early mortality. As described in more recent literature, the traditional definition of MT tends to dilute the critical population with patients who are less sick and does not capture the group who dies early (before the 10-unit RBC threshold can be met).^{5,6,7}

In recent years, other surrogate metrics have been developed that better account for the earlier use of blood products and the wide variety of fluids that may be used during a trauma resuscitation. One such measurement, the Critical Administration Threshold (CAT), is defined as the administration of three or more units of RBCs within the first hour of resuscitation.⁷ Another such metric, the Resuscitation Intensity (RI), considers all fluid and blood products that may be administered to a trauma patient within the first 30 minutes of resuscitation.⁸ As previously defined, RI is the sum of each “unit” of resuscitative product, including each unit of blood product (RBC or plasma or platelets), every 500 mL of colloid solution, and every 1000 mL of crystalloid solution administered within the first 30 minutes. RI of 4 U, 6 U, and 8 U have been shown in previous studies to be increasingly predictive of mortality at 6 and 24 hours.⁸

However, CAT and RI have never been compared to one another, nor have they been validated in a large, multi-center cohort of trauma patients. The purpose of this study was to assess the validity of CAT and RI as surrogate metrics for early mortality in severe trauma and compare them to the traditional definition of MT.

METHODS

Study Design

The PROPPR study was a pragmatic phase III, multicenter, randomized trial that compared the effectiveness of two resuscitation strategies for bleeding patients. The study began August 3, 2012 and concluded enrollment December 2, 2013. Patients were randomized to receive a ratio of 1:1:1 or 1:1:2 of platelets:plasma:RBCs until hemorrhage was controlled. The study was approved by the US Food and Drug Administration (FDA) (Investigational New Drug No. 14929), Health Canada, NHLBI and the Department of Defense, as well as each individual site’s institutional review boards. The PROPPR study used exception from informed consent (21 CFR 50.24), including community consultation with delayed patient or legally authorized representative content.

This represents a secondary analysis of the original PROPPR study, investigating the validity of Resuscitation Index ≥ 4 U (RI4+) and the Critical Administration Threshold (CAT+) as surrogates for early mortality in severe trauma. Prior to starting the study, and as part of site training and verification, each site was evaluated for the ability of its blood bank to randomize, prepare, and deliver the first massive transfusion protocol (MTP) cooler to the bedside within ten minutes, as well as to prepare and deliver subsequent coolers on-demand. Because the delivery of blood products was collected and tracked, the amount of product transfused within a given time period could be ascertained with a high degree of accuracy. As part of an ongoing quality improvement initiative, the study protocol was evaluated and reevaluated at each site and then refined as necessary to ensure rigorous protocol fidelity.

Study Population

The PROPPR study was conducted at 12 North American level-1 trauma centers, screening those patients who were severely injured and who met local criteria for highest-level trauma activation. To meet the study's intended focus on those injured patients who were bleeding at the time of arrival, research team personnel were notified simultaneously with trauma team activation and were present prior to patient arrival. Given the aim of rapidly enrolling those patients with severe hemorrhage, inclusion criteria were as follows: (1) highest-level trauma team activation, (2) estimated age of 15 years or older or weight of 50 kg or greater if age unknown, (3) patient received directly from the injury scene, (4) having received at least one unit of any blood component transfused prior to hospital arrival or within 1 hour of admission and (5) predicted by an Assessment of Blood Consumption (ABC) score of 2 or greater or by physician judgment of the need for MT (defined as 10 U of RBCs within 24 hours).⁹ Patients were excluded if they: (1) did not receive at least one unit of a blood component within one hour of arrival to the hospital or during prehospital transport, (2) were expected to die within one hour of ED arrival from a devastating injury, or (3) improved during initial stabilization and did not require further transfusion. During the study period, 14,313 highest-level trauma activations occurred at the 12 sites, with 11,185 patients undergoing screening. Among these, 680 patients were enrolled and randomized (338 to the 1:1:1 group and 342 to the 1:1:2 group). All 680 patients were included in this secondary analysis.¹⁰

Outcomes and Definitions

The primary outcomes for this secondary analysis were mortality at 3, 6, and 24 hours. Secondary outcomes included 30-day mortality. A clinician blinded to group assignment and external to the trial site adjudicated each death, including death from exsanguination. Time to death was measured in both minutes and hours. Blood product use was recorded in units. Crystalloid and colloid use was recorded in milliliters. Massive transfusion (MT) was defined by the traditional definition of 10 U RBC in 24 hours. While CAT+ was previously defined as 3 U RBC during any one-hour period in the first 24 hours arrival, this definition seemed less relevant to the purpose of our study, which was to evaluate the predictive nature of these scores during the early resuscitation phase.⁷ Moreover, (1) as most deaths from hemorrhage occur in the first two to three hours of arrival, (2) the median time to death in both randomization groups in PROPPR was less than two hours, and (3) we planned to evaluate mortality as early as 3 hours, we felt that the performance of CAT during the first hour of arrival would be a more reasonable and relevant application of this tool. Resuscitation Intensity (RI) was defined as total products in the first 30 minutes of arrival (1 U RBC, 1 U plasma, 1000 mL crystalloid, 500 mL colloid each assigned a value of 1 U).⁸ RI was evaluated both as a continuous variable, and dichotomized as RI4+, where the RI 4 U (RI4+).

Statistical Analysis

Univariable and multivariable logistic regressions were used to evaluate associations between MT, RI and CAT on early mortality at 3, 6 and 24 hours, adjusting for age, site, penetrating injury, and randomization group (1:1:1 vs. 1:1:2). The goal was to compare the

predictive performance of RI and CAT metrics to the historical definition of MT. RI was evaluated both as a continuous variable and categorical variable to identify the optimal predictive value for early mortality. Mixed models with site as the random intercept were also performed for comparison. In addition, we evaluated the impact of RI and CAT on predicting deaths from exsanguination (or hemorrhage-related deaths). Odds ratios and 95% confidence levels are reported for all significant associations. Sensitivity and specificity of each metric (i.e. RI and CAT) were calculated, as were positive predictive values (PPV) and negative predictive values (NPV). Receiver operating curve statistics (ROC) were also performed to determine which cutoffs provided best prediction of early mortality. All analyses were performed using commercially available statistical software (STATA version 12.1; StataCorp, College Station, TX).

RESULTS

Baseline characteristics for the 680 patients have been previously reported.¹⁰ In summary, 80% of patients were male and 64% were white, with a median age of 34 (24, 51) years. Nearly half of the mechanisms of injury were penetrating, with an overall median Injury Severity Score (ISS) of 26 (17, 41) and weighted Revised Trauma Score (w-RTS) of 6.81 (4.09, 7.84). Of these 680 patients, 313 met the definition for MT, 521 were CAT+, 445 had a RI ≥ 4 (RI4+), 268 had a RI ≥ 6 (RI6+), and 142 had a RI ≥ 8 (RI8+). 153 patients (45.3%) in the 1:1:1 group and 160 patients (46.8%) in the 1:1:2 group met the traditional definition for MT. Considering CAT+ and RI4+, we observed that the patient characteristics were very similar between these groups (see TABLE 1). Patients were nearly equally distributed between the randomization groups, had similar age, gender, race distributions, admission vitals, and ISS.

However, the distribution of RI metrics was not the same across participating sites in the PROPPR trial. Sites 2, 4, 5, 6, 9, 10, and 11 had higher median RI values (greater than 4 units) compared to site 1 (referent site), as illustrated in FIGURE 1A. Conversely, nearly all hospital sites had a median RBC transfusion of 3 RBC units in the first three hours, with only sites 4, 7 and 9 displaying significantly higher administration of RBCs within the first hour compared to site#1 (referent site), as shown in FIGURE 1B. These figures illustrate the natural variability of resuscitative and transfusion product use across Level-1 trauma centers and the need to capture more than just RBCs during the acute phase of resuscitation.

Despite the variability of resuscitative products, patients who were RI4+ received similar median numbers of blood products and resuscitative fluids. Interestingly, these patients received a median of 10 units of product within the first hour of their hospital admission (TABLE 1), with 8 of these units generally being a type of blood product (i.e. RBC, plasma, platelet). Given these similar blood and fluid loads, these subjects experienced similar times to hemostasis of 130–135 minutes (TABLE 1).

100 study patients died within 24 hours, with 90% of these being CAT+ and 80% being RI4+. (TABLE 2) Interestingly, 37 patients (~10%) did not receive at least 10 units of RBC, therefore making them ineligible to meet the definition for MT. However, all met the CAT+

and RI4+ definitions. For the entire study population, 3-hour, 6-hour and 24-hour mortality were 52 (7.6%), 78 (11.5%), and 100 (14.7%) respectively.

The ability of each to predict death at 3, 6, and 24 hours was determined by calculating the sensitivity, specificity, PPV, and NPV and summarized in TABLES 3–5. For MT, sensitivity at 3, 6, and 24 hours ranged from 51% to 64%, while specificity was remained stable at around 58%. For CAT, sensitivity at 3, 6, and 24 hours was higher at around 92%, while specificity was lower at about 25%. For RI4+, sensitivity was approximately 78%, while specificity was approximately 36%. Sensitivity decreased at RI 6 (about 61%) and RI 8 (about 49%), while specificity improved (63% for RI 6 and 83% for RI 8).

CAT and RI were also evaluated for their ability to predict death primarily due to exsanguination. Both CAT and RI were positive predictors of exsanguinating deaths. When RI was treated as a continuous variable, every 1-unit increase in RI corresponded to a 20% increase in hemorrhage-related death (OR 1.20; 95% CI [1.12–1.29], $p<0.05$; FIGURE 2), when adjusting for age, penetrating injury, randomized group, and site. As RI increases there is an exponential increase in the risk for early mortality at both 6 and 24 hours. Nearly half of subjects with a RI>10 U experienced an early death within 24 hours (FIGURE 2).

DISCUSSION

The traditional definition of MT appears to have been derived from open-heart surgery patients who received a near complete blood volume transfusion (5000 mL) in 24 hours). The 10 U portion of this clinical definition may very well have been translated from the initial 10 U of whole blood used (each unit roughly 500–550 mL) which would be equivalent to the original 5000 mL description.¹¹ Application of this term first appeared in the trauma literature in 1955, but without a specific stated volume or number of units transfused.¹² About the time that blood bankers and transfusion medicine began fractionating whole blood into components, the term “massive transfusion” was applied to transfusion of 10 or more units of RBCs in 24 hours, though the volume was significantly less (3000 mL) than that initially described.^{13,14} The classic definition for MT has been shown to have several intrinsic flaws that impact its relevance in identifying trauma patients at risk for early mortality. First, by definition, it does not reflect resuscitation that includes blood products other than RBCs. With the advent of DCR and clear scientific evidence that demonstrates that a balanced ratio of plasma, platelets, and RBCs is associated with favorable outcomes, the era of RBC-only resuscitation is over.¹⁵ In addition, some of the most critical trauma patients may succumb to their injuries within 24 hours and *well before* a total of 10 units of RBCs can be delivered. In fact, 37 patients enrolled in this study died before receiving their 10th unit of RBC, thus making them ineligible to meet the definition of MT. A patient who is transfused nine units of RBC and nine units of plasma but dies in an hour would not meet the definition, while one who receives their tenth unit of RBCs at 23 hours and lives would be included. As MT is plagued with such biases and limitations, it is no longer useful as a surrogate measurement for transfusion needs and early mortality.

The limitations of the traditional definition of massive transfusion are further highlighted by the fact that MT captures the fewest patients of the three measurements evaluated in the

current study. In fact, of the patients that it did capture, MT had the lowest sensitivity (63%) in predicting mortality at 24 hours. The risk of early in-hospital mortality at 3, 6, and 24 hours after hospital admission was increased more than twofold in patients receiving three or more units of RBCs (i.e. CAT+) in the first hour or receiving four or more units of resuscitative fluids in the first 30 minutes of arrival (i.e. RI4+), compared to those receiving less resuscitative products. However, both CAT+ and RI4+ metrics demonstrated relatively poor positive predictive values for mortality. Only 90 out of the 521 CAT+ subjects experienced death within 24 hours and 80 out of 445 who were RI4+ experienced death within 24 hours. This means that CAT+ and RI4+ metrics, while associated with relative increased use of blood products and mortality and demonstrated improved identification of massively hemorrhaging patients compared to the traditional MT definition, they are limited in their ability to be the sole predictors of in-hospital mortality.

In attempts to create metrics less susceptible to the survival bias of MT, the RI+ and CAT+ metrics were designed to provide quick snapshots based on the first 30 and 60-minute resuscitation and transfusion and activities in hospital, respectively. In this study, CAT+ and RI4+ both out-performed MT in predicting transfusion need and mortality. First, both metrics captured more of the patients enrolled in the PROPPR trial (521 for CAT+ and 445 for RI4+), with more than half of these subjects receiving >10 units of resuscitative products within the first hour of hospital admission. Second, both metrics demonstrated improved sensitivity when predicting mortality at 3 hours (92% for CAT+ and 77% for RI4+), 6 hours (91% for CAT+ and 78% for RI4+), and 24 hours (90% for CAT+ and 80% for RI4+). Specificity of these metrics was lowest for CAT+ (25% vs. 37% for RI4+). Specificity for RI was also low but became incrementally better at higher RI cutoffs. For example, RI6+ demonstrated moderately high specificity and sensitivity levels, both greater than 60%. Both metrics had consistently better negative predictive values for all mortality rates at 3, 6 and 24 hours than MT. Altogether, these results are promising for CAT+ and RI4+, since both measurements are available to clinicians sooner. While not specifically intended to be decision-making tools for the clinician in real time in the trauma bay, both metrics provide an enhanced awareness of the trajectory of a resuscitation. Crossing the threshold into CAT+ or RI4+ should prompt physicians to recognize the significantly increased risk of early mortality and closely evaluate the methods by which definitive control of bleeding is being obtained. While the predictive values for CAT+ and RI4+ were similar in this study, we believe that RI provides additional benefit by evaluating all resuscitative fluids in the first 30 minutes, instead of blood products only or RBCs only as done by CAT and MT. Therefore, RI could potentially serve as a more universal metric across all trauma hospitals worldwide.

There are several limitations in this study. First, these metrics were not designed to predict mortality and were not primary outcomes in the original PROPPR study. Resuscitation fluids/products and times to administration were collected intentionally and prospectively, but PROPPR was not specifically designed to test the predictive ability of these measurements. Secondly, given that PROPPR was designed to randomize subjects at risk for massive hemorrhage and treat by administering blood products, this study cohort is biased towards subjects who receive substantial blood products. Thus, it is possible that specificity and sensitivity of these metrics could be higher than calculated here if a more comprehensive trauma population that don't receive blood products (e.g. screen failures),

were included in the study. As a result, all of the metrics (i.e. MT, CAT and RI) were better at predicting who *would not* die than at predicting who *would*. MT, CAT, and RI4+ all had poor specificity and positive predictive values in the PROPPR study trial cohort. The specificity of RI improved as intensity increased (RI = 8, for example, had specificities in excess of 80% at 3, 6, and 24 hours), however this improvement in specificity came at the expense of its sensitivity. No single measurement provided both high sensitivity and high specificity. Further, there were only 100 subjects (out of 680) who experienced early mortality in the PROPPR trial. This is a relatively low rate of mortality and likely to be largely influenced by the early administration of blood products. While their value likely lies more in replacing MT to identify those at risk of mortality from bleeding, RI4+ and CAT+ are better predictors of blood product usage than mortality, especially when these mortalities are being prevented by the early use of balanced blood products and administration of other life-saving interventions.

CONCLUSION

Both RI and CAT performed better than MT at identifying trauma patients at risk for early mortality. However, because the sensitivities for CAT and RI4+ were significantly better than their specificities, each measurement was better at identifying patients that *would not die* at 24 hours than those who would. Although specificity could be dramatically improved by increasing the RI threshold to = 8, this was done to the detriment of the sensitivity. Since both measurements can be completed much earlier than MT (30 minutes for RI, 60 minutes for CAT), both are available to clinicians earlier and may be used to help guide decision-making during resuscitation. Continued research is necessary to refine a surrogate measurement that predicts early mortality with a high degree of sensitivity *and* specificity.

Acknowledgments

This work was supported with grant U01HL077863 from the US National Heart, Lung, and Blood Institute (NHLBI), including a subcontract to Dr. Elaheh Rahbar (Sub-award No. 0010612B) and funding from the US Department of Defense, the Defence Research and Development Canada in partnership with the Canadian Institutes of Health Research-Institute of Circulatory and Respiratory Health (grant CRR-120612).

References

1. Riskin DJ, Tsai TC, Riskin L, Hernandez-Boussard T, Purtill M, Maggio PM, Spain DA, Brundage SI. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. *J Am Coll Surg*. 2009; 209(2):198–205. [PubMed: 19632596]
2. Radwan ZA, Bai Y, Matijevic N, del Junco DJ, McCarthy JJ, Wade CE, Holcomb JB, Cotton BA. An emergency department thawed plasma protocol for severely injured patients. *JAMA Surg*. 2013; 148(2):170–175. [PubMed: 23426594]
3. Meyer DE, Vincent LE, Fox EE, O’Keeffe T, Inaba K, Bulger E, Holcomb JB, Cotton BA. Every minute counts: Time to delivery of initial massive transfusion cooler and its impact on mortality. *J Trauma Acute Care Surg*. 2017 Jul; 83(1):19–24. [PubMed: 28452870]
4. Malone DL, Hess JR, Fingerhut A. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *J Trauma*. 2006; 60:S91–96. [PubMed: 16763487]
5. Mitra B, Cameron PA, Gruen RL, Mori A, Fitzgerald M, Street A. The definition of massive transfusion in trauma: a critical variable in examining evidence for resuscitation. *Eur J Emerg Med*. 18:137–142. 011.

6. Nascimento B, Rizoli S, Rubenfeld G, Lin Y, Callum J, Tien HC. Design and preliminary results of a pilot randomized control trial on a 1:1:1 transfusion strategy: the trauma formula-driven versus laboratory-guided study. *J Trauma*. 2011; 71:418–426. [PubMed: 21248647]
7. Savage SA, Zarzaur BL, Croce MA, Fabian TC. Redefining massive transfusion when every second counts. *J Trauma Acute Care Surg*. 2013 Feb; 74(2):396–400. discussion 400–2. [PubMed: 23354230]
8. Rahbar E, Fox EE, del Junco DJ, Harvin JA, Holcomb JB, Wade CE, Schreiber MA, Rahbar MH, Bulger EM, Phelan HA, et al. PROMMTT Study Group. Early resuscitation intensity as a surrogate for bleeding severity and early mortality in the PROMMTT study. *J Trauma Acute Care Surg*. 2013 Jul; 75(Suppl):S16–23. [PubMed: 23778506]
9. Baraniuk S, Tilley BC, del Junco DJ, Fox EE, van Belle G, Wade CE, Podbielski JM, Beeler AM, Hess JR, Bulger EM, et al. PROPPR Study Group. Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial: design, rationale, and implementation. *Injury*. 2014; 45(9):1287–95. [PubMed: 24996573]
10. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, et al. PROPPR Study Group. 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; 313:471–482. [PubMed: 25647203]
11. Ulin AW, Gollub SW, Winchell HS, Ehrlich EW. Hemorrhage and Massive Transfusion. *JAMA*. 1958; 168:1971–1973.
12. Artz CP, Sako Y, Bronwell AW. Massive Transfusion in the Severely Wounded: Report of a patient receiving 23,350 cc of blood in the first twenty-four hours. *Surgery*. 1955; 37:469–472. [PubMed: 14359071]
13. Wilson RF, Mammen E, Walt AJ. Eight years of experience with massive blood transfusions. *J Trauma*. 1971; 11:275–85. [PubMed: 5313649]
14. Massive transfusion in surgery and trauma. Proceedings of the XIVth annual scientific symposium of the American Red Cross. *Prog Clin Biol Res*. 1982; 108:1–319. [PubMed: 7178146]
15. Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, Dubose JJ, Fox EE, Inaba K, Rodriguez CJ, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: A practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg*. 2017; 82:605–617. [PubMed: 28225743]

Figure 1.

RI and CAT metrics across participating sites in the PROPPR trial. (A) RI4+ (*i.e.*, 4 units in first 30 min) is illustrated by the dotted line. Sites 2, 4, 5, 6, 9, 10 and 11 had higher median RI values compared to site#1 (referent site). (B) CAT+ (*i.e.*, 3 RBC Units in first hour) is illustrated by the dotted line. Nearly all sites had a median CAT value $\geq$ 3 RBC units in the first hour. Sites 4, 7 and 9 had significantly more patients receiving $\geq$ 3 RBC units in the first hour compared to site #1 (referent site).

Figure 2. Resuscitation intensity versus 24-hour mortality. Increasing RI is associated with an exponential increase in risk of early mortality.

Table 1

Summary of patient characteristics based on the three metrics: MT, CAT and RI. Median and IQR are reported. Categorical variables are presented as n(%).

	MT (N=301)	CAT+ (N=521)	RI4+ (N=445)
Randomization Group			
1:1:1, n (%)	149 (49.5%)	240 (46%)	217 (48.7%)
1:1:2, n (%)	152 (50.5%)	281 (54%)	228 (51.2%)
Age, y	33 (24, 51)	34 (24, 49)	34 (24, 51)
Male, n (%)	241 (80%)	421 (81%)	356 (80%)
Penetrating, n (%)	134 (44%)	263 (50%)	217 (49%)
ABC Score 3	198 (66%)	353 (68%)	305 (68.5%)
GCS	13 (3, 15)	13 (3, 15)	13 (3, 15)
w-RTS	6.37 (4.09, 7.55)	6.37 (4.09, 7.55)	6.38 (4.09, 7.55)
ISS	33 (22, 42)	27 (18, 41)	29 (18, 41)
<i>Vital Signs</i>			
Systolic Blood Pressure, mmHg	100 (80, 124)	99 (79, 125)	92 (76, 120)
Diastolic Blood Pressure, mmHg	70 (55, 87)	68 (50, 91)	61 (47, 87)
Heart Rate, bpm	116 (90, 130)	116 (97, 134)	116 (97, 135)
Respiratory Rate, bpm	20 (16, 24)	20 (17, 26)	20 (17, 25)
Base Deficit (mEq/L)	-10.3 (-14.2, -6.4)	-9 (-14, -5)	-9 (-13.4, -5.1)
pH	7.19 (7.07, 7.27)	7.21 (7.1, 7.29)	7.21 (7.11, 7.29)
Hemoglobin (g/dL)	11.3 (9.5, 12.9)	11.6 (9.9, 13.1)	11.5 (9.9, 13.2)
Hematocrit (%)	34.1 (28.6, 37.8)	34.7 (30, 39.1)	34.5 (30, 39)
<i>Resuscitative Products</i>			
1-hr Total RBC units	6 (4, 8)	5 (4, 7)	5 (4, 7)
1-hr Total Plasma units	3 (1, 5)	2 (1, 4)	2 (1, 4)
1-hr Total Platelets units	1 (0, 1)	1 (0, 1)	1 (0, 1)
1-hr Total Crystalloid units	2 (1, 3)	2 (1, 3)	2 (1, 4)
1-hr Total Colloid units	0 (0, 0)	0 (0, 0)	0 (0, 0)
<i>Clinical Outcomes</i>			
Time to Hemostasis (min)	183 (130, 279)	132 (90, 210)	135 (88, 208)
3-hr mortality	27 (8.9%)	48 (9%)	40 (9%)
6-hr mortality	50 (16.6%)	71 (14%)	61 (14%)
24-hr mortality	63 (21%)	90 (17%)	80 (18%)
Death due to Exsanguination	63 (21%)	78 (15%)	65 (15%)

Table 2

Baseline and arrival data dichotomized by 24-hour mortality. Median and inter-quartile range (IQR) reported. For categorical data, n(%) reported.

	Survivors at 24 hrs (n=580)	Non-Survivors at 24 hrs (n=100)	p-value
Male gender	81%	77%	0.352
Age, years	34 (25, 49)	39 (24, 56)	0.223
White Race	63%	68%	0.336
Blunt Mechanism	51%	62%	0.042
ISS	25 (17, 37)	36 (25, 48)	<0.001
w-RTS	6.90 (4.09, 7.84)	4.09 (3.80, 6.37)	<0.001

Medians are expressed with 25th and 75th interquartile range. ISS: injury severity score; w-RTS: weighted revised trauma score.

Table 3

MT, RI, and CAT metrics predicting mortality at 3 hours.

	MT	CAT+	RI4+	RI6+	RI8+
PPV	9%	9.21%	8.98%	11.94%	19.01%
NPV	92%	97.48%	94.89%	95.15%	95.35%
Specificity	51%	24.68%	35.51%	62.42%	81.69%
Sensitivity	56%	92.31%	76.92%	61.54%	51.92%

MT: massive transfusion; CAT: critical administration threshold; RI: resuscitation intensity; PPV: positive predictive value; NPV: negative predictive value

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 4

MT, RI and CAT metrics predicting mortality at 6 hours.

	MT	CAT+	RI4+	RI6+	RI8+
PPV	16%	13.63%	13.71%	17.54%	26.76%
NPV	92%	95.59%	92.76%	92.47%	92.56%
Specificity	64%	25.25%	36.21%	63.28%	82.72%
Sensitivity	58%	91.03%	78.21%	60.25%	48.72%

MT: massive transfusion; CAT: critical administration threshold; RI: resuscitation intensity; PPV: positive predictive value; NPV: negative predictive value

Table 5

MT, RI, and CAT metrics predicting mortality at 24 hours.

	MT	CAT+	RI4+	RI6+	RI8+
PPV	20.93%	17.27%	17.98%	22.76%	33.09%
NPV	90.24%	93.71%	91.49%	90.53%	90.15%
Specificity	58.96%	25.69%	37.07%	64.31%	83.62%
Sensitivity	63%	90%	80%	61%	47%

MT: massive transfusion; CAT: critical administration threshold; RI: resuscitation intensity; PPV: positive predictive value; NPV: negative predictive value