Early predictors of massive transfusion (MT) would prevent undertriage of patients likely to require MT. This study validates scores using the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study.

METHODS: All patients in PROMMTT were analyzed. The initial emergency department triggers at each center were compared. A single trigger (international normalized ratio [INR], systolic blood pressure, hemoglobin, base deficit, positive result for Focused Assessment for the Sonography of Trauma examination, heart rate, temperature, and penetrating injury mechanism) was compared for patients receiving MT (≥10 U of packed red blood cells in 24 hours) versus no MT. Adjusted odds ratios (ORs) for MT are reported using multiple logistic regression. If all triggers were known, a Massive Transfusion Score (MTS) was created, with 1 point assigned for each met trigger.

RESULTS: A total of 1,245 patients were prospectively enrolled with 297 receiving an MT. Data were available for all triggers in 66% of the patients including 67% of the MTs (199 of 297). INR was known in 87% (1,081 of 1,245). All triggers except penetrating injury mechanism and heart rate were valid individual predictors of MT, with INR as the most predictive (adjusted OR, 2.5; 95% confidence interval, 1.7–3.7). For those with all triggers known, a positive INR trigger was seen in 49% receiving MT. Patients with an MTS of less than 2 were unlikely to receive MT (negative predictive value, 89%). If any two triggers were present (MTS ≥2), sensitivity for predicting MT was 85%. MT was present in 33% with an MTS of 2 greater compared with 11% of those with MTS of less than 2 (OR, 3.9; 95% confidence interval, 2.6–5.8; p < 0.0005).

CONCLUSION: Parameters that can be obtained early in the initial emergency department evaluation are valid predictors for determining the likelihood of MT. (J Trauma Acute Care Surg. 2013;74: 59–68. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Diagnostic, level II.

KEY WORDS: PROMMTT; transfusion triggers; massive transfusion; INR.

Defining when to initiate massive transfusion: A validation study of individual massive transfusion triggers in PROMMTT patients

Rachael A. Callcut, MD, MSPH, Bryan A. Cotton, MD, Peter Muskat, MD, Erin E. Fox, PhD, Charles E. Wade, PhD, John B. Holcomb, MD, Martin A. Schreiber, MD, Mohammad H. Rahbar, PhD, Mitchell J. Cohen, MD, M. Margaret Knudson, MD, Karen J. Brasel, MD, MPH, Eileen M. Bulger, MD, Deborah J. del Junco, PhD, John G. Myers, MD, Louis H. Alarcon, MD, Bryce R.H. Robinson, MD, on behalf of the PROMMTT Study Group, San Francisco, California

BACKGROUND: Early predictors of massive transfusion (MT) would prevent undertriage of patients likely to require MT. This study validates triggers using the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study.

METHODS: All patients in PROMMTT were analyzed. The initial emergency department triggers at each center were compared. A single trigger (international normalized ratio [INR], systolic blood pressure, hemoglobin, base deficit, positive result for Focused Assessment for the Sonography of Trauma examination, heart rate, temperature, and penetrating injury mechanism) was compared for patients receiving MT (≥10 U of packed red blood cells in 24 hours) versus no MT. Adjusted odds ratios (ORs) for MT are reported using multiple logistic regression. If all triggers were known, a Massive Transfusion Score (MTS) was created, with 1 point assigned for each met trigger.

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LEVEL OF EVIDENCE: Diagnostic, level II.

KEY WORDS: PROMMTT; transfusion triggers; massive transfusion; INR.
Using the entire patient cohort from the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study, the predictive ability of individual transfusion triggers common to previously reported scoring systems are prospectively investigated. The goal is to determine the utility of individual triggers compared with a Massive Transfusion Score (MTS) for expeditious identification of who is likely to benefit from damage-control resuscitation.

PATIENTS AND METHODS

Study Population

PROMMTT was a prospective, multicenter observational cohort study conducted at 10 Level I trauma centers in the United States from July 2009 to October 2010. The primary objective of PROMMTT was to investigate in-hospital mortality in all patients surviving for at least 30 minutes after emergency department (ED) admission. To be included in the PROMMTT cohort, patients had to be major trauma patients at least 16 years old, requiring trauma team activation, arriving from the scene, and receiving at least 1 U of RBC within 6 hours. The original PROMMTT study as well as this secondary analysis was approved by the institutional review boards of each study site and the Data Coordinating Center (DCC). The US Army Human Research Protections Office also provided second-level review and approval of the PROMMTT study.

Trigger Selection

The Individual Transfusion Trigger study (Cincinnati ITT Study, CITT) and the Assessment of Blood Consumption (ABC) score have shown promise in the literature for predictive utility of MT and ease of use in the civilian population. The CITT triggers were adapted from previously published military triggers. The CITT triggers included systolic blood pressure (SBP) of less than 90 mm Hg, hemoglobin (Hgb) level of less than 11 g/dL, temperature of less than 35.5°C, international normalized ratio (INR) of greater than 1.5, and base deficit (BD) of 6 or greater. The ABC score includes SBP of less than 90 mm Hg, heart rate (HR) 120 beats per minute (bpm) or greater, positive result for Focused Assessment for the Sonography of Trauma (FAST), and penetrating mechanism of injury. From the CITT and ABC studies, eight unique triggers were identified for study inclusion.

Data Collection

Data collection was conducted under the standard operating procedure manual and site coordinators of the PROMMTT study. Research assistants were available 24/7 in the study sites and responded to all major trauma activations to record real-time collection of relevant data variables. The observers recorded exact times of transfusion products, fluids, interventions, and patient outcomes. Following conclusion of the active resuscitation phase of the observation as defined by PROMMTT, patients were followed up on a daily basis until discharge or death.

The PROMMTT study was intended to prospectively assess individual triggers as one of the secondary aims, and thus, all of the relevant triggers were included on the data collection sheets for real-time collection. The initial ED value for each trigger was recorded and verified in the medical records when possible before submission to the DCC. As in previous work, the first laboratory data available on arrival were counted as the ED laboratory result if they were drawn in the ED or performed as a point-of-care test in the ED.

Data Analysis

The DCC provided the data as a deidentified patient level data set containing all relevant study variables including demographics, injury characteristics, ED vital signs, arrival times, transfusion data, ED interventions, laboratory studies, radiographic studies, operative interventions, and outcomes. Cause of death was determined by the treating attending physician. Initial ED values were used to determine if a patient met each trigger cutoff value. The DCC was responsible for auditing, cleaning, and assessing data collection.

For each trigger, comparison was made between patients receiving an MT versus no MT within specific time intervals. Patients were classified in the MT at 24 hours (MT24h) group if they received or 10 or more units of RBCs within 24 hours of initial ED presentation. Alternatively, a separate analysis was done for MT at 6 hours (MT6h) if patients received 10 or more units of RBCs within 6 hours. To address potential survivor bias, sensitivity analysis was performed including early hemorrhagic deaths with each MT variable (MT24h+ plus hemorrhagic deaths within 24 hours [MT24h+]; MT6h+ plus hemorrhagic deaths within 6 hours [MT6h+]).

To determine individual predictive utility of a trigger for predicting MT, the odds ratio (OR) and 95% confidence interval (CI) of receiving an MT was calculated using logistic regression. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each trigger. The percentage of correct classification (true-positive results plus true-negative results divided by the total) was determined. χ², t test, and Mann-Whitney U-tests were used to compare relevant groups as applicable. All data analysis was performed using SAS/STAT (version 9.2, Cary, NC) and SPSS (version 18).

Determination of the FAST Trigger

FAST was reported (rFAST) in only 67% of the cohort. Some centers did not perform FAST in certain patients (penetrating trauma), and those in extremis may have gone directly to the operating room without a FAST. Given data were likely not missing at random, a result was substituted for those with missing FAST using a modified method described in the Prince of Wales Hospital transfusion score.

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The DPL result was determined by the attending surgeon at the time of the procedure. If a patient went to the operating room from the ED with no FAST or DPL (ORFAST), repair of major solid-organ or vascular abdominal injury was substituted for a positive FAST result because these injuries would frequently be associated with significant hemorrhage on abdominal entry. For those with no immediate abdominal operation but who did have an ED abdominal computed tomographic scan, a FAST result was determined from the presence or absence of intra-abdominal hemorrhage. If none of the these were available,
a FAST variable was not reported. The derived FAST (dFAST) represented the reported or surrogate results and was determinable for 96% of the cohort (Table 1). Sensitivity analysis was performed with dFAST included and not included in each model.

**Massive Transfusion Score**

If data were not available or determinable for a trigger in at least 75% of the patients, it was not included as a variable in the MTS. In the subset of patients for whom data were available for all triggers (ALL group), the adjusted ORs for MT of each trigger were determined using a hierarchical mixed effects logistic regression nested for study site. Center effects were included in the analysis to account for unmeasured confounding attributable to variations across study sites. Two analyses were then performed to identify the best predictive MTS. First, each criterion based on the individual predictive adjusted ORs was assigned a weighted value if the trigger was met. Alternatively, each criterion was equally weighted with 1 point assigned for each trigger met.

Total scores were calculated at the patient level, and comparison was made between those receiving MT and no MT based on threshold scores. The overall accuracy for prediction of MT were determined for the final MTS models (criterion equally weighted) using the area under the receiver operating characteristic curve (AUC). Correlation coefficients of predicting MT using MTS were calculated. The OR for requiring MT was determined for an MTS of 2 or greater.

### RESULTS

**Overall**
The PROMMTT cohort included 1,245 patients from a total screened potentially eligible population of 12,561. Penetrating trauma was the mechanism of injury in 35%. Based on transfusion data, 297 (24%) received an MT24h (>10 U of RBCs in the initial 24 hours). The percentage of patients receiving MT24h was equivalent between those with a rFAST, DPL, and ORFAST (Table 1). For each trigger, data were available for a variable number of patients with temperature being the least frequently known parameter (51%) (Table 2). INR was available in 87% (1,081 of 1,245).

**Utility of Individual Transfusion Triggers**
For all triggers except temperature, if the trigger was met, the mean units of transfused RBCs was greater in the group who met that target than the group that did not meet the target (Table 2). The largest difference in RBC use was seen for the INR trigger (13.5 U vs. 6.6 U, \( p < 0.0001 \)).

On univariate analysis, the likelihood of requiring MT24h was greatest when the INR target was exceeded (OR, 3.4; 95% CI, 2.5–4.7), followed by BD (OR, 2.8; 95% CI, 2.0–3.9), and SBP (OR, 2.6; 95% CI, 1.9–3.4) (Table 2). The INR trigger was positive in 19% of patients, and 43% of these patients got an MT24h. If any individual trigger was met, at least 22% (range, 22–43%) of the patients went on to receive MT24h (Table 2).

To account for patients who would have likely received MT24h but died of hemorrhage before receiving 10 U of RBCs, a sensitivity analysis was performed including these patients in the MT group (MT24h+). This analysis had little effect on the predictability of the individual transfusion triggers with the exception of an increase in the likelihood of receiving MT (OR, 4.0) and the number receiving MT (49%) for the INR trigger (Table 2).

Sensitivity, specificity, NPV, and correct classification percentage for each individual trigger was also unaffected by including hemorrhagic deaths within 24 hours (Table 3). NPV for MT24h+ for each trigger exceeded 75%, with BD being the highest (85%) followed by temperature (82%), and Hgb (82%). For each trigger, using only that single trigger, patients were correctly classified 57% to 75% of the time with INR having the highest rate.

**MT at 6 Hours**
The individual transfusion triggers were also predictive of MT at 6 hours (MT6h+). INR remained the most predictive, followed by BD and Hgb (Table 2). If any trigger was exceeded, MT was seen within 6 hours in between 21% and 40% of patients exceeding the relevant trigger. Sensitivity and NPV were increased for each trigger at 6 hours compared with 24 hours (Table 3). Correct classification was also improved with the exception of a slight decrease for the BD trigger.

**Massive Transfusion Score**
Given that temperature did not distinguish between RBC use (Table 2) and data were available in only 51% of the cohort, it was excluded from the MTS. When dFAST was used, 66% of the patients (822 of 1,245) had all 7 remaining triggers known (ALL group) including 67% of those receiving an MT24h (199 of 297). Using mixed effects hierarchical multiple logistic regression, adjusted ORs for MT were calculated for the ALL group (Table 4). INR remained the most significant predictor in each model.

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**TABLE 1. Derivation of the dFAST Variable**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort, n (%)</th>
<th>MT, %</th>
<th>OR MT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST or DPL reported</td>
<td>FAST reported (rFAST)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 874 total)</td>
<td>838 (67)</td>
<td>26†</td>
<td>2.1 (1.5–2.9)</td>
</tr>
<tr>
<td>FAST or DPL reported</td>
<td>36 (3)</td>
<td>36†</td>
<td></td>
</tr>
<tr>
<td>No FAST/DPL, but went to OR (ORFAST) (n = 263 total)</td>
<td>No abdominal operation</td>
<td>160 (13)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Abdominal operation</td>
<td>103 (8)</td>
<td>28</td>
</tr>
<tr>
<td>No FAST/DPL/OR but ED CT scan dFAST</td>
<td>Total</td>
<td>63 (5)</td>
<td>5 N/A</td>
</tr>
</tbody>
</table>

*FAST or DPL reported versus ORFAST, \( p = 0.5 \) (Mann-Whitney U-test).
†rFAST versus DPL, \( p = 0.2 \) (Mann-Whitney U-test).
N/A, not applicable.
Using the adjusted ORs to determine a relative point value for each trigger, a weighted score was calculated for each patient in the ALL group. The accuracy of predicting MT was then determined (data not shown) for various cutoff values (c-statistic, 0.60–0.68). Alternatively, the criterion was assigned an equal weight of 1 point for each trigger met and the total summed (MTS). This equally weighted score provided the best overall accuracy of receiving an MT at both 24 hours and 6 hours when hemorrhagic deaths were accounted for (c-statistic > 0.70, Table 5).

Using the equal weighted model, as the MTS increased, it was highly predictive of who received MT24h+ (Fig. 1). Patients with an MTS of less than 2 were unlikely to receive MT24h+ (NPV, 99%). If any two triggers were met, the sensitivity for predicting MT24h+ was 85%, and PPV was 33% (Table 4). MT24h+ was present in 33% of patients with an MTS of 2 or greater compared with 11% of those with MTS of less than 2 (OR, 8.2; 95% CI, 2.5–28.5; p < 0.0005). The MTS also demonstrated even higher sensitivity (90%), NPV (95%), and correlation for MT prediction within 6 hours (Table 5).

Inclusion of the dFAST variable in the MTS improved the sensitivity of the models while not biasing the contribution of each individual trigger. For example, the ORs of all the triggers for prediction of MT24h+ and the overall model ORs for MT remained nearly identical with and without inclusion of the dFAST (Tables 4 and 5). Moreover, penetrating trauma and HR were not independent predictors of MT; however, inclusion of the variables in the MTS improved the sensitivity (MT24h+, 75–85%).

To explore the utility of the MTS if not all seven triggers were known for a given patient, the model was applied in the remaining 34% of the cohort (NOT ALL group, n = 423). The model remained predictive of receiving an MT (R² = 0.94; c-statistic, 0.80) as the number of triggers met increased. Sensitivity and NPV for predicting MT24h+ remained high at 82% and 89%, respectively. Overall in the NOT ALL group, 35% of patients required MT24h+ if the MTS is 2 or greater compared with 11% for those with MTS of less than 2 (OR, 4.4; 95% CI, 2.5–7.5, p < 0.0005).

**DISCUSSION**

Previous studies have shown a survival advantage to early balanced resuscitation for patients ultimately requiring MT.8–12 Despite these advances, early identification of patients with a high likelihood of needing significant transfusion remains a challenge in the trauma bay.

A number of predictive scores have been developed from retrospective data; however, the scores have variable accuracy and sensitivity.5–12,24,25 The Trauma Associated Severe Hemorrhage (TASH)-weighted score remains to be most promising

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**TABLE 2. Likelihood of MT and Mean RBC Transfusion Volume for Individual Transfusion Triggers**

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Data Available, n</th>
<th>Data Available, %</th>
<th>Mean Units RBCs Transfused</th>
<th>Likelihood of MT (OR, 95% CI)</th>
<th>Percentage of MT if Trigger Exceeded (PPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &gt; 1.5</td>
<td>1,081</td>
<td>87</td>
<td>13.5 ± 1.0</td>
<td>6.6 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP &lt; 90 mm Hg</td>
<td>1,213</td>
<td>97</td>
<td>11.2 ± 0.7</td>
<td>6.5 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hgb &lt; 11 g/dL</td>
<td>1,198</td>
<td>96</td>
<td>10.3 ± 0.6</td>
<td>6.8 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BD ≥ 6</td>
<td>960</td>
<td>77</td>
<td>10.5 ± 0.6</td>
<td>5.5 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>dFAST (+)</td>
<td>1,199</td>
<td>96</td>
<td>12.0 ± 0.7</td>
<td>7.0 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HR ≥ 120 bpm</td>
<td>1,218</td>
<td>98</td>
<td>9.9 ± 0.6</td>
<td>7.3 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Penetrating</td>
<td>1,242</td>
<td>100</td>
<td>9.0 ± 0.6</td>
<td>7.7 ± 0.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Temperature &lt;35.5°C</td>
<td>630</td>
<td>51</td>
<td>7.7 ± 0.8</td>
<td>6.4 ± 0.4</td>
<td>0.11</td>
</tr>
</tbody>
</table>

MT 24h, ≥10 U of RBCs in 24 hours; MT24h+, ≥10 U of RBCs in 24 hours plus hemorrhagic deaths within 24 hours; MT6h+, ≥10 U of RBCs at 6 hours plus hemorrhagic deaths within 6 hours.

**TABLE 3. Utility of Individual Transfusion Triggers**

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Percentage of Correctly Classified</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &gt;1.5</td>
<td>MT 24h</td>
<td>74</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>SBP &lt; 90 mm Hg</td>
<td>MT 24h</td>
<td>69</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>Hgb &lt; 11 g/dL</td>
<td>MT 24h</td>
<td>65</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>BD ≥ 6</td>
<td>MT 24h</td>
<td>56</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>dFAST (+)</td>
<td>MT 24h</td>
<td>68</td>
<td>68</td>
<td>71</td>
</tr>
<tr>
<td>HR ≥ 120 bpm</td>
<td>MT 24h</td>
<td>64</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Penetrating</td>
<td>MT 24h</td>
<td>58</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>Temperature &lt;35.5°C</td>
<td>MT 24h</td>
<td>71</td>
<td>70</td>
<td>73</td>
</tr>
</tbody>
</table>

MT 24h, ≥10 U of RBCs in 24 hours; MT24h+, ≥10 U of RBCs in 24 hours plus hemorrhagic deaths within 24 hours; MT6h+, ≥10 U of RBCs at 6 hours plus hemorrhagic deaths within 6 hours.

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score, which requires complex calculations and thus limits its ease of use.\textsuperscript{19,24,25} In addition, all but one civilian score excluded INR,\textsuperscript{24} and it has been recently shown to be a significant individual predictor in a retrospective cohort of patients who required early operative intervention (CITT).\textsuperscript{1}

The present study is the first to prospectively examine the predictive ability of individual triggers to expeditiously identify those who are likely to receive MT. This cohort represents a diverse population more closely reflective of the patient spectrum encountered in civilian trauma centers compared with previous studies.\textsuperscript{7} Although this is the best currently available prospective cohort for testing transfusion triggers, it is important to acknowledge that patients needed to receive at least 1 U of RBCs for enrollment.

All triggers from the CITT except temperature remained significant individual predictors of MT. Although the correct classification rate and MT rate with a positive INR trigger were slightly lower in the present study compared with CITT,\textsuperscript{1} the results remain consistent with INR as the best individual trigger followed by SBP, BD, and Hgb. Importantly, all the individual triggers remained significant negative predictors (NPV > 80\%) of MT. Given the clinical utility of the laboratory parameters hypothesized in the CITT study and validated in the present prospective cohort, particular effort should be undertaken to obtain these parameters as rapidly as possible on patient arrival.

The parameters of FAST, HR of 120 bpm or greater, and penetrating injury mechanism also had significant ability to discriminate between those requiring and not requiring significant RBC volumes. The inclusion of the dFAST variable, which uses surrogate data to derive a FAST parameter when the data were missing, provided an improvement in sensitivity of the models without biasing the outcomes of interest. As an example, the ORs of prediction of MT at 24 hours and 6 hours remained essentially statistically unchanged. However, it is important to note that if FAST data are not known, a limited MTS (no FAST included) was still useful for predicting likelihood of needing an MT.

In this study, an equally weighted MTS had no tradeoff in accuracy compared with a weighted score. In addition, the MTS that resulted in a screening test with the best sensitivity and reliability given the consequences of delayed resuscitation was desired. The sensitivity or ability of a test to identify correctly those who have the condition of interest should be high when the consequences for missing a positive case are significant.\textsuperscript{1} Driving a model to a higher sensitivity trades off a degree of accuracy, which was tolerable in this clinical scenario, given that consequences for overtreatment are minimal compared with the substantially increased mortality with undertriage.

The MTS was sensitive in predicting MT at 24 hours or 6 hours as the number of positive triggers increased. In addition, the NPV was improved with combining the triggers into

### TABLE 5.

Performance of the Model for Prediction of MT With an MTS of 2 or Greater

<table>
<thead>
<tr>
<th>MTS ≥ 2</th>
<th>MT at 24 h</th>
<th>MT at 24 h + Hemorrhagic Deaths Within 24 h</th>
<th>MT at 6 h + Hemorrhagic Deaths Within 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dFAST (n = 822)</td>
<td>No FAST (n = 847)</td>
<td>dFAST (n = 822)</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>85</td>
<td>81</td>
<td>85</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>41</td>
<td>47</td>
<td>41</td>
</tr>
<tr>
<td>PPV, %</td>
<td>31</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>NPV, %</td>
<td>89</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.95</td>
<td>0.93</td>
<td>0.95</td>
</tr>
<tr>
<td>C-statistic (95% CI)</td>
<td>0.69 (0.65–0.74)</td>
<td>0.68 (0.64–0.72)</td>
<td>0.70 (0.66–0.74)</td>
</tr>
<tr>
<td>OR MT (95% CI)</td>
<td>3.9 (2.5–5.9)</td>
<td>3.7 (2.5–5.5)</td>
<td>3.9 (2.6–5.8)</td>
</tr>
</tbody>
</table>

Boldface indicates statistical significance, $p < 0.05$.  

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the MTS compared with using individual triggers alone. In fact, the ability to exclude (NPV, 95%) the likelihood of MT using the score was excellent when considering early significant hemorrhage (MT6h+). Thus, if patients had less than 2 positive triggers (MTS $< 2$), they were highly unlikely to receive an MT by 6 hours. Importantly, the score was also useful for prediction of MT even if data were not available for every trigger.

Previously published transfusion scores with equal weighting and thus, ease of use, have focused on high accuracy over sensitivity owing to concern for overtriage. This has resulted in poorer model sensitivity (53–75%) compared with the current MTS model (85% MT24h+, 90% MT6h+). The sensitivity of previous scores has been especially poor when validation studies have been attempted. Reliance on the MTS alone would result in initiating balanced resuscitation in a proportion of patients who would ultimately not require MT. Although inappropriate use and risk of RBCs and plasma transfusion are of concern, there are data to suggest that balanced resuscitation may still benefit severely injured trauma patients who do not ultimately require MT volumes. Although the utility of individual triggers are validated in this study, the combined MTS should be further studied in future prospective studies.

Previous work has been unable to account for survivor bias in determining predictive MT algorithms given the retrospective nature of the data collection. One of the major strengths of the PROMMTT study for transfusion trigger analysis was that cause-of-death variables were available. Thus, the timing of deaths from early exsanguination was known, and an attempt to minimize survivor bias was possible. By performing a sensitivity analysis assuming these patients would have required MT if they had survived long enough to receive 10 U of RBCs, the model performance remained consistent.

Despite being an observational study with no mandate for changes to an individual trauma centers routine clinical practice, the ascertainment and availability of data for the individual triggers across the various centers was quite complete (with the exception of temperature). In addition, the method of data collection was standardized across centers and audited by the centralized DCC. The inclusion of a DCC in the study insured the integrity of data collection and likely contributed to

Figure 1. Prediction of MT based on the MTS. MT 24h, $\geq 10$ U of RBCs in 24 hours; MT24h+, $\geq 10$ U of RBCs in 24 hours plus hemorrhagic deaths within 24 hours; MT6h+, $\geq 10$ U of RBCs at 6 hours plus hemorrhagic deaths within 6 hours.
the completeness of trigger data availability. The site-specific ordering and recording practices reflect the practices across Level I trauma centers, and center effects were included in the analysis to account for unmeasured confounding attributable to variations across study sites.

CONCLUSION

Parameters that can be obtained early in the initial ED evaluation are valid predictors for determining likelihood of MT. The overall sensitivity for predicting significant blood volume needs was improved by combining the triggers into the MTS. The score can be applied with ease in an expeditious manner early in the patient course as a guide to avoid undertriage of patients most likely to benefit from balanced resuscitation of platelet, plasma, and RBCs.

AUTHORSHIP


DISCLOSURES

J.B.H. reports serving on the board for Tenaxis, Winklewerder Company, the Regional Advisory Council for Trauma, and the National Trauma Institute; providing expert testimony for the Department of Justice; grants funded by Haemonetics Corporation and KCI USA, Inc., and patent royalties paid through his institution.

C.E.W. reports serving on the Science Board for Resuscitation Products, Inc. and the Advisory Board for AstraZeneca.

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REFERENCES


**DISCUSSION**

**Dr. Timothy C. Fabian** (Memphis, Tennessee): I would like to compliment the authors on a biostatistical tour de force, and chide Dr. Coimbra and the program committee for offering up this defenseless pilgrim as the discussant. I damn near fell out when I ran into “using mixed effects hierarchical multiple logistic regression!” I should have listened to Marilyn vos Savant, “Be able to analyze statistics, which can be used to support or undercut almost any argument.”

They have performed a post hoc analysis of the PROMMTT database, an observational study designed to investigate in-hospital mortality in trauma patients requiring team activation, arriving from the scene, and receiving at least 1 U of red blood cells (RBCs) within 6 hours. The intent of this post hoc analysis was to define emergency department triggers for massive transfusion (MT) and to develop a MT score. I will make a few observations on methodology and a couple of comments regarding data analysis.

They make the caveat that to be in the PROMMTT study, patients had to receive at least 1 U of RBC but do not expand on the implications relative to evaluating the seven selected triggers and developing the MT score. I believe this is a crucial issue relative to any practical clinical application. The issue becomes, what about patients who received no units, and that issue is not trivial. The sensitivities of the seven triggers may not suffer since any patient receiving MT defined as 10 U or greater in 24 hours would obviously all have received the first unit. However, the specificity and positive predictive values of the triggers would certainly decrease if all patients receiving trauma team activation were included in the study because some percentage of those would not receive any RBCs but would have some of the seven triggers positive. That would lead to unnecessary activation of MT protocols. The authors suggest that overtriage is preferred over undertriage. However, I am not so sure this is a free lunch. Please comment on this concern.

It is stated in Methods section that, “If data were not available in at least 75% of the patients, it was not included as a variable in the MTS.” Yet, Focused Assessment for the Sonography of Trauma (FAST) was reported in only 67% of the patients. Thus, a derived FAST (dFAST) was developed based on three surrogates for FAST: diagnostic peritoneal lavage, going directly to the operating room from the emergency department, or abdominal computed tomography showing hemorrhage. The diagnostic peritoneal lavage and computed tomography groups were small, and definitions of positivity were not stated. More problematic is the larger group of patients who went to the operating room (ORFAST). Only 41% of those patients had an abdominal operation. Presumably, most of the others had orthopedic procedures. Why not just drop FAST as a trigger in the study? Please comment.

You developed a statistical rationale to apply an equal weighted model for the triggers to predict MT and develop the MT score. However, trigger positivity ranged from 22% to 43%, with international normalized ratio of greater than 1.5 being the most sensitive. The equal weighting may have held up to your statistical methodology, but a doubling of the sensitivity range makes me a little uneasy. Please comment.

There were 297 patients (24%) who received MT during the 15-month study period in the 10 trauma centers. That averages out to two patients per month per center. It seems likely there were some with more and some less. Did you evaluate for any center effects?

To address potential survivor bias, you divided the population into four cohorts: MT24h, MT24h plus hemorrhagic deaths within 24 hours (MT24+), MT6h, and MT6h plus deaths within 6 hours (MT6+). I think that was a good idea, but I could not find the numbers of patients in those four cohorts. What were the mortality numbers? While the tables demonstrated sensitivity, specificity, negative predictive values, and odds ratios for three of the cohorts, I could find no results for these for the MT6h cohort. Please help.

I will come full circle with this final observation concerning overtriage. The authors support the concept of using a MT score of 2 or greater to avoid undertriage, although acknowledging that it “would result in initiating balanced resuscitation in a proportion of patients who would ultimately not require MT.” Their data demonstrate that proportion would be 2 of 3 of their study population. Remember again, the false-positive patient number would be even higher in real world rather than PROMMTT study population that was selected by having at least 1 U of RBCs. They note that, “although inappropriate use risk of RBCs and plasma transfusion are of concern, there are data to suggest that balanced resuscitation may still benefit severely injured trauma patients who do not ultimately require MT volumes.” As there are, indeed, identified risks associated with transfusion of both RBCs and plasma, I would respond that sometimes “free lunches” are more expensive than the ones you pay for.

I thank Dr Callcut for an excellent presentation, and the Association for the privilege of the floor.

**Dr. Hasan B. Alam** (Boston, Massachusetts): During your very nice presentation, I was thinking about how I am going to use this information taking care of the patients tomorrow, so two very simple questions. One is that all of this is post-hoc analysis of the data, and its looks very good, but how practical is it to use it in real life? Is it possible to look at all these variables and generate the predictive score in real-time?

When you do that, is it really any better than a seasoned surgeon just looking at the patient and saying, “this patient is really messed up, please activate the MT protocol?”

**Dr. Juan A. Asensio** (Valhalla, New York): Very nice paper. However, without some of the initial admission data and even initial admitting arterial blood gas data, I am confused.

Having spent most of my life in trauma centers that have dealt with large volumes of penetrating injuries, I find that your statement on penetrating trauma does not account for some of your findings. Therefore, I wonder how many thoracotomies, how many major laparotomies, and how many abdominal vascular injuries have you encountered.

In our own article that reported 548 patients who exsanguinated, which actually set the criteria for when to institute damage control, we could accurately predict patients who would need MT. (Am J Surg. 2001;182(6):743–751).

Furthermore, even on other articles from our institution, we could predict with reasonable certainty when to stop transfusions, as we had patients, albeit outliers, that survived with hundreds of units.
So I must say, not having seen the article, that most of these patients did not have major vascular, thoracic, or cardiac injuries or required emergency department thoracotomy. Could you please clarify this information? In my opinion, many of these patients did not sustain the life-threatening injuries that would usually require activation of this protocol.

**Dr. Babak Sarani** (Washington, D.C.): The ABC score that you alluded to has already been validated by one of the authors of the PROMMTT study so why bother creating yet another validation score?

ABC is easier to calculate than what you had, as Dr. Alam just pointed out. Your graphs show that they are equally effective.

**Dr. Norman McSwain** (New Orleans, Louisiana): Unless I misread or misheard what you said, an hematocrit of 28 was one of your trigger points. If hematocrit was 28, you do not look at the amount of blood the patient has lost.

A lot of our patients function at an hematocrit of 30 all the time, so the drop of the hematocrit to 28 is less than 1 U of blood loss. That is certainly not an indication for an MT. Would you please comment?

It is true that the PROMMTT study group is a select patient group; however, this is the best available cohort of multicenter prospective patients that we have to date. When you do an observational prospective study, you have to make some relative inclusion criteria that makes sense. Although it is a select patient population, we believe that the score will probably hold up and plan to validate this in subsequent prospective studies that are ongoing.

With regard to the sensitivity, specificity, and positive predictive value of the individual triggers, those results are based on univariate analysis. We know from prior work that the triggers have some collinearity. This means that the individual predictors likely overestimate a certain degree of the predictive ability and therefore, that's why we used a summation score. Thus, equal weighting of triggers may not be superior to differential weighting because the vast majority of the distribution of the effect of an individual factor may be collinear with another factor in the model.

To speak to the question of center effect, this was accounted for in our nested analysis. There are clearly some center effects. We have other data from the PROMMTT study that we have discussed and in the process of publishing showing that there are some differences across the centers with regard to some degree the way the patients were resuscitated, although it is fairly consistent.

Given that, we've shown we can control for center effect using the nested study design that controlled specifically for center differences.

With regard to using the individual triggers, the point of this is not for you guys to focus on one trigger over another but really the summation of all the triggers because, you are absolutely right, an individual trigger such as hemoglobin with a single drop in a lab, and especially in a civilian patient population, may not mean as much as putting the triggers together.

This study was is in no way done to suggest that the MTS is a substitute for clinical judgment. The real fine point of this particular story is we still struggle with not trying to figure out who clearly needs massive transfusion and who clearly doesn't need massive transfusion but the vast majority of severely injured patients who might need massive transfusion. This particular scoring has the opportunity to actually decipher who that patient population is in order to initiate massive transfusion earlier.

To just speak to the ABC Score, the reason we did not use just the ABC Score and we used another score and proposed another score is that in subsequent studies every prediction algorithm that's been published to date, including the ABC Score, when it's been applied to other patient population besides the one that it was originally validated in has not performed as well as it performs in the original validation study.

This difference in performance probably speaks a little bit to the survivor bias issue as well as to the issue of selection. So that's why we created another scoring system that captures some of the other triggers and pulls them in from other work that's shown that the addition non-ABC triggers are also actually important.

In regard to the remaining number of the thoughtful questions raised, including the illness level of the patients, derivation of the D-FAST, and the ease of use of our score, further detail is provided in our paper and the original PROMMTT outcomes paper which is in press to be published in the Archives of Surgery in October 2012. The patients were an ill cohort of all comers including more than half suffering from hemorrhage in the abdomen or chest, a median ISS of 25, and one-third were victims of penetrating trauma.

I just also want to speak DFAST really quickly to that. We present in our paper both the data, which I did not show for time's sake, with the FAST included and with the FAST not included and the effect persists.

We also took this data and applied it to the one-third of the patients who did not have every trigger available, and the effect continues to persist and the algorithm actually continues to be predictive. This is part of the advantage to the MTS over ABC. You do not need every element to be known in the MTS to still be useful.

Thank you very much to all the fellow PROMMTT investigators and everyone who has contributed a great deal of effort to getting this to this point. I appreciate everyone's comments. Thank you.

**APPENDIX**

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