An Evaluation of the Impact of Apheresis Platelets Used in the Setting of Massively Transfused Trauma Patients

Jeremy G. Perkins, MD, Cap P. Andrew, MD, PhD, Philip C. Spinella, MD, Lorne H. Blackbourne, MD, Kurt W. Grathwohl, MD, Thomas B. Repine, MD, Lloyd Ketchum, MD, Paige Waterman, MD, Ruth E. Lee, Alec C. Beekley, MD, James A. Sebesta, MD, Andrew F. Shorr, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

Introduction: Trauma is a major cause of morbidity and mortality worldwide. Of patients arriving to trauma centers, patients requiring massive transfusion (MT, ≥10 units in 24 hours) are a small patient subset but are at the highest risk of mortality. Transfusion of appropriate ratios of blood products to such patients has recently been an area of interest to both the civilian and military medical community. Plasma is increasingly recognized as a critical component, though less is known about appropriate ratios of platelets. Combat casualties managed at the busiest combat hospital in Iraq provided an opportunity to examine this question.

Methods: In-patient records for 8,618 trauma casualties treated at the military hospital in Baghdad more than a 3-year interval between January 2004 and December 2006 were retrospectively reviewed and pa-

tients requiring MT (n = 694) were identified. Patients who required MT in the first 24 hours and did not receive fresh whole blood were divided into study groups defined by source of platelets: (1) patient receiving a low ratio of platelets (<1:16 apheresis platelets per stored red cell unit, aPLT:RBC) (n = 214), (2) patients receiving a medium ratio of platelets (1:16 to <1:8 aPLT:RBC) (n = 154), and (3) patients receiving a high ratio of platelets (≥1:8 aPLT:RBC) (n = 96). The primary endpoint was survival at 24 hours and at 30 days.

Results: At 24 hours, patients receiving a high ratio of platelets had higher survival (95%) as compared with patients receiving a medium ratio (87%) and patients receiving the lowest ratio of platelets (64%) (log-rank *p* = 0.04 and *p* < 0.001, respectively). The survival benefit for the

high and medium ratio groups remained at 30 days as compared with those receiving the lowest ratio of platelets (75% and 60% vs. 43%, *p* < 0.001 for both comparisons). On multivariate regression, plasma:RBC ratios and aPLT:RBC were both independently associated with improved survival at 24 hours and at 30 days.

Conclusion: Transfusion of a ratio of ≥1:8 aPLT:RBC is associated with improved survival at 24 hours and at 30 days in combat casualties requiring a MT within 24 hours of injury. Although prospective study is needed to confirm this finding, MT protocols outside of investigational research should consider incorporation of appropriate ratios of both plasma and platelets.

Key Words: Apheresis platelets, Penetrating injury, Component therapy, Massive transfusion, Combat trauma.

J Trauma. 2009;66:S77–S85.

Trauma is a the leading cause of death and disability in adults worldwide.[1] The vast majority of reversible death is due to hemorrhage, which tends to occur within 6 to 24 hours after injury.[2–6] Transfusion of blood is critical in managing hemorrhage and 1% to 3% of civilian trauma admissions[7,8] may require massive transfusion (MT), commonly defined as 10 units of blood within 24 hours.[9] Injured patients

frequently manifest coagulopathy on admission and this has been associated with increased mortality.[10–12] Management of trauma-related coagulopathy in part includes transfusion of coagulation factors and platelets,[13] though optimal transfusion strategies remain poorly understood. Appropriate plasma to red blood cell (RBC) ratios has been identified as a critical component in managing massively transfused patients,[14–18] though fewer data exist regarding the appropriate ratios for platelets.[19,20]

At the US Army's Combat Support Hospital (CSH) in Baghdad, Iraq, stored RBCs, fresh frozen plasma (FFP), and cryoprecipitate (cryo) were routinely available to treat casualties requiring massive resuscitation. In November 2004, the CSH obtained apheresis machines allowing for collection and use of apheresis platelets (aPLT) in the management of casualties. The availability of such aPLT offered an opportunity to examine the outcomes of massively transfused combat casualties related to different platelet to RBC ratios.

PATIENTS AND METHODS
Patients

We performed a retrospective review of trauma patients admitted to the CSH located at Ibn Sina Hospital in Baghdad, Iraq between January 2004 and December 2006. Patients who received a MT defined as 10 or more units of blood within 24

	Form Approved
# Report Documentation Page	OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 APR 2009	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
An evaluation of the impact of apheresis platelets used in the setting of massively transfused trauma patients	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)	5d. PROJECT NUMBER
Perkins J. G., Cap A. P., Spinella P. C., Blackbourne L. H., Grathwohl K. W., Repine T. B., Ketchum L., Waterman P., Lee R. E., Beekley A. C., Sebesta J. A., Shorr A. F., Wade C. E., Holcomb J. B.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234	

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**	**UU**	**9**	

hours were identified. Patients who were treated initially at forward surgical units/local hospitals before transfer to Ibn Sina Hospital, or who received their MT as a complication during their hospital course/not on the day of their admission (e.g., after the first 24 hours as with an excision/grafting of burns, or for gastrointestinal bleeding) were excluded from analysis. Because of difficulty comparing the equivalence of platelets from fresh whole blood to those receiving aPLT, patients receiving fresh whole blood were also excluded from the analysis.

Three groups of patients were defined and evaluated: (1) patient receiving a low ratio of platelets (<1:16 apheresis platelets per stored red cell unit, aPLT:RBC), (2) patients receiving a medium ratio of platelets (1:16 to <1:8 aPLT: RBC), and (3) patients receiving a high ratio of platelets (≥1:8 aPLT:RBC). We chose ≥1:8 aPLT:RBC as the high platelet ratio group based on previously published data with survivors receiving 1:7.7 apheresis units:RBC as compared with nonsurvivors (1:11.9).[20] The primary endpoint was survival at 24 hours and at 30 days. Stored blood products (RBCs, FFP, and cryo) were obtained almost exclusively from the United States through the Armed Services Blood Program. aPLT were collected using the Hemonectics' Component Collection System (Braintree, MA) from healthy donors at the hospital, and a MT protocol was in place for the hospital to guide resuscitation.[21]

Data Sources

The data presented here were obtained under a human use protocol that received Institutional Review Board approval through the Department of Clinical Investigation at Brooke Army Medical Center in San Antonio, TX. Theater transfusion records maintained within the Department of Defense Armed Services Blood Program Office database in Falls Church, VA were used to identify massively transfused patients and individual blood products. The Joint Theater Trauma Registry (JTTR) maintained at the US Army Institute for Surgical Research at Ft. Sam Houston in San Antonio, TX was used to determine baseline patient demographics and determine outcomes for evacuated patients. For United States military casualties discharged from the hospital before 30 days, out-patient visits were noted in the joint patient tracking application, which provides information on location and status of soldiers near real time through a web-based application. Mortality and dates of death were cross referenced with Social Security Death Index records and listing of casualties provided on the online website Iraq Coalition Casualty Count (www.icasualties.org).

Individual patient chart review was performed on in-patient records to verify vitals, laboratory reports, blood product transfusions, and outcomes before evacuation or transfer from the CSH. Such charts were viewed directly or by using the Patient Administration Systems and Biostatistics Activity system, which receives all in-patient records from deployed medical units. Blood product usage and timing of blood product administration were identified from the chart, and were compared against the JTTR and the ASBPO Blood Bank transfusion record. Discrepancies were reconciled by comparing the times recorded on blood transfusion slips, anesthesia records, intensive care unit records, operative reports, and discharge summaries. Most discrepancies occurred in the context of missing/incomplete blood transfusion slips, double counting of carbon copies of blood transfusion slips, misdocumentation of blood products (e.g., RBCs recorded as FFP, or FFP recorded as RBCs), inaccurate documentation on anesthesia records, or failure to attribute emergency release blood products to the specific recipient by the blood bank. The comparison of multiple databases with correlation to the patient record represents the most accurate and complete dataset possible.

Data Collection

After identification, patient charts were evaluated for age, gender, admission vital signs, Glasgow Coma Scale, admission laboratory tests, mechanism of injury, documented injuries, 24 hour blood product administration (RBC, FFP, cryo, and aPLT), and recombinant factor VIIa (rFVIIa) administration and dosage. Plasma ratios (%) were calculated as (FFP/RBC) × 100. Apheresis platelet ratios (%) were calculated as (aPLT/RBC) × 100. Revised Trauma Scores (RTS) were calculated using admission vitals signs.[22] Abbreviated injury scales and Injury Severity Scores (ISS) were centrally scored and calculated by trained research nurses and staff using ISS-98 after patient discharge.[23] Trauma and Injury Severity Scores were calculated using age, mechanism of injury, RTS, and ISS-98.[24]

The primary outcomes evaluated were survival at 24 hours and at 30 days. US soldiers were tracked for survival as they reached higher echelons of care. Iraqi casualties who were discharged before 30 days were generally lost to follow-up unless they were seen as out-patients in follow-up or were readmitted to the combat hospital. Secondary outcomes, including causes of death from central nervous system injury, exsanguination, airway failure, multisystem organ failure (in patients surviving >24 hours), and arterial or venous embolism were evaluated using the JTTR and available in-patient records from Ibn Sina Hospital, US military hospitals in Germany, and US military hospitals in the continental US.

Statistical Analysis

Baseline characteristics, blood product transfusion, rFVIIa usage, and survival at 24 hours and at 30 days were compared between patient groups. Data were evaluated for normality using Kolmogorov-Smirnov, Shapiro-Wilk, and normality plots. Analysis of variance was used to compare parametric data between groups. Kruskal-Wallis and pairwise Mann-Whitney U was used to compare nonparametric data between groups. Pearson χ^2 was used to compare dichotomous variables between groups. Kaplan-meier log-rank was used to

```
┌─────────────────────────────────────────────────────┐
│        Time Period: January 2004 – December 2006      │
└─────────────────────────────────────────────────────┘
                          ↓
┌─────────────────────────────────────────────────────┐
│           8,618 Trauma Patients Arrived at CSH         │
└─────────────────────────────────────────────────────┘
                          ↓
┌─────────────────────────────────────────────────────┐
│        2,024 (23%) Received Blood Transfusions         │
└─────────────────────────────────────────────────────┘
                          ↓
┌─────────────────────────────────────────────────────┐
│  694 (8.1%) Received ≥ 10 u Blood (RBC + FWB) in 24 hours │
└─────────────────────────────────────────────────────┘
                          │→ ┌──────────────────────────────────────┐
                          │   │ 18 MT occurred during hospital course, not on │
                          │   │ admission                             │
                          │   │                                       │
                          │   │ 84 treated at forward surgical teams/hospitals │
                          │   │ prior to transfer to CSH              │
                          │   │                                       │
                          │   │ 128 received fresh whole blood        │
                          │   └──────────────────────────────────────┘
                          ↓
┌─────────────────────────────────────────────────────┐
│            462 charts reviewed for analysis            │
└─────────────────────────────────────────────────────┘
```

214 received <1:16 units of apheresis platelets per RBC unit (Low Platelet Ratio)	154 received from 1:16 to <1:8 units of apheresis platelets per RBC unit (Medium Platelet Ratio)	96 received ≥1:8 units of apheresis platelets per RBC unit (High Platelet Ratio)

CSH = Combat Support Hospital, RBC = red blood cell, MT = massive transfusion
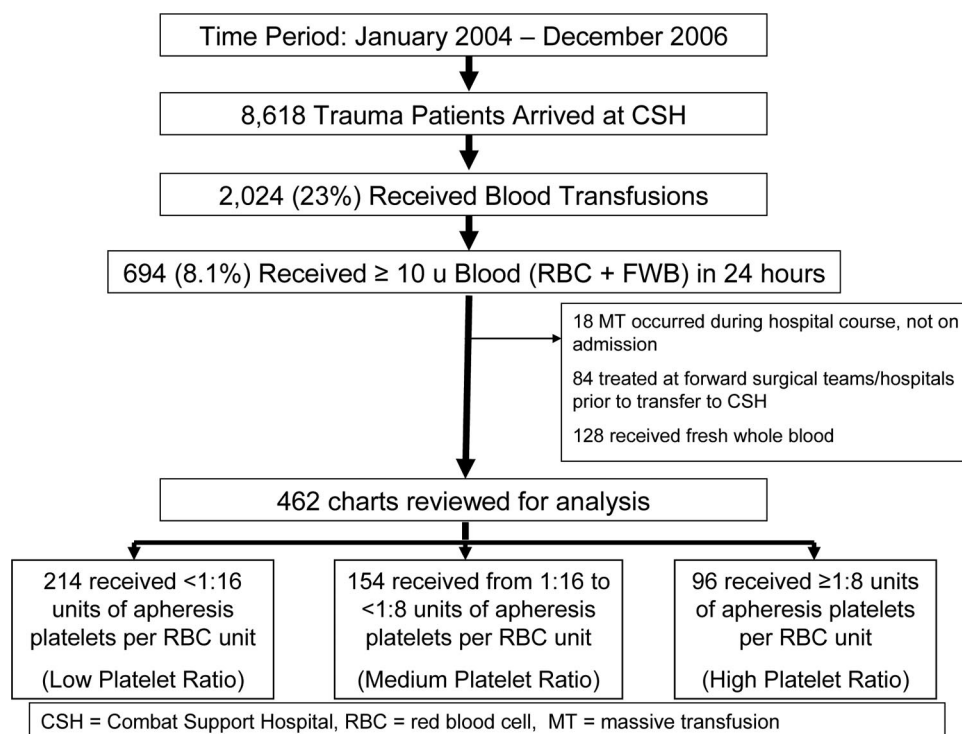
Fig. 1. *Flow chart of all trauma patients admitted to the combat hospital between January 2004 and December 2006.*

compare groups for survival at 24 hours and at 30 days. Continuous data are presented as median (range) for nonparametric data or mean (SD) for parametric data, as indicated. Statistical significance was set at a p £0.05 for all group comparisons.

To adjust for potential confounders, we used multivariable logistic-regression analysis of 24-hour survival and Cox-proportional hazards model of 30-day survival for baseline variables, excluding variables subsumed within other variables (e.g., systolic blood pressure, respiratory rate, and Glasgow Coma Scale are used to calculate RTS). Variables with $p < 0.1$ on univariate analysis were included in the multivariate analyses. To control for confounding, a propensity score was calculated from a logistic regression as the probability of receiving a platelets given variables that would influence the decision to administer platelets (abbreviated injury severity by body region, admission temperature, admission platelet count, admission systolic blood pressure, admission international normalized ratio (INR), admission base deficit, RBC units given over 24 hours, FFP units given over 24 hours, the plasma ratio in first 24 hours, and rFVIIa dosage over 24 hours). This logistic regression model for propensity to administer platelets had a receiver operating characteristic area under the curve = 0.91. This propensity score was then forced into the logistic and Cox-proportional hazards models for survival to adjust for confounding. Regressions were also performed without the propensity score and relationships between variables were unaffected (data not shown). Statistical analysis was performed with SPSS 15.0 (Chicago, IL).

RESULTS

Over the 36-month period between January 2004 and December 2006, the CSH received 8,618 patients with traumatic injuries, of which 2,024 (23%) were transfused with 694 (8.1%) identified as having received 10 or more units of RBCs within 24 hours at the hospital (Fig. 1). On review of in-patient records, 230 patients were excluded from the analysis: 18 patients had a MT during their hospital course and not within 24 hours of admission (e.g., during excision and grafting of burns, or gastrointestinal bleeding), 84 patients were treated at forward surgical teams or local hospitals before transfer to the combat hospital, and 128 patients received fresh whole blood. Of the remaining 462 patients, 214 patients received <1:16 aPLT:RBC (low platelet ratio group), 154 patients received between 1:16 to <1:8 aPLT:RBC (medium platelet ratio group), and 96 patients received ≥1:8 aPLT:RBC (high platelet ratio group).

Characteristics of the Patients

The three groups were similar (Table 1) on the basis of admission demographics, ISS, RTS, vital signs, and admission laboratory studies. The patients were primarily young (median age, 27–28), male (>95%), with median ISS 20 to 21, and the vast majority had a penetrating mechanism of injury (>90%). There were no differences between groups for admission vitals, or admission laboratories with groups tending to be acidotic (median pH, 7.24–7.25, median base deficit of 7–8 mEq/L), slightly anemic (median hemoglobin, 11.1–11.4 g/dL), and with median INR of 1.4 to 1.5. There

Table 1 Baseline Characteristics of Massively Transfused Patients by Platelet Ratio Group*

Characteristic	Low Platelet Ratio (N = 214)	Medium Platelet Ratio (N = 154)	High Platelet Ratio (N = 96)	$p^\dagger$
Age (yr)	28.7 (±9.1)	27.0 (±7.1)	28.2 (±7.4)	NS
Gender (male)	213/214 (99.5%)	149/154 (96.8%)	92/96 (95.8%)	NS
Weight (kg)	80.0 (±13.3)	77.6 (±11.2)	81.5 (±12.7)	NS
Injury severity score	20 (9–75)	21 (9–75)	21 (9–75)	NS
Revised trauma score	7.00 (0–7.84)	7.11 (0–7.84)	7.11 (0–7.84)	NS
TRISS probability	95% (0.8–99%)	96% (0.4–99%)	96% (0.1–99%)	NS
Penetrating mechanism of injury	93.0%	94.1%	91.7%	NS
Admission vitals				
Heart rate (beats/min)	115 (±32)	117 (±25)	119 (±26)	NS
Systolic blood pressure (mm Hg)	98 (±40)	100 (±31)	102 (±34)	NS
Temperature (°C)	36.2 (±1.3)	36.2 (±1.2)	36.4 (±1.2)	NS
Glasgow Coma Score	11.6 (±4.7)	12.4 (±3.9)	12.5 (±3.8)	NS
Admission labs				
pH	7.24 (6.56–7.55)	7.25 (6.76–7.52)	7.24 (6.67–7.49)	NS
Base deficit (mEq/L)	7 (0–30)	7 (0–30)	8 (0–30)	NS
Hemoglobin (g/dL)	11.1 (±2.9)	11.1 (±2.6)	11.4 (±2.2)	NS
Platelet count (1000/mm^3)	261 (±127)	272 (±102)	255 (±101)	NS
INR	1.4 (0.5–10.0)	1.4 (0.5–8.0)	1.5 (0.5–8.0)	NS

* Low ratio, <1:16 apheresis platelets/red cell units; medium ratio, 1:16 to <1:8, high ratio, ≥1:8. Data are expressed as median (range), mean (±SD), or %.
† Parametric data compared using ANOVA, nonparametric data compared Kruskal-Wallis, and dichotomous variables compared using Pearson's χ^2.
TRISS, Trauma and Injury Severity Score; INR, international normalized ratio.

Table 2 Resuscitation Management of Massively Transfused Patients in First 24 Hours by Platelet Ratio Group*

Resuscitation Product	Low Platelet Ratio (N=214)	Medium Platelet Ratio (N=154)	High Platelet Ratio (N=96)	$p^\dagger$
Transfusion products				
Stored red blood cell units	14 (10–56)[a,b]	17 (10–58)[a,c]	20 (10–54)[b,c]	<0.001
Apheresis platelet units	0 (0–3)[a,b]	2 (1–6)[a,c]	3 (2–9)[b,c]	<0.001
Fresh frozen plasma units	7 (0–37)[a,b]	12 (4–32)[a,c]	14 (4–42)[b,c]	<0.001
Plasma ratio‡	49% (±32%)[a,b]	71% (±24%)[a]	74% (±22%)[b]	<0.001
Cryoprecipitate units	0 (0–38)[a,b]	10 (0–52)[a]	10 (0–50)[b]	<0.001
Recombinant factor VIIa				
No. patients/total No. patients (%)	96/207 (46.4%)[a,b]	94/151 (62.3%)[a,c]	75/75 (78.1%)[b,c]	<0.001
Dose (mg) when given	7.2 (2.4–21.6)[a]	7.2 (2.4–28.8)[b]	9.6 (2.4–36.0)[a,b]	<0.001

* Low ratio, <1:16 apheresis platelets/red cell units; medium ratio, 1:16 to <1:8, high ratio ≥1:8. Data are expressed as median (range) or %.
† p value shown is for group comparisons, values with same superscripts (a, b, and c) are different from one another on pairwise comparison ($p < 0.05$), nonparametric data compared using Kruskal-Wallis/Mann-Whitney U and dichotomous variables compared using Pearson's chi square.
‡ Plasma ratio = (fresh frozen plasma/stored red cell units) × 100.

were multiple differences between groups regarding resuscitation management (Table 2), but in general the low platelet ratio group received the fewest stored RBC, FFP, aPLT, and cryo units as well as the lowest FFP:RBC ratio as compared with the medium and high platelet ratio groups ($p < 0.001$ for all pairwise comparisons). The high platelet ratio group received more RBC, FFP, and aPLT as compared with the medium platelet ratio group ($p = 0.02$, 0.01, and <0.001 for pairwise comparisons respectively), though these two groups received similar plasma ratios and cryo units. All groups differed from one another with respect to rFVIIa administration with 78%, 62%, and 46% of patients receiving rFVIIa in the high, medium, and low platelet ratio groups, respectively

($p < 0.01$ for all pairwise comparisons). When administered, the dose of rFVIIa was highest in the high platelet ratio group (median, 9.6 mg) as compared with both the low and medium platelet ratio groups (both with median of 7.2 mg, and $p < 0.001$ and $p = 0.02$ for pairwise comparisons versus the high platelet ratio group, respectively).

Outcomes

The primary outcome of survival (Table 3) at 24 hours was 64%, 87%, and 95% in the low, medium, and high platelet ratio groups, respectively (χ^2, $p < 0.001$ for low versus medium and high platelet ratio group comparisons, χ^2, $p = 0.04$ for medium versus high platelet ratio group com-

Table 3 Outcomes of Massively Transfused Patients by Platelet Ratio Group*

	Low Platelet Ratio (N=214)	Medium Platelet Ratio (N=154)	High Platelet Ratio (N=96)	$p^\dagger$
Survival				
24-h survival	134/209 (64.1%)[a,b]	131/151 (86.8%)[a,c]	91/96 (94.8%)[b,c]	<0.001
30-day survival	64/150 (42.7%)[a,b]	51/85 (60.0%)[a]	45/60 (75%)[b]	<0.001
Time to death (h), median (range)	2.3 (0.5–505)[a,b]	7.6 (1.2–441)[a]	80.2 (2.6–325)[b]	<0.001
Cause of death				
Exsanguination	60/210 (28.6%)[a,b]	13/151 (8.6%)[a,c]	2/96 (2.1%)[b,c]	<0.001
CNS death	14/210 (6.7%)	4/151 (2.6%)	3/96 (3.1%)	NS
Multiorgan failure syndrome[‡]	6/134 (4.5%)	12/131 (9.2%)	9/91 (9.9%)	NS
Airway	2/210 (1.0%)	3/151 (2.0%)	1/96 (1.0%)	NS
Venous/arterial embolism	1/210 (0.5%)	0/151 (0.0%)	0/96 (0.0%)	NS
Death other	3/210 (1.4%)	2/151 (1.3%)	0/96 (0.0%)	NS

* Low ratio, <1:16 apheresis platelets/red cell units; medium ratio, 1:16 to <1:8; high ratio ≥1:8. Data are expressed as number (%), percentages may not total 100 because of rounding.

[†] p value shown is for group comparisons, values with same superscripts (a, b, and c) are different from one another on pairwise comparison ($p < 0.05$), compared using χ^2.

[‡] Multiorgan failure deaths examined specifically in patients living ≥24 h from admission.
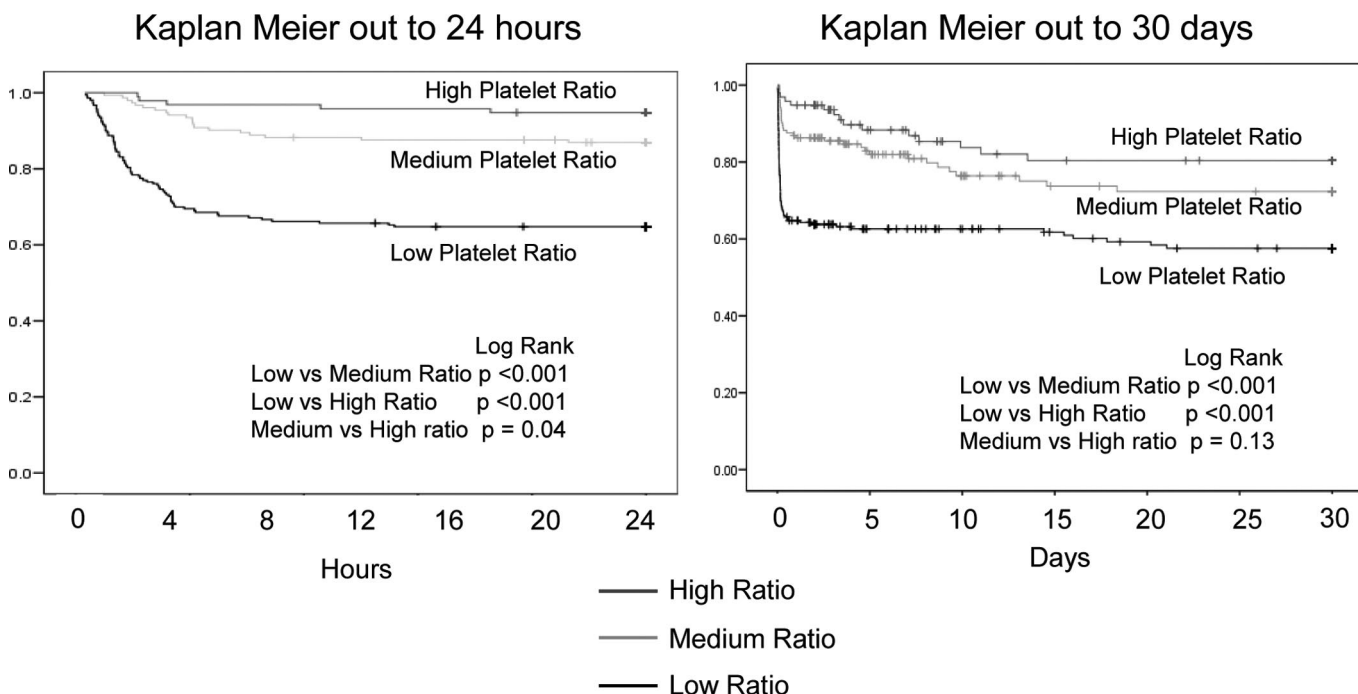
CNS, central nervous system.

Fig. 2. *Twenty-four hours and 30-day survival curves by platelet ratio group.*

parisons), and most deaths in the first 24 hours occurred within 6 hours of admission (Fig. 2). Differences in 30-day survival between the low platelet ratio (42.7%) group as compared with the medium (60%) and high platelet ratio (75%) groups remained highly significant ($p < 0.001$ log-rank for both comparison). Because of the number of patients lost to follow-up, the difference in 30-day survival between the medium and high platelet ratio groups could not be established (Log-rank, $p = 0.13$).

Regarding secondary outcomes, the median time to death was shorter in the low platelet ratio group (2.3 hours) as compared with the medium (7.6 hours) and high (80.2 hours)

platelet ratio groups ($p < 0.001$ both comparisons). Exsanguination represented 28.6%, 8.6%, and 2.1% of the causes of death in the low, medium, and high platelet ratio groups, respectively, ($p < 0.001$ for low versus medium and high platelet ratio group comparisons, $p = 0.04$ for medium versus high platelet ratio group comparisons). Other causes of death to include central nervous system, multiorgan failure syndrome, airway failure, and embolism were similar between groups.

Because of differences in the resuscitation management, a univariate regression analysis of variables was performed examining mortality at 24 hours and 30 days (Table 4).

Table 4 **Univariate Regression of Variables Associated With Mortality at 24 h and 30 Days**

Variable	24-h Survival		30-Day Survival	
	OR (95% CI)*	$p^\dagger$	HR (95% CI)*	$p^\ddagger$
Demographics-trauma scores				
Age	0.99 (0.96–1.02)	0.41	1.00 (0.98–1.02)	0.79
Gender	0.65 (0.16–2.55)	0.54	0.56 (0.23–1.36)	0.20
Weight	0.99 (0.97–1.01)	0.23	0.99 (0.98–1.01)	0.33
Blunt mechanism of injury	1.97 (0.92–4.24)	0.08	1.45 (0.80–2.62)	0.22
Injury severity score	1.06 (1.04–1.08)	<0.001	1.04 (1.03–1.05)	<0.001
Revised trauma score	0.55 (0.48–0.64)	<0.001	0.67 (0.63–0.72)	<0.001
Vitals-laboratory tests				
Heart rate (beats/min)	1.00 (0.99–1.01)	0.66	1.00 (0.99–1.01)	0.72
Temperature (°C)	0.76 (0.63–0.92)	0.01	0.88 (0.76–1.01)	0.08
Hemoglobin (g/dL)	0.82 (0.75–0.90)	<0.001	0.90 (0.85–0.97)	0.003
Platelet count (1000/mm³)	0.99 (0.99–0.997)	<0.001	0.996 (0.994–0.998)	<0.001
Base deficit (mEq/L)	1.13 (1.09–1.17)	<0.001	1.08 (1.06–1.11)	<0.001
INR§	1.88 (1.47–2.42)	<0.001	1.39 (1.27–1.53)	<0.001
Blood components and rFVIIa§				
Stored red blood cell units	1.04 (1.02–1.07)	<0.001	1.02 (1.01–1.04)	0.001
Cryoprecipitate units	0.96 (0.93–0.99)	0.01	0.97 (0.95–0.996)	0.02
Plasma ratio (%)	0.95 (0.94–0.96)	<0.001	0.97 (0.97–0.98)	<0.001
Apheresis platelet ratio (%)	0.88 (0.84–0.92)	<0.001	0.93 (0.91–0.96)	<0.001
rFVIIa dose§	0.98 (0.95–1.02)	0.40	1.01 (0.98–1.03)	0.59

* Odds/hazard ratio >1 denotes increased mortality, <1 denotes decreased mortality.
† Survival at 24 h compared using logistic regression.
‡ Survival at 30 d compared using Cox-proportional hazards regression.
§ INR, international normalized ratio; rFVIIa, recombinant factor VIIa.

Table 5 **Multivariate Regression of Variables associated with Mortality at 24 h and 30 Days**

Variable	Multivariate Regression at 24 h*		Multivariate Regression at 30 d*	
	OR (95% CI)†	$p^\ddagger$	HR (95% CI)†	$p^\S$
Injury severity score	1.10 (1.05–1.15)	<0.001	1.06 (1.04–1.08)	<0.001
INR	1.71 (1.07–2.74)	0.04	1.16 (1.01–1.32)	0.03
Plasma ratio (%)	0.94 (0.91–0.96)	<0.001	0.98 (0.97–0.99)	0.01
Apheresis platelet ratio (%)	0.82 (0.72–0.93)	0.002	0.91 (0.86–0.95)	<0.001
Revised trauma score	0.80 (0.60–1.07)	0.138	0.81 (0.72–0.91)	<0.001
Cryoprecipitate units	0.93 (0.87–0.997)	0.04	0.97 (0.94–1.003)	0.07
Stored red blood cell units	1.08 (1.004–1.16)	0.04	1.03 (0.996–1.07)	0.08
Temperature (°C)	0.82 (0.57–1.18)	0.29	1.06 (0.88–1.28)	0.55
Hemoglobin (g/dL)	0.99 (0.82–1.20)	0.95	1.03 (0.94–1.13)	0.59
Platelet count (1000/mm³)	1.00 (0.99–1.01)	0.41	1.00 (0.998–1.002)	0.808
Base deficit	1.06 (0.98–1.14)	0.15	1.04 (0.997–1.08)	0.07
Mechanism of injury	1.81 (0.29–11.3)	0.53		

* Propensity score for platelet-product transfusion was forced into regression models, regressions included variables with $p < 0.1$ on univariate in addition to variables with biologic plausibility.
† Odds/hazard ratio >1 denotes increased mortality, <1 denotes decreased mortality.
‡ Survival at 24 h compared using Logistic Regression, Nagelkerke $R^2 = 0.64$, and ROC AUC = 0.94.
§ Survival at 30 d compared using Cox-Proportional Hazards regression.
INR, international normalized ratio; CI, confidence interval; HR, hazards ratio; ROC AUC, receiver operating characteristic area under the curve.

Variables influencing survival with $p < 0.1$ on univariate analysis were then used for multivariate analysis at 24 hours and 30 days (Table 5). Variables independently associated with increased mortality at 24 hours included ISS (odds ratio [OR], 1.10), admission INR (OR, 1.71), and stored RBC units (OR, 1.08). Variables independently associated with decreased mortality at 24 hours included the plasma ratio (OR, 0.94), apheresis platelet ratio (OR, 0.82), and cryo units (OR, 0.93). The 24-hour multivariate logistic regression model had a $R^2 = 0.64$ with receiver operating characteristic area under the curve = 0.94. Variables independently associated with increased mortality at 30 days included ISS (hazards ratio [HR], 1.06) and admission INR (HR, 1.16). Variables independently associated with decreased mortality at 30 days included the plasma ratio (HR, 0.98), apheresis platelet ratio (HR, 0.91), and RTS (HR, 0.81).

DISCUSSION

This article represents the largest comparative analysis examining the impact of platelet ratios in massively transfused combat casualties with penetrating injury published to date. Corroborating what has been noted in the civilian literature, both platelets and plasma seem to be key components in managing massively transfused trauma patients.[18] These data are important as clinically relevant thrombocytopenia has previously been considered a delayed complication of MT based on data published during the era of stored whole blood transfusion, which showed that circulating platelet counts dropped to $<50 \times 10^3/mm^3$ only after multiple blood volume replacements.[25] However, assumptions of "clinically relevant thrombocytopenia" do not take into account platelet dysfunction in trauma due to acidosis, hypothermia, or outpatient medications with activity against platelets such as aspirin/nonsteroidal antiinflammatory drugs (NSAIDS) or clopridogrel.[26–28] The optimal timing of platelet administration has not been clearly defined by these data and given that the majority of deaths occurred by 6 hours, it would be appropriate to examine this time point more closely. Such data in combat casualties are not available at the time of this publication, but are forthcoming.

The optimal ratio of platelets to administer during a MT has also not been precisely defined. We chose $\geq1:8$ aPLT:RBC as the high platelet ratio group based on previously published data in forty-five massively transfused patients with survivors receiving 1:7.7 apheresis units:RBC as compared with nonsurvivors (1:11.9).[20] For centers using pooled platelets instead of aPLT, assuming that one unit of aPLT is approximately equal to 6 units of pooled platelets, the equivalent ratio would be 0.75:1 or 4:6 pooled platelets:RBC. This pooled-platelet:RBC ratio is supported by data from a study examining fifty-eight massively transfused patients showing that survivors received higher ratios of pooled platelets (0.8:1) as compared with nonsurvivors (0.5:1).[19] Both of these studies were reported out of civilian trauma centers that have a higher proportion of blunt mechanism injuries (e.g., motor vehicle accidents and falls). Our data add to the evidence of an association between platelets and survival in a cohort of combat casualties suffering primarily from penetrating injuries (e.g., high-velocity gun shot wounds and fragmentation injuries).

As this is a retrospective analysis, these data are hypothesis generating as they only show an association between the platelet ratio and survival and cannot be used to make definitive conclusions about the best care for trauma casualties. The exclusion of patients receiving less than 10 units of blood in 24 hours may have inadvertently introduced bias in that patients may have died quickly before being able to receive 10 units, though very few of such patients would have received platelet products. The exclusion of patients undergoing surgery at forward surgical hospitals may also have introduced bias because platelets would have been transfused much longer after injury than in patients arriving de novo to the hospital. This being said, an informal examination of survival in patients treated at forward surgical hospitals showed similar 30-day survival trends between the different ratio groups (43%, 62%, and 73% in the low, medium, and high platelet ratio groups, respectively, $p = NS$). This was a retrospective study in patients where clinical decisions were made at the bedside and treatment groups were not assigned. Some casualties may have been so severely injured that the surgeon may have made a triage decision that the casualty did not warrant the commitment of resources necessary to consume a relatively limited resource such as aPLT. One might also argue that there is a survival bias inherent for patients who receive more aPLT as this blood product may have been reserved for late in the resuscitation. This is somewhat supported by the fact that the median time to aPLT transfusion was 2.5 hours (interquartile range, 1.4–4.4 hours), whereas the median time to death of patients in the low platelet ratio group was 2.3 hours (interquartile range, 1.2–3.8 hours). A propensity analysis was performed to account for such decision making, but it remains possible that patients received platelets because they lived as opposed to living because they received platelets. Given the significant differences in resuscitation between groups, one might wonder whether this is a reflection on changing patterns in resuscitation during time. An analysis of this was performed and patients in the low platelet ratio group did come from earlier in the time period than patients in the other two groups, which can be partially explained by the fact that aPLT were unavailable before November 2004 (when apheresis machines were deployed to the hospital). There were no such time period differences between the medium and high platelet ratio groups. An additional limitation is that we did not report on important outcomes secondary such as ventilator days, intensive care unit days, or hospital length of stay. Finally, the findings of this study are limited to patients receiving a MT in the setting of trauma and care should be taken before extrapolating these results to patients undergoing elective surgery or patients expected to receive less than 10 units of blood.

In conclusion, increased platelet:RBC and plasma:RBC ratios are associated with increased survival in the setting of MT. Randomized trials are needed to examine the optimal timing of platelet administration (such as proactively administering platelets before the 8th unit of blood as opposed to reactively after receiving the 8th unit of blood) and the optimal ratios for transfusing platelets. Until such data are available, transfused platelets should be considered an integral component in patients requiring MT and incorporated into transfusion protocols at medical facilities managing trauma.

REFERENCES

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet.* 2006;367:1747–1757.

2. Bellamy RF, Maningas PA, Vayer JS. Epidemiology of trauma: military experience. *Ann Emerg Med.* 1986;15:1384–1388.

3. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma.* 1995;38:185–193.

4. Peng R, Chang C, Gilmore D, Bongard F. Epidemiology of immediate and early trauma deaths at an urban Level I trauma center. *Am Surg.* 1998;64:950–954.

5. Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level I trauma center. *J Am Coll Surg.* 1998;186:528–533.

6. Demetriades D, Murray J, Charalambides K, et al. Trauma fatalities: time and location of hospital deaths. *J Am Coll Surg.* 2004;198:20–26.

7. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma.* 2003;54:898–905; discussion 905–897.

8. Huber-Wagner S, Qvick M, Mussack T, et al. Massive blood transfusion and outcome in 1062 polytrauma patients: a prospective study based on the Trauma Registry of the German Trauma Society. *Vox Sang.* 2007;92:69–78.

9. 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–S96.

10. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma.* 2003;54:1127–1130.

11. Niles SE, McLaughlin DF, Perkins JG, et al. Increased mortality associated with the early coagulopathy of trauma in combat casualties. *J Trauma.* 2008;64:1459–1463; discussion 1463–1455.

12. McLaughlin DF, Niles SE, Salinas J, et al. A predictive model for massive transfusion in combat casualty patients. *J Trauma.* 2008; 64:S57–S63; discussion S63.

13. College of American Pathologists. Practice parameters for the use of fresh frozen plasma, cryoprecipitate and platelets. Fresh-Frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. *JAMA.* 1994;271:777–781.

14. Como JJ, Dutton RP, Scalea TM, Edelman BB, Hess JR. Blood transfusion rates in the care of acute trauma. *Transfusion.* 2004; 44:809–813.

15. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma.* 2007;63:805–813.

16. Maegele M, Lefering R, Paffrath T, et al. Red blood cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiply injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft fur Unfallchirurgie. *Vox Sang.* 2008;95:112–119.

17. Cotton BA, Gunter OL, Isbell J, et al. Damage contol hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma.* 2008;64:1177–1182; discussion 1182–1173.

18. Holcomb JB, Wade CE, Michalek JE, et al. Increased Plasma and Platelet to RBC ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg.* 2008;248:447–458.

19. Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. *J Trauma.* 1997;42:857–861; discussion 861–852.

20. Cinat ME, Wallace WC, Nastanski F, et al. Improved survival following massive transfusion in patients who have undergone trauma. *Arch Surg.* 1999;134:964–968; discussion 968–970.

21. Repine TB, Perkins JG, Kauvar DS, Blackborne L. The use of fresh whole blood in massive transfusion. *J Trauma.* 2006;60:S59–S69.

22. Champion HR, Sacco WJ, Copes WS, Gann DS, Gennarelli TA, Flanagan ME. A revision of the Trauma Score. *J Trauma.* 1989; 29:623–629.

23. *The Abbreviated Injury Scale 1990 Revision-Update 98.* IL: Association for the Advancement of Automotive Medicine Des Plains; 1998.

24. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. *J Trauma.* 1987;27:370–378.

25. Miller RD, Robbins TO, Tong MJ, Barton SL. Coagulation defects associated with massive blood transfusions. *Ann Surg.* 1971; 174:794–801.

26. Wolberg AS, Meng ZH, Monroe DM III, Hoffman M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. *J Trauma.* 2004;56:1221–1228.

27. Zhang JN, Wood J, Bergeron AL, et al. Effects of low temperature on shear-induced platelet aggregation and activation. *J Trauma.* 2004;57:216–223.

28. Marumo M, Suehiro A, Kakishita E, Groschner K, Wakabayashi I. Extracellular pH affects platelet aggregation associated with modulation of store-operated $Ca(2^+)$ entry. *Thromb Res.* 2001; 104:353–360.

DISCUSSION

Bryan Cotton: I would like to thank the ATACCC group for the invitation to discuss this work by Dr. Perkins and his colleagues. I would also like to thank ATACC and the presiding officers for the privilege of the floor.

Dr. Perkins and his colleagues have evaluated the impact of various apheresis platelets (aPLT) ratios as part of a massive transfusion protocol used at the US Army's Combat Support Hospital (CSH) in Baghdad, Iraq. The author's exclusion of several patient groups seems to be methodically sound. However, one group that they excluded from analysis was those patients receiving their platelet transfusion source from whole blood. The reason stated for this is completely understandable, that is, the difficulty of comparing the equivalence of platelets from fresh whole blood to those receiving aPLT. This brings me, though, to my first question for the authors: although I understand the reasoning behind excluding these patients, given the controversy surrounding the use of whole blood, could the whole blood group not have served as a control group for comparing with the aPLT group as whole or by ratios? Such a comparison might provide some insight into superiority of aPLT or validation of the quite controversial whole blood strategy. At a minimum, I would hope the authors would at least plan for future analysis to include these additional patients.

Three groups of patients were constructed based on their previous published experience. These included patients receiving a low ratio of aPLT: RBC (<1:16 ratio), patients receiving a medium ratio of platelets (1:16 to <1:8), and those receiving a high ratio of platelets (≥1:8). The primary endpoint was survival at 24 hours and at 30 days. This brings me to my second question for the authors: given the previous data from the ISR group demonstrating a more proximal "cut point" for survivors, why did Dr. Perkins and his colleagues not look at six (6) hour survival differences?

Although laboratory values do not equate directly with survival, the authors, devote a significant amount of their discussion section to platelet values and the potential need to

revisit previously accepted transfusion triggers for platelets. My third question is why did the authors choose not to look at differences between the three groups with respect to platelet values and other coagulation parameters at various points during the resuscitation process?

As to their choice to evaluate the data with a propensity score model, I have a few comments and a question for the authors. Propensity scoring is a statistical method where investigators match on a single summary measurement in an attempt to create "pseudo randomization" from a retrospective cohort. However, this method is most useful and applicable in the following situations: (1) there is a limited number of patients exposed and a much larger number not exposed to a particular intervention and (2) when there are only a few events (usually less than 7) per confounder or covariate being considered. In these situations, propensity scoring is less biased and more robust than multivariate regression models. In the absence of these scenarios, however, pure or traditional multivariate regression analyses are preferred. Therefore, my fourth question is, given the larger number of covariates examined and the high number of exposure events, why not simply stratify or adjust with a traditional regression model?

Next, during construction of the propensity score, the authors used logistic regression to determine the risk of receiving platelet transfusions. By using the logistic regression method, this gives the authors a "yes or no" answer. The authors, however, have set out to look at platelet ratios in three groups with a wide range of platelets being received. My question to this then is why not use linear regression in generating the propensity score to allow for expression of the likelihood of receiving platelet transfusion as a continuous measure of risk?

The authors found the three groups to be very similar with respect to standard demographics and injury and physiological severity. Despite this, the groups seemed to have received completely different resuscitation strategies with respect to both plasma and platelet ratios. For example, the low aPLT:RBC group received significantly lower overall transfusions of plasma, RBC, and cryoprecipitate and more recombinant VIIa. Can the authors please explain these dramatic differences? In other words, did these ratios represent changes of practice overtime and thus these three groups would be better served to undergo a time series analysis?

Although the authors noted 24-hour and 30-day survival was highest in the higher aPLT:RBC group and was lowest in the low aPLT:RBC, they also found the median time to death in the low ratio group was just more than 2 hours, whereas that of the high ratio group was more than 3 days. In addition, almost one third of deaths in the low ratio group were from exsanguination compared with that of the high ratio aPLT:RBC group, which was just more than 2%. One potential explanation for the ratio-survival differences put forth by the authors in the article is that patients in the high ratio group may have simply lived long enough to receive higher ratios compared with the fairly rapid time to death in the low ratio group who may not have had time alive and in the hospital to achieve these higher ratios. This seems to be one very reasonable explanation; however, I have another possible explanation to their findings. Several years ago, Manny Rivers found that early and aggressive catheter directed resuscitation of septic shock patients results in improved survival. These patients received dramatically larger volumes of resuscitation fluids in the first 6 hours but less fluids, blood, and vasopressors in the subsequent 24 hours and overall. By addressing the pathophysiology quicker and more aggressively, the authors found they were able to "keep up" rather than "play catch up" with septic shock and use fewer resources to achieve these results. Perhaps, the earlier transfusion of higher amounts of platelets (and plasma) result in getting a "finger in the dike" quicker, allowing for more rapid achievement of hemostasis and allowing of adequate time for surgical correction of hemorrhage. Given this, my final question is can the authors make any comments on the differences in timing of platelet transfusions in the resuscitation of the three groups of patients? In other words, were the higher ratio groups receiving more platelets (or at least a higher percentage of their platelets) upfront, thereby resulting in a reduction in their risk of early mortality, specifically from exsanguination?

I would like to congratulate the authors on a solid article and a significant contribution to the topic of damage control resuscitation. I would also like to thank the meeting organizers again for the privilege of the floor and the opportunity to discuss this article.