Increased Mortality Associated With the Early Coagulopathy of Trauma in Combat Casualties

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Background: **Recent civilian studies have documented a relationship between increased mortality and the presence of an early coagulopathy of trauma diagnosed in the emergency department (ED). We hypothesized that acute coagulopathy (international normalized ratio ≥1.5) in combat casualties was associated with increased injury severity and mortality as is seen in civilian trauma patients.**

Methods: **A retrospective study of combat casualties who received a blood transfusion at a single combat support hospital between September 2003 and December 2004 was performed. Coagulation status, pH, base deficit, and temperature were recorded at arrival to the ED. These were analyzed by Injury Severity Score (ISS), associated injury patterns, and mortality.**

Results: **A total of 3,287 patients were treated at the combat support hospital during the study period. Of these, 391 patients were transfused and primarily admitted, thus meeting the study criteria, 347 had coagulation data, and 92% had a penetrating mechanism. The prevalence of acute coagulopathy in transfused casualties measured with point-of-care devices at arrival in the ED was 38%. Mortality in those who were coagulopathic at arrival to the ED was 24% (32/133) versus 4% (8/214) in those not presenting with coagulopathy ($p < 0.001$). The prevalence of mortality by coagulopathy increased as ISS increased. Coagulopathy and acidosis were associated with mortality, odds ratio (OR), 5.38 [95% confidence interval (CI), 1.55–11.37] and 6.9 (95% CI, 2.1–19.5), respectively. Temperature did not affect outcomes (OR, 1.1; 95% CI, 0.4–2.6).**

Conclusions: **The early coagulopathy of trauma was rapidly diagnosed in the ED and present in more than one-third of combat casualties who received a transfusion, similar to the incidence found in civilian trauma patients. Coagulopathy, independent of hypothermia but strongly correlated with acidosis and ISS, was associated with mortality in combat casualties, similar to that found in civilian trauma patients. Early diagnosis and treatment of acute traumatic coagulopathy with new resuscitation paradigms may improve outcomes.**

Key Words: **Coagulopathy, Early coagulopathy, Combat casualties.**

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Coagulopathy has been cited as part of the lethal triad which includes acidosis and hypothermia.[1–5] These three factors perpetuate one another, are challenging to reverse, and when present contribute to death. The lethal triad is initiated by injury and significant hemorrhage and frequently compounded by an iatrogenic resuscitation injury that exacerbates and perpetuates this cycle.[6–11] Previously, it was assumed that acidosis and hypothermia were primary responses to hemorrhagic shock and that the coagulopathy component of the lethal triad developed over time. We now know this is not true.

Previous studies of trauma-induced coagulopathy frequently measured the laboratory changes that occurred in the operating room or intensive care unit after dilution with crystalloid and packed red blood cells (PRBC), concluding that traumatic coagulopathy was a byproduct of resuscitation or hypothermia.[4,5] Diagnosis was delayed because of a lack of point-of-care testing capability, and treatment was frequently slowed simply because of the logistics of ordering and receiving multiple blood components from the blood bank based on the laboratory data. The early coagulopathy of trauma has now been recognized as a primary response to injury in 25% of civilian trauma patients admitted to Level I trauma centers.[12,13] Prolonged coagulation values at arrival to the emergency department (ED), before the initiation of resuscitation, and independent of hypothermia have been described in the civilian trauma population with blunt injuries.[12–14] This unique coagulopathy is likely caused by blood loss, acidosis, hypothermia, consumption, fibrinolysis, and dilution.[15–21] Another recently hypothesized physiologic mechanism for traumatic coagulopathy is tissue hypoperfusion, measured through base deficit (BD), resulting in the release of protein C, an anticoagulant, which circulates in the plasma.[20] In contrast to civilian trauma where blunt injuries represent approximately 90% of admissions, penetrating injuries are responsible for more than 90% of the injuries seen in the ongoing war in Iraq and Afghanistan.[22,23] Furthermore, massive transfusion (≥10 units of red blood cells) occurs

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three times more often in combat verses civilian trauma admissions,[24,25] and truncal hemorrhage from these penetrating injuries is the leading cause of potentially preventable morbidity and mortality.[22,23] Although the mechanism of the early coagulopathy of trauma is currently unknown, it occurs frequently and is associated with increased mortality in civilian trauma patients.

Similar to the civilians with blunt injuries suffering hemorrhagic shock and coagulopathy, but with a uniquely different wounding mechanism, we thought that our combat-injured patient population was at significant risk for acute coagulopathy and increased mortality. Our study objectives therefore were to determine the prevalence of the early coagulopathy of trauma in transfused combat casualties and analyze its associations with injury severity, acidosis, hypothermia, and mortality.

MATERIALS AND METHODS

The data presented here were obtained under a human use protocol that received Institutional Review Board approval at Brooke Army Medical Center in San Antonio, TX. Using the Joint Theater Trauma Registry (JTTR) maintained at the U.S. Army Institute of Surgical Research at Ft. Sam Houston in San Antonio, TX, we performed a retrospective analysis of data for trauma patients admitted to one combat support hospital (CSH) in Iraq between September 2003 and December 2004. Enemy combatants and patients who received prior treatment at a medical facility and were transferred in were excluded from the study. Mortality was recorded for all in-hospital events.

Red blood cell transfusions were PRBC, fresh whole blood, or a combination of these. All transfusions in this study were within 24 hours after admission. A massive transfusion was defined as $\geq$10 units of a combination of PRBC or fresh whole blood in the initial 24 hours. The current study did not focus on coagulopathy reversal, so the use or effect of fresh frozen plasma, cryoprecipitate, and platelets were not analyzed. Coagulopathy was defined using the International Normalized Ratio (INR) value, which was obtained at arrival to the CSH. An INR of 1.0 is the reference for normal, and an INR $\geq$ 1.5 defined a clinically significant coagulopathy.[25–27] Consistent activated partial thromboplastin times were not available in the chart review for this analysis. Acidosis was defined as a BD $\geq$ 6, whereas hypothermia was defined as a temperature $\leq$35°C. Abbreviated Injury Scores (AIS-95) were used to calculate the Injury Severity Score (ISS).

Patient demographics, transfusions, injuries, and outcomes were all obtained from the JTTR. The JTTR is a database established by the Department of Defense to capture data prospectively from multiple nonintegrated clinical and administrative systems. This database provides data abstraction of all available clinical data from the point of injury through discharge from military treatment facilities for coalition and foreign national patients and from point of injury through acute care discharge for U.S. patients.

Laboratory data were collected by two researchers (S.E.N. and D.F.M.) through individual patient chart review in the Patient Administration Systems and Biostatistics Activity (PASBA) system. PASBA is a division of the Program Analysis and Evaluation Directorate, U.S. Army Medical Command. PASBA receives all Inpatient Records from deployed medical units that do not have access to the Composite Health Care System once that unit returns from theater. PASBA reviews, performs data quality checks, codes, enters the record information into a number of databases, and then forwards them to the National Personnel Records Center.[28]

Analysis of coagulopathic versus noncoagulopathic and their relationship to outcomes of ISS and mortality were described by prevalence and relative risk (RR) with 95% confidence intervals (95% CIs). Odds ratios (ORs) were calculated for acidosis, hypothermia, and coagulopathy related to mortality. RR was used to determine the probability of developing coagulopathy in all exposed patients. ORs were used in variables that may be used for logistic regression. INR, BD, and ISS were compared using Spearman correlation coefficient. Data were analyzed using STATA 9.2 (StataCorp LP., College Station, TX), SAS 9.1.3 (SAS Institute, Inc., Cary, NC), and EPI INFO (Version 3.3.2; Centers for Disease Control and Prevention, Atlanta, GA).

Data are presented as median $\pm$ interquartile ranges or means. Continuous variables were compared using a Student *t* test and dichotomous variables were compared with χ^2 or Fisher Exact analysis as appropriate. A *p* value of less than 0.05 denoted statistical significance.

RESULTS

Patient demographics are seen in Table 1. Between September 2003 and December 2004, 3,287 patients were seen at the CSH. Of these patients, 688 (21%) received a blood

Table 1 Patient Demographics

Patient Demographics (n = 391)	N (%)
Status	
Armed forces	224 (57)
Iraqi	155 (40)
Contractor	12 (3)
Age (yrs)	
18–24	160 (41)
25–34	103 (26)
≤35	65 (17)
Unknown	63 (16)
Sex	
Male	366 (94)
Female	25 (6)
Primary mechanism of injury (n = 390)*	
Gunshot wound	107 (27)
Explosive	255 (65)
Motor vehicle collision	18 (5)
Other	10 (3)

* Mechanism of injury unknown for one patient.

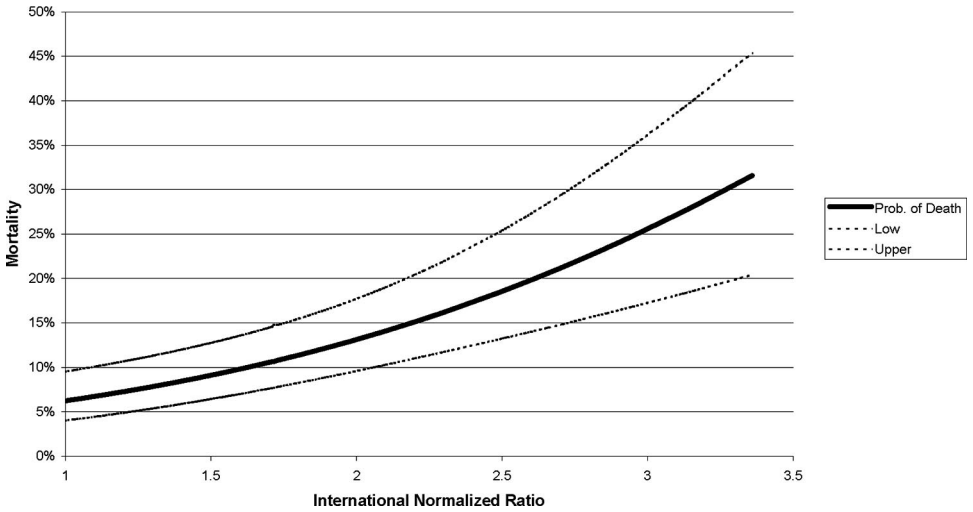

Fig. 1. *The trend of INR associated with mortality with 95% CI by univariate analysis.*

transfusion. Of patients receiving a transfusion, 171 were seen at a Level II facility before arrival (transferred patients) at the CSH (Level III) and 126 were designated as potential or known Security Internees. These 297 patients were excluded. The total study population was 391 patients.

The primary mechanism of injury was penetrating, representing 92% of all injuries, and 65% were from explosions. About 84% of blood transfusions were PRBC alone, 15% a combination of PRBC and whole blood, and 1% whole blood alone. The median primary RBC transfusion number was 4 (interquartile range, 2–9). About 49% (194/391) of patients received at least 1 unit of FFP. The incidence of massive transfusion (≥10 units of PBRC + whole blood) was 25%. Thirty-seven patients (9.5%) received rFVIIa. The case fatality rate in the study population was 14% (55/391).

Coagulation status at admission (INR) was available for 347 patients. The prevalence of acute traumatic coagulopathy (INR ≥ 1.5) in transfused patients was 38% (133/347). The case fatality rate based on coagulopathy was 24% (32/133) versus those who presented without coagulopathy 4% (8/214). The RR of death associated with coagulopathy was 5.38 (95% CI, 1.55–11.37; $p < 0.001$). Figure 1 represents the trend of mortality associated with INR with 95% CI by univariate analysis. The probability of death began to increase at an INR of 1.5 with a range of 7% to 12% at this level. With an INR of 2.0, the probability of death rose to 10% to 17%. At an INR of 3.0, the probability of death was between 17–35%.

The relationship between coagulopathy measured through INR and other variables were pursued. These variables include ISS, acidosis measured by BD, and temperature. The outcome relationship in the later two variables was mortality. The median cohort ISS was 17 (IQR, 10–26). The prevalence of coagulopathy increases as injury severity increases only in the casualties with a BD ≥ 6 (Fig. 2). Coagulopathy across ISS category was assessed for risk of mortality (Fig. 3). A significant difference in mortality between coagulopathic and noncoagulopathic patients was seen in the highest ISS category ≥25 with a mortality of greater than 40% in coagulopathic patients versus less than 10% in those who were not coagulopathic.

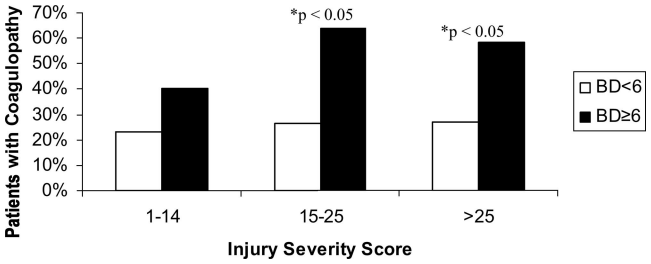

Fig. 2. *Prevalence of coagulopathy by ISS and BD in patients requiring a blood transfusion.*

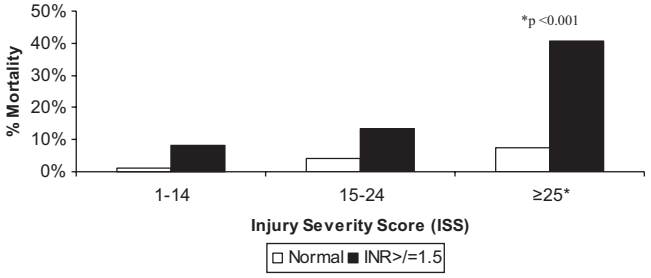

Fig. 3. *Coagulopathy across ISS categories increases the risk of mortality.*

Admission temperature (<35°C) was not associated with mortality (OR, 1.1; 95% CI, 0.4–2.6). Acidosis measured at admission BD was associated with mortality with an OR of 6.9 (95% CI, 2.1–19.5). BD was analyzed for its correlation with INR. This relationship was then compared with the relationship between INR and ISS. The correlation coefficient between INR and BD was 0.45. This relationship was compared with the correlation between INR and ISS. These were not as closely related at 0.12. Thus, the correlation

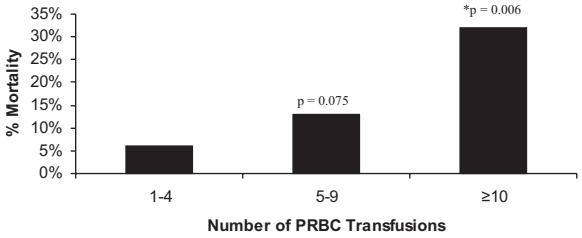

Fig. 4. *Prevalence of mortality with number of PRBC transfusions.*

between BD and INR was three times the strength of the association between INR and ISS. There was not any interaction found between these three variables.

Finally, mortality was compared with number of PRBCs transfused. Patient mortality increases with the number of PRBC transfusions. Mortality doubled between 1 to 4 units and 5 to 9 units (6%–14%) and also between 5 to 9 units and ≥10 units (14%–32%). A statistically significant increase in mortality is seen when 10 or more units of PRBCs are transfused (Fig. 4).

DISCUSSION

Remarkably similar to the two civilian cohort of patients described by Brohi and MacLeod;[12,13] more than one-third of combat casualties who required a blood transfusion arrived at the combat hospital coagulopathic. These patients had only received treatment equivalent to emergency medical service care during rapid helicopter transport, which typically included small amounts of isotonic crystalloid solution, analgesics, and airway support. Although the percentage of patients with coagulopathy was similar, inclusion for this study was limited to those casualties that received at least one red blood cell transfusion. Previous civilian studies were on patients who were admitted to a trauma center, with or without receiving a blood transfusion. Additionally, very different from civilian trauma, more than 90% of our patients' injuries were from penetrating trauma and in 25% of these patients whom received a transfusion a massive transfusion was required.

Similar to Brohi's initial work, ISS was directly associated with an increase in the prevalence of coagulopathy.[13] In this analysis, a greater incidence of coagulopathy was seen in comparison with Brohi (25% vs. 38%).[13] This difference is likely caused by the different inclusion criteria for the two studies. However, in our study, for a given ISS, mortality rates were lower, likely related to the preponderance of penetrating injuries. Whether this is an affect of the younger cohort of fit patients seen in the military population or an effect of interventions such as early rFVIIa, or increased plasma:red blood cell ratio remains to be clarified.[25,29,30] The overall risk of death associated with coagulopathy was five times that of not being coagulopathic (Fig. 3). This risk is similar to that seen in patients with an overall injury severity more than 25, or the most severe group in our cohort. Coagulopathic patients with an ISS of 1 to 14 have a mortality similar to that of the noncoagulopathic patients with an ISS ≥ 25. This leads us to assume that coagulopathy and acidosis are more related to the physiologic status, rather than the amount of tissue injury. Whether the excess risk of death associated with coagulopathy is only present in those with high injury severity is difficult to determine from our current data. Although the risk seems to be present across all injury groups, the number of deaths at the lower ISS range is too few for noncoagulopathic patients, making this association inadequately powered in this study. Future studies to determine whether early coagulopathy may predict outcomes in patients with less severe injuries needs to be examined.

Our data in combat casualties is consistent with civilian data correlating high injury severity, shock, and increased mortality with the early coagulopathy of trauma.[12,13,20] Whether the coagulopathy is secondary to hemorrhage resulting in loss of coagulation factors, tissue hypoperfusion, or extensive tissue injury resulting in the release of tissue factors causing the coagulopathy cannot be determined from this study.

There are several limitations in this study. Most studies describing coagulopathy have used prothrombin time or partial prothrombin time. INR is more readily used in our CSH; thus test variation may account for some difference in rates of coagulopathy compared with prior studies. Based on study design, a direct cause and effect relationship cannot be established between coagulopathy and mortality. In our full cohort, one-third of deaths did not have initial ED laboratory information. Further, in our group of patients who required a massive transfusion, 10% were missing initial ED laboratory data. With more than 50% of our missing data being in patients with the highest risk factors for poor outcomes, the data presented may be an underrepresentation of the true burden of acute coagulopathy. Second, mortality in this study was recorded only during the time the patients were at the CSH. Many coalition combat casualties are transported after initial stabilization and within 24 to 72 hours after arrival to the CSH. Iraqi patients' typically stay in the intensive care unit for 3 to 5 days before transfer to a local hospital. Final long-term outcomes are not available for these patients. As the overall mortality could only increase, mortality may be underestimated in this study. Balancing this limitation is that most (>80%) of combat mortality occurs during the first 24 hours. Future studies using long-term outcomes would be beneficial to further define the impact of the early coagulopathy of trauma in combat casualties. This information may provide insight into what interventions may be most beneficial to both treat and prevent the early coagulopathy of trauma, potentially improving outcomes.

CONCLUSIONS

The overall prevalence of the early coagulopathy of trauma in transfused combat casualties is 38%. Coagulopathy was correlated with BD and both have a similar risk to mortality. As demonstrated with prior civilian studies, the early coagulopathy of trauma increases in prevalence as

shock or injury severity increases and is predictive of mortality. An acute coagulopathy (INR $\geq$ 1.5) in combat casualties is one of the easily measurable point-of-care laboratory values associated with a significant risk factor for mortality. Awareness of this diagnosis is of critical importance. Early and aggressive management of this devastating physiologic state may improve survival in trauma patients with severe injuries.[31] Further studies to determine the mechanism of this unique coagulopathy, as well as more effective resuscitation strategies with new blood products, amounts, and ratios, are needed to optimize management of severely injured military and civilian casualties.

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DISCUSSION

Dr. Anna M. Ledgerwood (Detroit, Michigan): Thank you, Dr. Fabian, Dr. Britt, members and guests. The authors report that a third of their patients who arrived at the combat hospital and required a blood transfusion had coagulopathy.

My first question to the authors is what new information is being reported in this study? McCloud et al. from the Ryder Trauma Center in Miami reported similar findings four years ago with a 35 percent increase in mortality with an elevated PT and a 326 percent increase in mortality in patients with an abnormal PTT.

Dr. Niles, you report essentially the same findings using INR instead of PT and PTT. Burleigh et al. from the Royal London Hospital also reported four years ago that 24 percent of over 1,000 patients admitted by helicopter had a coagulopathy as measured by PT, APTT and TT.

And, furthermore, this increase in coagulopathy was associated with an increased ISS and increased mortality.

They postulated that tissue trauma results in the release of mediators that are responsible for the development of coagulopathy. Have you measured any mediators?

Have you tried to determine what causes this increase in coagulopathy since we've known this occurs for at least four years?

Were you able to evaluate prehospital times or time from injury to arrival at your ED or when your blood samples were drawn? And was there a difference?

What type of volume and what type and what volume of fluids were given prior to arrival? In particular, were colloid solutions used since we know that the use of colloids can alter coagulation protein content as well as activity?

Was there a difference in the volume of fluids used prior to arrival? Why did the 32 of 133 patients with coagulopathy on arrival die? How long after arrival did they die? And did they bleed to death?

Your manuscript implies that correction of coagulopathy with early administration of FFP and activated factor VII may improve survival. I'm not convinced.

I have never known these substances to plug a hole in the aorta, the iliac vein, or other causes of what I refer to as "audible bleeding." It appears to me that coagulopathy on admission is simply a reflection of the physiologic aspects of injury.

I would plead with our military colleagues to find out what causes this and also would caution against the need to correct what I refer to as an abnormal laboratory value unless you're doing it in a randomized prospective manner.

Dr. Philip S. Barie (New York, New York): A small point perhaps but one worth mentioning, the international normalized ratio or INR was used in a couple of your data slides to index your results.

And the point that I rise to make is that the international normalized ratio is a correction factor used by hematology laboratories to adjust for different prothrombin time assays and it does not have any inherent biological relevance.

The international normalized ratio, furthermore, is a valid indicator only in patients who are on warfarin on a stable dose.

So I would strongly encourage you to rework your data to index it to prothrombin time which would be the correct and interpretable form. And I look forward to your comments.

Dr. Jeffry L. Kashuk (Denver, Colorado): I would like to compliment the military on their series. And it's very important for us in the civilian population to learn from these experiences.

But we need ask presented from your data is in excess of I think 60 to 70 percent blast injuries compared to conventional trauma in your series.

In our experiences in Israel we reported that there was significant differences between blast injury and the conventional trauma. The blast injury, ISS, and multi-dimensional injury was not predictor of those particular injuries.

Secondly, I would surmise that in the blast injury with associated soft tissue injury, thoracic injuries, etc, the potential for coagulation disorders are much greater than the conventional injuries that we're used to treating.

So my question to you is, did you separate out your blast injuries from your conventional injuries in terms of identifying the coagulation disorders that you describe?

Dr. Michell Cohen (San Francisco, California): We in San Francisco are interested in the cause of early coagulopathy and actually working with Mr. Brohi who published that paper in the Journal of Trauma in 2003.

We found because of our very early transport times that it seems that our patients are making thrombin, which is the commonly thought to be cause of acidosis and hypothermic coagulopathy, but they're still coagulopathic.

As we have discussed, we think it's due to protein C. So I'm wondering what your transport times are and your time to measurement of coagulopathy.

And I'm wondering if you have looked at the patients who received a small amount of blood or no transfusions? What happened to that large group of patients because I think there can be some clue as to the cause of coagulopathy, acidosis-induced versus non-acidosis-induced in that patient population?

Dr. Richard J. Mullins (Portland, Oregon): Are some of the patients arriving in CSH in Baghdad considered moribund and unsalvageable? Are some judged to be so severely injured that no effort is made to really treat them other than to provide comfort? If there are patients considered moribund, are they included in these analyses that identify early coagulopathy is associated with death?

Dr. Sarah E. Niles (Silver Springs, Maryland): Dr. Ledgerwood and other commenters, thank you for all of your questions.

As for what new information and why we looked into this study was really based on the fact that we agree there are similar situations. Hemorrhagic shock is happening in civilian patients as well as in ours.

However, they had a very different mechanism of injury and very different injury pattern and we wanted to see whether the recommendations built on our damage control resuscitation were based on the same, were finding the same outcomes with the different injury types.

As for other questions about the time to injury that was asked by yourself as well as several other people, the time to injury were at some times recorded. They were not analyzed in this study and could be looked at further to see the different transportation times.

In terms of fluid resuscitation prior to patients arriving, we did not have that information for this set of patients.

The military uses a very strict regiment for the amount of prehospital fluid resuscitation that they do receive but we didn't have that measurement for this data right now.

Hemorrhagic shock has been looked at as to why they died and whether or not they died from bleeding.

Hemorrhagic shock has been documented to definitely be a major cause of death in combat casualties and believe that many of our patients in the study definitely did die from hemorrhage from their wounds.

In terms of PTT, why PT was used versus INR, more, I do know that INR is based on the PT. In our patient population we measure INR more frequently which was also represented here by Dr. Moore's paper that was presented at the AAST as well as by Dr. Schreiber as a used indicator. And because it was more used we decided to evaluate that laboratory data point for our patients.

In terms of Dr. Kashuk's question on whether or not we separated out blast versus conventional injuries, we did not look at them separately, although 92 percent of our injuries were from explosions, not from the other ones and that would be probably what drives the majority of our data, being the vast majority of the injury pattern seen.

And Dr. Cohen asked about whether or not we looked at the patients that were not transfused versus those that were. The inclusion criteria for the study was just based on having a blood transfusion.

We felt that these patients were at a very high risk of hemorrhagic shock and wanted to look closely at their outcomes. The other patients are there and continued analysis would be a great study to go ahead and look at that.

In terms of the physiologic basis of why these patients and what is happening with their coagulopathy in terms of long term outcome, it's a retrospective study design and unfortunately a good prospective study design from the very beginning watching what happens and going ahead into the future and measuring the different mediators involved would be necessary to determine a cause and effect relationship.