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Prospective multicenter evaluation of coagulation abnormalities in dogs following severe acute trauma

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Abstract

Objectives – To describe coagulation abnormalities in dogs following severe acute trauma and to evaluate the relationship between coagulation, clinical, and laboratory variables, and disease and injury severity, as well as the ability of coagulation variables to predict the presence of body cavity hemorrhage (BCH), necessity of blood product administration, and outcome.
Design – Prospective, multicenter, observational study.
Setting – Two university teaching hospitals.
Animals – Forty client-owned dogs sustaining severe blunt or penetrating trauma.
Interventions – Blood samples were collected within 12 hours of the traumatic incident for measurement of blood gases, lactate concentration, platelet count, activated clotting time, prothrombin time, activated partial thromboplastin time (aPTT), fibrinogen concentration, antithrombin activity, D-dimer concentration, protein C activity, plasmin inhibition, plasminogen activity, and kaolin-activated thromboelastography.
Results – Decreased platelet count was a risk factor for the presence of BCH ($P = 0.006$) and decreased platelet count ($P < 0.001$), protein C activity ($P = 0.001$), angle (α) ($P = 0.001$), maximum amplitude (MA) ($P < 0.001$), and clot strength (G) ($P = 0.002$) were risk factors for blood product administration. Nonsurviving dogs were hypocoagulable with prolonged aPTT ($P = 0.008$), decreased plasmin inhibition ($P = 0.033$), decreased α ($P = 0.021$), and decreased MA ($P = 0.038$) compared to surviving dogs. Multivariate analysis accounting for disease severity showed that prolonged aPTT ($P = 0.004$, OR = 1.74) was the strongest predictor of nonsurvival. Prolonged aPTT was positively correlated with APPLE-fast score ($P < 0.001$, $r^2 = 0.35$), lactate concentration ($P < 0.001$, $r^2 = 0.35$), and negative base excess ($P = 0.001$, $r^2 = 0.27$). Acute traumatic coagulopathy, as defined by 2 or more abnormal coagulation tests, was diagnosed in 15% of dogs at hospital admission and was more common in dogs with increased disease severity ($P = 0.002$), decreased systolic blood pressure ($P = 0.002$), and increased lactate concentration ($P = 0.011$).
Conclusions – In dogs with severe traumatic injuries and hypoperfusion, measurement of thromboelastography and aPTT should be considered to support clinical assessments in predicting the need for blood product administration and nonsurvival.

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Keywords: hemostasis, hemorrhage, hypotension, lactate, perfusion, thromboelastography

Abbreviations

ACT	activated clotting time
aPTT	activated partial thromboplastin time
AT	antithrombin
ATC	acute traumatic coagulopathy
BCH	body cavity hemorrhage

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BE	base excess
DBP	diastolic blood pressure
FAST	focused assessment sonography for trauma
G	clot strength
INR	international normalized ratio
ISS	injury severity score
K	clot formation time
LY30	30 minute clot lysis
MA	maximum amplitude
MAP	mean arterial pressure
NCSU-VHC	North Carolina State University Veterinary Health Complex
NSAIDs	nonsteroidal anti-inflammatory drugs
OVC-HSC	Ontario Veterinary College Health Sciences Centre
PT	prothombin time
R	reaction time
SBP	systolic blood pressure
TEG	thromboelastography

Introduction

Trauma accounts for over 10% of veterinary hospital admissions and involves serious injuries in approximately 35% of cases.[1–3] Mortality rates are approximately 10% in dogs, whose injuries are typically the result of blunt trauma sustained in motor vehicle accidents.[2–4] Posttrauma hemorrhage and coagulopathies have not been extensively studied in veterinary patients. Retrospectively, fewer than a quarter of dogs with severe blunt trauma have documented hemothorax or hemoabdomen and approximately 25% of dogs with severe blunt trauma require a blood product transfusion.[4] However, the introduction of focused assessment using sonography for trauma (FAST) in veterinary medicine has increased the detection of posttrauma hemorrhage, with incidences of hemoabdomen ranging from 27–43% in dogs sustaining blunt trauma.[5,6]

In people, trauma is the leading cause of death and disability worldwide, with in-hospital mortality rates of approximately 20%.[7] Recovery after trauma in people is largely determined by the primary injuries, the patient's physiologic reserves, and secondary injuries that occur due to suboptimal or delayed care.[8] Evidence suggests that coagulopathy associated with severe trauma is a major source of secondary injury and also a key contributor to posttrauma hemorrhage.[8] Second only to head injuries, posttrauma hemorrhage causes 40% of all deaths and is the leading cause of potentially preventable death due to trauma in people.[8]

Acute traumatic coagulopathy (ATC), also referred to as coagulopathy of trauma, trauma-induced coagulopathy, and acute coagulopathy of trauma-shock, is a coagulopathy diagnosed in 24–34% of severely injured people upon arrival to the emergency room.[9–12] A formal definition does not exist for ATC; however, most studies use a 50% prolongation in prothrombin time (PT) or activated partial thromboplastin time (aPTT), measured upon hospital admission, as a diagnostic criterion.[12] Numerous factors contribute to ATC including severe tissue injury, shock, hemodilution during fluid resuscitation, hypothermia, acidosis, and inflammation.[13–15] Injury severity is closely associated with the degree of ATC and people diagnosed with ATC have approximately a 4-fold higher mortality rate compared to those without ATC.[9–12]

The association of ATC and posttrauma hemorrhage in dogs and its impact on outcome is currently unknown. Acute traumatic coagulopathy has only recently been described in dogs.[16] Coagulation variables including resonance thrombography have been investigated in a group of dogs presenting to a veterinary teaching hospital within 24 hours of blunt trauma.[17,18] Several variables were significantly altered compared to healthy dogs including platelet count, PT, aPTT, fibrinogen concentration, and clotting factor activity.[18] However, most coagulation variables still remained within reference intervals and associations between coagulation abnormalities and posttrauma hemorrhage or outcome were not investigated. The objective of the present study was to describe coagulation abnormalities in dogs following severe acute trauma and to evaluate the association of coagulation and thromboelastography (TEG) variables with clinical and laboratory variables, as well as disease and injury severity, and to assess the ability of coagulation and TEG variables to predict the presence of body cavity hemorrhage (BCH), necessity of blood product administration, and outcome. It was hypothesized that severely injured dogs would demonstrate hypocoagulability after trauma that would be predictive of the presence of BCH, the need for blood product administration, and nonsurvival.

Materials and Methods

Study population

Dogs were considered for inclusion if they were admitted to the hospital within 12 hours of a blunt (eg, motor vehicle accident, fall from height) or penetrating (eg, animal altercation) traumatic incident with injuries involving > 1 organ system and an anticipated requirement for hospitalization for at least 3 days. Dogs < 1 year old, weighing < 10 kg, diagnosed with a congenital coagulopathy, previously treated with hypertonic saline, synthetic colloids, blood products, or anticoagulant medications, with injuries localized to an extremity (eg, limb fracture), or hospitalized only for IV fluid therapy or

analgesia were excluded. Informed consent was obtained prior to enrolment of dogs and the institution's animal use committee approved all aspects of the study.

Recorded variables

Clinical variables recorded upon hospital admission included the signalment, body weight, animal trauma triage (ATT)[19] and acute patient physiologic and laboratory evaluation- (APPLE-) fast[1] scores, prior treatment with crystalloids, glucocorticoids, or nonsteroidal anti-inflammatory drugs (NSAIDs), as well as the type (blunt or penetrating) and cause of trauma. Clinical and laboratory variables recorded upon hospital admission and every other day up to and including the fifth day of hospitalization included vital signs, blood pressure (Doppler or oscillometric), SpO_2 (pulse oximetry), PCV, total plasma protein (refractometry), venous blood gases and electrolytes, and plasma lactate concentrations. Administration of glucocorticoids, NSAIDs, oxygen supplementation, synthetic colloids, hypertonic saline, or blood products during hospitalization were also recorded, as well as the presence of BCH, which was considered a positive FAST[6] or a hemorrhagic abdomino- or thoracocentesis. Outcome was recorded as survival (to hospital discharge) or nonsurvival (died or euthanized due to a perceived grave prognosis). Dogs euthanized for financial reasons were excluded from analyses.

Blood collection

Blood samples were collected as soon as possible after hospital admission and then every other day until hospital discharge or death for a total of 3 sample collections. Blood was collected using nontraumatic direct jugular, cephalic, or saphenous venipuncture, or from an indwelling central venous or arterial catheter. When blood samples were obtained from indwelling catheters, a discard sample of 3 times the volume of the catheter was removed prior to acquisition of the blood sample using a 3-syringe technique. Approximately 7.5 mL of whole blood was collected and divided between an activated clotting time (ACT) tube[a] (0.5 mL), a tube containing potassium EDTA[b] (0.5 mL), and 2 tubes containing 3.2% sodium citrate (1.8 mL and 4.5 mL).[c] The ACT tube was immediately used to determine the ACT using a human axilla for incubation.[20] The EDTA tube was submitted to the institution's laboratory for a platelet count[d,e,f] and slide analysis for platelet clumping. The 1.8 mL citrate tube was allowed to rest at room temperature for 30 minutes prior to TEG analysis. The 4.5 mL citrate tube was centrifuged for 15 minutes at 4°C (39°F) at 700 × *g*. The supernatant (citrated plasma) was immediately separated into polypropylene tubes and stored at –80°C until submission for batch analysis.

Coagulation testing

Citrated plasma was submitted to the Comparative Coagulation Section of the Animal Health Diagnostic Center at Cornell University for batch analysis of coagulation variables after no more than 6 months of storage. All of the assays were performed using an automated coagulation instrument.[g] A coagulation panel consisting of PT, aPTT, and clottable (Clauss) fibrinogen was performed using commercial reagents[h,i,j] and reaction conditions as previously described.[21] The fibrinogen content of the standard was measured by a gravimetric method.[22] Antithrombin (AT) activity was measured in a functional assay configured to measure thrombin inhibition (anti-IIa assay) using a commercial chromogenic kit.[k] Plasmin inhibition and plasminogen activity were measured using commercial chromogenic kits[l,m] configured to detect the amidolytic activity of plasmin. The plasminogen assay was modified by the substitution of urokinase,[n] rather than streptokinase, to activate plasminogen in the test sample, as previously described.[23] Protein C activity was measured using a chromogenic kit[o] as previously described.[24] The D-dimer concentration was measured using a quantitative, immunoturbidometric method, and commercial kit[p] as previously described.[25,26] Pooled canine plasma (prepared from 20 healthy, adult dogs) was used as the assay standard or control for all coagulation tests except the plasmin inhibition and D-dimer assays, which used the manufacturer's human calibration reagents.[q,r]

Thromboelastography

TEG was performed with recalcified citrated whole blood using a commercial thromboelastograph[s] according to the manufacturers' recommendations. For each analysis, 1 mL of citrated whole blood was placed into a vial containing kaolin[t] provided by the manufacturer. The kaolin-containing vial was then gently inverted 5 times to ensure mixing. Then 340 μL of kaolin-activated citrated whole blood was added to 20 μL of calcium chloride (0.2 M)[u] in warmed (37°C) TEG cups.[v] All tracings were recorded for a minimum of 120 minutes or until the maximum amplitude (MA) was reached. The variables reported for this study include reaction time (R, minutes), clot formation time (K, minutes), angle (α, degrees), maximum amplitude (MA, millimetres), clot strength (G, dyne/cm^2), and 30 minute lysis (LY30, %).

Acute traumatic coagulopathy

For the purpose of this study, ATC was defined as 1 or more of the following variables on hospital admission: ACT > 105 seconds, platelet count < the lower limit of the reference interval, PT or aPTT > 1.5 times the upper

limit of the reference interval, and MA or α < the lower limit of the reference interval.

Statistical analyses

Descriptive statistics (number, mean, SD, median, range) were calculated for all clinical, laboratory, coagulation, and TEG variables. Continuous variables were analyzed for standard normal distribution with a Shapiro-Wilk test and values not normally distributed were log transformed prior to analysis. All values were presented as mean and SD. Depending on normal distribution, a Pooled Student or Wilcoxon Mann–Whitney test was used to assess differences in the mean or median for clinical, laboratory, coagulation, and TEG variables between surviving and nonsurviving dogs. Univariate exact conditional logistic regression was used to assess clinical, laboratory, coagulation, and TEG variables as risk factors for the presence of BCH, necessity of blood product administration, and nonsurvival. Multivariate exact conditional logistic regression was then used to assess significant variables as risk factors for the presence of BCH, necessity of blood product administration, and nonsurvival when included with ATT and APPLE scores. Pearson's correlation analysis was used to estimate the correlation between coagulation and TEG variables and ATT score, APPLE-fast score, rectal temperature, pH, base excess (BE), lactate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). A value of $r^2 >$ 0.90 was considered an excellent correlation, $r^2 > 0.70$–0.89 was considered a very good correlation, $r^2 > 0.50$–0.69 was considered a good correlation, $r^2 > 0.20$–0.49 was considered a fair correlation, and $r^2 < 0.20$ was considered a poor correlation.

Univariate exact conditional logistic regression was used to assess rectal temperature, SBP, DAP, and MAP, ATT score, APPLE-fast score, pH, BE, and lactate as risk factors for ATC. A Wilcoxon Mann–Whitney test was used to assess the difference in survival between dogs with or without ATC. ANOVA for repeated measures was used to assess for significant changes over time in coagulation and TEG variables measured on admission and every other day until hospital discharge. Because coagulation variables were measured over time, the AKAIKE information criterion was used to determine an error structure for the auto-regression. The assumptions of the ANOVA were assessed by comprehensive residual analyses. Residuals were plotted against predicted values and explanatory variables (dog and day) to look for patterns in the data suggesting outliers or unequal variance. If the overall *f*-test was significant, a Dunnett's going back to baseline (admission) was applied. Data analyses were performed by use of computer software.[w] A value of $P < 0.05$ was considered significant for all comparisons.

Results

A total of 40 dogs were included in this study including 26 dogs enrolled at the Ontario Veterinary College Health Sciences Centre (OVC-HSC) and 14 dogs enrolled at North Carolina State University Veterinary Health Complex (NCSU-VHC). During the 18-month study period (June 2009–December 2010), 141 dogs were admitted to OVC-HSC following traumatic events. 115 dogs were excluded from the study for the following reasons: body weight < 10 kg ($n = 37$), presentation > 12 hours after the traumatic incident ($n = 33$), age < 1 year old ($n =$ 22), injury limited to an extremity ($n = 14$), anticipated < 24 hours of hospitalization ($n = 4$), prior administration of synthetic colloids ($n = 4$), and prior administration of hypertonic saline ($n = 1$). Admission and exclusion information was not available from NCSU-VHC as this information was lost while moving into a new hospital. Because the medical records coding system for diagnoses also changed, it was not possible to collect the information retrospectively either.

The included dogs were 50% female (2 intact females, 18 spayed females) and 50% male (8 intact males, 12 neutered males). Blunt trauma occurred in 80% (32/40) of dogs, all due to motor vehicle accidents. Penetrating trauma occurred in 20% (8/40) of dogs due to animal altercations (7/8, 88%) and gunshot wounds (1/8, 12%). Prior to admission, 5 dogs (13%) received glucocorticoids, 9 dogs (23%) received NSAIDs, and 1 dog (3%) received both glucocorticoids and NSAIDs. Admission clinical and laboratory variables from the dogs are included in Table 1. During hospitalization, no dogs received glucocorticoids and 26 dogs (65%) received NSAIDs including meloxicam[x] (19/26, 73%) or carprofen[y] (7/26, 27%). Almost half of the dogs (18/40, 45%) received oxygen supplementation, 6 dogs (15%) received synthetic colloids, 2 dogs (5%) received hypertonic saline, and none of the dogs received anticoagulant therapy during hospitalization. Evidence of BCH was present in 25% (10/40) of dogs and was evenly distributed between hemothorax (5/10, 50%) and hemoabdomen (5/10, 50%). Almost all of these dogs (8/10, 80%) received a blood product including whole blood (2/8, 25%), packed red blood cells (2/8, 25%), fresh frozen plasma (2/8, 25%), an autotransfusion (1/8, 12.5%), and all of the preceding 4 blood products (1/8, 12.5%). Thirty-one dogs survived (31/40, 77.5%); of the 9 (22.5%) nonsurvivors, 8 dogs (8/9, 89%) were euthanized due to a perceived grave prognosis and 1 dog (1/9, 11%) experienced cardiopulmonary arrest and died. No dogs were euthanized for financial reasons.

Table 1: Clinical and laboratory variables from surviving and nonsurviving dogs upon hospital admission within 12 hours following acute traumatic events

	All dogs			Survivors			Nonsurvivors		
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Weight (kg)	40	27.6	10.1	31	26.5	10.9	9	31.0	6.9
Age (years)	40	4.2	3.3	31	4.2	3.4	9	4.2	3.4
Hospital stay (days)	40	5.1	4.2	31	6.1	4.2	9	1.7	0.9
ICU stay (days)	37	3.6	2.2	28	4.2	2.2	9	1.7	0.9
Temperature (°C)	38	37.7	1.1	29	37.7	1.1	9	37.9	1.1
HR (per min)	40	119	39	31	112	34	9	142	46
RR* (per min)	27	40	17	21	40	17	6	40	20
SpO_2 (%)	24	97	3	19	96	4	5	97	4
MAP (mm Hg)	31	108	26	25	108	27	6	110	23
SAP (mm Hg)	39	147	34	31	148	29	8	141	49
DAP (mm Hg)	30	82	24	25	84	24	5	75	19
ATT score	40	5	2	31	4	2	9	7	2
APPLE-fast score	33	21	7	26	20	7	7	25	6
PCV (%)	40	44	10	31	43	9	9	47	13
TS (g/dL)	40	5.6	1.2	31	5.6	1.1	9	5.6	1.5
TS (g/L)	40	56	12	31	56	11	9	56	15
pH	39	7.34	0.06	31	7.35	0.05	8	7.31	0.08
PO_2 (mm Hg)	39	54.6	23.6	31	55.0	25.0	8	52.7	18.9
PCO_2 (mm Hg)	39	42.5	8.6	31	42.2	8.9	8	43.7	7.9
HCO_3 (mmol/L) (mEq/L)	39	22.4	3.1	31	22.7	3.0	8	21.3	3.4
Base excess (mmol/L) (mEq/L)	38	−3.1	3.0	30	−2.6	2.7	8	−4.6	3.8
Sodium (mmol/L) (mEq/L)	36	145	3	28	146	3	8	144	3
Potassium (mmol/L) (mEq/L)	36	3.7	0.3	28	3.7	0.3	8	3.6	0.4
Chloride (mmol/L) (mEq/L)	26	115	3	20	115	2	6	116	4
iCa (mmol/L)	36	1.31	0.08	28	1.31	0.08	8	1.28	0.08
iCa (mg/dL)	36	5.24	0.32	28	5.24	0.32	8	5.12	0.32
Lactate (mmol/L)	40	2.2	1.5	31	1.9	1.0	9	3.4	2.3
SO_2 (%)	39	79.0	14.6	31	79.8	12.7	8	75.9	21.5
Glucose (mmol/L)	40	7.2	1.9	31	7.2	1.6	9	7.3	2.8
Glucose (mg/dL)	40	129.7	34.2	31	129.7	28.8	9	131.5	50.5

HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ATT, animal trauma triage; APPLE, acute patient physiologic and laboratory evaluation; TS, total solids; iCa, ionized calcium.
*Dogs documented as "panting" did not have an RR recorded.

The first blood sample was collected a median of 6.25 hours (range, 1–12 hours) after the traumatic event. The majority of dogs (28/40, 70%) received IV crystalloids at the referring veterinary clinic or after hospital admission, but prior to collection of their first blood sample. Admission coagulation and TEG variables are listed in Table 2. Admission coagulation and TEG variables that predicted the presence of BCH and necessity of blood product administration are listed in Tables 3 and 4. At hospital admission, prolonged aPTT ($P = 0.008$, OR = 1.26, 95% CI = 1.04–1.66), decreased plasmin inhibition ($P = 0.033$, OR = 0.97, 95% CI = 0.93–1.00), decreased α ($P = 0.021$, OR = 0.93, 95% CI = 0.84–0.99), and decreased MA ($P = 0.038$, OR = 0.93, 95% CI = 0.86–1.00) were predictive of nonsurvival. Using multivariate analysis with APPLE-fast score to account for disease severity, only prolonged aPTT ($P = 0.004$, OR = 1.74, 95% CI = 1.10–4.16) and decreased α ($P = 0.048$, OR = 0.84, 95% CI = 0.84–1.00) remained predictive of non-survival. ROC curve analysis revealed that an aPTT ≥ 16.6 seconds (reference interval: 10–17 seconds) was 67% sensitive and 83% specific for predicting nonsurvival (Figure 1; AUC = 0.726). Using multivariate analysis with ATT score to account for injury severity, none of the coagulation or TEG variables were predictive of nonsurvival.

At hospital admission, aPTT was positively correlated with APPLE-fast score ($P < 0.001$, $r^2 = 0.35$), lactate concentration ($P < 0.001$, $r^2 = 0.35$), and negative base excess ($P = 0.001$, $r^2 = 0.27$); AT activity was negatively correlated with APPLE-fast score ($P < 0.001$, $r^2 = 0.35$); fibrinogen concentration was negatively correlated with ATT score ($P < 0.001$, $r^2 = 0.31$); and platelet count was positively correlated with MAP ($P = 0.007$, $r^2 = 0.29$). When assessing all coagulation and TEG variables measured during hospitalization, lactate concentration was positively correlated with ACT ($P < 0.001$, $r^2 = 0.29$), negatively correlated with fibrinogen concentration

Table 2: Coagulation and TEG variables from surviving and nonsurviving dogs upon hospital admission within 12 hours of acute traumatic events

			Survivors			Nonsurvivors			
Variable	**Units**	**Reference Interval**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	***P*-value**
ACT	Seconds	70–105	31	84	18	8	128	117	0.292
Platelet count*	$\times 10^3/\mu L$ ($\times 10^9/L$)	> 200	26	216	72	6	197	28	0.532
aPTT	**Seconds**	**10–17**	**29**	**14.6**	**2.2**	**9**	**23.2**	**13.0**	**0.008**
PT	Seconds	11–16	29	14.1	1.5	9	19.2	10.8	0.055
Fibrinogen	mg/dL	147–479	29	425	361	9	272	197	0.073
Fibrinogen	μmol/L	4.3–14.1	29	12.5	10.6	9	8.0	5.8	0.073
Antithrombin	% activity	65–145	29	97	17	9	80	32	0.121
D-dimer†	ng/mL	< 250	29	788	1039	9	1065	922	0.264
Protein C	% activity	75–135	29	81	19	9	64	33	0.118
Plasmin inhibition	**% activity**	**65–120**	**29**	**89**	**27**	**9**	**63**	**37**	**0.033**
Plasminogen	% activity	60–170	29	94	26	9	82	23	0.254
R	Minutes	1.7–6.1	31	3.4	1.1	9	3.3	0.9	0.697
K	Minutes	0.9–3.1	31	1.9	0.7	9	5.0	5.3	0.622
α	**Degrees**	**48.7–75.2**	**31**	**65.3**	**7.1**	**9**	**54.2**	**19.2**	**0.021**
MA	**mm**	**46.0–64.2**	**31**	**58.3**	**8.5**	**9**	**48.3**	**18.2**	**0.038**
G	dynes/cm^2	4.2–8.0	31	7.6	3.3	9	5.7	3.5	0.121
LY30	%	0.0–2.0	31	0.4	0.7	9	6.3	11.4	0.078

ACT, activated clotting time; aPTT, activated partial thromboplastin time; PT, prothrombin time; R, reaction time; K, time to clot formation; α, angle; MA, maximum amplitude; G, clot strength; LY30, 30 minute clot lysis.

*Platelet counts with platelet clumps observed on the blood smear were excluded from analyses.

†Not normally distributed (log transformed for analysis). **Bolded** variables were significantly different ($P < 0.05$) between survivors and non-survivors. ACT reference interval determined at OVC-HSC using 13 healthy dogs.[26] Reference intervals for conventional coagulation tests were determined by the Comparative Coagulation Section of the Animal Health Diagnostic Center at Cornell University using 30–50 healthy adult dogs. TEG reference intervals determined at OVC-HSC using 40 healthy dogs.[27]

Table 3: Admission coagulation and TEG variables assessed as significant risk factors for the presence of BCH in dogs presenting within 12 hours acute traumatic events

	Univariate analysis			**Multivariate analysis with ATT score**			**Multivariate analysis with APPLE-fast score**		
Variable	***P*-value**	**Odds ratio**	**95% CI**	***P*-value**	**Odds ratio**	**95% CI**	***P*-value**	**Odds ratio**	**95% CI**
Platelet count	**0.006**	**0.98**	**0.96–0.99**	**0.038**	**0.98**	**0.97–0.99**	**0.021**	**0.980**	**0.95–0.99**
aPTT	0.024	1.20	1.02–1.55	0.232			0.564		
Fibrinogen	0.035	0.99	0.99–1.00	0.243			0.315		
Antithrombin	0.029	0.96	0.92–1.00	0.220			0.525		
D-dimer	0.031	1.00	1.00–1.01	0.031	1.00	1.00–1.01	0.034	1.001	1.00–1.01
Protein C	0.003	0.94	0.88–0.98	0.099			0.330		
Plasmin inhibition	0.019	0.96	0.93–1.00	0.168			0.474		
Plasminogen	0.037	0.97	0.93–1.00	0.077			0.056		
α	0.004	0.90	0.82–0.97	0.013	0.90	0.81–0.98	0.146		
MA	0.002	0.89	0.79–0.96	0.007	0.89	0.79–0.97	0.102		
G	0.003	0.59	0.39–0.87	0.009	0.59	0.35–0.90	0.080		

BCH, body cavity hemorrhage; aPTT, activated partial thromboplastin time; α, angle; MA, maximum amplitude; G, clot strength. **Bolded** variable is considered the strongest predictor of the presence of BCH.

($P < 0.001$, $r^2 = 0.25$), negatively correlated with plasmin inhibition ($P < 0.001$, $r^2 = 0.35$), positively correlated with K ($P < 0.001$, $r^2 = 0.45$), negatively correlated with α ($P < 0.001$, $r^2 = 0.29$), negatively correlated with MA ($P < 0.001$, $r^2 = 0.34$), and positively correlated with LY30 ($P < 0.001$, $r^2 = 0.37$) and pH was positively correlated with plasmin inhibition ($P < 0.001$, $r^2 = 0.20$) and negatively correlated with K ($P < 0.001$, $r^2 = 0.22$). None of the coagulation or TEG variables were correlated with rectal temperature, SBP, or DAP measured on admission or combined throughout hospitalization.

When ATC was defined as at least 1 abnormal admission coagulation or TEG variable, 38% (15/40) of dogs were diagnosed with ATC. Those dogs had an increased risk of blood product administration ($P = 0.0075$, OR = 16.4, 95% CI = 1.74–1000) and their mortality rate was

Table 4: Coagulation and TEG variables assessed as significant risk factors for necessity of blood product administration in dogs upon hospital admission within 12 hours of acute trauma

	Univariate analysis			Multivariate analysis with ATT score			Multivariate analysis with APPLE-fast score		
Variable	***P*-value**	**Odds ratio**	**95% CI**	***P*-value**	**Odds ratio**	**95% CI**	***P*-value**	**Odds ratio**	**95% CI**
Platelet count	**<0.001**	**0.96**	**0.93–0.99**	**<0.001**	**0.95**	**0.88–0.98**	**0.006**	**0.87**	**0.40–0.99**
aPTT	0.008	1.25	1.04–1.64	0.081			0.163		
PT	0.022	1.30	1.02–2.08	0.130			0.085		
Fibrinogen	0.009	0.99	0.98–1.00	0.253			0.058		
Antithrombin	0.002	0.93	0.87–0.98	0.033	0.94	0.87–0.99	0.061		
Protein C	**0.001**	**0.92**	**0.85–0.98**	**0.011**	**0.91**	**0.81–0.99**	**0.031**	**0.94**	**0.87–0.99**
Plasmin inhibition	0.036	0.97	0.93–1.00	0.475			0.246		
α	**0.001**	**0.88**	**0.78–0.96**	**0.030**	**0.90**	**0.80–0.99**	**0.003**	**0.82**	**0.60–0.96**
MA	**< 0.001**	**0.87**	**0.76–0.95**	**0.025**	**0.88**	**0.76–0.99**	**0.006**	**0.85**	**0.65–0.97**
G	**0.002**	**0.53**	**0.29–0.83**	**0.038**	**0.60**	**0.32–0.98**	**0.008**	**0.50**	**0.18–0.88**

aPTT, activated partial thromboplastin time; PT, prothrombin time; α, angle; MA, maximum amplitude; G, clot strength. **Bolded** variables are considered strong predictors of the necessity of blood product administration.

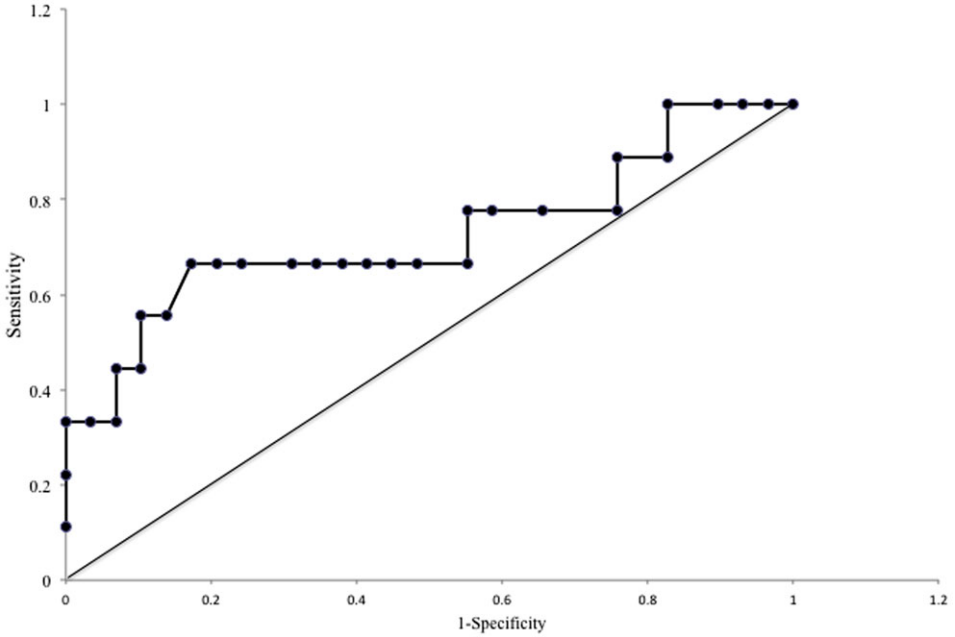

Figure 1: ROC curve analysis of aPTT prolongation as a predictor of nonsurvival following acute traumatic incidents in dogs.

27%, compared to 20% for dogs not diagnosed with ATC ($P = 0.484$). When ATC was defined as at least 2 abnormal admission coagulation or TEG variables, 15% (6/40) of dogs were diagnosed with ATC. Those dogs had increased APPLE-fast scores ($P = 0.002$, OR = 1.43, 95% CI = 1.10–2.24), decreased SBP ($P = 0.002$, OR = 0.92, 95% CI = 0.82–0.98), and increased lactate concentration ($P = 0.011$, OR = 2.34, 95% CI = 1.20–5.51) and their mortality rate was 50%, compared to 18% for dogs not diagnosed with ATC ($P = 0.131$). A diagnosis of ATC on admission using any number of abnormal coagulation or TEG variables was not predicted by rectal temperature, DBP, or MAP.

Measured coagulation and TEG variables throughout hospitalization in surviving dogs are recorded in Table 5. Compared to admission, platelet count decreased on day 3 and increased on day 5 and aPTT increased on day 3 and then returned to baseline on day 5. Conversely, fibrinogen concentration, protein C activity, plasmin inhibition, α, MA, and G increased and K decreased throughout hospitalization compared to baseline.

Discussion

In this group of severely injured dogs, approximately one quarter of dogs exhibited BCH and 80% of those

Table 5: Coagulation and TEG variables on days 1, 3, and 5 following acute traumatic incidents in surviving dogs

			Day 1			Day 3			Day 5		
Variable	**Units**	**Reference interval**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
ACT*	Seconds	70–105	31	84	18	30	98	21	17	96	21
Platelet count*‡	$\times 10^3/\mu L$	> 200	26	216	72	26	175	80	16	248	109
aPTT*	Seconds	10–17	29	14.6	2.2	28	17.5	8.8	16	15.0	3.8
PT	Seconds	11–16	29	14.1	1.5	28	13.7	1.1	16	13.4	1.8
Fibrinogen*†	mg/dL	147–479	29	425	235	28	957	225	16	983	226
Fibrinogen*†	μmol/L	4.3–14.1	29	12.5	6.9	28	28.1	6.6	16	28.9	6.6
Antithrombin	% activity	65–145	29	97	17	28	90	18	16	96	17
D-dimer	ng/mL	< 250	29	789	1040	28	645	670	16	650	438
Protein C*†	% activity	75–135	29	81	19	28	101	23	16	109	22
Plasmin inhibition*†	% activity	65–120	29	89	27	28	142	27	16	134	24
Plasminogen†‡	% activity	60–170	29	94	26	28	100	31	16	139	45
R	Minutes	1.7–6.1	31	3.5	1.1	30	3.9	1.5	17	3.6	1.2
K*†	Minutes	0.9–3.1	31	1.9	0.7	30	1.4	0.4	17	1.2	0.5
α*†‡	Degrees	48.7–75.2	31	65.3	7.1	30	69.8	5.6	17	74.1	5.0
MA*†	mm	46.0–64.2	31	58.3	8.5	30	70.0	7.3	17	72.8	10.3
G*†	$dyne/cm^2$	4.2–8.0	31	7.6	3.3	30	12.8	5.2	17	15.2	5.6
LY30	%	0.0–2.0	31	0.4	0.7	30	0.2	0.4	17	0.5	1.4

ACT, activated clotting time; aPTT, activated partial thromboplastin time; PT, prothrombin time; R, reaction time; K, time to clot formation; α, angle; MA, maximum amplitude; G, clot strength; LY30, 30 minute clot lysis.

*Significant difference between measurements on Day 1 and Day 3 ($P < 0.05$).

†significant difference between measurements on Day 1 and Day 5 ($P < 0.05$.

‡significant difference between measurements on Day 3 and Day 5 ($P < 0.05$). ACT reference interval determined at OVC-HSC using 13 healthy dogs.[26] Reference intervals for conventional coagulation tests were determined by the Comparative Coagulation Section of the Animal Health Diagnostic Center at Cornell University using 30–50 healthy adult dogs. TEG reference intervals determined at OVC-HSC using 40 healthy dogs.[27]

dogs required transfusion of blood products. Decreased platelet count was predictive of both the presence of BCH and necessity of blood product administration, whereas, TEG variables consistent with decreased clot formation and clot strength were predictive of the requirement for blood product administration. These findings are consistent with human studies revealing that adult trauma patients with evidence of decreased clot strength as defined by TEG-MA < 50 mm[29] or rotational thromboelastometry (ROTEM) clot amplitude at 5 minutes ≤ 35 mm[30] after trauma are more likely to require packed red blood cell, fresh frozen plasma, or platelet transfusions. Similarly, people diagnosed with ATC based on prolongation of aPTT, PT, or international normalized ratio (INR) also have increased transfusion requirements.[12,31,32] Interestingly, one study revealed that PT and TEG-platelet mapping were predictive of the need for transfusions; however, routine TEG variables including MA were not.[33] However, another study using the rapid-TEG protocol, which involves dual activation of noncitrated blood with both tissue factor and kaolin, showed that TEG-R was superior to PT in guiding transfusion requirements such as the need for fresh frozen plasma after trauma in people.[34] In the present study, although PT and aPTT were predictors of the presence of BCH or necessity of blood product administration on univariate analysis, multivariate analysis with APPLE-fast score and ATT score revealed that platelet count and TEG variables were better predictors of the presence of BCH or requirement for blood product transfusion.

In this group of traumatized dogs, aPTT was the best predictor of nonsurvival when taking into account disease severity by including APPLE-fast score in the multivariate analysis. Conversely, when ATT score was used in the multivariate analysis to account for injury severity, none of the coagulation or TEG variables remained associated with nonsurvival. This suggests that in this group of traumatized dogs, ATT score was a better predictor of survival compared to the measured coagulation and TEG variables. Several studies in people have investigated the ability of coagulation test results to predict outcome following major trauma. An INR > 1.5 or aPTT > 60 seconds is a significant independent risk factor associated with death within 24 hours of major trauma in people.[35] Similar findings are apparent in other human studies revealing that patients with a prolonged PT or INR > 1.5 have a 4-fold higher mortality than those without a prolonged PT.[9–12] The most

recent retrospective multicenter human study investigating admission INR in 3,646 severely injured trauma patients revealed that people with an INR > 1.5 had a mortality rate of 28%, which was 4-fold higher than those patients with a normal INR.[12] While PT was not predictive of outcome in the present study, aPTT appears to be the strongest predictor of nonsurvival in this group of traumatized dogs. When using a cut-off of ≥ 16.6 seconds, which is near the upper end of the reference interval (17 seconds) for the laboratory used, aPTT predicted nonsurvival with moderate sensitivity (67%) and high specificity (83%), suggesting its potential utility as a prognostic indicator in dogs following acute trauma.

TEG and ROTEM have also been investigated in people as predictors of outcome following severe trauma. Studies investigating human trauma patients reveal that TEG and ROTEM variables indicative of decreased clot strength and increased fibrinolysis are associated with increased mortality.[29,33,36–38] Specifically, MA is significantly smaller in people that die following trauma and remains an independent predictor of mortality, even after adjusting for injury severity and age.[29] In the present study, univariate analysis revealed that decreased MA was associated with nonsurvival in dogs following trauma. Additionally, hyperfibrinolysis, as measured with TEG or ROTEM, is also associated with increased mortality in severely traumatized people.[36–38] Although hyperfibrinolysis was not significantly associated with mortality in the present study, increases in clot lysis at 30 minutes trended toward significance in nonsurviving dogs. Interestingly, when studies compare traditional coagulation tests with TEG variables, TEG variables are more sensitive for detecting hypercoagulability and hyperfibrinolysis.[39,40] Therefore, given the increased availability of viscoelastic testing such as TEG and ROTEM in veterinary hospitals and its point-of-care utility, further investigation of decreased clot strength and hyperfibrinolysis using these tests is warranted in traumatized dogs.

Several factors are believed to contribute to the development of coagulopathies following trauma including the degree of tissue injury and shock.[13–15] Although correlation does not equal causation, there were several clinical and laboratory variables correlated with coagulation and TEG variables in the present study, which might have contributed to the coagulopathies that occurred. Most notably, disease severity as indicated by increased APPLE-fast score, was moderately correlated with increased PTT. Similarly, increased injury severity as indicated by increased ATT score, was mildly correlated with decreased fibrinogen. Therefore, in this group of traumatized dogs, more severe injuries and disease correlated with measures of hypocoagulability. Injury severity is closely related to the incidence of ATC in people. A large retrospective study investigating 1,867 human trauma patients demonstrated that patients with higher injury severity scores (ISSs) were more likely to have significant coagulopathies.[9] This is suspected to be the result of tissue injury and endothelial damage, which causes exposure of subendothelial type III collagen and tissue factor that subsequently activate thrombin and fibrin formation.[15]

It appears that hypoperfusion also has a very important role in the development of coagulopathies, independent of the severity of injury and soft tissue trauma. Human trauma patients with high ISSs do not exhibit coagulopathies when hypoperfusion is not present; conversely, those with lower ISSs and concurrent negative BE have prolonged PT and aPTT.[41] Similarly, laboratory measures of hypoperfusion in the present study including increased lactate, negative BE, and decreased pH were moderately correlated with hypocoagulability including increased ACT and PTT, decreased fibrinogen, and decreased α and MA. Increased lactate and decreased pH were also mildly correlated with measures of hyperfibrinolysis including decreased plasmin inhibition and increased LY30. The mechanism by which shock induces coagulopathies is somewhat unclear; however, hypoperfusion seems to lead to an anticoagulant and hyperfibrinolytic state by causing widespread endothelial disruption and activation, resulting in increased thrombomodulin and activation of protein C.[15] The activated protein C might then lead to consumption of plasminogen activator inhibitor-1 or decreased activation of thrombin-activatable fibrinolysis inhibitor, thereby resulting in a hyperfibrinolytic state.[15] Additionally, hypoperfusion prevents removal of residual thrombin from the site of vascular injury, thereby perpetuating continued coagulation and anti-fibrinolysis.[15]

Even though acidosis can occur in trauma patients due to shock or administration of large volumes of chloride-containing fluids, reductions in the activity of coagulation factor complexes on cell surfaces do not occur unless the pH is < 7.2.[15] An acidosis of this severity does not occur commonly in dogs following trauma.[4] And while decreased pH was correlated with some hypocoagulable variables in the present study, it is more likely that the hypocoagulability was due to decreased perfusion and increased lactate, rather than the acidosis itself, as the average pH in this group of dogs was 7.34. Similarly, although hypothermia is suggested to contribute to the development of coagulopathies after trauma, the degree of hypothermia required to induce a coagulopathy (< 34°C) rarely occurs in patients with naturally occurring trauma.[15] Rectal temperature was not correlated with any of the coagulation or TEG variables in dogs in the present study.

Unfortunately, no formal definition exists for ATC; therefore, comparing studies that investigate risk factors for or consequences of ATC is difficult. A qualitative international survey of clinical practice among senior physicians revealed that physicians diagnose ATC based on blood loss, body temperature, pH, platelet count, PT, aPTT, or overall clinical assessment.[42] Given the disparity among respondents, the survey highlighted the need for a common definition of ATC, as well as a standardized approach to treatment.[42] In the present study, 50% prolongations in PT or aPTT, as well as deviations of other coagulation or TEG variables outside of the reference interval, were arbitrarily chosen to diagnose ATC in dogs. Using one or more of these abnormal coagualation tests, dogs diagnosed with ATC in the present study were more likely to require a blood product transfusion. Using 2 or more of these abnormal coagulation tests, dogs in the present study diagnosed with ATC had almost a 3-fold higher mortality rate than those not diagnosed with ATC, although the difference was not statistically significant.

Interestingly, a diagnosis of ATC using 2 or more abnormal coagulation or TEG variables in dogs in the present study occurred more commonly in dogs with increased APPLE-fast scores, decreased SBP, and increased lactate, consistent with proposed etiologies for ATC including increased injury severity and shock. Many human studies have also investigated risk factors for ATC following severe trauma and consistently find that increased injury severity and shock occur more commonly in patients with ATC. A prospective study investigating 436 human patients with traumatic brain injury revealed that decreased Glasgow coma scale scores, increased injury severity scores, and decreased systolic blood pressure were all independent risk factors for ATC.[43] Another study investigating 8,724 human trauma patients revealed an incidence of ATC of 41% in people with a lactate > 2.2 mmol/L versus an incidence of 25% in people with a normal lactate.[11] Thus, increased injury severity and decreased perfusion or shock appear to be consistently associated with and perhaps prerequisites for a diagnosis of ATC in people and dogs.

While many studies investigate coagulation variables at the time of injury or upon hospital admission after trauma, few studies investigate the change in coagulation variables over time. In the present study, dogs appeared to exhibit coagulation and TEG variables consistent with hypocoagulability after the traumatic incident, but the variables seemed to normalize or become relatively hypercoagulable over time. Studies in people investigating coagulation variables over time typically compare variables from baseline or at the time of the injury to postresuscitation or in-hospital. These studies reveal that fluid resuscitation causes only minor changes in TEG-R[44] and that other TEG variables (MA and α) become relatively hypercoagulable over time.[39] However, other studies investigating human trauma patients with less severe or nonbleeding injuries (eg, burn patients) reveal that the majority of people are hypercoagulable on admission TEG analysis and normalize over time.[40,45,46] The relatively hypercoagulable changes over time in the present study might have also been due to the development of anemia, which can alter blood viscosity secondary to a decrease in RBC mass and relative increase in plasma protein concentration. In a previous study, when the blood of healthy dogs was diluted with aliquots of autologous plasma to decrease the Hct measurement, the MA increased.[z] However, the effect of anemia on TEG variables measured in vivo is unknown at this time.

Limitations exist in this study and should be considered when interpreting the results. First, dogs receiving glucocorticoids or NSAIDs, both of which can influence coagulation status, were not excluded from enrollment.[47,48] Unfortunately, given that the study took place at referral hospitals, it was common that dogs would initially be treated by a referring veterinarian and glucocorticoids or NSAIDs administered prior to hospital admission. Additionally, dogs also received NSAIDs after admission, which could have affected coagulation and TEG variables measured over time. Platelet function tests were not specifically performed in the present study and would be needed to further investigate the effect of glucocorticoid or NSAID administration in dogs following trauma. Secondly, fluid resuscitation occurred in the majority of dogs prior to the initial sample collection. Although fluid resuscitation is a proposed factor contributing to ATC, human studies suggest that hemodilution caused by fluid resuscitation has minimal effect on coagulation and TEG variables.[9,44] Additionally, in vitro studies suggest that 20–40% hemodilution with crystalloids or synthetic colloids is required to alter coagulation tests.[49] While it was not possible to quantify the amount of fluid administered intravenously to all dogs enrolled in the present study, it is clinically unlikely that the volume was sufficient to result in the degree of hemodilution required to affect measured coagulation and TEG variables. Thirdly, a small number of dogs in the present study received hypertonic saline, synthetic colloids, or blood products during hospitalization, which could also have affected coagulation or TEG variables measured over time.

Additional limitations include that blood collection was not standardized with regards to the sampling location or procedure (eg, vacutainer aspiration) and although TEG analyses were performed at 2 different institutions only 1 reference range was used. Recent investigations in dogs reveal that the method of blood sampling can significantly affect TEG results and should be taken

into account when designing studies.[50,51] However, the use of kaolin activation for TEG analysis in the present study might have mitigated some of the effects of non-standardized sampling and interoperator variability.[28,50] Additionally, it is unclear whether reference ranges for TEG must be established at each individual institution, or whether one reference range can be used. One human study investigating TEG-ROTEM reference ranges from 6 different institutions found that the reference ranges were not statistically different from one another, therefore, one reference range could be used.[52] Finally, the results of this study should be interpreted with caution, given that a small number of dogs was included, specifically those that had evidence of BCH, required blood transfusions, or died. Therefore, some of the prediction analyses were underpowered and most of the variables had fair correlation. The results also do not confirm that any of the coagulation tests are superior to clinical assessment regarding the requirement for blood product administration or prediction of outcome. Larger prospective studies are needed to confirm these results and strengthen the conclusions.

Conclusions

In this group of dogs, hypocoagulability and decreased clot strength were risk factors for the presence of BCH or the need for blood product administration after severe trauma. Likewise, prolonged aPTT was strongly predictive of nonsurvival and was also correlated with increased disease severity and decreased perfusion as measured by increased lactate and negative base excess. ATC, as defined by one or more abnormal coagulation or TEG variables, predicted the requirement for blood product administration, whereas ATC, as defined by two or more abnormal coagulation or TEG variables, was diagnosed in a small number of dogs whose mortality rate almost three times higher than those dogs not diagnosed with ATC. Therefore, in dogs presenting with severe traumatic injuries and hypoperfusion, measurement of TEG and aPTT should be considered to support clinical assessments in predicting the need for blood product administration and survival.

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Footnotes

[a] Actalyke MAX-ACT, Helena Laboratories, Beaumont, TX.
[b] Capiject, Terumo Medical Corporation, Elkton, ND.
[c] BD Vacutainer, Franklin Lakes, NJ.
[d] Advia 2120, Siemens Healthcare Diagnostics, Tarrytown, NY.
[e] Advia 120, Siemens Diagnostics, Deerfield, IL.
[f] HemaTrue Veterinary Hematology Analyzer, Heska Corporation, Loveland, CO.
[g] STA Compact, Diagnostica Stago, Parsippany, NJ.
[h] Dade Actin FS, Dade Behring, Newark, DE.
[i] Thromboplastin LI, Helena Diagnostics.
[j] Fibrinogen, Diagnostica Stago, Parsippany, NJ.
[k] Stachrom ATIII, Diagnostica Stago.
[l] Stachrom Antiplasmin, Diagnostica Stago.
[m] Stachrom Plasminogen, Diagnostica Stago.
[n] Human urokinase, American Diagnostica, Stamford, CT.
[o] Stachrom Protein C, Diagnostica Stago.
[p] HemosIL D-dimer, Instrumentation Laboratory, Bedford, MA.
[q] HemosIL D-dimer calibrator, Instrumental Laboratory.
[r] Unicalibrator, Diagnostica Stago.
[s] TEG 5000, Thromboelastograph Hemostasis Analyzer, Haemonetics Corporation, Braintree, MA.
[t] TEG Hemostasis System Kaolin, Haemonetics Corporation.
[u] TEG Hemostasis System Calcium Chloride, Haemonetics Corporation.
[v] TEG Hemostasis System Plain Cups and Pins, Haemonetics Corporation.
[w] SAS OnlineDoc 9.1.3, SAS Institute, Cary, NC.
[x] Metacam, Boehringer Ingelheim, Burlington, ON.
[y] Rimadyl, Pfizer Animal Health, Kirkland, QC.
[z] Jacquith SD, Brown AJ, Scott MA. Effects of decreased hematocrit on canine thromboelastography (abstr). J Vet Emerg Crit Care 2009; 19(suppl 1):A4.

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