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Exposing the bidirectional effects of alcohol on coagulation in trauma

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Complete Manuscript Title: Exposing the Bidirectional Effects of Alcohol on Coagulation in Trauma: Impaired Clot Formation and Decreased Fibrinolysis in Rotational Thromboelastometry

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Abstract

Background—Alcohol has been associated with altered viscoelastic testing in trauma, indicative of impaired coagulation. Such alterations, however, show no correlation to coagulopathy-related outcomes. Other data suggests that alcohol may inhibit fibrinolysis. We sought to clarify these mechanisms following traumatic injury using thromboelastometry (ROTEM), hypothesizing that alcohol-related clot formation impairment may be counter-balanced by inhibited fibrinolysis.

Methods—Laboratory, demographic, clinical, and outcome data were prospectively collected from 406 critically-injured trauma patients at a Level 1 Trauma Center. ROTEM and standard coagulation measures were conducted in parallel. Univariate comparisons were performed by alcohol level (EtOH), with subsequent regression analysis.

Results—Among 274 patients (58%) with detectable EtOH, median EtOH was 229 mg/dL. These patients were primarily bluntly injured and had lower GCS ($p<0.05$) than EtOH-negative patients, but had similar admission pH and injury severity (p=NS). EtOH-positive patients had prolonged ROTEM clotting time (CT) and rate of clot formation (CFT/α); they also had decreased fibrinolysis (max lysis %; all $p<0.05$). In linear regression, for every 100mg/dL increase in EtOH, CT increased by 13s and fibrinolysis decreased by 1.5% (both $p<0.05$). However, EtOH was not an independent predictor of transfusion requirements or mortality. In high-EtOH patients with coagulopathic ROTEM tracings, transfusion rates were significantly lower than expected, relative to EtOH-negative patients with similar ROTEM findings.

Conclusions—As assayed by ROTEM, alcohol appears to have a bidirectional effect on coagulation in trauma, both impairing initial clot formation and inhibiting fibrinolysis. This balancing of mechanisms may explain lack of correlation between altered ROTEM and coagulopathy-related outcomes. Viscoelastic testing should be utilized with caution in intoxicated trauma patients.

Study Type—Epidemiological study. Type III.

Keywords

Alcohol, ethanol; coagulation disorders; acute traumatic coagulopathy; ROTEM, rotational thromboelastometry; trauma

BACKGROUND

Trauma remains the leading cause of death in the young worldwide, and mortality from injuries surpasses that from HIV/AIDS, malaria, and tuberculosis combined across all age groups (1). Acute hemorrhage remains a major driver of early traumatic death (2), and is often complicated by disordered coagulation, a phenomenon termed acute traumatic coagulopathy (3, 4). As such, recent efforts in trauma care have focused on improving diagnostic and therapeutic approaches to the bleeding patient (5). The emergence of viscoelastic testing in this setting has been hailed as a significant improvement on standard plasma coagulation assays, despite lack of prospective validation, to the point that some centers have abandoned such assays altogether in the initial evaluation of critical trauma patients (6).

Though alcohol has been established as a major risk factor for traumatic injury, with acute alcohol intoxication found in up to half of all trauma patients (7), the relationship between alcohol and coagulation after trauma remains unclear. In vitro studies would suggest that alcohol impairs platelet aggregation (8, 9), and that alcohol consumption may lead to decreased levels of coagulation factors (10); such mechanisms have been advanced as explanations for the known association between long-term moderate alcohol intake and reduced risk of thrombogenic cardiovascular disease (11). Epidemiological studies would seem to support a model of alcohol inhibiting coagulation (12, 13), as would studies of healthy subjects (14, 15). Nonetheless, acute cute alcohol intake has also been associated with marked inhibition of fibrinolysis, both *in vitro* and in healthy subjects (16–18).

Known interactions between alcohol and coagulation dynamics notwithstanding, the impact of alcohol on outcomes in trauma patients is a subject of considerable debate (19, 20). Despite its known role as a risk factor for sustaining trauma in the first place, alcohol has been posited as having a *protective* effect in those who are critically injured. Recent studies have identified a possible survival benefit associated with alcohol intoxication (21, 22), and alcohol has been linked to attenuation of acute traumatic coagulopathy as a possible explanatory mechanism (23). In a recent prospective cohort study that sought to address this question, acutely intoxicated trauma patients were found to have altered thromboelastography (TEG) on admission, consistent with impaired clot formation (24). Such alterations, however, showed no correlation to bleeding or other coagulopathy-related

outcomes. Based on these findings, the question remained whether the observed effect represented a true biological phenomenon or an anomaly specific to functional coagulation testing.

Given the known inhibitory effects of alcohol on both platelet function and fibrinolysis, we hypothesized that the previously assayed apparent decrease in clot formation is a true, reproducible effect that may be balanced by a concomitant reduction in fibrinolysis, leading to no significant net impact on clinical coagulation dynamics. In order to test this hypothesis, and to establish that prior findings were not simply vagaries of the TEG test itself, we sought to identify any such changes in a trauma cohort using another global viscoelastic assay, rotational thromboelastometry (ROTEM).

METHODS

Plasma and whole blood samples were prospectively collected from a cohort of 442 critically injured patients who had blood alcohol (EtOH) levels collected at the time of admission to a Level 1 Trauma Center between 2005 and 2014. Adult patients aged 18 years to 95 years were included in the study if they met center criteria for top-level trauma activation, using an established algorithm accounting for field vital signs, clinical status, and injury mechanism. Patients with end stage renal disease and cirrhosis were excluded (n = 23), as were those on systemic anticoagulants including aspirin (n = 50). Following exclusions, the final cohort consisted of 406 patients. A waiver of consent was applied for initial blood draws upon admission, and informed consent was obtained from all patients in the cohort, under a protocol approved by the University of California Committee on Human Research.

Blood samples were collected at the time of initial placement of 16-gauge or larger intravenous catheters in the trauma bay of the emergency department. Standard vacuum tubes with 3.2% sodium citrate (0.109 mol/L) were used for all draws. Point-of-care viscoelastic testing was performed with the ROTEM delta machine (Pentapharm GmbH; Munich, Germany) using INTEM and EXTEM reagents (star-TEM recalcifier; in-TEM ellagic acid intrinsic pathway activator, ex-TEM tissue factor intrinsic pathway activator). Each sample was warmed to 37°C in the TEM cup, prepared according to manufacturer specifications with the use of an automated pipette, and the test initiated within 20 seconds of mixing 300uL of whole blood with the recalcifier and respective activator. Our whole blood viscoelastic testing protocol has been described previously (25). Standard coagulation assays (eg prothrombin time) were performed by the clinical lab at San Francisco General Hospital.

Massive transfusion was defined as 10 units or more of packed red blood cells (pRBCs) received within 24 hours of admission; to account for survivor bias, patients who did not survive 24 hours were considered as massive transfusion recipients if they were transfused 5 or more units of pRBCs within 12 hours, or 2.5 or more units of pRBCs within 6 hours, as previously described (24). Multiorgan failure was defined using the Denver Postinjury Multiple Organ Failure Score (26). Acute respiratory distress syndrome was determined by two-physician blinded adjudication of chest radiographs during the first seven days of

admission, as described previously (27). Coagulopathy by standard measures was defined as international normalized ratio (INR) of 1.3 or higher. During the study period, there were no explicit changes to transfusion practices or protocols, and at no point was ROTEM (or other viscoelastic testing) utilized to guide clinical decision-making.

Demographics, clinical data including quantitative resuscitation measures, and outcomes were collected in parallel with laboratory data. Data are presented as mean (standard deviation), median (interquartile range), or percentage, depending on data type and distribution. Univariate comparisons were made using the Student's *t* test for parametrically distributed data, the Wilcoxon rank sum test for skewed data, and Fisher's exact test for proportions. Linear regression analysis was used to assess correlation between alcohol and specific coagulation parameters, incorporating known and potential confounders of the alcohol-coagulation relationship (e.g. injury severity, gender) to clarify any such correlations. In similar fashion, multiple logistic regression was used to assess predictors of coagulopathy-related outcomes, including transfusion requirements and mortality. An α of <0.05 was considered significant. All statistical analysis was performed by the authors using Stata version 12 (StataCorp, College Station, TX).

RESULTS

Of 406 total patients in the cohort, 237 (58.3%) had detectable EtOH >10 mg/dL; these patients were substantially intoxicated, with a median EtOH of 229 mg/dL, nearly three times above the legal limit for operating a motor vehicle in the state of California. In keeping with the known demographics of a trauma population, the majority of patients were male, and relatively young in age; though there was a higher percentage of male patients in the EtOH-positive group, this did not reach statistical significance (Table 1). EtOH-intoxicated patients had a higher rate of blunt injury (70% vs. 56%, p=0.006); they also had slightly lower median GCS (13 vs 14, p=0.004) and lower mean temperature (36.2 vs. 36.6 °C, p<0.001) at admission, but these differences did not appear clinically significant. As shown in Table 1, though the alcohol-intoxicated patients had a slightly higher initial mean base deficit (reported as excess, −3.46 vs. −1.83 mEq/L, p=0.029), there were no differences in initial pH or injury severity score (ISS) between the groups.

The two groups demonstrated multiple differences with regard to admission coagulation testing. As shown in Table 1, there was a statistically significant but clinically insignificant difference in INR between intoxicated and non-intoxicated patients. There were no significant differences in other standard plasma coagulation tests, including partial thromboplastin time (PTT), platelet count, and fibrinogen level. However, viscoelastic testing revealed notable differences in clotting dynamics: by INTEM, Clotting Time (CT) was prolonged in EtOH-intoxicated patients (166 vs. 151 seconds, p<0.001), as was Clot Formation Time (CFT) (72 vs. 68 seconds, p=0.006), and α angle was decreased (75 vs. 77 degrees, p=0.007), all consistent with impaired clot formation. Maximum Clot Formation (MCF) in INTEM did not differ in the two groups, but median maximum degree of fibrinolysis (as a percentage of MCF) was decreased in the EtOH-intoxicated patients (12% vs. 14%, p=0.008). In EXTEM, clot formation variables were again decreased in EtOH-positive patients (CFT 96 vs. 88 sec, p=0.003; α angle, 72 vs. 74 degrees, p=0.017), total

clot strength by MCF was similar, and median maximum fibrinolysis was decreased (12% vs. 14%, p=0.001).

Despite these differences in functional coagulation testing parameters, there were no corresponding differences in basic clinical outcomes. As shown in Table 2, EtOH-positive patients did not have increased rates of blood or platelet transfusions, and they actually had significantly lower rates of plasma transfusion (17% versus 27%, p=0.018). There were no differences in rate of massive transfusion, and EtOH-positive patients had no increased rates of ARDS or multiple organ failure. Length of stay in the ICU and in the hospital overall were not different by group, and there were no significant differences in early mortality. The EtOH-positive group actually experienced decreased mortality at discharge compared to their sober counterparts (7% vs. 15%, p=0.008).

To better characterize the relationship between EtOH and viscoelastic coagulation testing parameters, a series of linear regression analyses were performed. Univariate linear regression confirmed that with increased EtOH, INTEM clotting time significantly increased (Figure 1a); increased EtOH was also linearly related to decreased maximum degree of fibrinolysis in INTEM (Figure 1b). Similar findings were identified in EXTEM.

In order to control for any effects of patient gender or injury severity, these relationships were further analyzed using multiple linear regression. As shown in Table 3, for every 100 mg/dL increase in EtOH, INTEM clotting time increased by 13 seconds (p=0.033), and maximum degree of fibrinolysis decreased by 1.5% (p=0.028). Trends were observed toward prolonged clot formation time and decreased α angle. Similar trends were observed in EXTEM, where maximum degree of fibrinolysis decreased 1.6% for every 100 mg/dL increase in EtOH (p=0.028).

To assess the influence of alcohol on coagulopathy-related clinical outcomes, a series of logistic regressions were performed. Univariate analysis showed that blood alcohol content at admission was actually a negative predictor of blood product transfusion within 24 hours of admission (OR 0.82 per 100 mg/dL EtOH, 95% CI 0.71 – 0.95, p=0.009). However, in multiple logistic regression controlling for injury severity, degree of shock as assayed by base deficit, admission GCS, and INR (all variables that were significant on univariate analysis), EtOH was not a statistically significant predictor of 24-hour transfusion (Table 4). In similar multiple logistic regression analyses, EtOH was not a predictor of massive transfusion or other coagulopathy-associated outcomes, including mortality within 24 hours and mortality at discharge (data not shown).

A sub-analysis was conducted to assess patients who presented with abnormal or hypocoagulable-appearing ROTEM tracings, stratified by EtOH status at admission. These patients had admission ROTEM parameters that were out of the normal range per the manufacturer. To gauge the impact of EtOH on the interpretation of such "hypocoagulable" ROTEM tracings, EtOH-negative patients were compared to those with a high EtOH level (above 229 mg/dL, the median level in EtOH-positive patients). As Table 5 demonstrates, EtOH-negative patients presenting with abnormal ROTEM results had higher rates of transfusion and increased mortality than high-EtOH patients with similarly abnormal

ROTEM parameters. Transfusion within the first 24 hours was 38% in the EtOH-negative patients but only 24% in those with high EtOH (p=0.054); the transfusion rates of plasma and platelets were significantly higher in the EtOH-negative group (28% vs. 9% for FFP, p=0.002; 15% vs. 4% for platelets, p=0.032). Overall mortality at discharge was notably higher in the EtOH-negative group than the high-EtOH group (15% vs. 4%, p=0.031). Thus abnormal admission ROTEM parameters have a markedly different clinical significance based on EtOH level.

An additional sub-analysis was performed in the most severely-injured patients, with ISS > 25. In these 136 patients, key findings were unchanged, including the effects of EtOH on ROTEM by both univariate and linear regression analysis, and the relationship of EtOH to clinical outcomes by logistic regression (data not shown).

DISCUSSION

Given the frequency with which alcohol intoxication is associated with trauma, multiple studies have attempted to delineate the effects of elevated blood EtOH level on the response to injury. In both animal models (28) and clinical investigations (29), EtOH appears to have a blunting effect on the normal catecholamine surge that accompanies hemorrhagic shock; how such an effect correlates to clinical outcomes remains unknown. The lack of concordance in the trauma literature is likely due to differences in study methodology, and to the difficulty of extrapolating EtOH intoxication from associated risk factors (e.g. high-risk behavior, interpersonal violence, driving under the influence, etc) (30). After finding that EtOH intoxication was associated with *improved* survival in traumatic brain injury patients (22), investigators at a major U.S. trauma center identified decreased coagulation abnormalities as a potential mechanism (in addition to blunted adrenergic response) by which EtOH may affect outcome.

In an attempt to clarify the effects of EtOH on coagulation in trauma, we recently conducted a prospective study of critically injured patients who had TEG performed upon hospital arrival (24). Our main finding was that the EtOH-intoxicated patients had admission TEG tracings indicative of impaired clot formation, consistent with acute traumatic coagulopathy – however, this did not correlate to clinical outcomes associated with bleeding. In several patients, the TEG tracing normalized within 12 hours of admission, independent of resuscitation or transfusions and coincident with the metabolism of EtOH. As these viscoelastic findings did not correlate to any changes in standard plasma coagulation tests (PT, PTT), it was not clear whether the results were indicative of a true physiologic phenomenon or a mere *in vitro* anomaly associated with TEG.

In the current study, we used ROTEM to demonstrate that the effect of EtOH on viscoelastic testing is not limited to the TEG modality alone. The replicated finding of impaired clot formation in ROTEM suggests that this may represent a true biological phenomenon after all. If so, it would correspond to the well-known inhibitory effects of EtOH on platelet activation, which constitutes a substantial component of clot initiation in whole blood assays such as ROTEM and TEG. The lack of difference in final clot strength suggests that these seemingly anticoagulant effects do not last beyond the early stages of clot initiation; this

may also explain the lack of difference in standard plasma coagulation tests like INR and PTT.

As in our prior study, viscoelastic changes associated with EtOH did not correspond to adverse clinical outcomes in extensive regression analyses. While the reasons for this were unclear in the previous study's TEG findings (wherein no effect was observed with regard to fibrinolysis), the decreased fibrinolysis observed in ROTEM here may provide a mechanistic explanation for the lack of overall clinical impact. In EtOH-intoxicated patients, inhibited clot formation appears to be balanced by a decrease in fibrinolysis, such that the coagulation process is both slower to initiate and slower to degrade. These mechanisms could result in a net even effect on coagulation and bleeding overall, helping to explain to lack of association between abnormal ROTEM results and clinical sequelae.

Such a phenomenon was observed *in vitro* by Engstrom and colleagues, who found that healthy whole blood "spiked" with increasing concentrations of EtOH demonstrated impaired clot formation by ROTEM, with no change in overall clot strength, and a profound inhibition of fibrinolysis (17). Spoerke et al studied acute EtOH intoxication in healthy subjects and obtained similar results in TEG, with impaired clot formation parameters and inhibition of fibrinolysis (15). Another healthy subjects study focusing on coagulation factors concluded that the primary effects of EtOH on the hemostatic balance appear to be mediated via platelet activity and fibrinolysis (31). Our results thus correspond well to the existing literature, and provide a compelling clinical extension of known *in vitro* and healthy subject-derived mechanistic findings.

An abnormal ROTEM tracing appears to have a very different clinical meaning in EtOH-intoxicated versus non-intoxicated patients. In the patients with high EtOH, ROTEM may be sensitive to EtOH-induced changes that mimic the impaired clot formation characteristic of acute traumatic coagulopathy (32), without the associated dire clinical implications. In an era of increasing reliance on viscoelastic testing in the initial assessment of injured patients, this represents a significant concern, as EtOH-induced ROTEM or TEG tracings could lead to misdiagnosis; clinicians might then implement inappropriate resuscitation practices in such patients, leading to unnecessary transfusions and associated complications. As such, we recommend caution in using viscoelastic testing to guide resuscitation in EtOH-intoxicated trauma patients.

This study faces the same limitations of any single center prospective cohort study, namely those of generalizability and unmeasured confounding, and our findings should be replicated in a larger series and at other centers. Our analysis was limited to patients who had admission blood alcohol data, and relied on their ability to provide an accurate medical history. It should be noted that in attempting to control for possible confounding of the relationship between EtOH and coagulation parameters by active smoking status, we repeated our central analyses including current smoking as an additional variable, but found that it had no bearing on the parameters in question, and did not change the significance or magnitude or our regression analyses. It should be also noted that, though we collected thorough clinical histories, it may be that patients with acute intoxication were less likely to report chronic conditions that would otherwise warrant exclusion, including chronic

alcoholism; however, if this did occur, it would presumably bias the data to show more adverse coagulopathy-related events in the alcohol-positive group. Analysis was limited to patients for whom blood alcohol level data was available; as previous work has shown, this discrepancy may be non-random, as patients with alcohol data may tend to be less severely injured than their counterparts (22), and this could contribute to selection bias within our cohort – however, this should not affect the ability of our data to shed light on the relationship between ROTEM and alcohol, especially given the high percentage of severely injured patients (ISS>25) in our cohort.

It should be noted that some of the ROTEM differences noted in this study, while statistically significant, may not represent major clinical differences, and may fall within the larger "normal range" of reported ROTEM values. Still, the significant bidirectional trends in ROTEM parameters remain, and it should be noted that ROTEM normal ranges have not been thoroughly validated in a population of injured patients. Recent studies have also indicated that ROTEM may not be ideally sensitive to changes in fibrinolysis (33), and our findings should be confirmed with plasmin-antiplasmin levels or the equivalent. As Pieters and colleagues have shown, EtOH intake leads to a significant increase in plasminogen activator inhibitor 1 (PAI-1), with associated decreases in tissue plasminogen activator (tPA); though these factors were not available from our cohort, they could be used in future investigations to confirm the mechanism by which EtOH influences fibrinolysis.

To conclude, we present here the first reported clinical evidence of a bidirectional effect of alcohol on coagulation dynamics in trauma. As assayed by ROTEM, EtOH appears to impair initial clot formation and inhibit fibrinolysis; this balancing of mechanisms may explain the observed discordance between abnormal ROTEM and coagulopathy-related outcomes in this population. These findings correspond to known inhibitory mechanisms of EtOH with regard to platelet function and fibrinolysis. In light of these findings, viscoelastic testing should be interpreted with caution in guiding the resuscitation of EtOH-intoxicated trauma patients.
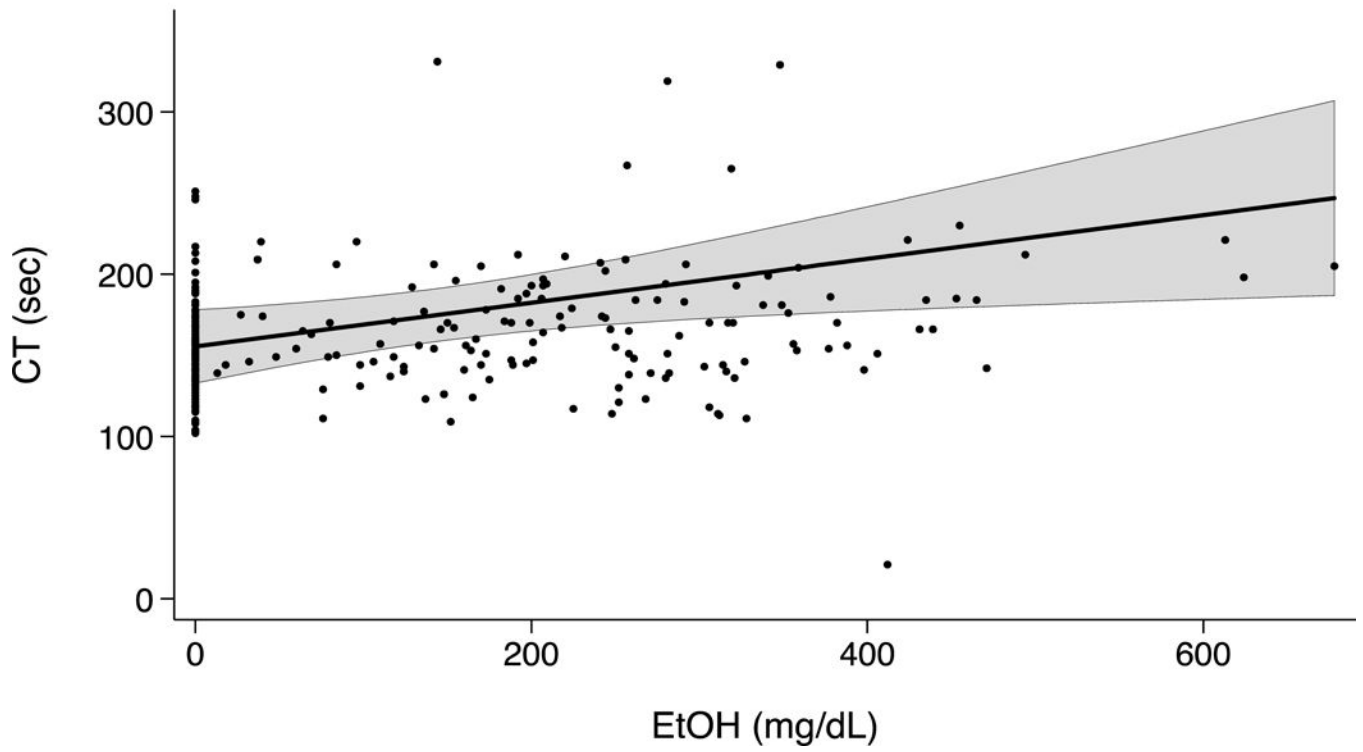
Acknowledgments

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Figure 1a. Clotting Time By Blood Alcohol Level
As EtOH increases, INTEM clotting time increases by 13.5 seconds per 100 mg/dL EtOH
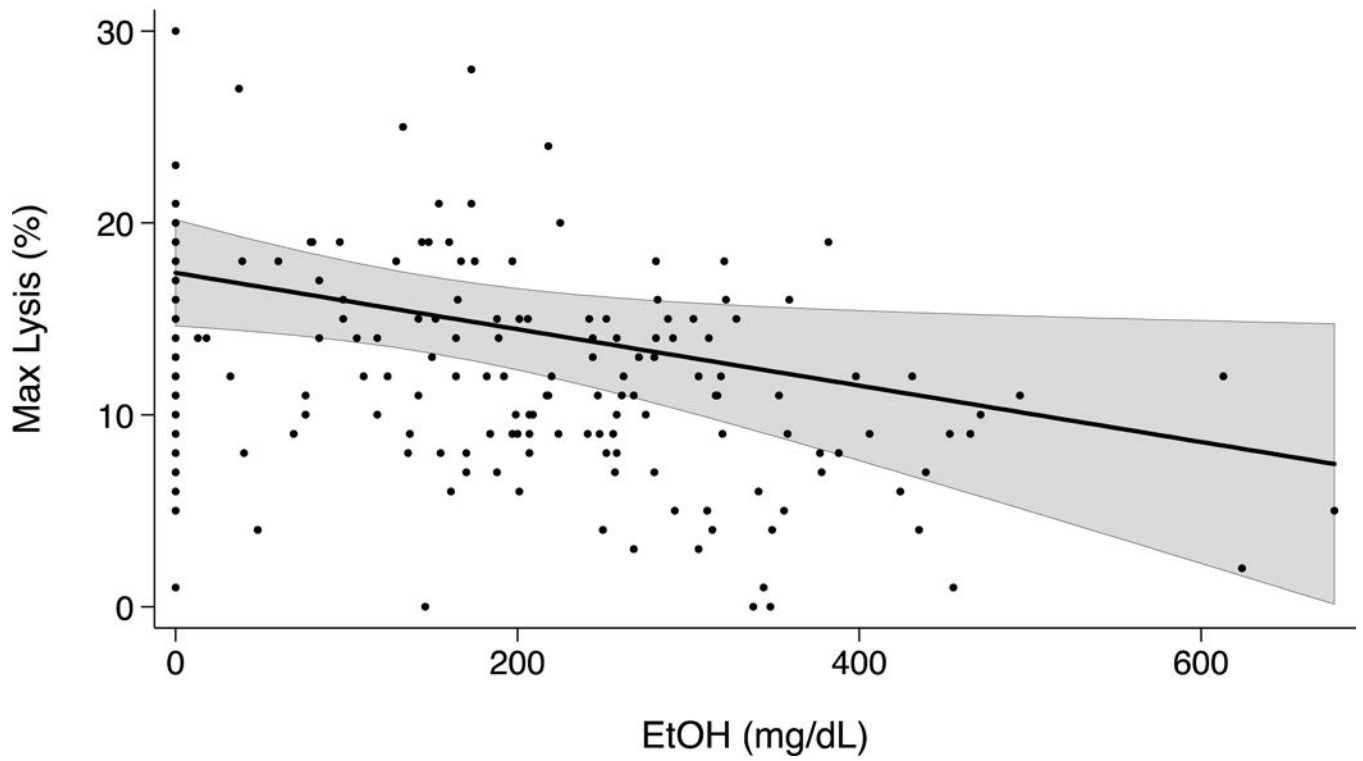(95% CI 2.7 - 24.3, p = 0.015).

Figure 1b. Fibrinolysis By Blood Alcohol Level
As EtOH increases, INTEM degree of maximum fibrinolysis decreases by 1.5% per 100 mg/dL EtOH (95% CI 0.2 - 2.8, p = 0.029).

Table 1

Admission Demographics and Coagulation Parameters

	Negative EtOH (<10mg/dL) N = 169	Positive EtOH (>10mg/dL) N = 237	*p*-value
Age (years)	35 (26 - 53)	31 (25 - 46)	0.053
Male	80	86	0.105
Blunt Mechanism	56	70	0.006
Injury Severity Score	10 (1 - 27)	10 (2 - 24)	0.769
AIS Head	0 (0 - 4)	1 (0 - 3)	0.190
GCS	14 (8 - 15)	13 (7 - 15)	0.004
Temperature (°C)	36.6 (0.6)	36.2 (0.8)	<0.001
Base Excess (mEq/L)	−1.83 (6.28)	−3.46 (5.66)	0.029
pH	7.31 (0.14)	7.29 (0.11)	0.357
Admit INR	1.15 (0.21)	1.14 (0.38)	0.026
Admit PTT (seconds)	28 (26 - 32)	28 (26 - 30)	0.064
Admit Platelets (x 1000)	263 (217 - 321)	274 (225 - 327)	0.399
Admit Fibrinogen (mg/dL)	227 (99)	228 (100)	0.949
Admit INTEM CT (sec)	151 (131 - 174)	166 (144 - 191)	<0.001
Admit INTEM CFT (sec)	68 (56 - 80)	72 (62 - 89)	0.006
Admit INTEM α angle (°)	77 (74 - 79)	75 (73 - 78)	0.007
Admit INTEM MCF (mm)	61 (5)	61 (7)	0.318
Admit INTEM Max Lys (%)	14 (11 - 16)	12 (8 - 15)	0.008
Admit EXTEM CT (sec)	58 (49 - 68)	58 (49 - 69)	0.775
Admit EXTEM CFT (sec)	88 (66 - 104)	96 (82 - 111)	0.003
Admit EXTEM α angle (°)	74 (69 - 77)	72 (68 - 75)	0.017
Admit EXTEM MCF (mm)	63 (6)	62 (7)	0.177
Admit EXTEM Max Lys (%)	14 (11 - 18)	12 (8 - 17)	0.001

Legend: Data presented as percentage unless stated, mean (SD), or median (25% - 75%). Statistical testing performed with Student's t test, Wilcoxon rank sum test, or Fisher's exact test. BMI, Body Mass Index; AIS, Abbreviated Injury Scale; GCS, Glasgow Coma Scale; International Normalized Ratio; PTT, partial thromboplastin time; CT, clotting time; CFT, clot formation time; MCF, maximum clot formation; Max Lys, maximum fibrinolysis.

Table 2

Outcomes by Alcohol Status

	Negative EtOH (<10mg/dL)	Positive EtOH (>10mg/dL)	
	N = 169	N = 237	*p*-value
Transfused pRBCs in 24h	36	30	0.280
Transfused FFP in 24h	27	17	0.018
Transfused plts in 24h	14	8	0.098
Massive Transfusion	5	4	0.477
ARDS	13	7	0.149
Multi-Organ Failure	10	8	0.484
Total Hospital Days	4 (2 - 13)	4 (2 - 11)	0.393
Total ICU Days	1 (0 - 5)	2 (0 - 4)	0.768
Mortality at 24h	4	2	0.250
Mortality at Discharge	15	7	0.008

Legend: Data presented as percentage unless stated, mean (SD), or median (25% - 75%). Statistical testing performed with Student's t test, Wilcoxon rank sum test, or Fisher's exact test. pRBCs, packed red blood cells; FFP, fresh frozen plasma; plts, platelets; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

Table 3

Multiple Linear Regression by Blood Alcohol Level

	per 100 mg/dL EtOH	95% CI	*p*	R²
Admit INTEM CT (sec)	12.7	1.0 – 24.4	0.033	0.043
Admit INTEM CFT (sec)	3.3	−0.8 - 7.4	0.119	0.043
Admit INTEM α angle (°)	−0.4	−0.9 - 0.2	0.197	0.045
Admit INTEM MCF (mm)	0.02	−0.4 - 0.5	0.911	0.081
Admit INTEM Max Lys (%)	−1.5	−2.8 - −0.2	0.028	0.105
Admit EXTEM CT (sec)	4.4	−2.2 - 11.1	0.193	0.022
Admit EXTEM CFT (sec)	7.6	−1.5 - 16.7	0.099	0.033
Admit EXTEM α angle (°)	−0.2	−0.9 - 0.4	0.490	0.050
Admit EXTEM MCF (mm)	−0.3	−0.8 - 0.3	0.355	0.083
Admit EXTEM Max Lys (%)	−1.6	−3.1 - −0.2	0.028	0.101

Legend: Multiple linear regression models, controlled for injury severity score and gender. CI, confidence interval; , change; CT, clotting time; CFT, clot formation time; MCF, maximum clot formation; Max Lys, maximum fibrinolysis.

Table 4

Multiple Logistic Regression - Predictors of Transfusion in 24 hours

	Odds Ratio	95% CI	p
Injury Severity Score	1.11	1.08 - 1.15	<0.001
Admit base excess	0.95	0.89 - 1.01	0.085
Admit GCS	1.07	0.98 - 1.16	0.131
Admit INR	2.92	0.51 - 16.8	0.230
EtOH (by 100 mg/dL)	0.84	0.65 - 1.10	0.212

Legend: Multiple logistic regression model controlled for injury severity score, admission base excess, GCS, INR, and EtOH, with N=192. INR, International Normalized Ratio; OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale; EtOH, blood alcohol level. AUC (area under receiver operating characteristic curve) 0.86.

Table 5

Clinical Outcomes in Patients with Abnormal ROTEM

	Negative EtOH (<10mg/dL) N = 124	High EtOH (230mg/dL) N = 68	p-value
Any transfusion in 24h	38	24	0.054
Transfused pRBCs in 24h	36	24	0.076
Transfused FFP in 24h	28	9	0.002
Transfused platelets in 24h	15	4	0.032
Massive Transfusion	7	3	0.333
Mortality at 24h	5	3	0.714
Mortality at Discharge	15	4	0.031

Legend: Abnormal ROTEM defined as CT > 240 seconds, CFT > 110 seconds, α angle < 70°, MCF < 50mm, ML 15% per manufacturer ranges. Data presented as percentages. Statistical testing performed with Fisher's exact test. 24h, 24 hours; pRBCs, packed red blood cells; FFP, fresh frozen plasma.