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Do Not Resuscitate Orders in Trauma Patients May Bias Mortality-Based Effect Estimates: an evaluation utilizing the PROMMTT study

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Abstract

Background—The impact of do not resuscitate (DNR) orders have not been systematically evaluated in acute trauma research. We determined the frequency, timing and impact on mortality-based effect estimates for patients with DNR orders in the the PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study.

Methods—Trauma patients surviving at least 30 minutes and transfused ≥ 1 RBC unit within 6 hours of admission (n=1245) from ten Level 1 centers were enrolled. We report descriptive statistics and results from survival analysis to compare the association of blood product transfusion ratios with outcome defined as mortality and as a composite, DNR and death.

Results—DNRs were reported for 95 patients (7.6%) with 94 in-hospital deaths. There were 172 deaths without DNRs. Of 90 known DNR order times, the median was 53 hours (IQR=9-186 hours) after admission; the median DNR-to-death time was 10 (2-32) hours. DNRs were for comfort measures only (43%), no CPR (40%), and no intubation or CPR (16%). Compared with the 116 non-DNR deaths that occurred after the earliest DNR order (2-hours), the DNR decedents were significantly older with a less severe base deficit, fewer RBC and plasma transfusions, and a later median time of death: 98 (21-230) vs. 17 (4-91) hours. In multivariable Cox models that accounted for time-varying blood product ratios, the associations were consistent regardless of whether outcome was defined as mortality or the composite.

Conclusion—DNR orders were instituted after the 24-hour period of highest mortality risk and more often in older patients not in severe shock. Findings from the primary PROMMTT analyses of the impact of blood product ratios on survival did not materially change when the original mortality outcome was redefined as a composite of DNR or death. DNR orders are potentially an important mediating variable that should be systematically evaluated in trauma research.

Keywords

survival; resuscitation; withdrawal of care

Introduction

Efficacy studies of initial interventions in the care of the patient with traumatic injuries use 28-30 day survival as the primary endpoint.^{1, 2} Historically the impetus for this endpoint was the tri-modal distribution of mortality when a significant number of deaths occurred beyond seven days after injury.³⁻⁵ Though this pattern is no longer observed the 28-30 day mortality endpoint is still employed.⁶⁻⁸ Recent work has shown the majority of deaths due to traumatic injuries occur within three days after hospital admission. There is a period of early deaths within the first 6-24 hours and a second population at 24 to 72 hours. In fact, less than eight percent of the deaths associated with traumatic injury now occur after seven days.⁶⁻⁸

A potential factor impacting deaths occurring beyond 24 hours is the implementation of do not resuscitate (DNR) orders. Among trauma patients, these orders are initiated in 5 to 7% percent of the population.^{9, 10} In contrast, the proportion of medical patients with a DNR order is 15 to 18%.^{11, 12} The average time of implementation of a DNR order is 24-48 hours after admission in trauma patients.^{9, 10, 13} Furthermore the mortality risk in trauma patients with these orders in place is 43% to 94%.^{9, 10, 13, 14} Whereas the mortality risk with a DNR in place is 23 to 37% for general surgery patients, but in some cases may be as high as 82%.¹⁵⁻¹⁷ Franklin et al. suggested that because of the presence of DNR orders after traumatic injury that medical care could not have been expected to impact 62% of trauma deaths.¹⁸

It is clear that DNR orders could be an important mediating variable in the 30-day survival paradigm utilized by regulatory bodies. In light of these findings we proposed to determine the impact of DNR orders on the hazard ratios associating mortality with high vs. low plasma:RBC and platelet:RBC ratios the primary outcome analysis of the PROspective Observational Multicenter Major Trauma Transfusion (PROMMTT) study. Of specific interest is the validity of the 30-day survival endpoint when DNR orders are considered.

Methods

The PROMMTT study was a prospective, multicenter observational cohort study conducted at ten Level 1 trauma centers in the US. At each study site and the Data Coordinating Center, the local institutional review board approved the study as did the US Army Human Research Protections Office.^{19, 20}

Patients with severe traumatic injuries were enrolled in PROMMTT and data collection was initiated upon hospital arrival. Patients were eligible if they required the highest level of trauma activation at the center, were age 16 or older, and were transfused at least one unit of RBCs in the first six hours after admission. Patients were excluded if: 1) transferred from other facilities; 2) declared dead within 30 minutes of admission; 3) received more than 5 minutes of CPR prior to or within 30 minutes of admission; 4) prisoners; 5) burn injury > 20% of total body surface area; 6) inhalation injury diagnosed by bronchoscopy; or 7) pregnant. No changes in clinical practice were implemented in this observational study. A massive transfusion protocol was in place at all centers.

Data collection and management procedures have previously been described in detail.^{19, 20} In the data collection forms it was recorded if there was a do not resuscitate (DNR) order in place. DNR orders were documented in the data collection forms. If the response was "yes" the nature of the order was further broken down into the following categories: 1) comfort measures only, 2) no CPR, and 3) no intubation or CPR. In addition, the time of initiation of the DNR order was documented.

Statistical Analysis

To examine the extent to which DNR orders influenced mortality-based effect estimates in the entire PROMMTT study population (n=1,245), survival, regardless of DNR, was compared with DNR-free survival using Kaplan Meier survival curves, in which outcome was defined as a composite of either the time of a DNR order or the time of death. Of the patients declared DNR after ED admission, all but one later died in-hospital, and the group of decedent DNR patients was compared with the group of decedent non-DNR patients who died in-hospital without receiving a DNR order. Between-group differences were assessed using the Pearson chi square test for categorical variables and the nonparametric Wilcoxon rank sum two-sample tests for continuous variables. To assess whether DNR orders influenced the magnitude of association between a life-saving intervention i.e., blood component transfusions, and outcome, we compared results from Cox proportional hazards models defining outcome first as in-hospital mortality (published previously)²⁰ and then as a composite outcome (time of DNR order or time of death). The rationale for the original analysis has been published previously.²⁰ All analyses were performed using SAS/STAT and Stata/MP software packages.^{21, 22}

Results

Trauma patients surviving at least 30 minutes and transfused 1 RBC unit within 6 hours of admission from ten Level 1 centers were enrolled (n=1,245). There were 266 (21.4%) deaths of which 172 (64.7%) were not preceded by a DNR order. DNRs were reported for 95 patients (7.6%) with 94 in-hospital deaths, thus 99% of the patients with a DNR died. The implementation of DNR orders varied between centers from 0 to 16.5% of the patient population of the center. DNR order times were known on 90 patients with a median of 53 hours (IQR=9-186 hours) after admission; the median DNR-to-death time was 10 (2-32) hours. DNRs were for comfort measures only (43%), no CPR (40%), and no intubation or CPR (16%).

Compared with the 116 non-DNR patients whose deaths occurred sometime after the earliest DNR order (2-hours post admission), DNR decedents were significantly older (Table 1) with less severe base deficit, and fewer RBC and plasma transfusions (Table 2). Patients with a DNR in place had a later median time of death: 99 (21-230) vs. 17 (4-91) hours (p<0.001).

Clinical characteristics for the total study population of 1,245 PROMMTT patients and for the analysis sub-cohort of 905 patients who received 3 or more total blood product transfusions within 24 hours have been reported.²⁰ DNR orders did not materially influence the overall Kaplan Meier survival curves in PROMMTT patients as illustrated by the similarity of the curves and the overlap in their 95% confidence intervals (Figure 1). The graphs reflect the PROMMTT eligibility criterion that patients had to survive the first 30 minutes post ED admission.

In the multivariable Cox models that accounted for time-varying blood product ratios among the 905 patients receiving three or more total blood product transfusions within 24 hours, the associations were consistent regardless of whether outcome was defined as mortality or the composite, DNR/death (Tables 3, 4 and 5). While overall outcome analysis was not significantly altered there were specific observations of interest. For example the contribution of platelet:RBCs ratio became significant with the analysis of DNR/death within 6 hours (Table 3). The analyses of deaths from 6-24 hours and 24 hours to 30 days were not significantly impacted by employing the composite of the time of death and the time of DNR.

Discussion

In patients with traumatic injuries the use of DNR orders is highly variable between centers with an overall average of about 7%.^{9, 10} The average rate of the presence of a DNR order in the PROMMTT study, that was comprised of 10 level I trauma centers, was 7.6%. The reported mortality rates of trauma patients with a DNR order ranges from 40 to 94%.^{9, 10, 13, 14} In the PROMMTT study the mortality was 99% for patients with a DNR order. Of the in-hospital deaths associated with traumatic injuries 48-61% have a DNR order in place.^{9, 13, 23} In the present study 36% of the deaths were preceded by a DNR order. This difference is, in part, a result of the study population, those patients requiring a transfusion and presumed to be hemorrhaging and thus at risk for an early death. In the present study 50% of the deaths occurring in the first 24 hours were predominantly associated with hemorrhage.²⁰ The institution of a DNR order usually occurs 24 to 48 hours after admission similar to that noted in the present study (median of 53 hours).^{9, 10, 24} Thus those patients enrolled in PROMMTT with early deaths were not amenable to having DNR order instated in part accounting for the lower percentage of overall deaths with a DNR. This is further supported by the admission physiological differences between patient who died prior to institution of a DNR order and those with a DNR order (Table 2). Most importantly, the profile of frequency and timing of DNR orders in PROMMTT provides a unique opportunity to assess the impact, if any, on the evaluation of outcomes, specifically in the present study the ratios of blood product ratios on survival.

In the clinical evaluation of various resuscitation procedures, fluids and blood products, long-term survival has been readily accepted as it is an outcome that is understood by everyone, an important clinical endpoint, a clear objective criterion, and one that is accepted by regulatory agencies.^{1, 2} Though a clear endpoint, improved survival has been difficult to demonstrate with 30 day mortality and its utility questioned.¹ One of the issues is the timing of deaths. In the case of early deaths, the alteration of resuscitation procedures may be readily apparent, but later impacted by the complexity of care and variations in treatment days if not weeks beyond the initial intervention. Important to this time-dependent variable is the effect of competing risks of mortality, such that patients surviving a near-fatal hemorrhage may later die of their head injuries. An additional confounder is the initiation of DNR orders. Franklin et al assessed the impact of withdrawal of care and futile care on mortality in trauma patients.¹⁸ In their study there were 347 deaths of which 43% had DNR orders or were provided futile care. The overall mortality rate was 6.4% however mortality was only 2.4% in those patients they were allowed to treat. For 62% of the deaths it was deemed “that medical care could not have been reasonably expected to impact survival.” A similar finding was reported by Scarborough et al in general surgery patients.¹⁷ These studies demonstrated that there are a high percentage of deaths that present a limited chance of survival, especially when the decision is made to withdraw or limit care. This is clearly demonstrated in the PROMMTT study in that death occurred within hours of initiation of a DNR order (median 10 [2-32] hours).

The impact of DNR orders has not been systematically evaluated in acute trauma research. This is important because most trauma studies (by design) strive to enroll patients that will suffer high mortality rates. Small differences in rates, via institution of DNR orders, may alter outcomes of these studies. In the PROMMTT study, the use and timing of DNR orders appeared to be similar to those in the overall trauma population.^{9, 10, 13} To assess the impact of initiation of DNR orders on analysis of the effect of increased ratios of plasma and platelets to red cells on survival we determined the frequency and timing for patients with DNR orders in the PROMMTT study. While the initiation of DNR orders occurred later in the course of care, death happened shortly thereafter. Thus, while a significant portion of

deaths were associated with DNR orders, especially late deaths, in the present analysis there was not a significant impact in the overall analysis of survival.

While no significant effect was noted on the present analysis, initiation of DNR orders should be considered in future studies. This is of particular importance in those studies of interventions applied later in the course of care when patients who die acutely are eliminated from the study population. In the present study a significant number of deaths (36%) occurred in the first six hours after admission.²⁰ If a study was assessing outcomes of a population that excludes this group of patients the deaths associated with DNR orders would increase from 36% to 55%.

In the present study DNR orders were classified as comfort measures only, no CPR, and no intubation or CPR. These definitions were inadequate to clearly define what care the patient received. At present end of life care is poorly delineated.^{9, 25, 26} Finally, the sustainment of life support for the harvest of tissues may also affect survival time. In the formulation of studies these endpoints should be defined in order to assure uniformity across institutions to adequately account for care decisions in the analysis of survival.

The PROMMTT study was a prospective observational study with the inherent limitations with this type of study design. The present analysis was limited by possible under-ascertainment of DNR orders in patients who survived to discharge or the thirtieth hospital day, the absence of a uniform definition of DNR, as noted above, and variance of implementation of DNR orders between centers (data not presented). In addition, there was not a systematic evaluation of life saving interventions throughout hospitalization to adequately evaluate the impact of care on survival, which should be considered in future studies.

In conclusion, a significant number of deaths are associated with presence of DNR orders in patients with traumatic injuries. The initiation of DNR orders occurs well after the period of initial resuscitation, the period of highest mortality risk, and is followed shortly thereafter by death in a high percentage of patients. In PROMMTT the presence of a DNR order did not materially change the outcome of the survival analysis when the original mortality outcome was redefined as a composite of DNR order or death. We conclude that DNR orders are an important outcome that should be systematically evaluated in trauma research.

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Figure 1. Kaplan-Meier Survival estimated for 30 days for Death as Outcome (right) and Declared DNR or Death as Outcome (left).

Table 1

PROMMTT Demographic and Clinical Factors among DNR and Non-DNR Patients Who Died In-Hospital.

Variable	Whole Group (N = 206) Mean ($\pm$ SD) ^a Median (IQR) ^a	Non-DNR Patients (N = 116; 56.3%) Mean ($\pm$ SD) Median (IQR)	DNR Patients (N = 90; 43.7%) Mean ($\pm$ SD) Median (IQR)	P-Value ^b
Age	46.2 (22.0) 45.0 (25.0, 61.25) 0	42.2 (20.9) 40.0 (24.0, 56.5) 0	51.2 (22.6) 51.0 (29.5, 70.25) 0	0.004
Gender				
Female	55 (26.7%)	28 (24.1%)	27 (30.0%)	0.35
Male	151 (73.3%)	88 (75.9%)	63 (70.0%)	
Missing	0	0	0	
Mechanism				
Blunt	169 (82.4%)	93 (80.2%)	76 (85.4%)	0.33
Penetrating	36 (17.6%)	23 (19.8%)	13 (14.6%)	
Unknown/Missing/Both	1	0	1	
ISS	35.1 (14.0) 34.0 (26.0, 43.0) 0	35.0 (14.2) 34.0 (26.0, 43.0) 0	35.2 (13.9) 34.0 (26.75, 41.50) 0	0.95
Time interval at entry to analysis cohort [*]	3.1 (2.1) 2 (1, 4) 35	2.5 (1.9) 1 (1, 3.5) 18	3.8 (2.3) 3 (1, 4) 17	0.14
Ineligible ^{**}				
Bleeding site: head				
Yes	90 (43.7%)	47 (40.5%)	43 (47.8%)	0.32
No	116 (56.3%)	69 (59.5%)	47 (52.2%)	
Missing	0	0	0	
Bleeding site: chest				
Yes	39 (18.9%)	26 (22.4%)	13 (14.4%)	0.16
No	167 (81.1%)	90 (77.6%)	77 (85.6%)	
Missing	0			
Bleeding site: limb				
Yes	57 (27.7%)	35 (30.2%)	22 (24.4%)	0.43
No	149 (72.3%)	81 (69.8%)	68 (75.6%)	
Missing	0	0	0	

^{*} Time intervals at cohort entry (received ≥ 3 transfusions post ED admission): 1=hour 0.5-0.75; 2=hour 0.75-1; 3=hour 1-1.5; 4=hour 1.5-2; 5=hour 2-2.5; 6=hour 2.5-3; 7=hour 3-3.5; 8=hour 3.5-4; 9=hour 4-4.5; 10=hour 4.5-5; 11=hour 5-5.5; 12=hour 5.5-6; 13=hour 6-24.

^{**} Ineligible = received <3 transfusions within 24 hours of ED admission and thus ineligible for analysis cohort.

Table 2

PROMMTT Continuous Demographic and Clinical Factors Among DNR and Non-DNR Patients Who Died In-Hospital (-6 hour deaths).

Variable	Whole Group (N = 206) Mean ($\pm$ SD) ^a Median (IQR) ^a	Non-DNR Patients (N = 116; 56.3%) Mean ($\pm$ SD) Median (IQR)	DNR Patients (N = 90; 43.7%) Mean ($\pm$ SD) Median (IQR)	P-Value ^b
Systolic Blood Pressure	112.8 (36.5)	108.0 (34.5)	118.6 (38.2)	0.09
	110.0 (85.5, 132.5)	108.0 (79.5, 130.25)	116.0 (90.0, 142.0)	
Missing	13	10	3	
Heart Rate (ED)	104.7 (33.4)	104.2 (34.4)	105.3 (32.4)	0.79
	103.0 (81.0, 126.0)	104.5 (83.0, 127.75)	103.0 (80.5, 123.5)	
Missing	5	4	1	
Temperature (ED) (F°)	96.4 (2.2)	96.4 (2.3)	96.4 (2.1)	0.66
	96.8 (95.4, 97.8)	96.94 (95.27, 97.90)	96.8 (95.5, 97.65)	
Missing	127	74	53	
ED FAST Results				0.07
Negative	98 (68.1%)	50 (61.7%)	48 (76.2%)	
Positive	46 (31.9%)	31 (38.3%)	15 (23.8%)	
Missing	62	35	27	
GCS	5.6 (4.4)	5.7 (4.6)	5.4 (4.1)	0.84
	3.0 (3.0, 7.0)	3.0 (3.0, 8.0)	3.0 (3.0, 6.0)	
Missing	17	7	10	
Base Deficit	-8.3 (6.7)	-9.4 (7.5)	-6.9 (5.5)	0.04
	-7.0 (-12.0, -4.0)	-7.15 (-14.0, -4.05)	-7.0 (-10.9, -3.0)	
Missing	35	24	11	
PH	7.2 (0.2)	7.2 (0.2)	7.2 (0.1)	0.05
	7.23 (7.09, 7.32)	7.2 (7.045, 7.31)	7.24 (7.14, 7.3275)	
Missing	33	23	10	
PTT (ED)	40.4 (21.9)	43.4 (24.4)	36.9 (18.1)	0.05
	34.2 (28.5, 44.7)	36.0 (29.3, 49.325)	31.2 (27.4, 42.6)	
Missing	33	22	11	
PT (ED)	18.6 (8.6)	19.0 (7.5)	18.3 (9.5)	0.76
	16.1 (14.4, 18.95)	16.4 (14.025, 20.55)	16.0 (14.75, 18.15)	
Missing	49	40	9	
INR (ED)	1.6 (0.9)	1.6 (0.6)	1.7 (1.2)	0.98
	1.4 (1.2, 1.645)	1.4 (1.2, 1.72)	1.39 (1.2, 1.6)	
Missing	25	17	8	

Variable	Whole Group (N = 206) Mean ($\pm$ SD) ^a Median (IQR) ^a	Non-DNR Patients (N = 116; 56.3%) Mean ($\pm$ SD) Median (IQR)	DNR Patients (N = 90; 43.7%) Mean ($\pm$ SD) Median (IQR)	P-Value ^b
Platelet (ED)	207.8 (91.9)	201.5 (102.9)	215.8 (75.5)	0.07
	202.0 (160.0, 252.0)	187.0 (152.0, 247.0)	214.0 (171.75, 257.25)	
Missing	11	7	4	
HGB (ED)	11.5 (2.4)	11.4 (2.7)	11.6 (2.1)	0.60
	11.7 (10.2, 13.3)	11.5 (10.1, 13.325)	11.8 (10.2, 13.375)	
Missing	8	6	2	
MT				0.01
No	118 (57.3%)	57 (49.1%)	61 (67.8%)	
Yes	88 (42.7%)	59 (50.9%)	29 (32.2%)	
Missing	0	0	0	
Substantial Bleeding				0.04
No	109 (52.9%)	54 (46.6%)	55 (61.1%)	
Yes	97 (47.1%)	62 (53.4%)	35 (38.9%)	
Missing	0	0	0	
6 Hour Total RBC	12.7 (14.7)	15.9 (16.5)	8.7 (11.0)	0.001
	6.0 (3.0, 17.0)	9.0 (3.5, 24.5)	4.0 (2.0, 10.0)	
Missing	10	7	3	
6 Hour Total Plasma	9.8 (12.0)	11.8 (13.4)	7.3 (9.6)	0.03
	5.0 (2.0, 13.0)	6.0 (2.0, 18.5)	4.0 (2.0, 10.0)	
Missing	10	7	3	
6 Hour Total Platelets	7.3 (10.9)	8.8 (12.6)	5.4 (7.9)	0.15
	0.0 (0.0, 12.0)	6.0 (0.0, 12.0)	0.0 (0.0, 6.0)	
Missing	10	7	3	

^aP-values for the categorical data were calculated using Pearson Chi-Square

Table 3

For the first 6 hours Post ED admission a comparison of Death as Outcome and Declared DNR or Death as Outcome using a Multivariable Cox Time-dependent Analysis.

	Death as Outcome (876 patients with 3,606 hours at risk, 94 deaths)			Declared DNR or Death as Outcome (876 patients with 3,585 hours at risk, 98 failures including 12 DNRs)		
Covariate	Adjusted Hazard Ratio	95% Confidence Intervals	P value	Adjusted Hazard Ratio	95% Confidence Intervals	P value
*Plasma:RBC Ratio	0.31	0.17-0.57	<0.0005	0.36	0.20-0.64	0.001
*Platelet:RBC Ratio	0.55	0.28-1.07	0.080	0.51	0.27-0.99	0.047
Age	1.01	1.00-1.02	0.032	1.01	1.00-1.02	0.029
ISS	1.02	1.01-1.04	0.001	1.02	1.01-1.04	<0.0005
Bleeding Chest	1.53	0.96-2.44	0.076	1.44	0.91-2.29	0.118
Bleeding Limb	0.54	0.31-0.93	0.027	0.55	0.32-0.93	0.026
Bleeding Head	3.71	2.29-6.03	<0.0005	3.95	2.45-6.36	<0.0005
Entry Time	0.73	0.64-0.84	<0.0005	0.75	0.66-0.85	<0.0005
*Cumulative Sum of Transfusions	1.05	1.04-1.07	<0.0005	1.06	1.05-1.07	<0.0005

Table 4

At 6-24 hours Post ED admission a comparison of Death as Outcome and Declared DNR or Death as Outcome using a Multivariable Cox Time-dependent Analysis.

Covariate	Death as Outcome (809 patients with 14,070 hours at risk, 37 deaths)			Declared DNR or Death as Outcome (805 patients with 14,007 hours at risk, 37 failures including 13 DNRs)		
	Adjusted Hazard Ratio	95% Confidence Intervals	P value	Adjusted Hazard Ratio	95% Confidence Intervals	P value
*Plasma:RBC Ratio	0.34	0.14-0.79	0.012	0.32	0.13-0.78	0.012
*Platelet:RBC Ratio	0.81	0.44-1.48	0.492	0.95	0.64-1.42	0.811
Age	1.01	0.98-1.04	0.501	1.01	0.99-1.04	0.407
ISS	1.02	0.99-1.04	0.104	1.02	0.99-1.04	0.103
Bleeding Chest	0.87	0.37-2.08	0.759	0.81	0.33-2.00	0.649
Bleeding Limb	0.96	0.45-2.02	0.905	1.28	0.61-2.68	0.518
Bleeding Head	8.46	3.86-18.55	<0.0005	7.68	3.41-17.30	<0.0005
Entry Time	0.84	0.72-0.98	0.026	0.88	0.75-1.00	0.057
*Cumulative Sum of Transfusions	1.04	1.02-1.05	<0.0005	1.04	1.02-1.05	<0.0005

Table 5

At 24 hours-30 days Post ED admission a comparison of Death as Outcome and Declared DNR or Death as Outcome using a Multivariable Cox Time-dependent Analysis.

	Death as Outcome (773 patients with 491,670 hours at risk, 88 deaths)			Declared DNR or Death as Outcome (769 patients with 490,511 hours at risk, 85 failures including 60 DNRs)		
Covariate	Adjusted Hazard Ratio	95% Confidence Intervals	P value	Adjusted Hazard Ratio	95% Confidence Intervals	P value
*Plasma:RBC Ratio	1.20	0.93-1.57	0.166	1.21	0.93-1.57	0.155
*Platelet:RBC Ratio	0.79	0.62-1.01	0.058	0.78	0.60-1.00	0.051
Age	1.03	1.02-1.05	<0.0005	1.03	1.02-1.04	<0.0005
ISS	1.03	1.02-1.05	<0.0005	1.03	1.02-1.05	<0.0005
Bleeding Chest	0.43	0.22-0.85	0.016	0.51	0.27-0.97	0.041
Bleeding Limb	1.16	0.72-1.87	0.548	1.04	0.64-1.70	0.866
Bleeding Head	5.81	3.50-9.66	<0.0005	6.10	3.69-10.09	<0.0005
Entry Time	0.96	0.89-1.05	0.388	0.97	0.89-1.05	0.445
*Cumulative Sum of Transfusions	1.02	1.01-1.03	<0.0005	1.02	1.01-1.03	<0.0005