Massive transfusion and the response to prehospital plasma: It is all in how you define it

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BACKGROUND: A recent analysis derived from the Prehospital Air Medical Plasma trial data set demonstrated no significant independent plasma survival benefit in those who required massive transfusion (≥10 units of red cells in 24 hours). The definition of massive transfusion has evolved over time to minimize bias and predict those at highest risk of death. We sought to characterize the definition of massive transfusion, their associated mortality risks and the survival benefit associated with prehospital plasma.

METHODS: A secondary analysis was performed using data from a recent prehospital plasma trial. Patients transferred directly from the scene were characterized. We defined historic massive transfusion using ≥10 units red cells in 24 hours and critical administration threshold (CAT) as ≥3 units per hour in the first hour (CAT1hr) or in any of the first 4 hours (CAT4hr) from arrival. The primary outcome was 30-day mortality. Kaplan-Meier analysis and Cox hazard regression were used to characterize the survival benefit of prehospital plasma.

RESULTS: There were a total of 390 enrolled patients who were transferred from the scene and represent the study cohort. Overall, 126 patients were positive for the CAT1hr metric, 183 patients were positive for the CAT4hr metric and 84 patients were positive for historic massive transfusion metric. The overall study mortality rate for those patients who met each transfusion definition was 13.1%, 17.4% and 10.0%, respectively. The CAT4hr metric had the lowest potential for survival bias. Kaplan-Meier survival analysis demonstrated a prehospital plasma survival benefit in the patients who were CAT4hr positive.

CONCLUSION: The current analysis demonstrates the superior utility of the CAT4hr definition with optimization of survival bias while conserving mortality risk prediction. This transfusion definition was associated with a prehospital plasma survival benefit and may be the most appropriate definition of massive transfusion for pragmatic studies which focus on hemorrhagic shock. (*J Trauma Acute Care Surg.* 2020;89: 43–50. Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Epidemiologic, Level II

KEY WORDS: Prehospital; plasma; massive transfusion; critical administration threshold.

A recent call for zero preventable deaths by the National Academies of Sciences, Engineering, and Medicine focuses on needed strategies to counter the physiologic consequences of severe hemorrhage.[1] Despite major improvements over the last two decades in trauma resuscitation following arrival to the hospital, patients continue to suffer high rates of mortality due to hemorrhage in the first few hours of arrival.[2–5] This persistent early mortality highlights the importance of prehospital environment interventions, implemented as close to the time of injury as possible, that result in improved outcome differences for hemorrhagic shock. Recent randomized evidence from the Prehospital Air Medical Plasma (PAMPer) trial demonstrated a survival benefit in trauma patients at risk of hemorrhagic shock treated with early prehospital thawed plasma during air medical transport to definitive trauma care.[6]

A recent secondary analysis derived from the PAMPer trial data set demonstrated the most robust prehospital plasma survival benefit was in patients with moderate transfusion requirements and found no significant independent plasma survival benefit in those who required massive transfusion defined as receiving 10 units red cells or greater in initial 24 hours.[7] More recent transfusion definitions focusing on shorter periods have been characterized as equivalent in their hemorrhage associated mortality risk but with minimization of inherent survival bias.[8–10] These newer transfusion definitions have not been assessed using data derived from a pragmatic, prehospital, interventional trial.

The overall objective of the current secondary analysis of the PAMPer study cohort was to characterize different transfusion metrics, their mortality risk prediction capabilities and the associated benefits of prehospital plasma for each transfusion definition. We hypothesized that these novel transfusion definitions would have improved mortality risk prediction capabilities relative to the historical massive transfusion definition and that prehospital plasma would be associated with a survival benefit when they are used.

METHODS

The current analysis is a secondary analysis using data derived from the Prehospital Air Medical Plasma (PAMPer) trial. The original study was a multicenter, cluster-randomized trial involving injured patients who were transported by air medical transport to a level 1 trauma center, either directly from the scene or from a referring hospital.[6] Patients enrolled in PAMPer received two units of either group AB or group A with a low anti-B antibody titer (<1:100) thawed plasma or received standard air medical care during prehospital transport to a participating trauma center. Standard care consisted of goal-directed, crystalloid-based resuscitation on the basis of hemodynamic status for air transport teams at 14 of the 27 participating air medical bases. Air transport teams at the other 13 participating air medical bases also carried 2 units of universal donor red blood cells (RBCs) on all flights. If a patient remained hypotensive after the plasma infusion or had obvious bleeding, transfusion of RBCs then proceeded according to the local standard care protocol. Randomization was at the level of the air medical base for 1-month periods. Importantly, prehospital plasma was administered prior to other resuscitative fluids once the patient met all inclusion and no exclusion criteria.[6]

Inclusion criteria for the current secondary analysis mirrored the inclusion criteria of the primary trial. Enrolled participants

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TABLE 1. Patient and Injury Characteristics for Study Cohort Patients Stratified by Three Transfusion Definitions CAT1hr, CAT4hr, and hMR

Variables	CAT1hr (n = 126)	CAT4hr (n = 183)	hMT (n = 84)
Median age (IQR), y	40.5 (26–59.25)	42 (27–61)	44 (27–63)
Male sex, n (%)	91 (72.2)	131 (71.6)	63 (75.0)
Race, n (%)			
White	110 (87.3)	160 (87.4)	73 (86.9)
Black	12 (9.5)	16 (8.7)	8 (9.5)
Asian	0	1 (0.5)	0
Other	0	1 (0.5)	2 (2.4)
Unknown	7 (5.6)	5 (2.7)	1 (1.2)
Hispanic ethnic group, n (%)	3 (2.4)	4 (2.2)	1 (1.2)
Any injury caused by blunt trauma, n (%)	108 (85.7)	157 (85.8)	73 (86.9)
Fall from height	2 (1.6)	4 (2.2)	3 93.6)
Motor vehicle collision	59 (46.8)	85 (46.4)	37 (44.0)
Motorcycle collision	25 (19.8)	39 (21.3)	22 (26.2)
Pedestrian or bicycle collision	9 (7.1)	12 (6.6)	7 (8.3)
Assault	6 (4.8)	7 (3.8)	4 (4.8)
Other	5 (4.0)	8 (4.4)	0
Any injury caused by penetrating trauma, n (%)	19 (15.1)	28 (15.3)	12 (14.3)
Firearm	13 (10.3)	18 (9.8)	10 (11.9)
Impalement or stabbing	6 (4.8)	10 (5.5)	2 (2.4)
Median prehospital volume of crystalloid solution (IQR), mL	725 (0–1400)	600 (0–1480)	800 (0–1575)
Prehospital red-cell transfusion, n (%)	56 (44.4)	79 (43.2)	40 (47.6)
Initial Glasgow Coma Scale score <8, n (%)	67 (53.2)	94 (51.4)	42 (50.0)
Median prehospital systolic blood pressure (IQR), mm Hg	72 (60–83)	71 (60–82)	69 (60.0–81.8)
Median prehospital heart rate (IQR), bpm	120 (109–133.5)	119 (105.5–132.3)	122 (110–144)
Prehospital intubation, n (%)	92 (73.0)	127 (69.4)	59 (70.2)
Prehospital cardiopulmonary resuscitation, n (%)	11 (8.7)	11 (6.0)	2 (2.4)
Median prehospital transport time (IQR), min	39 (32.5–50)	40 (33–55)	39 (33–50)
Median ISS (IQR)	27 (17–41)	26.5 (17–36.5)	27 (17–41)
Median 24-h RBC units (IQR)	8 (5–15)	7 (5–13)	15 (11–21.75)
Median 24-h plasma units (IQR)	3 (0–8)	3 (0–8)	9 (4–13.75)
Median 24-h platelet units (IQR)	1 (0–2)	1 (0–2)	2 (1–3)
Median crystalloid volume (IQR), mL	5030 (3000–7665.75)	5290 (3250–7800)	5487.5 (3250–8161.5)
Abbreviated injury scale score for head			
Median (IQR)	2 (0–4)	2 (0–3)	0.5 (0–3)
Score > 2, n (%)	56 (44.4)	77 (42.1)	31 (36.9)
History of treatment with vitamin K antagonist, n (%)	1 (0.8)	2 (1.1)	1 (1.2)
History of treatment with antiplatelet medication, n (%)	5 (4.0)	8 (4.4)	5 (6.0)

were hypotensive (Systolic Blood Pressure [SBP] < 90 mm Hg) and tachycardic (heart rate [HR] >108) or severely hypotensive (SBP < 70 mm Hg) without the tachycardia requirement at any period in the prehospital environment. Exclusion criteria included prisoner status, known pregnancy, isolated penetrating injury to the head, ground level fall, asystole, or cardiopulmonary resuscitation (>5 minutes) or those wearing opt-out bracelets. For the current secondary analysis, patients transferred from a referral emergency department were also excluded due to the longer prehospital times and bias associated with surviving to be transferred. The primary clinical outcome for the current analysis was 30-day mortality.

All analyses were carried out in the intention-to-treat randomized patients used in the published study who were

TABLE 2. PPV, NPV, Sensitivity and Specificity of Each Transfusion Definition for 24 Hour and 30-Day Mortality

24 Hour Mortality	CAT1hr	CAT4hr	hMT	30-Day Mortality	CAT1hr	CAT4hr	hMT
PPV	34.1	29.5	35.7	PPV	41.5	37.8	46.4
NPV	85.9	87.4	83.5	NPV	73.8	74.9	73.4
Sensitivity	54.4	68.4	37.5	Sensitivity	44.3	59.1	33.6
Specificity	72.5	57.3	82.4	Specificity	71.4	55.6	82.5

TABLE 3. Calculation of the Percentage of Patients That Died Within the Period Specified by the Transfusion Definition That Did Not Meet the Transfusion Threshold for the Associated Definition

	CAT1hr	CAT4hr	hMT
Died within transfusion definition period	17	54	80
Died within definition period without meeting transfusion threshold	11	15	50
Percent of patients that died within the definition period without meeting transfusion threshold	65%	28%	63%
Percent of patients with hemorrhagic shock cause of death who met massive transfusion definition	43%	46%	56%

transferred from the scene. We characterized multiple transfusion definitions to quantify a patient's magnitude of hemorrhage. A historical definition of massive transfusion (hMT) was defined as 10 units RBCs or greater within 24 hours of hospital arrival.[11–15] A more recently characterized critical administration threshold (CAT) was defined as ≥3 units of RBCs during any single 1-hour period.[8–10] Patients who were CAT+ were further categorized by whether they reached CAT in the first hour of arrival (CAT1hr) or in the first 4 hours (CAT4hr) of hospital arrival. The CAT periods were selected based upon the early separation of the plasma and standard care arms at 3 hours in the 24-hour survival curves of the primary study.[6] Importantly, the massive transfusion definitions were not exclusive and patients who met a respective massive transfusion definition may also meet the requirement of the other definitions. Transfusion definitions were calculated following arrival to definitive trauma care and do not include prehospital blood product transfusions provided during transport because not all patients had access to such prehospital interventions. For all deaths in the original study, a single attributable cause of death was adjudicated by the site principal investigator prospectively throughout the enrollment period of the trial.

First, patient demographics, injury severity, mechanism of injury, prehospital injury characteristics, history of antithrombotic medications, and 24-hour resuscitation requirements were described across patients satisfying the CAT1hr, CAT4hr, and hMT definitions. The sensitivity, specificity, and negative predictive values (NPV) and positive predictive values (PPVs) of each transfusion definition for predicting both 24-hour and 30-day mortalities were then determined. To compare the degree of inherent survival bias for each definition, we determined the percentage of patients that died prior to meeting the specific transfusion threshold in the time allotted for each definition (i.e., 1 hour for CAT1hr, 4 hours for CAT4hr and 24 hours for hMT). Kaplan-Meier survival analysis and log rank comparison were then performed comparing the treatment effect of prehospital plasma versus standard care on 30-day mortality stratified by those patients who met hMT, CAT1hr or CAT4hr transfusion definitions. To verify these unadjusted findings, we then performed multivariate analysis using Cox proportional-hazard regression for each transfusion definition subgroup after controlling for important and relevant confounders. Finally, survival curves of those patients who died of hemorrhagic shock, as adjudicated by site investigators, were created in attempts to characterize the early timing of death for these patients.

Regression models passed the proportional-hazards assumption on the basis of Schoenfeld residuals. The identical model was utilized for all Cox-regression analyses. The model included age, sex, Injury Severity Score (ISS), prehospital blood transfusion (yes/no), prehospital crystalloid volume (mL), prehospital systolic blood pressure (<70 mm Hg, yes/no), prehospital GCS and

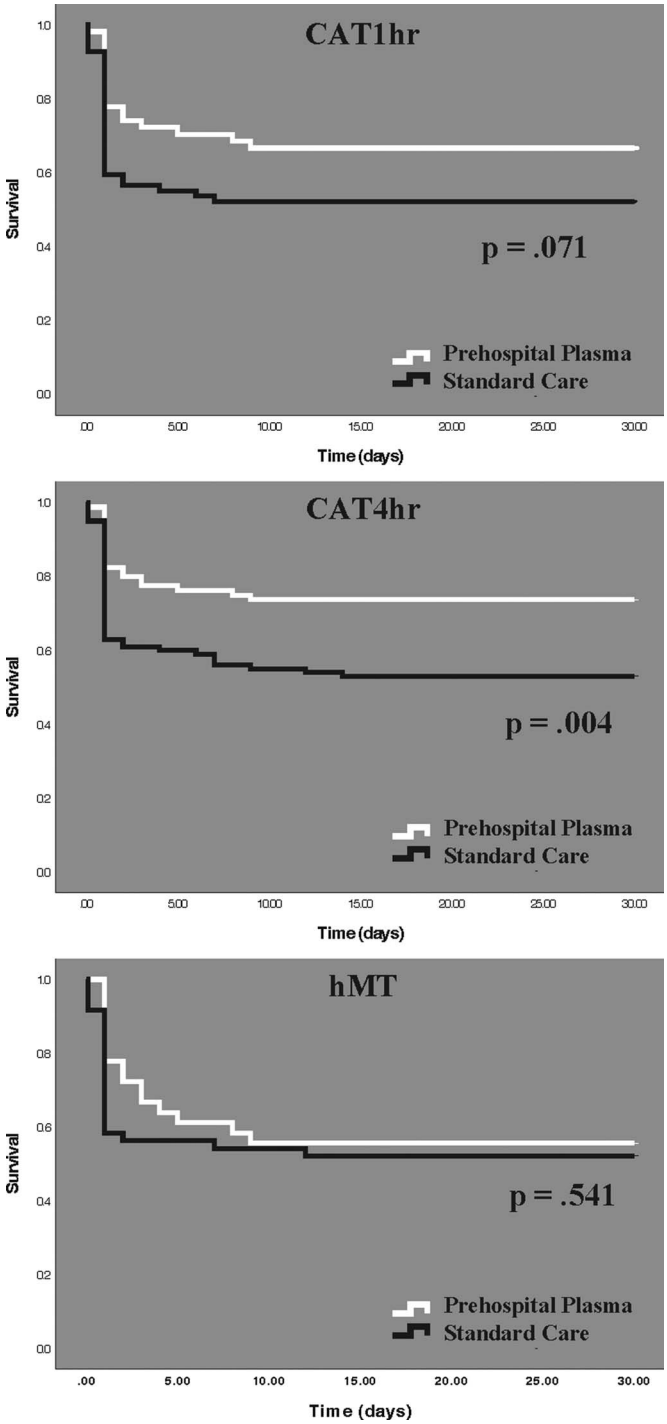

Figure 1. Kaplan Meier survival curves of 30-day mortality comparing plasma versus standard care treatment arms for patients who met the CAT1hr, CAT4hr and MT definitions.

TABLE 4. Characteristics of the Patients Who Met the CAT4hr Definition Across Prehospital Plasma and Standard Care Treatment Arms

	CAT4hr		
	Plasma (n = 81)	**Standard of Care (n = 102)**	***p***
Median age (IQR), y	42 (30–63)	38.5 (24–59.25)	0.178
Male sex, n (%)	67.9	74.5	0.969
Penetrating mechanism, n (%)	16	14.7	0.684
Median prehospital SBP (IQR), mm Hg	71 (60–83.5)	70 (60.75–80)	0.547
Median scene HR (IQR)	122 (109.25–133.75)	118 (100–129)	0.117
Prehospital time (IQR), min	41 (33.5–50.5)	38 (31–50)	0.371
Median prehospital crystalloid (IQR), mL	50 (0–1025)	950 (0–1500)	0.008*
Prehospital red cell transfusion, n (%)	26 (32.1)	53 (52.0)	0.006*
Median 24-h RBC units (IQR)	7 (5–12)	8 (5–14.25)	0.536
Median 24-h plasma units (IQR)	3 (0–7)	3 (0–9)	0.848
Median 24-h platelet units (IQR)	1 (0–2)	1 (0–2)	0.58
Median crystalloid volume (IQR), mL	6,000 (3,521–8,000)	4,900 (3,035.25–7,688.25)	0.139
ISS (IQR)	27 (17.5–39.5)	26 (17–34.5)	0.312
GCS <8, n (%)	36 (44.4)	58 (56.9)	0.202
Median AIS head (IQR)	2 (0–3)	2 (0–4)	0.382
AIS head score > 2, n (%)	30 (37.0)	47 (46.1)	0.197

Groups marked with * indicate a significant difference, $p \leq 0.05$.

mechanism of injury (penetrating vs. blunt). Robust variance estimators were used in all models to account for clustering at the center level.

Descriptive statistics were used to characterize the demographics and injury characteristics of patients for each transfusion definition. Categorical variables were presented as frequencies and percentages and tested using the χ^2 test. Continuous variables were expressed as medians and interquartile ranges (IQRs) and were tested using the *t* test or Mann-Whitney test as appropriate. Statistical significance was determined at the $p < 0.05$ level (two-sided). All data were analyzed using SPSS Inc. released 2019, version 26.0.

RESULTS

Of the original 501 patients enrolled for the primary study, 390 (78%) patients were transferred directly from the drop and a median ISS of 22 (IQR, 13–30). There was excellent randomization in the original study across plasma and standard care arms.

Of the 390 patients included in the current study, 46% received prehospital plasma and 54% received standard care, which is identical to the original study. For the current study cohort, 126 patients were positive for the CAT1hr metric, 183 patients were positive for the CAT4hr metric and 84 patients were positive for hMT metric. The overall study mortality rate for those patients who met each transfusion definition was 40.5%, 37.2%, and 46.4%, respectively. Patient demographic and injury characteristics were similar across transfusion definitions (Table 1). Patients had similar demographics, mechanism of injury, prehospital characteristics, and ISS across the different transfusion definitions. Patients who were positive for CAT1hr had the highest percentage that received prehospital cardiopulmonary resuscitation and the patients who met the hMT definition had a lower percentage of severe head injury (abbreviated injury scale for head >2). As expected, patients who met the hMT definition required higher median blood component transfusion at 24 hours due to having the largest red cell requirement of the three definitions characterized.

The ability of each definition to predict death at 24 hours and 30 days was determined by calculating the sensitivity, specificity, PPV, and NPV (Table 2). Metrics were similar at 24 hours and 30-day mortality. The CAT4hr had the highest sensitivity and NPV for both mortality time points, indicating its utility in ruling out patients at high-risk of mortality. Specificity and PPV for 24 hour and 30-day mortality were highest for the hMT metric.

In determining the potential level of survival bias inherent with each definition, the percentage of patients that died within

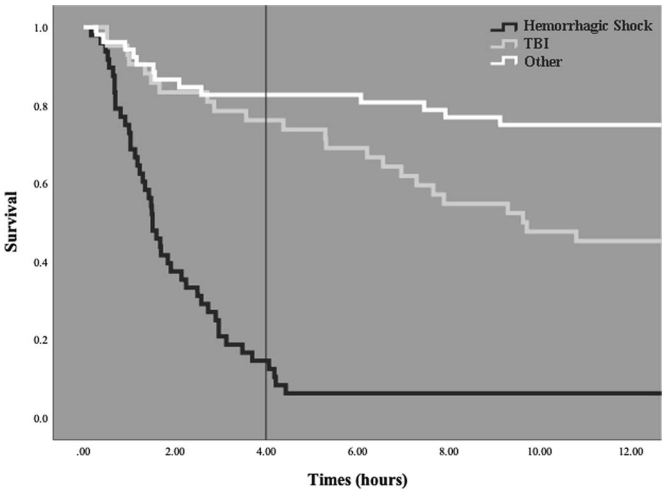

Figure 2. Kaplan Meier survival curves for 30-day mortality of patients who died from hemorrhagic shock (median time to death, 1.6 hours), TBI (median time of death, 9.3 hours) or other causes (median time to death, 60.0 hours). Time axis was set to a maximum of 12 hours to highlight early death. X-axis reference line positioned at 4 hours.

the specified period from arrival without meeting the transfusion threshold were calculated for each definition (Table 3). Of patients that died in the first hour of arrival, 65% of patients did not meet the CAT1hr transfusion threshold. Of patients that died in the first 4 hours from arrival, 28.3% of patients did not meet the CAT4hr transfusion threshold. Of the patients that died within 24 hours of arrival, 62.5% of patients did not meet the hMT transfusion threshold. These results suggest that the CAT4hr definition is associated with the lowest potential for survival bias in the current study cohort.

The three definitions were further evaluated for any association with a prehospital plasma survival benefit. Kaplan-Meier survival curves for 30-day mortality stratified into subgroups who met each transfusion definition were constructed. Prehospital plasma was associated with a significant survival benefit via log rank comparison in CAT4hr patients ($p = 0.004$) while no significant survival differences were found for patients who met CAT1hr ($p = 0.071$) or hMT ($p = 0.541$) definitions (Fig. 1).

To further characterize the CAT4hr subgroup, plasma and standard care treatment groups were compared. There were no differences in patient demographics, mechanism of injury, prehospital injury characteristics, injury severity, or 24-hour resuscitation requirements in-hospital (RBC, plasma, platelets, and crystalloid). The treatment arms demonstrated similar differences as in the original published analysis, with standard care patients being more likely to receive prehospital RBC transfusions and prehospital crystalloid infusions due to the lack of prehospital plasma capabilities and the crystalloid-based nature of the standard care treatment arm (Table 4).

To verify the unadjusted survival analysis findings for each transfusion definition subgroup, Cox-Hazard regression verified that for CAT4hr patients, prehospital plasma was associated with an independent survival benefit (HR, 0.55; 95% confidence interval [CI], 0.34–0.89; $p = 0.02$) after adjusting for all important confounders. There were no significant, independent associations with survival in the multivariate models for either the CAT1hr (HR, 0.74; 95% CI, 0.49–1.12; $p = 0.16$) or hMT (HR, 0.63; 95% CI, 0.29–1.36; $p = 0.24$) definition.

Finally, to characterize the timing of mortality and cause of death for the study cohort we plotted survival curves for those who died in the trial stratified by adjudicated cause of death. The two most common causes of death adjudicated by the respective site investigator for the study cohort were hemorrhagic shock (36%) and traumatic brain injury (31%) with the remaining resulting from a variety of less common causes (Fig. 2). While the time course of mortality for brain injury and other causes were much slower, the vast majority of deaths attributable to hemorrhagic shock occurred within the first 4 hours of enrollment, suggesting the benefit of using the CAT4hr definition in the current pragmatic, prehospital enrolled clinical trial.

DISCUSSION

Over the last two decades, trauma resuscitation has changed dramatically with the most current attention being placed on initiating the principles of damage-control resuscitation during the earliest phase of care, as close to the time of injury as feasible.[16–20] Prehospital interventions, such as plasma, have been shown to be safe and beneficial in those patients transported via air medical transport with typical longer transport times.[6,21] The importance of tailoring these types of early resuscitation practices to those patients who receive the greatest benefit is essential.

Massive transfusion was historically defined as receiving 10 or greater units of red cells over an initial 24-hour period. The original studies which demonstrated benefit of early "hemostatic resuscitation" or high fresh frozen plasma / packed red blood cell (FFP/PRBC) transfusion ratios utilized this historic massive transfusion (hMT) definition.[12,14] The limitations of using this definition and the retrospective nature of the preliminary studies resulted in the potential for survival bias. More appropriate prospective studies which mitigated the risk of bias and randomized trials were subsequently performed verifying the benefits of damage-control resuscitation.[4,22–24]

During this same period, more novel transfusion definitions have been characterized which maintain mortality prediction capabilities with limited risk of bias by incorporating both a rate and volume of transfusion that can be measured in shorter windows of time.[8–10,25] The CAT transfusion definition within 1-hour of arrival has been recently validated using data from a recent prospective randomized trial which focused on early hemostatic resuscitation.[26] Those results validated the utility of positive CAT at 1-hour and the ability of this transfusion metric to predict early mortality as compared to the hMT definition. This prior analysis also demonstrated a high sensitivity of the CAT at 1-hour definition and the relative lower specificity for early mortality.

The results of the current analysis not only confirm the ability of the CAT transfusion metric to define a cohort of injured patients at high risk of mortality from hemorrhagic shock but also provide insight into the most appropriate time window to be utilized for a prehospital trial which focuses on hemorrhagic shock. The CAT4hr definition included the largest number of enrolled patients as compared with the other transfusion definitions and represents a time window where the majority of hemorrhagic deaths occur for the current study. The CAT4hr metric also had the lowest percentage of patients who died not meeting the transfusion threshold, suggesting the lowest potential for survival bias. The sensitivity of the CAT4hr definition was the highest of the three metrics demonstrating that those who do not meet the transfusion definition are unlikely to suffer mortality. The CAT4hr metric correspondingly also had the lowest specificity, suggesting that not all patients who meet the transfusion metric will actually suffer mortality. Of most interest, the current analysis suggests that the CAT4hr definition subgroup is independently associated with a prehospital plasma survival benefit. This likely results from including the largest population of patients defined by the transfusion metric relative to the other definitions, by minimizing those patients who die prior to meeting the transfusion threshold, while maintaining the mortality prediction capability. The larger population who met the CAT4hr metric provides the survival analysis more power to detect significant differences when prehospital plasma was analyzed. Prior studies using the PAMPer study cohort have demonstrated no significant prehospital plasma benefit in patients who required massive transfusion.[7] The current results

suggest that how massive transfusion is defined may be important when determining intervention benefits in hemorrhagic shock trials.

The CAT1hr definition had a lower sensitivity and much higher specificity but the short time window was associated with a 65% rate of patients dying without meeting the CAT threshold. This suggests that the timing of mortality in the current prehospital enrolled study may be somewhat delayed or the transfusion rate was somewhat slower relative to prior studies which have previously characterized the CAT transfusion metric in the first hour.[26] This may be due to utilization of different inclusion criteria relative to prior studies or enrollment in the prehospital setting using pragmatic vital sign criteria alone. The hMT definition similarly described a cohort with a high percentage of patients dying prior to reaching the transfusion threshold, yet hMT metric had the highest specificity for 24 hour and 30-day mortality due to the large volume transfusion requirement inherent with its definition.

The most robust transfusion metric that has both a high prediction of mortality and negates all limitations including survivor and collider bias may be difficult to find. It may be that the most appropriate definition of massive transfusion for a specific study may vary based upon the inclusion criteria, the environment of enrollment and magnitude of hemorrhage the cohort suffers. The current analysis would suggest that the CAT definition represents the correct volume of transfusion with appropriate mortality prediction capabilities but the time window which it is measured may need to be tailored to the individual study.

The current study does have limitations. It is a secondary analysis which was not prespecified in the initial protocol of the primary study, and data were not specifically recorded to answer the hypotheses proposed. The study was not specifically powered to appropriately characterize large volume transfusion definitions and the regression results for subgroup analysis may demonstrate survival association with larger patient populations. There remains a significant risk of survivor and collider biases as the study is looking at variables which occur (in-hospital transfusion) following randomization of prehospital plasma. The results of the prehospital plasma relationships described should only be considered hypothesis generating. Patients on specific helicopters had access to prehospital red cell transfusions which may alter the results and conclusions formulated. As all patients did not have prehospital red cells, these were not included in the transfusion totals used for each massive transfusion definition. Although we controlled for relevant differences via a robust statistical approach in our multivariate models, the potential of residual confounding exists. The cohorts described by the respective massive transfusion definitions were not mutually exclusive and patients who met the CAT1hr may also have met the CAT4hr or hMT definitions. The current analysis represents only patients when transferred directly from the scene. Alternative results may be demonstrated in study cohorts that include both interfacility transfers as well as scene patients. The most robust-specific transfusion definition utilized by other trials may vary by the inclusion criteria used, the environment of enrollment, the magnitude of hemorrhage, and the specific injury characteristics of patients enrolled. Although no patients received whole blood in the current clinical trial, whole blood resuscitation is becoming more common in busy trauma centers across the country. Counting a whole blood unit as a single red cell unit may alter the relationships of massive transfusion definitions and attributable mortality outcomes.

In conclusion, the CAT metric represents a robust rate and volume transfusion definition that has consistently demonstrated excellent hemorrhage related mortality prediction with minimization of survival bias. The specific definition used for massive transfusion in a pragmatic, prehospital interventional trial has important implications and can alter mortality associations. A positive CAT in the first 4 hours after arrival in the current study cohort encompasses the majority of patients who suffer mortality due to hemorrhagic shock and is independently associated with a prehospital plasma survival benefit.

AUTHORSHIP

All authors meet authorship criteria for this article as described below. All authors have seen and approved the final manuscript as submitted. The first author (E.S.S.) had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. E.S.S., J.L.S., F.X.G., J.B.B. participated in the conception and design. E.S.S., J.L.S., F.X.G., J.B.B., B.J.D., R.S.M., B.G.H., J.A.C., H.A.P. participated in the acquisition of data. E.S.S., J.L.S., F.X.G., J.B.B. participated in the analysis and interpretation of data. All authors participated in the article preparation and editing.

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DISCLOSURE

The authors declare no conflicts of interest.

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CRITIQUE

JOHN A. HARVIN, MD, MS, FACS: The work Sim and colleagues again illustrates the severe limitations of the "historic" definition of massive transfusion (hMT). Massive transfusion is an important concept as it aids in performance improvement and, ideally, might provide some real-time prognostic information as we treat the sickest of our patients. That the already validated Critical Administration Threshold (CAT) and the proposed CAT4hr were superior to hMT was unsurprising. Not only does hMT have the largest survivor bias of all definitions, it also lacks clinical importance and is antiquated in light of the advances made in hemostatic resuscitation over the previous two decades.

However, like CAT and hMT, the proposed CAT4hr also fails to reflect current transfusion practices. The three definitions fail to account for prehospital transfusions. The current study was a post hoc secondary analysis of the Prehospital Air Medical Plasma (PAMPer) Trial, which revealed improved survival in patients receiving prehospital plasma. Prehospital transfusion are now commonplace and must be included.

Additionally, these three definitions continue counting only packed red blood cells. The transfusion of high ratios of red blood cells to plasma to platelets is now considered standard of care in the management of hemorrhagic shock. Additionally, as supported by PAMPer, early transfusion of plasma and platelets are common. This is a stark difference than the days when red blood cells were given exclusively until coagulopathy developed and then plasma administered. Moreover, in light of its benefits in the military setting, whole blood is now gaining popularity in civilian trauma. Plasma, platelets, whole blood, and, potentially, crystalloid and colloid would be included in the ideal definition of massive transfusion making it nimble between different center transfusion practices.

In summary, the CAT4hr proposed by Sim and colleagues is a novel new definition of massive transfusion. It, and CAT, are improvements over the arbitrary and antiquated hMT as they could be used in real time and limit survivor bias. However, the CAT4hr continues to suffer the same limitations that an ideal definition needs to overcome, namely the accounting of prehospital transfusions and the inclusion of resuscitation volumes other than red blood cells.