Earlier time to hemostasis is associated with decreased mortality and rate of complications: results from the Pragmatic Randomized Optimal Platelet and Plasma Ratio (PROPPR) trial

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Abstract

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Introduction: Clinicians intuitively recognize that faster time to hemostasis is important in bleeding trauma patients, but these times are rarely reported.

Methods: Prospectively collected data from the PROPPR trial were analyzed. Hemostasis was predefined as no intraoperative bleeding requiring intervention in the surgical field or resolution of contrast blush on interventional radiology. Patients who underwent an emergent (within 90 minutes) OR or IR procedure were included. Mixed-effects Poisson regression with robust error variance (controlling for age, injury severity score [ISS], treatment arm, injury mechanism, base excess on admission [missing values estimated by multiple imputation], and time to OR/IR as fixed effects and study site as a random effect) with modified Bonferroni corrections tested the hypothesis that decreased time to hemostasis was associated with decreased mortality and decreased incidence of acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), sepsis, and venous thromboembolism (VTE).

Results: Of 680 enrolled patients, 468 (69%) underwent an emergent procedure. Patients with decreased time to hemostasis were less severely injured, had less deranged base excess on admission, and lower incidence of blunt trauma (all p<0.05). In 408 patients (87%) in whom hemostasis was achieved, every 15 minute decrease in time to hemostasis was associated with decreased 30-day mortality (RR 0.97, 95% CI 0.94–0.99), AKI (RR 0.97, 95% CI 0.96–0.98), ARDS (RR 0.98, 95% CI 0.97–0.99), MOF (RR 0.94, 95% CI 0.91–0.97), and sepsis (RR 0.98, 95% CI 0.96–0.99), but not VTE (RR 0.99, 95% CI 0.96–1.03).

Conclusion: Earlier time to hemostasis was independently associated with decreased incidence of 30-day mortality, AKI, ARDS, MOF, and sepsis in bleeding trauma patients. Time to hemostasis should be considered as an endpoint in trauma studies and as a potential quality indicator.

Level of evidence: Level III (Therapeutic / Care Management)

Introduction

Hemorrhage is the leading cause of preventable trauma mortality[1,2,3] with median time to exsanguination of 2–3 hours after hospital arrival.[4,5] Optimal treatment of the hemorrhaging trauma patient includes transfusion of a balanced ratio of blood products and measures to rapidly acquire mechanical hemorrhage control, i.e. hemostasis.[6] Clinicians intuitively recognize that minimization of blood loss by more rapidly obtaining hemostasis reduces physiologic derangement and ischemic organ injury, thereby improving patient outcomes. Several studies have reported that minimizing times to laparotomy,[7,8] interventional radiology (IR),[9] and plasma and platelet transfusion (hemostatic resuscitation)[4,10,11] are associated with improved outcomes in trauma patients, likely by minimizing the time to hemostasis and degree of blood loss. However, time to hemostasis is not routinely reported. [12] The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial found that bleeding trauma patients randomized to high (1:1:1) ratios of plasma and platelets to red blood cells (RBCs) were more likely to have achieved hemostasis and less likely to have

died from hemorrhage within the first 24 hours compared to patients randomized to a low (1:1:2) ratio, although there were no differences in 24-hour or 30-day mortality.[5] In patients achieving hemostasis, the time from hospital arrival to hemostasis was similar between treatment arms (median 144 vs 131 min, p=0.17). We hypothesized that early achievement of hemostasis was independently associated with reduced mortality and risk of complications.

Methods

Patients and data collection

This was a pre-specified secondary analysis of the PROPPR study, a pragmatic, phase 3, multicenter trial which randomized 680 bleeding trauma patients predicted to require massive transfusion to resuscitation with 1:1:1 versus 1:1:2 plasma to platelets to RBCs during a 17-month period in 2012–2013. This study was approved by the institutional review boards of all 12 participating sites.[5]

Definitions

Hemostasis was declared by the attending trauma surgeon and defined a priori as no intraoperative bleeding requiring intervention in the surgical field or resolution of contrast blush on IR. Active resuscitation was ended when hemostasis was achieved and the attending surgeon and anesthesiologist agreed that the patient was adequately resuscitated based on improving patient physiology (normalizing vital signs, increasing urine output, or decreasing vasopressor requirement). We included patients who underwent an emergent procedure defined as any operating room (OR) or IR procedure for hemorrhage control within 90 minutes of hospital arrival, consistent with previous studies.[13,14] Severe injury was defined as abbreviated injury scale (AIS) 3. Definitions of complications were those from the primary paper and were standardized across all institutions.[5] Acute kidney injury (AKI) was defined as serum creatinine increase of at 0.3 mg/dL or 50%, glomerular filtration rate (GFR) decrease of 25%, or urine output of <0.5 ml/kg/hr. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin criteria.[15] Multiple organ failure (MOF) was defined using the Denver MOF scoring system. Sepsis was defined as systemic inflammatory response syndrome and suspected or known infection. Venous thromboembolism (VTE) was defined as deep venous thrombosis identified by autopsy or imaging, or pulmonary embolism identified on CT angiogram.

Statistical analysis

Stata 14.1 (Stata Corp., College Station, TX) was used for all calculations. Data are summarized as median and interquartile range (IQR) or proportions as appropriate. Patients requiring emergent OR or IR were separated into groups based on time to hemostasis to facilitate univariate and sensitivity analyses. Patients were divided into quartiles based on time to hemostasis with a fifth group created for patients who did not achieve hemostasis. Non-parametric univariate comparisons of continuous data were performed using the Kruskal-Wallis test. Comparisons of categorical data were performed with chi-squared test or Fisher's exact test for categories with 5 expected members. Locally weighted scatterplot

smoothing (LOWESS) was used to estimate the incidence of complications versus time to hemostasis.

Mixed-effects Poisson models with robust error variance (which have been previously used to analyze dichotomous outcomes)[16] were used to analyze mortality at 24 hours and 30 days, as well as five inflammatory complications (AKI, ARDS, MOF, sepsis, and VTE) to test the hypothesis that decreased time to hemostasis was independently associated with improved outcomes. Out of the 23 predefined complications analyzed in PROPPR, we chose the above complications to analyze in the present study because they were prevalent, clinically important, and thought to be potential consequences of the prolonged ischemia and increased inflammation secondary to delayed hemostasis. Of note, 6-hour mortality was not analyzed because only one patient who achieved hemostasis died within 6 hours of ED arrival. Unadjusted models controlled for study site as a random effect. Adjusted models controlled for study site as a random effect and the following as fixed effects: age, ISS, injury mechanism, treatment arm, admission base excess, and time to OR/IR. These were selected because of their clinical significance and/or statistical significance at the 0.1 level on univariate analysis. Missing admission base excess data were estimated using multiple imputation with predictive mean matching using age, injury mechanism, and ISS as predictors. Modified Bonferroni corrections were performed to control for multiple comparisons. Because these analyses use time to hemostasis as a continuous variable, only patients who achieved hemostasis were included. Sensitivity analyses were then performed which included patients who exsanguinated before hemostasis was achieved. A two-tailed alpha level of 0.05 was used for all statistical tests.

Results

Summary of hemostasis and between-site comparisons

Of 680 patients enrolled, 468 (69%) underwent an emergent OR/IR procedure. These patients had greater incidence of severe abdominal injury (60% vs 27%), decreased incidence of severe head injury (17% vs 34%), and decreased incidence of TBI-related death (6% vs 17%) compared to those not undergoing an emergent OR/IR procedure (all p<0.01).

Among patients undergoing emergent OR/IR, hemostasis was achieved in 87% (n=408) with no significant differences between study sites on the chi-squared test (range: 71–91% per site, p=0.43). We examined the time to emergent OR/IR, time from OR/IR to hemostasis, and overall time to hemostasis, which is schematically depicted in Figure 1. Time from OR/IR to hemostasis accounted for the majority of overall time to hemostasis (median 77%, IQR 63–87%). There were significant between-site differences in proportion of blunt trauma (range: 8–57%), use of emergent IR instead of OR (range: 0–20%), as well as time to emergent OR/IR, time from OR/IR to hemostasis, and overall time to hemostasis (all p<0.05). Overall time to hemostasis was significantly higher in blunt versus penetrating trauma (median 139 vs 119 min, p<0.01) and after IR versus OR (median 184 vs 127 min, p<0.01).

Demographics

Patients who underwent emergent OR/IR (n=468, 69%) were divided into quartiles based on time to hemostasis (group 1, <90 min; group 2, 90 to 129 min; group 3, 130 to 183 min; group 4, >183 min). A fifth group was created for patients who did not achieve hemostasis. There were no differences in age, admission systolic blood pressure or heart rate, or treatment arm between groups (Table 1). Higher group number was associated with increased ISS, more deranged base excess on admission, and higher incidence of blunt trauma. Multiple imputation with predictive mean matching was used to estimate missing admission base excess in 45 patients (10%) using age, ISS, and injury mechanism as predictors. Distribution of base excess before and after imputation was unchanged.

Outcomes

Higher group number was associated with increased transfusion of blood products during active resuscitation, consistent with increased hemorrhage (Table 2). There were no significant differences in mortality or time to death between the first four groups, although cause of death was somewhat different. In contrast, patients in group 5 died quickly (median 2.2 hours) from exsanguination. As group number increased, ICU-free days decreased and incidence of AKI, ARDS, MOF, and sepsis increased. LOWESS regression was used to estimate the rate of any complication (mortality, AKI, ARDS, MOF, sepsis, or VTE) versus time to hemostasis (Figure 3).

In 408 patients in whom hemostasis was achieved, mixed effects Poisson regression with robust error variance and modified Bonferroni corrections found that every 15 minute decrease in time to hemostasis was associated with decreased 30-day mortality (RR 0.97, 95% CI 0.94–0.99, p<0.001) and decreased incidence of AKI (RR 0.97, 95% CI 0.96–0.98, p<0.001), ARDS (RR 0.98, 95% CI 0.97–0.99, p<0.01), MOF (RR 0.94, 95% CI 0.91–0.97, p<0.001), and sepsis (RR 0.98, 95% CI 0.96–0.99, p<0.001), but not 24-hour mortality (RR 1.14, 95% CI 0.98–1.32, p=0.13) or VTE (RR 0.99, 95% CI 0.96–1.03, p=0.73). Results before and after adjustment for age, ISS, treatment arm, injury mechanism, time to OR/IR, and admission base excess are summarized in Figure 4.

Diagnostic studies were performed (Supplement). In terms of global goodness-of-fit, chi-squared tests of the deviance statistic were not significant (p>0.05). Visual inspection of deviance residuals versus predicted values revealed no outliers in three models and 1% outliers in four models (defined as deviance residual < −2 or > +2). Due to the dichotomous outcome, the residuals were not expected to be normally distributed. Instead, we used our models to generate simulated data; visual comparison of actual versus simulated residuals revealed moderate deviations in the sepsis model and no deviations in other models.

Sensitivity Analyses

Patients who did not achieve hemostasis had undefined time to hemostasis and were excluded from the primary analysis, likely leading to survival bias. Therefore, two sensitivity analyses were performed including the 60 patients who exsanguinated before hemostasis was achieved. First, these patients were assigned time to hemostasis of 315 minutes, which was at the 95th percentile for time to hemostasis. After modified Bonferroni correction,

decreased time to hemostasis was significantly associated with decreased risk of mortality at 24 hours (RR 0.93, 95% CI 0.91–0.95) and 30 days (RR 0.95, 95% CI 0.93–0.96), as well as decreased risk of AKI (RR 0.97, 95% CI 0.96–0.99) and MOF (RR 0.94, 95% CI 0.91–0.97), but not ARDS (RR 1.00, 95% CI 0.96–1.03), sepsis (RR 0.99, 95% CI 0.97–1.03), or VTE (RR 1.02, 95% CI 0.97–1.07). Another sensitivity analysis was performed in which group assignment (Table 1) was substituted for time to hemostasis. After modified Bonferroni correction, decreasing group number was significantly associated with decreased mortality at 24h and 30 days, as well as decreased risk of MOF, but not AKI, ARDS, sepsis, or VTE.

Discussion

We performed a pre-specified secondary analysis of the PROPPR study and found no significant differences in rate of hemostasis between sites, but there was significant variability in time to hemostasis between sites. We also found significant variability in use of IR between sites and increased time to emergent IR compared to emergent OR, consistent with a previous report.[17] Decreased time to hemostasis was independently associated with decreased incidence of 30-day mortality, AKI, ARDS, MOF, and sepsis, but not 24-hour mortality or VTE.

Components of hemostasis acquisition include recognition of significant hemorrhage, transport to the OR/IR suite, and the hemorrhage control procedure itself. Studies have reported improved outcomes with earlier time to operative[7,8] or IR intervention[9] in bleeding trauma patients. Several scoring methods have also been reported to rapidly identify bleeding patients in the trauma bay,[18,19,20] and catheter-based interventions in conjunction with hybrid operating suites may further reduce delays in initiating appropriate therapy.[21] However, clinical benefit is ultimately achieved by acquiring earlier definitive hemorrhage control (i.e. hemostasis). Determinants of time to hemostasis after arrival to OR/IR include factors which are non-modifiable (e.g. pattern of injury), modifiable (e.g. surgeons' skill level and judgment including decision for damage control versus definitive therapy), and potentially modifiable (e.g. availability of hybrid operating capability). Previous studies have used time to OR/IR as a surrogate for time to hemostasis, which does not take into account the actual time required to perform definitive hemorrhage control maneuvers. In the present study, we found that time from OR/IR to hemostasis accounted for most of the overall time to hemostasis (Figure 2).

Hemorrhagic death occurs rapidly with a median time to death of 2–3 hours after hospital arrival.[4,5] Oyeniyi et al performed a single-center retrospective study at a level 1 center and found that trauma mortality from hemorrhage significantly decreased after implementation of significant changes in control of bleeding and early resuscitation procedures as part of a hemorrhage control bundle.[22] These included earlier transfusion of plasma and platelets, earlier and increased use of temporizing hemorrhage control devices (extremity and junctional tourniquets, pelvic binders, hemostatic dressings, and resuscitative endovascular balloon occlusion of the aorta [REBOA]), and decreased time to OR/IR.[6,23,24] We have previously argued that outcomes of clinical studies should be consistent with the disease process being investigated, and have proposed using an outcome of all-cause mortality at 6

hours for future hemorrhage studies.[25] Given that purposeful action to effect earlier time to hemostasis will improve patient outcomes after trauma, the results of the current study support the use of time to hemostasis as a clinically significant endpoint for future hemorrhage studies. The overall complication rate was level until about 75 minutes, then steadily increased as time to hemostasis increased (Figure 3). Time to hemostasis may serve as a quality metric for trauma centers, but further studies are needed to identify modifiable and potentially modifiable determinants of time to hemostasis as well as an optimal benchmark.

The limitations of this study are as follows. Importantly, we could not control for several factors impacting time to hemostasis. Some injury patterns, such as retrohepatic caval injuries, result in substantial and difficult-to-control hemorrhage, and such injury patterns are not recapitulated by ISS. Other factors affecting time to hemostasis include the surgeons' technical skill and judgment, including the decision to perform damage control versus definitive therapy and knowing when to ask for help. Although hemostasis was defined a priori in the PROPPR study as no bleeding requiring intervention in the surgical field or resolution of contrast blush in IR, it is to some degree subjective and consequently subject to bias, possibly accounting for some of the between-study site variability in time to hemostasis. Study sites also had significant differences in rates of blunt versus penetrating injury, which may have also contributed to variation in time to hemostasis. However, we believe that our method of mixed effects regression (using study site as a random effect) accounts for this in our statistical models. Additionally, the ultimate goal of achieving early hemostasis is to reduce blood loss due to hemorrhage, but accurately measuring the volume of blood loss after trauma is prohibitively difficult. We have shown that time to hemostasis more accurately reflects the degree of blood loss compared to time to OR/IR, but time to hemostasis is nevertheless still a surrogate for volume of blood loss. Direct correlation between time to hemostasis and actual volume of blood loss is obfuscated by several factors including rate of hemorrhage. Interestingly, among all 680 patients in the PROPPR trial, the 1:1:1 group had increased *proportion* of hemostasis (86% versus 78%, p<0.01), but similar *time* to hemostasis (median 144 vs 131 min, p=0.17), compared to the 1:1:2 group,[5] suggesting that higher plasma:RBC and platelet:RBC reduced the rate of hemorrhage instead of allowing clinicians to achieve hemostasis more rapidly. We used time to hemostasis as a continuous variable in our multivariable models, which necessarily excluded 60 patients (15%) who exsanguinated before hemostasis could be achieved, resulting in survivor bias. Sensitivity analyses which included these 60 patients still found significant associations between time to hemostasis versus mortality, MOF, and possibly AKI. In the primary analysis of 408 patients who achieved hemostasis, we demonstrated that increased time to hemostasis was associated with increased incidence of several post-traumatic complications which was further correlated with increased 30-day mortality. Given that it takes time for these complications to manifest, it makes sense that there was no correlation with 24-hour mortality. These limitations are counterbalanced by the strengths of this study, which include our method of mixed-effects analysis, correction for multiple comparisons, and transparency in reporting diagnostics of our statistical tests.

In conclusion, time to hemostasis, but not rate of hemostasis, varied significantly between study sites in the PROPPR trial. Despite previous focus on time from hospital arrival to

OR/IR, time from OR/IR to hemostasis accounts for the majority of overall time to hemostasis. Decreased time to hemostasis was independently associated with decreased 30-day mortality as well as incidence of AKI, ARDS, sepsis, and MOF. We find it biologically plausible that delayed hemostasis would result in increased blood loss, greater end organ ischemia, greater organ dysfunction, and increased late mortality. Time to hemostasis should be considered as an endpoint in future hemorrhage studies, and further studies investigating its use as a potential quality metric for trauma centers are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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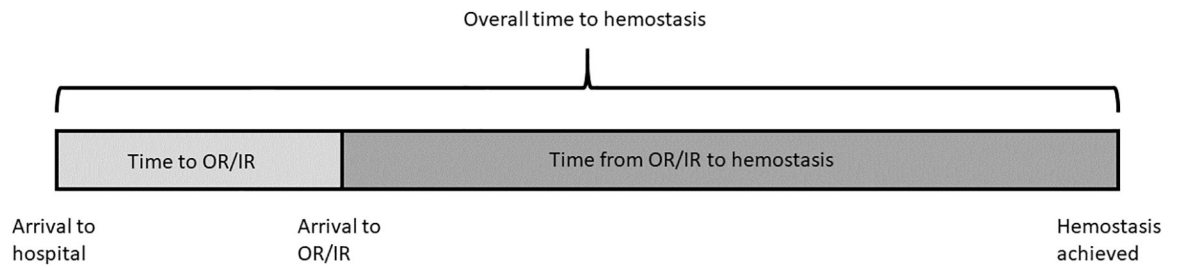
Figure 1.

Schematic representation of overall time to hemostasis, which consists of time from hospital arrival to OR/IR and time from OR/IR to hemostasis.
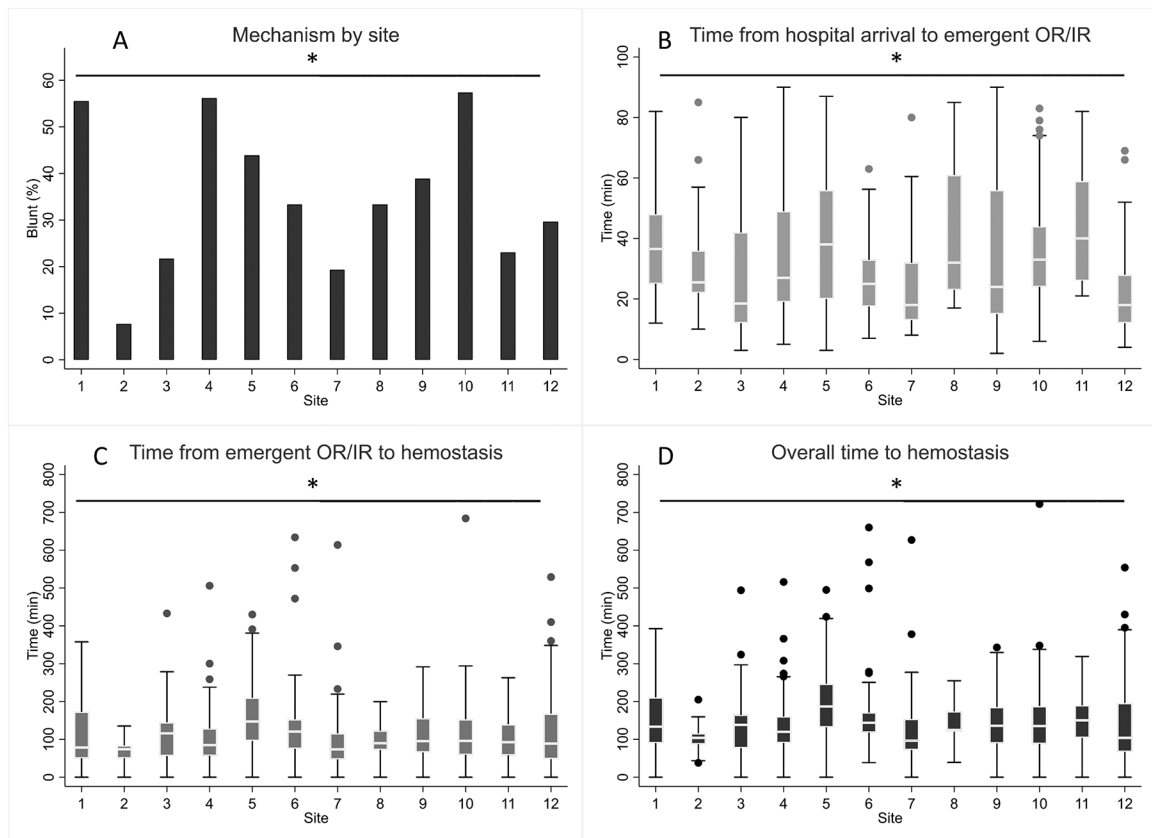
Figure 2A–D.
Between-site comparisons for patients requiring emergent OR/IR (n=468). Incidence of blunt (versus penetrating) trauma varied significantly between sites (A). Time from hospital arrival to emergent OR/IR (B), time from emergent OR/IR to hemostasis (C), and overall time to hemostasis (D) also varied significantly between sites. Time from emergent OR/IR to hemostasis accounted for median 73% (IQR 63%–87%) of overall time to hemostasis. *, $p<0.05$.
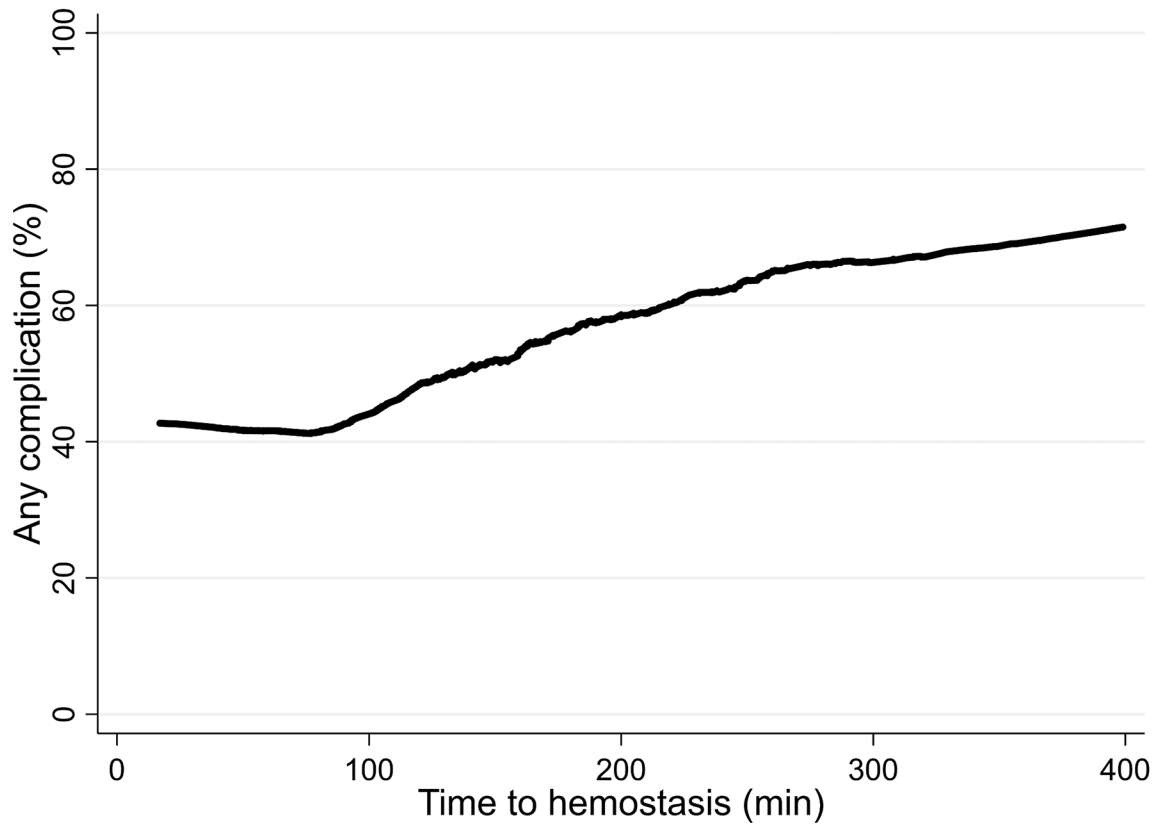
Figure 3.
Locally weighted scatterplot smoothing (LOWESS) regression of incidence of any complication (mortality, AKI, ARDS, MOF, sepsis, or VTE) versus time to hemostasis.
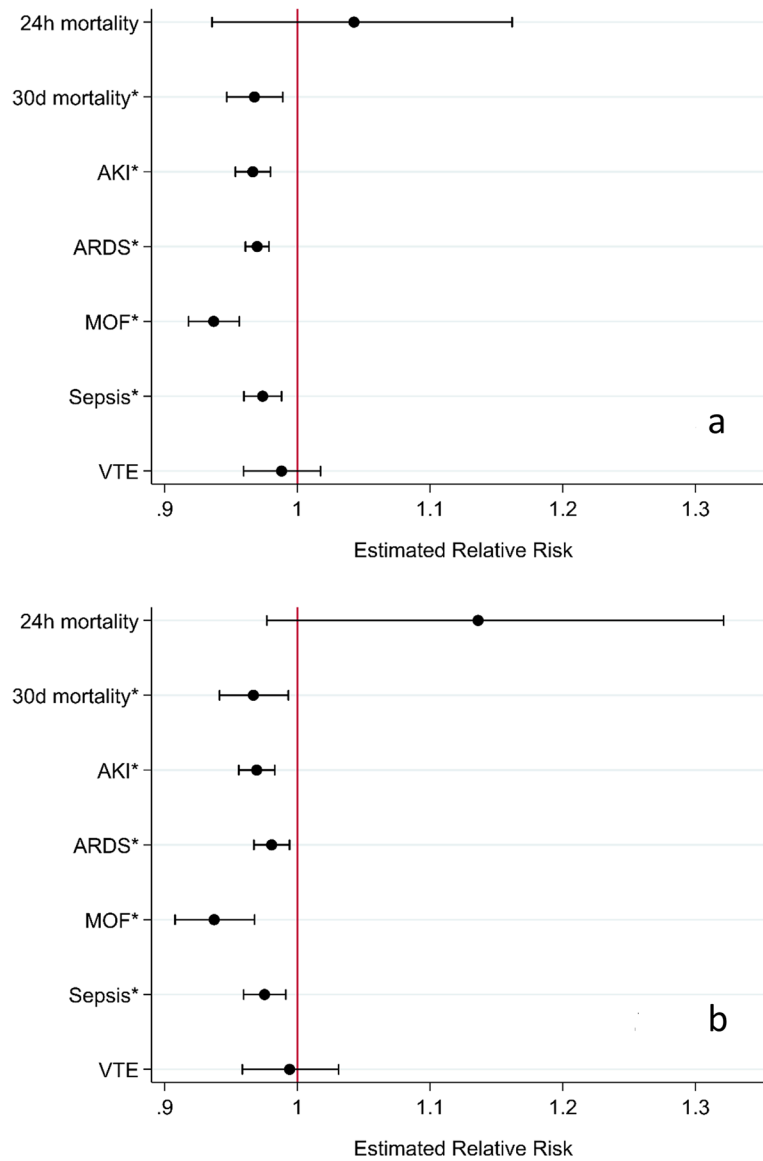
Figure 4A–B.
Mixed effects Poisson regression with robust error variance for patients requiring emergent OR/IR and who achieved hemostasis (n=408). Unadjusted models (A) control for study site as a random effect. Adjusted models (B) control for age, ISS, injury mechanism, time to OR/IR, treatment group, and admission base excess as fixed effects and study site as a random effect. *, statistically significant after modified Bonferroni correction.

Demographics of patients requiring emergent OR/IR (n=468)

Variable	Group 1 (n=102)	Group 2 (n=102)	Group 3 (n=104)	Group 4 (n=100)	Group 5 (n=60)	p
Time to hemostasis (min)	<90	90 to 129	130 to 183	>183	No hemostasis	-
Age (years)	32 (24, 47)	31 (24, 43)	33 (24, 45)	32 (24, 48)	34 (24, 54)	0.57
ISS	20 (13, 34)	25 (14, 38)	26 (18, 36)	29 (19, 41)	34 (25, 45)	<0.01
Base excess (mEq/L)	-7 (-11, -2)	-7 (-12, -4)	-7 (-12, -3)	-9 (-14, -6)	-17 (-19, -12)	<0.01
SBP (mmHg)	100 (79, 126)	106 (86, 130)	108 (86, 123)	104 (80, 130)	94 (78, 118)	0.17
Heart rate (bpm)	113 (93, 131)	107 (92, 127)	120 (97, 133)	122 (102, 136)	113 (82, 136)	0.09
Blunt mechanism (n, %)	29 (28%)	36 (35%)	47 (45%)	46 (46%)	28 (47%)	0.03
Treatment arm (n, %)						0.67
1:1:1	53 (52%)	53 (52%)	46 (49%)	49 (49%)	33 (55%)	
1:1:2	49 (48%)	49 (48%)	58 (51%)	51 (51%)	27 (45%)	
Emergent OR (n, %)	101 (99%)	101 (99%)	97 (93%)	91 (91%)	59 (98%)	<0.01
Emergent IR (n, %)	1 (1%)	1 (1%)	7 (7%)	9 (9%)	1 (2%)	
Time from hospital arrival to OR/IR (min)	20 (15, 28)	28 (19, 42)	31 (20, 57)	34 (21, 55)	25 (18, 45)	<0.01
Time from hospital arrival to hemostasis (min)	69 (56, 80)	111 (101, 120)	152 (141, 165)	245 (210, 303)	-	-

ISS, injury severity score

Table 2.

Outcomes of patients requiring emergent OR/IR (n=468)

Variable	Group 1 (n=102)	Group 2 (n=102)	Group 3 (n=104)	Group 4 (n=100)	Group 5 (n=60)	p*
Transfusions during active resuscitation						<0.01
RBC (units)	5 (4, 8)	7 (4, 11)	8 (5, 14)	13 (8, 24)	20 (11, 37)	
Plasma (units)	2 (1, 3)	3 (2, 6)	5 (2, 10)	8 (4, 15)	14 (6, 20)	
Platelets (units)	1 (0, 1)	1 (0, 2)	1 (1, 2)	2 (1, 3)	3 (1, 4)	
Mortality at 6 hours (n, %)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	55 (92%)	1.00
Mortality at 24 hours (n, %)	1 (1%)	2 (2%)	2 (2%)	1 (%)	59 (98%)	1.00
Mortality at 30 days (n, %)	8 (8%)	8 (8%)	8 (8%)	15 (15%)	60 (100%)	0.25
Time to death (days)	3.6 (1.3, 6.3)	2.8 (0.8, 11.9)	7.1 (1.5, 18.5)	8.8 (2.5, 11.2)	0.09 (0.05, 0.15)	0.74
Cause of death† (n, %)						0.01
Exsanguination	0 (0%)	2 (2%)	3 (3%)	0 (0%)	60 (100%)	
TBI	6 (6%)	4 (4%)	3 (3%)	10 (10%)	4 (7%)	
Respiratory	1 (1%)	0 (0%)	1 (1%)	0 (0%)	3 (5%)	
MOF	0 (0%)	0 (0%)	4 (4%)	6 (6%)	0 (0%)	
Sepsis	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	
PE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Other	1 (1%)	1 (1%)	0 (0%)	1 (1%)	1 (2%)	
ICU-free days	26 (17, 28)	25 (8, 27)	22 (11, 26)	16 (0, 25)	0 (0, 0)	<0.01
AKI (n, %)	13 (13%)	17 (17%)	29 (28%)	43 (43%)	2 (3%)	<0.01
ARDS (n, %)	10 (10%)	14 (14%)	23 (22%)	33 (33%)	5 (8%)	<0.01
MOF (n, %)	0 (0%)	2 (2%)	3 (3%)	14 (14%)	2 (3%)	<0.01
Sepsis (n, %)	21 (21%)	26 (25%)	43 (41%)	45 (45%)	0 (0%)	<0.01
VTE (n, %)	7 (7%)	10 (10%)	16 (15%)	14 (14%)	0 (0%)	0.20
Any complication§ (n, %)	38 (37%)	38 (37%)	61 (59%)	72 (72%)	60 (100%)	<0.01

*
for first four groups only

†
not mutually exclusive

§
includes mortality, AKI, ARDS, MOF, sepsis, or VTE

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RBC, red blood cells; TBI, traumatic brain injury; MOF, multiple organ failure; PE, pulmonary embolism; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; VTE, venous thromboembolism