Trauma Resuscitation Consideration: Sex Matters

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BACKGROUND: Sex dimorphisms in coagulation have been recognized, but whole blood assessment of these dimorphisms and their relationship to outcomes in trauma have not been investigated. This study characterizes the viscoelastic hemostatic profile of severely injured patients by sex, and examines how sex-specific coagulation differences affect clinical outcomes, specifically, massive transfusion (MT) and death. We hypothesized that severely injured females are more hypercoagulable and therefore, have lower rates of MT and mortality.

STUDY DESIGN: Hemostatic profiles and clinical outcomes from all trauma activation patients from 2 level I trauma centers were examined, with sex as an experimental variable. As part of a prospective study, whole blood was collected and thrombelastography (TEG) was performed. Coagulation profiles were compared between sexes, and association with MT and mortality were examined. Poisson regression with robust standard errors was performed.

RESULTS: Overall, 464 patients (23% female) were included. By TEG, females had a more hypercoagulable profile, with a higher angle (clot propagation) and maximum amplitude (MA, clot strength). Females were less likely to present with hyperfibrinolysis or prolonged activating clotting time than males. In the setting of depressed clot strength (abnormal MA), female sex conferred a survival benefit, and hyperfibrinolysis was associated with higher case-fatality rate in males.

CONCLUSIONS: Severely injured females have a more hypercoagulable profile than males. This hypercoagulable status conferred a protective effect against mortality in the setting of diminished clot strength. The mechanism behind these dimorphisms needs to be elucidated and may have treatment implications for sex-specific trauma resuscitation. (J Am Coll Surg 2019;228:760−768. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Sex dimorphisms in coagulation are well established, with females manifesting a more hypercoagulable profile.[1-3] Whether this dimorphism affects outcomes after trauma is timely, as trauma-induced hemorrhage remains a leading cause of early post-injury death.[4] The effect of sex dimorphisms on clinical outcomes after trauma, including complications and mortality, has been controversial.[5-12] Several multicenter studies report decreased

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Abbreviations and Acronyms

ACT = activated clotting time
DHMC = Denver Health Medical Center
ISS = Injury Severity Score
LY30 = percent clot lysis 30 minutes after reaching maximum amplitude
MA = maximum amplitude
MT = massive transfusion
PT/INR = prothrombin time/international normalized ratio
SBP = systolic blood pressure
TBI = traumatic brain injury
TEG = thrombelastography

morbidity and mortality among females, while other investigations have found increased mortality among females or failed to identify sex-related differences at all.[5,7-15] However, none of these studies have accounted for the whole blood hemostatic state. Despite potentially distinct coagulation profiles and responses to trauma between males and females, sex has often been controlled for during regression analysis in these large population investigations and is rarely treated as an experimental variable.

Differences in coagulation between males and females after trauma have yet to be evaluated using thrombelastography (TEG), a whole blood assay that provides a comprehensive description of hemostasis with measurements of clot initiation, propagation, strength, and fibrinolysis.[16] Although plasma-based conventional coagulation assays, such as prothrombin time/international normalized ratio (PT/INR), have been used to quantify deranged hemostasis in the setting of trauma, a growing body of literature suggests that these plasma-based assays overestimate coagulopathy in trauma and surgical patients.[17] Additionally, in contrast to PT/INR, the comprehensive description of the kinetics of clot formation provided by TEG can guide resuscitation in the setting of massive transfusion (MT) for specific blood component therapy.[18] As such, precise description and comparative evaluation of sex-specific coagulation profiles in severely injured patients are timely. The effects of sex dimorphism in relation to MT requirement and risk of mortality require evaluation. We sought to evaluate sex dimorphisms in coagulation by TEG after severe injury and to assess the effect of sex-related differences in coagulation on clinical outcomes. We hypothesized that females are more hypercoagulable than males and that this female-specific hypercoagulable phenotype decreases post-injury MT and mortality.

METHODS

Study design for evaluation after trauma

Data were prospectively collected at 2 urban level-1 trauma centers: Ernest E Moore Shock Trauma Center at Denver Health Medical Center (DHMC) in Colorado and Zuckerberg San Francisco General Hospital (SFGH) in California, from 2010 to 2017. These studies were approved by their respective regional Institutional Review Boards (DHMC COMIRB#13-3087 and SFGH IRB#10-04417) and were performed under waiver of consent. Criteria for inclusion in this study were patients 18 years old or older who presented to the emergency department as trauma activations with severe injuries (Injury Severity Score [ISS] >15). Criteria for MT at both institutions were based on the physiologic Resuscitation Outcome Consortium criteria: systolic blood pressure (SBP) < 70 mmHg or SBP 70 to 90 mmHg with heart rate (HR) ≥ 108 beats/minute), in addition to any of the following: penetrating torso wound, unstable pelvic fractures, or abdominal ultrasound suspicious of bleeding in more than 1 region.[19] Resuscitation is initiated based on clinical and injury criteria and starts with a ratio delivery of 2U fresh frozen plasma: 4U RBC. The TEG assessed on arrival then directs ongoing blood product resuscitation, including MT, by viscoelastic parameters, as we described previously.[18] Exclusion criteria were any patient younger than 18 years, pregnant, or incarcerated. Clinical data collected included age, sex, mechanism of injury, BMI, ISS, presence of traumatic brain injury (TBI), initial systolic blood pressure, Glasgow Coma Scale (GCS), international normalized ratio, partial thromboplastin time, prothrombin time, base deficit, and units of RBCs transfused. Significant TBI was defined as an Abbreviated Injury Scale (AIS) for head or neck ≥ 3.

Data measurements and clinical outcomes

Whole blood samples were collected in citrated tubes (3.5 mL, 3.2% sodium citrate, Greiner Bio-One) at the scene or on hospital arrival. Citrated Rapid TEG (CR-TEG) was performed using the TEG 5000 Thrombelastography Hemostasis Analyzer per manufacturer's instructions.[20] This whole blood assay involves the addition of tissue factor to blood to elicit a thrombin burst and accelerate clot formation, providing results within 15 minutes.[16] The rapidity of these results allows for prompt, clinically relevant assessment of the hemostatic profile of trauma patients to direct blood component resuscitation in real-time. The CR-TEG yields the following variables: activated clotting time (ACT, time from initiation of assay to clot formation in minutes), angle (rate of clot strength increase, degrees), maximum amplitude (MA; maximal clot strength achieved, millimeters), and percent clot lysis 30 and 60 minutes after reaching MA (LY30 and LY60, %). An ACT > 128 seconds, angle < 65 degrees, and MA < 55 mm are considered deranged coagulation measurements.[18] Due to its multimodal distribution, LY30 was expressed as previously published: fibrinolysis shutdown (LY30 0% to 0.8%), physiologic fibrinolysis (LY30 0.9% to 2.9%), and hyperfibrinolysis (LY30 ≥ 3%).[21]

We evaluated the initial coagulation status present on the admission TEG (with the aforementioned measurements) for prediction of need for transfusion and analysis of subsequent clinical endpoints, given serial TEGs during transfusion reflect changes in coagulopathy secondary to components received. Primary outcomes assessed included massive transfusion (defined as >10 units of RBCs transfused within 6 hours of presentation or death within 6 hours of presentation to account for survivor bias) and 30-day mortality, as well as hypercoagulable morbidities including venous thromboembolism (VTE), including both pulmonary emboli (PE) and deep venous thrombosis (DVT), and cerebral vascular accident (CVA). Deep venous thrombosis was determined by venous duplex ultrasound, and pulmonary embolism was diagnosed by CT angiography of the chest. Per current *Chest* guidelines, our institution does not routinely survey patients for venous thromboembolism; only symptomatic patients are submitted to clinical investigation.[22] Cerebral vascular accident was diagnosed by head CT.

Statistical analysis

Univariate analysis used *t*-tests and Wilcoxon tests or chi-square and Fisher Exact tests, as appropriate. Multivariate analysis was conducted using Poisson regression with robust standard errors to account for intra-center cluster effects. Effect modification was assessed including interactions in logistic regression models.

Because of the suspected role of sex hormones in coagulation dimorphisms, pre-menopausal and post-menopausal (based on age cut-off of 54 years) females were compared, and then an additional analysis of age-matched males and females (matching "nearest" 1:1) was conducted, accounting for tissue injury (ISS), shock (systolic blood pressure), and blunt mechanism.[6,7] Statistical analyses were performed using SAS for Windows version 9.4 (SAS Institute). All tests were 2-tailed, with significance established at $p < 0.05$.

RESULTS

Demographics and injury characteristics

Overall, 464 trauma patients were eligible for this study, 241 from San Francisco General Hospital and 223 from Denver Health Medical Center (Table 1). Differences were detected between institutions in ISS, TBI, and SBP (eTable 1). Women accounted for 23% of the overall sample. The median age of males was 34.0; females were older, with a median age of 48.0 years ($p = 0.001$). Blunt mechanism was more common among females (92% vs 72% in males, $p < 0.0001$), and time from injury to arrival was longer for females compared with males (28 vs 24 minutes, $p = 0.03$). The median ISS was 27.0, with no difference between sexes. There was no difference in lactate or base deficit; however, the median arrival SBP was lower in females (114 vs 128 mmHg in males, $p = 0.02$).

Hematology and thrombelastography values

Hemoglobin was lower and platelets were higher in females ($p = 0.01$) (Table 1). Whole blood TEG demonstrated sex dimorphisms in coagulation, while plasma-based conventional coagulation assays (PT/INR and PTT) failed to detect a difference. On univariate analysis, angle and MA were significantly higher in females compared with males (73.9 degrees vs 71.1 degrees, respectively, in males and 64.9 mm vs 61.5 mm in males, respectively; $p = 0.01$ and $p = 0.0001$) (Table 1). There were no sex-specific differences in ACT or LY30 as a continuous variable. In terms of fibrinolytic phenotypes, on univariate analysis, males were more likely to present with hyperfibrinolysis than females (26% vs 15% of females, $p = 0.03$). After adjusting for covariates (age, blunt mechanism, ISS, SBP, and TBI) on multivariate analysis, men were more likely to present with a prolonged ACT (>128 sec; RR 1.11, 95% CI 1.10 to 1.11) and decreased MA (<55 mm; RR 1.35, 1.13 to 1.60) (Table 2), and they were more likely to present in hyperfibrinolysis (RR 1.73, 95% CI 1.32 to 2.25).

Clinical outcomes and association with thrombelastography measurements

Overall mortality rate was not different between sexes (25% in men vs 33% in women) on unadjusted analysis, despite the fact that women were older, had longer time from injury to emergency department presentation, and lower arrival SBP ($p = 0.08$). On unadjusted analysis, there was no difference in case-fatality rate among hyperfibrinolytic patients (21% [20 of 94] in males vs 6% [1 of 16] in females, $p = 0.29$). However, all males with hyperfibrinolysis died from coagulopathy or hemorrhagic shock; only 1 woman with hyperfibrinolysis died, and the cause of her death was a devastating TBI, unrelated to coagulopathy. Case-fatality rate did not differ between males and females for physiologic lysis (11% in males vs 17% in females, $p = 0.30$) or fibrinolytic shutdown (7% in males vs 11% in females, $p = 0.50$).

Table 1. Trauma Population Characteristics by Sex (n = 464)

Characteristic	Female (n = 106)	Male (n = 358)	p Value*
Demographic, median (25th–75th IQR)			
Age, y	48.0 (27.8–61.6)	34.0 (25.3–51.0)	0.01
BMI, kg/m^2	25.3 (22.5–28.2)	25.8 (23.1–29.0)	0.18
Injury characteristic			
Time from injury to arrival, min	28 (20–38)	24 (19–32)	0.03
Blunt, n (%)	97 (91.6)	258 (72.1)	<0.01
ISS, median (25th–75th IQR)	29 (22–38)	27 (21–34)	0.06
GCS, median (25th–75th IQR)	10 (4–14)	11 (3–15)	0.55
TBI, n (%)	62 (58)	208 (58)	0.91
Physiologic marker, median (25th–75th IQR)			
SBP, mmHg	114 (90–142)	128 (104–148)	0.02
Base deficit, meq/L	8.4 (6.0–13.0)	7.0 (4.0–10.6	0.26
Lactate, mmol/L	4.1 (2.2–5.8)	4.2 (2.7–6.9)	0.21
Hematology/coagulation assay, median (25th–75th IQR)			
Hemoglobin, g/dL	12.6 (11.0–13.4)	13.8 (12.5–15.3)	<0.01
Hematocrit, %	38.2 (34.9–40.9)	41.8 (38.0–45.0)	<0.01
Platelets, 10^9/L	264 (216–369)	240 (191–301)	0.01
INR	1.2 (1.1–1.3)	1.2 (1.0–1.3)	0.96
PTT, sec	28.2 (25.2–34.4)	28.4 (25.0–35.0)	0.69
TEG measurement, median (25th–75th IQR)			
ACT, sec	113 (99–128)	113 (105–128)	0.37
Angle, degrees	73.9 (67.1–77.3)	71.1 (65.8–75.4)	0.01
MA, mm	64.9 (59.0–69.6)	61.5 (56.0–66.0)	0.01
LY30, %	1.4 (0.2–2.5)	1.4 (0.5–3.1)	0.72
Fibrinolytic phenotype, n (%)			
Fibrinolytic shutdown, LY30 < 0.9%	39 (37)	132 (37)	0.03
Physiologic lysis, LY30 0.9–2.9%	51 (48)	132 (37)	
Hyperfibrinolysis, LY30 ≥ 3.0%	16 (15)	94 (26)	
Outcome			
Mortality, n (%)	35 (33.0)	88 (24.6)	0.10
Transfusion (≥1U RBC) in first 24 h, n (%)	30 (28.3)	84 (23.5)	0.31
No. of U of RBC in first 6 h (among those transfused), median (25th–75th IQR)	6 (3–12)	6 (2–12)	0.98
Massive transfusion, n (%)	14 (13.2)	45 (12.6)	0.87
VTE, n (%)	13 (12)	29 (8)	0.25
CVA, n (%)	1 (1)	2 (1)	0.57
LOS, d, median (25th–75th IQR)	12 (6–20)	10 (4–18)	0.10
VFD-28, d, median (25th–75th IQR)	21 (0–26)	23 (0–27)	0.33
ICUFD-28, d, median (25th–75th IQR)	21 (6–25)	22 (9–25)	0.26

*p Values from Mann-Whitney and chi-square (2 outcomes for all categories except for fibrinolytic phenotype) as appropriate.
ACT, activated clotting time; CVA, cerebral vascular accident; GCS, Glasgow Coma Scale; ICUFD-28, intensive care unit free days at 28 d; INR, international normalized ratio; IQR, interquartile range; ISS, Injury Severity Score; LOS, length of stay; LY30, lysis 30 min after MA; MA, maximum amplitude; PTT, partial thromboplastin time; SBP, systolic blood pressure; TBI, traumatic brain injury; VFD-28, ventilator free days at 28 d; VTE, venous thromboembolism.

On adjusted analysis (age, blunt mechanism, ISS, SBP, and TBI), higher mortality was observed in hyperfibrinolytic and shutdown groups in both sexes, with equivalent case-fatality rates. Female sex conferred a survival benefit in the setting of decreased MA, with an increased risk of death in males (odds ratio [OR] 2.89, 95% CI 1.48 to 5.64) compared with females (OR 0.65, 95% CI 0.17 to 2.48) (Table 3). Sex was not found to have an effect on the association of abnormal ACT, angle, or LY30 with massive transfusion or death. There was no difference in transfusion

Table 2. Multivariate Analysis Assessing the Independent Effect of Sex (Female as the Reference Category) on Abnormal Thromboelastographic Measurements in Trauma Patients

Coagulation phenotype	Male relative risk	95% CI	p Value
Abnormal lysis, <0.9%, ≥3%	1.21	1.08−1.36	0.001
Hyperfibrinolysis, ≥3%	1.73	1.32−2.25	<0.0001
Fibrinolytic shutdown, <0.9%	1.02	0.91−1.13	0.100
Abnormal ACT, >128 s	1.11	1.10−1.11	<0.0001
Abnormal angle, <65 degrees	0.89	0.86−0.93	<0.0001
Abnormal MA, <55 mm	1.35	1.13−1.60	0.001

ACT, activating clotting time; MA, maximum amplitude.

requirement, MT, or hypercoagulable morbidities between sexes on univariate or multivariate analysis (Table 1).

Matched analysis

Before performing age-matched analysis, pre- and post-menopausal women were compared. Post-menopausal women had less severe indicators of shock (higher SBP, less base deficit, and less lactate), a shorter ACT, and decreased LY30, but higher angle and MA compared with pre-menopausal women (Table 4). The outcomes discussed in previously were also analyzed among a cohort of age-matched male and female trauma patients. Among 105 age-matched males and females, there were no differences in MT (14.3% in males vs 12.4% in females) or mortality (13.3% in both sexes) ($p = 0.84$ and 0.99, respectively). This lack of statistical difference persisted even when matching for mechanism, shock, and tissue injury, with an MT rate of 12.4% in females and 14.3% in males, and a mortality rate of 13.3% in females vs 12.4% in males ($p = 0.83$ and 0.99, respectively).

DISCUSSION

Female hypercoagulability has been described, but not characterized with comprehensive whole blood evaluation, such as TEG, in the setting of trauma.[3,23] The effect of this hypercoagulable state on clinical outcomes after trauma, including massive transfusion and mortality, is not well established. In the data presented here, when treating sex as an experimental variable, females had a more hypercoagulable profile than their male counterparts, presenting less coagulopathic after severe injury (less clot formation prolongation, higher MA and angle, and less hyperfibrinolysis). This hypercoagulability was protective and conferred a survival advantage in the setting of decreased clot strength (lower MA). Further, no females died from hemorrhage associated with hyperfibrinolysis, unlike their male counterparts.

Documenting a more hypercoagulable state among females compared with males is consistent with previous literature in healthy volunteers. Francis and colleagues[24] first described the citrated native profile of 40 healthy volunteers and noted sex-based differences: females demonstrated shorter R time and higher MA vs males. Gorton and associates[1] described similar native TEG results among healthy volunteers, specifically, 50 males, 50 pregnant females, and 50 nonpregnant, premenopausal females. Nonpregnant females demonstrated shorter R time and higher angle and MA, and these differences

Table 3. Multivariate Analysis of the Modification of the Association Between Abnormal Activating Clotting Time, Angle, Maximum Amplitude, and Fibrinolysis with Death, by Sex

Coagulation phenotype	Analysis of conditional maximum likelihood estimate	Standard error	p Value
Abnormal ACT	1.06	0.35	0.003
Abnormal ACT + male sex	0.18	0.32	0.58
Abnormal angle	0.53	0.36	0.14
Abnormal angle + male sex	0.46	0.34	0.18
Abnormal MA	0.32	0.38	0.41
Abnormal MA + male sex	0.74	0.38	0.04
Hyperfibrinolysis	0.85	0.32	0.60
Hyperfibrinolysis + male sex	-0.39	0.31	0.21
Fibrinolysis shutdown	-0.25	0.33	0.46
Fibrinolysis shutdown + male sex	0.17	0.33	0.60

Abnormal activated clotting time: >128 s; abnormal angle: <65 degrees; abnormal maximum amplitude: <55 mm; hyperfibrinolysis: LY30 (30 min after maximum amplitude) ≥3%; fibrinolysis shutdown: LY30 < 0.9%.
ACT, activated clotting time; LY30, lysis 30 min after maximum amplitude; MA, maximum amplitude.

Table 4. Female Patient Data, Stratified by Menopausal State

Data	Premenopausal female, ≤54 y (n = 66)	Postmenopausal female, >54 y (n = 40)	p Value
Demographic, median (25th–75th IQR)			
Age, y	31.8 (25.1–45.1)	67.5 (57.8–77.8)	<0.01
BMI, kg/m^2	25.3 (20.9–28.37)	25.1 (23.2–28.3)	0.57
Injury characteristic			
Time from injury to arrival, min, median (25th–75th IQR)	24 (18–37)	31 (24–46)	0.01
Blunt, n (%)	56 (85)	40 (85)	0.99
ISS, median (25th–75th IQR)	30 (22–41)	28 (22–37)	0.40
GCS, median (25th–75th IQR)	11 (3–14)	9 (5–15)	0.84
TBI, n (%)	32 (48)	30 (75)	0.01
Physiologic marker, median (25th–75th IQR)			
SBP, mm Hg	111 (90–134)	132 (91–161)	0.03
Base deficit, meq/L	8.0 (5.9–12.6)	2.2 (1.0–6.1)	<0.01
Lactate, mmol/L	4.1 (3.1–5.6)	2.0 (1.8–3.7)	<0.01
Hematology/coagulation assay, median (25th–75th IQR)			
Hemoglobin, g/dL	12.6 (11.2–13.5)	12.6 (11.4–13.5)	0.92
Hematocrit, %	38.0 (34.8–41.4)	38.5 (35.2–40.0)	0.66
Platelets, 10^9/L	273 (214–332)	232 (181–298)	0.13
INR	1.2 (1.1–1.3)	1.1 (1.0–1.2)	<0.01
PTT, s	28.7 (25.6–36.0)	28.5 (25.8–32.4)	0.75
TEG measurement, median (25th–75th IQR)			
ACT, s	113 (105–132)	105 (97–113)	0.01
Angle, degrees	71.6 (63.3–76.2)	76.9 (73.9–78.5)	<0.01
MA, mm	63.0 (55.9–68.8)	66.4 (62.1–71.0)	0.02
LY30, %	1.8 (0.7–2.7)	0.7 (0.0–2.0)	<0.01
Outcome			
Mortality, n (%)	16 (24)	19 (48)	0.02
Transfusion, ≥1U RBC in first 24 h, n (%)	35 (53)	24 (60)	0.55
No. of units of RBC in first 6 hours among those transfused, median (25th–75th IQR)	5 (3–13)	4 (3–6)	0.12
MT, n (%)	11 (17)	3 (8)	0.24
LOS d, median (25th–75th IQR)	12 (5–20)	12 (5–27)	0.51
VFD-28 d, median (25th–75th IQR)	23 (0–28)	16 (0–28)	0.66
ICUFD–28 (d, median (25th–75th IQR)	18 (4–26)	19 (7–28)	0.31

ACT, activated clotting time; GCS, Glasgow Coma Score; ICUFD-28, intensive care unit free days at 28 d; INR, international normalized ratio; IQR, interquartile range; ISS, Injury Severity Score; LOS, length of stay; LY30, lysis 30 min after MA; MA, maximum amplitude; PTT, partial thromboplastin time; SBP, systolic blood pressure; TBI, traumatic brain injury; VFD-28, ventilator free days at 28 d.

were further increased in pregnant females compared with nonpregnant females.[1] These data suggest that female sex hormones convey a hypercoagulable state. This highlights the importance of evaluating sex as an independent variable and accounting for estrus state of females when examining coagulation. The presented data support the contention that sex hormones contribute to a hypercoagulable state in that female patients had a more hypercoagulable profile than males. However, within our study, there were no differences in our findings when comparing pre-menopausal vs post-menopausal females with age-matched males. This suggests the mechanisms responsible for dimorphisms in outcomes are not explained by circulating sex hormone levels alone. For example, epigenetic or post-translational processes may exist from lifetime exposure to the milieu of female sex hormones, as suggested by the myriad of genomic and nongenomic effects of sex hormones on platelets.[25,26] This could impart functional alterations in female platelet progenitors or cellular clotting biology and result in hypercoagulable potential, which persists through menopause. Additionally, there are data from animal models and clinical work demonstrating low hemoglobin and elevated platelets confer a hypercoagulable profile on thrombelastography.[27-30] These data suggest that the relative anemia and elevated platelet count in females compared with males may partially explain their sex-specific hypercoagulability. Although the differences in hemoglobin and platelet levels between sexes themselves may not be clinically significant, their effect on coagulation must be considered. Ultimately, the mechanisms behind the sex-specific distinct coagulation profiles are likely multifactorial, complex, and include a composite of the previously mentioned variables.

The hypercoagulable profile described in healthy females in the previously mentioned literature persisted in the setting of trauma in our investigation. Male trauma patients presented with lower clot propagation and clot strength and were more likely to present with a prolonged time to clot formation (ACT) and hyperfibrinolysis than females. Given that penetrating trauma is associated with a higher rate of hyperfibrinolysis compared with blunt trauma, the higher rate of penetrating trauma within the male population suggests a partial explanation for this finding.[31] Another explanation may be that a higher angle and MA among females results in a stronger clot that is more resistant to fibrinolysis.

Despite the higher risk of hyperfibrinolysis in males, there was no difference in transfusion requirement or MT. This could be due to the fact that neither institution has a sex-specific trigger for massive transfusion, and all patients were resuscitated with TEG-based algorithms, as we described previously.[18] In our previously published randomized trial, a TEG-based resuscitation algorithm resulted in fewer blood product transfusions and improved survival. Therefore, detection of differences in transfusion and survival outcomes by sex, which may be observed in sex-indiscriminate fixed ratio transfusion strategies, may have been therapeutically mitigated or underestimated by TEG-based resuscitation. Ultimately, fixed ratio administration may result in females receiving more products than they need for hemostasis. Notably, seminal studies examining fixed ratio transfusion, such as the PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial and related studies, have not accounted for sex in transfusion practice or examined sex-based differences in transfusion requirement, highlighting the need to better characterize sex-specific transfusion triggers.[32,33] The lack of transfusion differences between males and females has been described in other studies, including a multicenter prospective cohort study of 2,007 trauma patients that found no difference in 24-hour transfusion requirement between males and females.[11,15] However, to our knowledge, current models to determine triggers for massive transfusion in trauma do not account for sex-related differences in coagulation and apply an empiric practice for males and females. Our data suggest that females may not need platelet transfusion for the same MA threshold as males, given their ability to tolerate a lower clot strength. These data ultimately support a consideration for the need to recalibrate the TEG-based thresholds for transfusion, which were previously established in a population with a male-dominated demographic.[18]

Despite an older age, longer time from injury to emergency department presentation, and lower arrival SBP, females did not have higher mortality. In fact, female sex-specific hypercoagulability was protective among trauma patients and conferred a survival advantage in the setting of decreased clot strength (lower MA). Additionally, the case-fatality rate among females with hyperfibrinolysis was lower than that of males. This sex-specific hypercoagulability did not appear to increase the risk of thrombotic morbidity. The findings from this study may serve to explain the reason for higher mortality among male trauma patients in larger scale studies, including a multicenter study of 47,295 trauma patients, an analysis of a trauma registry including 18,133 patients, and a review of 48,394 patients in the National Trauma Database, all of which describe a higher mortality rate among males.[5,7,10] Although another multicenter study of outcomes among trauma patients, stratified by coagulopathy (defined by INR >1.5), found increased mortality among females, those findings were in the context of defining coagulopathy by INR, not by TEG, as our study does.[11] The distinction of coagulopathy definitions by INR vs TEG is relevant, given recent work indicating that INR overestimates coagulopathy in trauma.[17]

The mechanism behind an inferior tolerance for decreased clot strength and hyperfibrinolysis among males is unclear. There are multifactorial effects on MA in males, including a lower fibrinogen and platelet count, as well as reduced platelet function, compared with females.[34,35] The increased functional fibrinogen level (FLEV) on citrated functional fibrinogen TEG (a measurement of fibrinogen contribution to clot strength in a fibrinogen-specific TEG in the healthy female volunteers [unpublished data]) suggests that fibrinogen in females may contribute more to clot strength than platelets compared with males, explaining a better tolerance to coagulopathy in females.[36] It may also be that coagulopathy associated with an abnormal MA does not increase mortality risk in females because they present with, or convert to, a more hypercoagulable profile earlier than their male counterparts, attenuating risk of death from hemorrhage. This has been suggested in serial blood draws and TEG of male vs female trauma ICU admissions.[23] Ultimately, platelets are known to be affected by shock, tissue injury, acidosis, and other elements present in trauma, therefore, the mechanism behind the survival advantage is likely a composite of several factors vs clot strength reflected by MA alone.[37]

Translationally, the hypercoagulability and increased tolerance of coagulopathy in females has treatment implications in that males in trauma-induced coagulopathy may need to be resuscitated earlier and more aggressively with blood components. Further, while we did not observe increased thrombotic morbidity in females, given their hypercoagulability, it calls into question the relative risk of thrombosis or transition to fibrinolysis shutdown with transfusions of cryoprecipitate or the administration of antifibrinolytics.

Limitations of this study include a relatively small sample size among the trauma population, which may contribute to a lack of power to detect morbidity and overall mortality differences. The small number of females in hyperfibrinolysis further limits the ability to draw firm conclusions on case-fatality; however, the fact that there were no deaths from hemorrhage in females with hyperfibrinolysis highlights a relationship worth investigating with a higher-powered study. Our findings support other larger-scale studies, which have found increased survival in females, and we believe this investigation, focused on sex-specific coagulopathy, suggests a potential mechanism behind this survival. However, wide application of these findings requires additional multicenter investigation to support this analysis. As previously mentioned, another limitation is the inability to correlate increased survival in females with a decreased MA (compared with males) to the TEG measurement itself; although MA and platelet function are affected by a myriad of factors, it is likely that the composite of these variables is what ultimately confers the improved survival. While this study includes venous thromboembolism, cerebrovascular accident, and acute lung injury as clinical events related to the hypercoagulable state, to comprehensively evaluate for all sequelae of hypercoagulability, a prospective, multicenter trial with screening duplex ultrasound and consistent definitions of clinical endpoints of hypercoagulability (myocardial infarction, cerebrovascular accident, venous thromboembolism) would better address these outcomes. Although all TEGs were conducted within 1 hour of venipuncture and conducted at the same time for each patient, some variability existed between time from venipuncture and running assays. Lastly, the trauma patient analysis did not include data on pharmacologic contraception or estrus cycle timing among females.

CONCLUSIONS

Sex-specific dimorphisms in coagulation persist in the setting of trauma such that after severe injury, female trauma patients are less coagulopathic. This female-specific hypercoagulability was protective from mortality in the setting of trauma-induced coagulopathy. These data challenge the clinical bias of unified transfusion strategy and suggest there should be a differential transfusion trigger and strategy for females given their more hypercoagulable profile or for males given their more coagulopathic profile. Our data also suggest that females may require less blood product transfusion and be less likely to require antifibrinolytics because of their hypercoagulable profile, and antifibrinolytic therapy may disproportionally increase the risk of venous thromboembolic events in females. The results of this study highlight the need to further investigate sex as a biologic variable in studies of trauma populations and how these sex dimorphisms may warrant differential transfusion practices or resuscitation after severe injury.

Author Contributions

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eTable 1. Comparison of Trauma Patients from Denver Health Medical Center and Zuckerberg San Francisco General Hospital (SFGH). Continuous data presented as median (25th–75th IQR).

	Female (n = 106)			Male (n = 358)		
Characteristic	**DHMC (n = 59)**	**SFMC (n = 47)**	**p Value**	**DHMC (n = 164)**	**SFMC (n = 194)**	**p Value**
Demographic, median (25th–75th IQR)						
Age, y	39.7 (26.1–50.4)	58.0 (39.0–75.0)	<0.01	32.6 (25.3–48.0)	36.0 (25.8–53.0)	0.25
BMI, kg/m^2	26.0 (22.7–24.5)	24.2 (21.0–27.8)	0.36	25.4 (23.2–28.6)	26.0 (23.0–29.7)	0.81
Injury characteristic						
Time from injury to arrival, min, median (25th–75th IQR)	29 (20–37)	27 (18–36)	0.83	25 (19–31)	25 (19–32)	0.85
Blunt, n (%)	52 (88.1)	45 (95.7)	0.27	111 (67.7)	147 (75.8)	0.10
ISS, median (25th–75th IQR)	29 (22–38)	30 (26–38)	0.38	26 (18–34)	29 (22–35)	0.02
GCS, median (25th–75th IQR)	13 (3–15)	9 (6–14)	0.71	14 (3–15)	11 (6–15)	0.70
TBI, n (%)	35 (59.3)	38 (80.9)	0.02	79 (48.2)	137 (71.1)	<0.01
Physiologic marker, median (25th–75th IQR)						
SBP, mm Hg	102 (83–130)	132 (107–159)	0.01	118 (90–140)	131 (112–155)	<0.01
BD, meq/L	8.4 (6.0–13.0)	1.8 (2.4–4.9)	0.16	7.0 (4.0–10.6)	3.0 (1.0–7.2)	0.33
Lactate, mmol/L	4.1 (2.0–6.4)	3.2 (2.2–4.9)	0.35	4.2 (2.7–6.9)	2.9 (2.3–5.6)	0.15
Hematology/coagulation assay, median (25th–75th IQR)						
Hemoglobin, g/dL	12.6 (10.8–13.6)	12.6 (11.0–13.2)	0.56	14.0 (12.5–15.5)	13.7 (12.6–15.0)	0.25
Hematocrit, %	38.6 (33.4–41.3)	37.8 (35.1–39.9)	0.86	42.4 (38.5–46.1)	40.7 (37.7–44.4)	0.30
Platelets, 10^9/L	264 (216–369)	245 (199–309)	0.14	240 (191–301)	261 (208–314)	0.03
INR	1.2 (1.1–1.3)	1.1 (1.1–1.2)	0.63	1.2 (1.0–1.3)	1.2 (1.1–1.3)	0.70
PTT, s	28.2 (25.2–34.4)	29.4 (25.7–32.8	0.43	28.4 (25.0–35.0)	29.1 (26.8–34.2)	0.33
TEG measurement, median (25th–75th IQR)						
ACT, s	121 (113–136)	97 (89–105)	<0.01	121 (113–136)	105 (89–121)	<0.01
Angle, degrees	72.2 (63.6–76.6)	76.8 (72.1–77.9)	0.01	69.7 (63.9–74.4)	72.5 (68.6–75.9)	0.05
MA, mm	63.8 (57.5–70.1)	66.4 (59.3–69.3)	0.16	60.5 (53.1–65.5)	62.1 (58.2–66.3)	0.66
LY30, %	1.6 (0.7–2.6)	0.8 (0.0–2.3)	0.13	1.9 (0.9–3.4)	0.8 (0.1–2.2)	0.01
Outcome						
Mortality, n (%)	14 (23.7)	21 (44.7)	0.04	37 (22.6)	51 (26.3)	0.46
Transfusion (≥1U RBC) in first 24 h, n (%)	30 (50.8)	23 (46.9)	0.99	84 (51.2)	65 (33.5)	0.01
No. of U of RBC in first 6 h, among those transfused, median (25th–75th IQR)	6 (3–12)	4 (3–9)	0.79	6 (2–12)	4 (2–8)	0.13
MT, n (%)	8 (13.6)	6 (12.8)	0.99	25 (15.2)	20 (10.3)	0.20
VTE, n (%)	4 (7)	9 (19)	0.07	10 (6)	19 (10)	0.24
CVA, n (%)	1 (2)	0 (0)	0.99	2 (1)	0 (0)	0.99
LOS, d, median (25th–75th IQR)	12 (6–20)	13 (4–29)	0.57	10 (4–18)	12 (5–25)	0.77
VFD–28, d, median (25th–75th IQR)	22 (0–26)	12 (0–25)	0.12	23 (0–27)	20 (0–26)	0.59
ICUFD–28, d, median (25th–75th IQR)	21 (6–25)	24 (10–25)	0.10	22 (8–25)	22 (14–26)	0.81

ACT, activated clotting time; CVA, cerebral vascular accident; DHMC, Denver Health Medical Center; GCS, Glasgow Coma Scale; ICUFD-28, intensive care unit free days at 28 d; INR, international normalized ratio; IQR, interquartile range; ISS, Injury Severity Score; LOS, length of stay; LY30, lysis 30 min after MA; MA, maximum amplitude; PTT, partial thromboplastin time; SBP, systolic blood pressure; BD, base deficit; SFGH, San Francisco General Hospital; TBI, traumatic brain injury; VFD-28, ventilator free days at 28 d; VTE, venous thromboembolism.